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Monitoring Technologies in Acute Care Environments

A Comprehensive Guide to Patient Monitoring Technology

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Preface

This book was written by world-renowned experts who specialize in developing, refining, and testing the technology that makes modern-day clinical monitoring possible. These individuals would like to share with you their excitement for what makes monitoring happen across a variety of acute care settings including the operating room, emergency department, and intensive care unit. Our goal in writing *Monitoring Technologies in Acute Care Environments* was to provide a concise, easy-to-use, and up-to-date introduction to how these technologies work.

Any individual working in an acute care environment will find this unique book incredibly useful – it covers both basic and advanced topics and includes an introductory section designed to help apply theoretical knowledge to real patient situations. As educators, we are indebted to generations of students and trainees who inspired us to write this text, and we are especially thankful for the support and expertise of our contributors at Vanderbilt University, the University of California at Irvine, and beyond. As physicians, we are privileged to work with an incredible group of individuals who support our clinical activities each day. This includes our surgical colleagues, nursing staff, and support services.

We are especially indebted to a number of individuals whose unending support and encouragement made this work possible. These include Drs. Warren Sandberg and Zeev Kain. We would also like to thank Diane Lamsback, Shelley Reinhardt, Joanna Perey, and the rest of the Springer team for making this manuscript possible. Finally, a special thanks to Judd Taback, Katharine Nicodemus, David and Josh Ehrenfeld, along with Claire, Elias, Esther, Gabrielle, and Dominique Cannesson for their tireless support, encouragement, and guidance.

As you discover the exciting world of monitoring, we hope that you find *Monitoring Technologies in Acute Care Environments* an essential tool!

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Part I

Fundamental Principles of Monitoring

Overview of Clinical Monitoring

1

James F. Szocik

What Is the Purpose of Monitoring?

Why do we monitor? Monitoring, in the best circumstances, results in an improved diagnosis, allowing for more efficacious therapy. This was recognized over a century ago by the noted neurosurgeon, Harvey Cushing, to quote:

> In all serious or questionable cases the patient's pulse and blood-pressure, their usual rate and level having been previously taken under normal ward conditions, should be followed throughout the entire procedure, and the observations recorded on a plotted chart. Only in this way can we gain any idea of physiological disturbances—whether given manipulations are leading to shock, whether there is a fall of blood-pressure from loss of blood, whether the slowed pulse is due to compression, and so on. [1]

Monitoring also allows titration of medication to a specific effect, whether it is a specific blood pressure, pain level, or electroencephalogram (EEG) activity. Despite all our uses of monitoring and technologies, clear data on their benefit is limited [2, 3]. Use of monitoring may not markedly change outcomes, despite changing intermediary events. However, simple logic dictates that we still need to monitor our patients, i.e., we do not need a randomized controlled trial (RCT) to continue our practice. This was humorously pointed out in a British Medical Journal article regarding RCT and parachutes: To paraphrase, those who don't believe parachutes are useful since they haven't been studied in an RCT, should jump out of a plane without one [4]. Our ability to monitor has improved over the years, changing from simple observation and basic physical exam to highly sophisticated technologies. No matter how simple or complicated our monitoring devices or strategies, all rely on basic physical and physiological principles.

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History of Monitoring

Historically, patients were monitored by simply observing or palpating or listening: Is the skin pink? Or blue? Or pale? Palpating the pulse, is it strong, thready, etc.? Are respirations audible as well as visible? Monitoring has progressed from these large, grossly observable signals, recorded on pen and paper, to much smaller, insensible signals, and finally to complex analyzed signals, able to be stored digitally and used in control loops.

Pressure Monitoring

These first observations as referenced by Dr. Cushing involved large signals that are easy to observe without amplification (e.g., inspiratory pressure, arterial pressure, venous pressure via observation of neck veins). Pressure was one of

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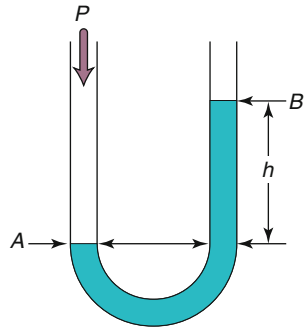

P = density • g • h,

Where density is the mass per volume of the indicator fluid, g is the acceleration of gravity, and h is the height difference between the menisci (due pressure [P]).

Fig. 1.1 Manometry. A difference in gas pressure (P) in the two arms of the manometer tube performs work by moving the indicator fluid out of the higher-pressure arm until it reaches that point where the gravitational force (g) on the excess fluid in the low-pressure arm balances the difference in pressure. If the diameters of the two arms are matched, then the difference in pressure is a simple function of the difference in height (h) of the two menisci (Reproduced from Rampil et al. [6]; with kind permission from Springer Science + Business Media B.V.)

the first variables to be monitored as the signal is fairly large, either in centimeters of water or millimeters of mercury. These historical units were physically easy to recognize and had a real-world correlate, i.e., the central venous pressure rose to a particular height in a tube marked with a scale, or the Korotkoff sounds were auscultated when the mercury column was at specific height. The use of the metric system and Systeme International is slowly replacing these units.

Monitoring pressure, while a large observable signal, is actually quite complex. In 1714 when Stephen Hales first directly measured arterial pressure in a horse by using a simple manometer, the column of blood rose to 8 ft 3 in. above the left ventricle [5]. Due to the height of the column, inertial forces, and practicality, this method is not used today. Pressures in the living organism are not static, but are dynamic and changing. Simple manometry as shown in Fig. 1.1 (allowing fluid to reach its equilibrium state against gravity in a tube) worked well for slowly changing pressures such as venous pressure, but the inertia of the fluid does not allow for precise measurement of the dynamic changes in arterial pressure [7]. Indirect measurement of blood pressure was pioneered by the method of Scipione Riva-Rocci in 1896 wherein the systolic blood pressure was determined by inflating a cuff linked to a mercury manometer until the radial pulse was absent. In 1905 Nicolai Korotkoff discovered that by auscultation, one could infer the diastolic pressure as well [5, 8]. In current use, arterial blood pressure is measured using computer-controlled, automated, noninvasive devices [9] or arterial cannulation [10] as well as the older methods. These methods may not have complete agreement, noninvasive blood pressure (NIBP) reading higher than arterial blood pressure during hypotension and lower during hypertension [11]. Use of the Riva-Rocci method (modified by using a Doppler ultrasound probe for detection of flow) has been reported to measure systolic blood pressure in patients with continuous flow left ventricular assist devices as the other noninvasive methods cannot be used [12]. What is old (measuring only systolic blood pressure by an occlusive method) is new again.

Development of pressure transducers as shown in Fig. 1.2 allowed analysis of the waveform to progress. Multiple technologies for pressure transducers exist. A common method is to use a device that changes its electrical resistance to pressure. This transducer is incorporated into an electronic circuit termed a Wheatstone bridge, wherein the changing resistance can be accurately measured and displayed as a graph of pressure versus time. Piezoelectric pressure transducers also exist which directly change their voltage output related to the pressure. These technologies, along with simple manometry, can be used to measure other pressures such as central venous pressure, pulmonary artery pressure, and intracranial pressure. The physiological importance

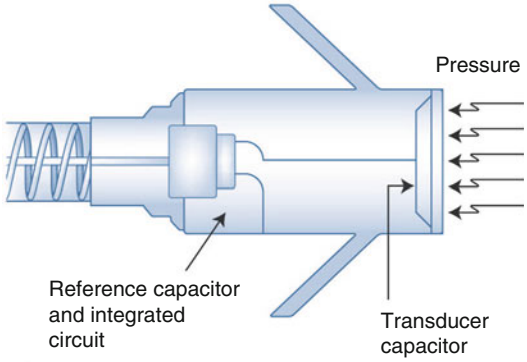

Fig. 1.2 Variable capacitance pressure transducers. Most pressure transducers depend on the principle of variable capacitance, in which a change in pressure alters the distance between the two plates of a capacitor, resulting in a change in capacitance. Deflection of the diaphragm depends on the pressure difference, diameter to the fourth power, thickness to the third power, and Young's modulus of elasticity (Reproduced from Cesario et al. [13]; with kind permission from Springer Science+Business Media B.V.)

and clinical relevance of course depends on all of these as well as the method of measurement.

Information about the state of the organism can be contained in both the instantaneous and long epoch data. Waveform analysis of the peripheral arterial signal, the pulse contour, has been used to try and determine stroke volume and cardiac output [7, 14]. Looking at a longer time frame, the pulse pressure variation induced by the respiratory signal has been analyzed to determine the potential response to fluid therapy [15]. Electronic transducers changed the pressure signal into an electronic one that could be amplified, displayed, stored, and analyzed.

Electrical Monitoring

With the advent of technology and electronics (and the elimination of flammable anesthetic agents) in the twentieth century, monitoring accelerated. Within the technological aspects of monitoring, the electromagnetic spectrum has become one of the most fruitful avenues for monitoring. Electrical monitoring yields the electrocardiogram (ECG), electroencephalogram (EEG) (raw and processed), somatosensory-evoked potentials (SSEP), and neuromuscular block monitors (simple twitch and acceleromyography). We could now measure the electrical activity of the patient, both for cardiac and neurologic signals. Computers facilitate analysis of complex signals from these monitors.

The first electrocardiogram was recorded using a capillary electrometer (which involved observing the meniscus of liquid mercury and sulfuric acid under a microscope) by AD Waller who determined the surface field lines of the electrical activity of the heart [16]. Einthoven used a string galvanometer in the early 1900s, improving the accuracy and response time over the capillary electrometer [17]. In 1928, Ernstene and Levine compared a vacuum tube amplifier to Einthoven's string galvanometer for ECG [18], concluding that the vacuum tube device was satisfactory. The use of any electronics in the operating theater was delayed until much later because the electronics were an explosion hazard in the presence of flammable anesthetics such as ether. Early intraoperative ECG machines were sealed to prevent any flammable gases or vapors from entering the area where ignition could occur.

The electroencephalogram (EEG) records the same basic physiology as the ECG (electrical activity summated by numbers of cells). However, the amplitude is tenfold smaller and the resistance much greater, creating larger technological hurdles. Using a string galvanometer, Berger in 1924 recorded the first human EEG from a patient who had a trepanation resulting in exposure of the cortex [19]. Further refinements led to development of scalp electrodes for the more routine determination of EEG. Processing the EEG can take the complex signal and via algorithms simplify it to a single, more easily interpreted number. The raw, unprocessed EEG still has value in determining the fidelity of the simple single number often derived from processed EEG measurements [20]. Somatosensory-evoked potentials can be used to evaluate potential nerve injury intraoperatively by evaluating the tiny signals evoked in sensory pathways and summating them over time to determine a change in the latency or amplitude of the signal [21].

The simple "twitch" monitor used to detect the degree of neuromuscular blockade caused by administration of either depolarizing or non-depolarizing muscle relaxants is a form of active electrical monitoring. Four supramaximal input stimuli at 0.5-s intervals (2 Hz) stimulate the nerve and the response is observed. Rather than simply seeing or feeling the "twitch," a piezoelectric wafer can be attached to the thumb and the acceleration recorded electronically. Acceleromyography may improve the reliability by decreasing the "human factor" of observation as well as optimizing the muscle response if combined with preloading of the muscle being stimulated [22]. Understanding that electromagnetic waves can interfere with each other explains some of the modes of interference between equipment [23].

Light Monitoring

Many gases of interest absorb light energy in the infrared range. Since multiple gases can absorb in this range, there can be interference, most notably for nitrous oxide [24], as well as false identifications. Intestinal gases such as methane can interfere as well [25]. Capnography has multiple uses in addition to detecting endotracheal intubation in the operating room, such as detection of cardiac arrest, effectiveness of resuscitation, and detection of hypoventilation [26]. In the arrest situation, it must be remembered that less CO_2 is produced, and other modalities may be indicated, such as bronchoscopy, which uses anatomic determination of correct endotracheal tube placement rather than physiological [27].

Pulse oximetry utilizes multiple wavelengths, both visible and IR, and complex processing to result in the saturation number displayed. In its simplest form, pulse oximetry can be understood as a combination of optical plethysmography, i.e., measuring the volume (or path length the light is traveling), correcting for the non-pulsatile (non-arterial) signal, and measuring the absorbances of the different species of hemoglobin (oxygenated, deoxygenated). The ratio of absorbances obtained is empirically calibrated to determine the percent saturation [28]. The use of multiple wavelengths can improve the accuracy of pulse oximetry and potentially provide for the measurement of other variables of interest (carboxyhemoglobin, methemoglobin, total hemoglobin) [29, 30].

Acoustic Monitoring

Sound is a longitudinal pressure wave. Auscultation with a stethoscope still has a place in modern medicine: An acute pneumothorax can be diagnosed by auscultation of decreased breath sounds, confirmed by percussion and hyperresonance, and treated by needle decompression (completing the process). A "simple" stethoscope actually has complex physics behind its operation. The bell and diaphragm act as acoustic filters, enhancing transmission of some sounds and impeding others to allow better detection of abnormalities [31].

Modern uses of sound waves have increased the frequency of the sound waves used to improve the spatial and temporal resolution, providing actual images of the internal structures in three dimensions [32]. Now only of historical use, A-mode ultrasonography (standing for amplitude mode) displayed the amplitude of the signal versus distance, useful for detecting a pericardial effusion or measuring fetal dimensions. B-mode ultrasound stands for "brightness mode" and produced a "picture" where the amplitude was converted to brightness. Multiple B-mode scans combine to produce the now common two-dimensional ultrasonography. M-mode echo displays the "brightness" over time, giving very fine temporal resolution [33]. These are still subject to physical limitations, i.e., sound transmission is relatively poor through air or bone (hence, the advantage of transesophageal echocardiography (TEE) vs. surface echocardiography), and fast-moving objects are better resolved using M-mode echo. The Doppler principle, involving the shift in wavelength by moving objects, can be used to detect and measure blood velocity in various vessels.

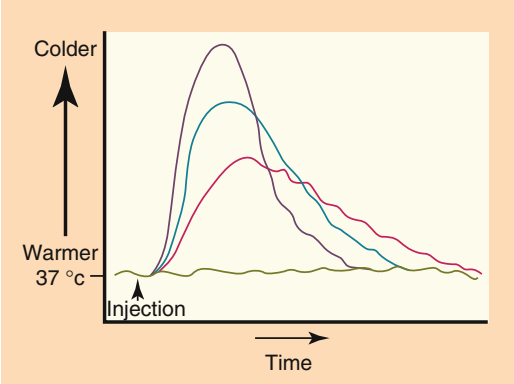

Fig. 1.3 Thermodilution for cardiac output measurement via Stewart-Hamilton indicator-dilution formula. The integral of change in temperature (area under the curve) is inversely related to cardiac output. A smooth curve with a rapid upstroke and slower delay to baseline should be sought. Sources of error include ventilatory variation, concurrent rapid-volume fluid administration, arrhythmias, significant tricuspid or pulmonary regurgitation, intracardiac shunt, and incomplete injection volume (causing overestimation of cardiac output). Lower cardiac output states result in relative exaggeration of these errors. Intraoperatively, ventilation can be temporarily suspended to measure cardiac output during exhalation, and several measurements should be averaged. If a second peak in the thermodilution curve is seen, a septal defect with recirculation of cooled blood through a left-to-right shunt should be suspected (Reproduced from Field [34]; with kind permission from Springer Science + Business Media B.V.)

Temperature Monitoring

Common household thermometers use liquid (or a combination of metals) that expands with heat, obviously impractical for intraoperative monitoring. For continual monitoring, a thermistor is convenient. A thermistor works as part of a Wheatstone bridge, wherein the change in resistance of the thermistor is easy calibrated and converted into a change in temperature. Small, intravascular thermistors are used in pulmonary artery catheters for thermodilution monitoring of cardiac output as shown in Fig. 1.3. Newer electronic thermometers use IR radiation at the tympanic membrane or temporal artery. Unfortunately, despite ease of use, the accuracy is not as good as other methods [35].

Chemical Monitoring

Glucose was one of the first chemistries monitored in medicine, being related to diabetes [36]. The evolution of glucose measurements parallels that of many other measurement values, starting with chemical reagents, such as "Benedict's solution," mixed in actual test tubes, to miniaturization, to enzyme associated assays. Current point-of-care glucometers were primarily designed for home use and self-monitoring and their accuracy can be suspect [37]. But controversy and disagreement between different methods of measurement is a long-standing tradition in medicine [38].

Blood gas analysis began with the Clark electrode for oxygen in the early 1950s [39], followed by Severinghaus electrode for CO_2 in the late 1950s [40, 41]. Other ions (calcium, sodium, etc.) can be measured by using ion-selective barriers and similar technologies. Most chemical measurements involve removing a sample from the patient. Optode technology allows continuous, invasive measurement directly in the patient. This technology uses optically sensitive reagent exposed to the body fluids via a membrane, and the information transmitted via a fiberoptic cable [42–44]. Advantages to these continuous techniques have yet to be seen.

Respiratory carbon dioxide was identified by chemist Joseph Black in the 1700s. He had previously discovered the gas in other products of combustion. Most respiratory analysis is done by infrared absorption. (Oxygen is a diatomic gas and does not absorb in the infrared range so either amperometric fuel cell measurements or paramagnetism is used.) Exhaled carbon dioxide can be detected and partially quantitated in the field by pH-induced color changes, akin to litmus paper. Of note, gastric acid can produce color changes suggestive of respiratory CO_2, providing a false assurance that the endotracheal tube is in the trachea, not in the esophagus [45]. More information is provided using formal capnography [27].

Point-of-care testing uses different reactions than standard laboratory test and results may not be directly comparable [46]. A test may be both

accurate and precise, but not clinically useful in a particular situation. Measurement of a single value in the coagulation cascade may contain insufficient information to predict the outcome of an intervention. For example, antiphospholipid antibodies can increase the measured prothrombin time, while the patient is actually hypercoagulable [47].

Flow Monitoring

> It is a source of regret that the measurement of flow is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure…
>
> Jarisch, 1928 [48]

Flow is one of the most difficult variables to measure. The range of interest can vary greatly, from milliliters per minute in blood vessels to dozens of liters per minute in ventilation. Multiple techniques can be used to attempt to measure flow. Flow in the respiratory system and the anesthetic machine can be measured using variations on industrial and aeronautical devices (pitot tubes, flow restrictors combined with pressure sensors) and have an advantage that the flow can be directed through the measuring device. Cardiac output and organ flow are much more difficult to measure.

Adolf Fick proposed measuring cardiac output in the late 1800s using oxygen consumption and the arterial and venous oxygen difference [49]. A variation of this method uses partial rebreathing of CO_2. Most measures of cardiac output are done with some variation of the indicator-dilution technique [14, 50]. Most techniques do not measure flow directly, but measure an associated variable. Understanding the assumptions of measurement leads to a better understanding of the accuracies and inaccuracies of the measurement. Indicator-dilution techniques work via integrating the concentration change over time and can work for various indicators (temperature, carbon dioxide, dyes, lithium, and oxygen) with different advantages and disadvantages. Temperature can be either a room temperature or ice-cold fluid bolus via a pulmonary artery catheter (with a thermistor at the distal end) or a heat pulse via a coil built into the catheter. Similar to injecting a hot or cold bolus, chemicals, such as lithium, can be injected intravenously and measured in an arterial catheter and the reading converted to a cardiac output [51]. An easy conceptual way to picture the thermodilution techniques (and to determine the direction of an injectate error) is to imagine trying to measure the volume of a teacup versus a swimming pool by placing an ice cube in each. The temperature change will be much greater in the teacup because of its smaller volume (correlates to the flow or cardiac output) than in the swimming pool. Decreasing the amount of injectate or increasing its temperature will overestimate the volume.

Measuring cardiac output by Doppler technique involves measuring the Doppler shift, calculating the velocity of the flow, measuring the cross sectional area and ejection time, and calculating the stroke volume. Then cardiac output is simply stroke volume times heart rate, assuming the measurement is made at the aortic root. Most clinical devices measure the velocity in the descending aorta and use a nomogram or other correction factors to determine total output [52].

Processed Information

Monitoring has progressed from large, grossly observable signals, recorded on pen and paper, to much smaller, unable to be sensed signals, and finally to complex analyzed signals, able to be stored digitally and used in control loops.

Data when obtained from monitoring can be stored using information systems or further analyzed in multiple manners. Processed data can reveal information that is not otherwise apparent. The SSEP can use data summation to elucidate a signal from a very noisy EEG background. Other processed EEG methods to measure depth of anesthesia use combinations of Fourier transform, coherence analysis, and various proprietary algorithms to output a single number indicating depth. Pulse oximetry and NIBP are two common examples of a complex signal being simplified into simpler numbers. Pulse contour analysis

attempts to extract stroke volume from the arterial waveform [53].

Interactive monitors (where the system is "pinged"), either via external means (NMB monitor, SSEP) or internal changes (systolic pressure variation, pulse pressure variation, respiratory variation), can be thought of as "dynamic indices" wherein the information is increased by monitoring the system in several states or under conditions of various stimulation [54].

Automated feedback loops have been studied for fluid administration, blood pressure, glucose, and anesthetic control [55–57]. Even if automated loops provide superior control under described conditions, clinically humans remain in the loop.

Conclusion

Although monitoring of patients had been ongoing for years, the ASA standards for basic anesthetic monitoring were first established in 1986 and periodically revised. Individual care units (obstetric, neuro intensive care, cardiac intensive care, telemetry) may have their own standards, recommendations, and protocols.

While not all monitoring may need to be justified by RCT, not all monitoring may be beneficial. The data may be in error and affect patient treatment in an adverse manner. Automated feedback loops can accentuate this problem. Imagine automated blood pressure control when the transducer falls to the floor: Sudden artifactual hypertension is immediately treated resulting in actual hypotension and hypoperfusion.

All measured values have some variation. Understanding the true accuracy and precision of a device is difficult. We have grown accustomed to looking at correlations, which provide some information but give a "good" value merely by virtue of correlation over a wide range, not true accuracy nor precision. A Bland-Altman analysis provides more information and a better method to compare two monitoring devices, by showing the bias and the precision. The Bland-Altman analysis still has limitations, as evidenced by proportional bias, wherein the bias and precision may be different at different values [58]. Receiver operator curves are yet another manner of assessment for tests that have predictive values.

The ultimate patient monitor would measure all relevant parameters of every organ, displayed in an intuitive and integrated manner; aid in our differential diagnosis: track ongoing therapeutic interventions; and reliably predict the future: the ultimate patient monitor is a physician.

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2 Monitoring in Acute Care Environments: Unique Aspects of Intensive Care Units, Operating Rooms, Recovery Rooms, and Telemetry Floors

Brian S. Rothman

Introduction

Patients in high-acuity settings such as the emergency department (ED), intensive care unit (ICU), telemetry unit, and the operating room (OR) are often defined as acutely "unwell," having rapidly changing physiologic states and associated abnormal vital signs [1]. "The art of managing extreme complexity" describes the ICU well and can easily describe other areas of high acuity. Facilities, resources, and personnel have been assembled in acute care settings in order to identify and treat significant injuries and medical conditions [2]. A major goal is to correct detrimental physiologic states while avoiding, preventing, or mitigating additional insults that could prevent optimal recovery [2]. Appropriate monitoring and patient safety are paramount since errors can have major deleterious impacts on this vulnerable population that is least able to recover from them.

Often, additional insults can result from suboptimal care. Suboptimal care may include "delays in diagnosis, treatment or referral, poor assessment and inadequate or inappropriate patient management" [3] and can result in further morbidity, mortality, or an increase in length of stay. Another definition offered is:

> Non-recognition of an abnormality clearly apparent from physiological recordings or laboratory but had not been identified in the case records or not acted upon with any obvious therapeutic intervention (i.e. no entry on the drug chart) or clearly inappropriate or inadequate treatment, although the case records showed that the abnormality had been identified by nursing or medical staff. [4]

Suboptimal care events are generally considered to be preventable or avoidable [4, 5], and yet often early signs of critical illness go undetected. This may be related to nonrecognition of a declining physiologic state as a consequence of inappropriate use or shortages of senior medical staff, resulting in suboptimal care provided by less-well-trained or less-experienced caregivers. Events might be detectable hours before severe physiologic decline, as is the case with cardiac arrest [6], which may be avoided or mitigated if early indicators are identified and acted upon promptly and appropriately [7].

High-acuity areas are ripe to have real-time data from monitors and bedside observations captured and applied through decision support engines to facilitate communication, and predict, identify, diagnose, and guide the treatment of evolving medical conditions. Through clinical education, training, and root-cause investigations of the origin and progression of errors, these systems could also guide and reinforce behaviors that will help providers avoid or prevent errors [8]. However, data collection of this magnitude is both time-consuming and monetarily intensive; implementation is further complicated by disparate sources, missing data,

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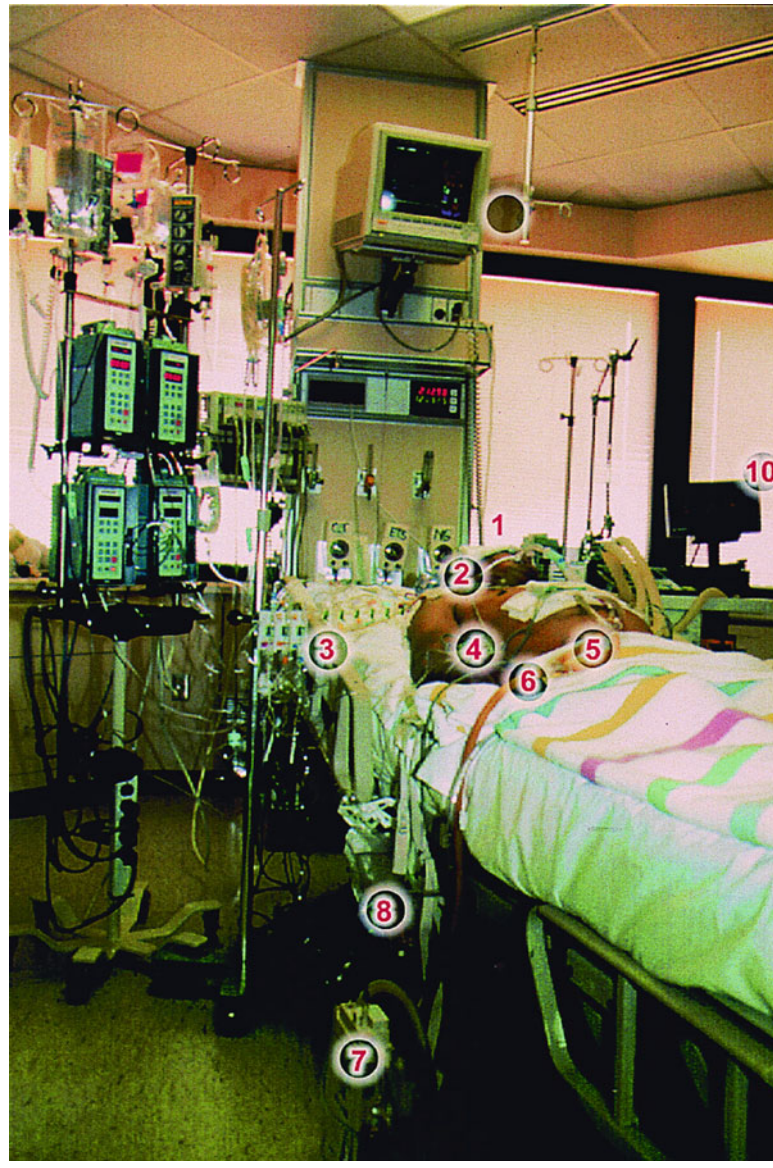

Fig. 2.1 Patient monitoring in the intensive care unit (Reproduced from Hilton et al. [10]; kind permission from Springer Science + Business Media B.V.)

incorrect data, time asynchrony, proprietary formats, computing power limitations, network and storage capacities, unproven algorithms, and government regulation [9]. This chapter will examine the many limitations of the monitors currently used in acute care environments, the elements required for real-time data and decision support, and current obstacles to implementation including care environment complexity and using this data to arrive at and prove improved outcomes.

Monitors and Alarms

High-acuity settings contain a multitude of devices (Fig. 2.1). Monitoring devices can measure a wide range of physiologic values both intermittently and/or continuously, and therapeutic devices serve to replace a patient's failed or failing organs or deliver medications. Many therapeutic devices also have the ability to monitor, such as the combined functionality found on ventilators that measure airway pressures [11].

At the bedside, monitor alarms perform important functions for high-acuity areas. Alarms are common in both monitoring and therapeutic devices and can be used for detection or diagnostic purposes, or both depending on their design. Detection examples include identification of life-threatening conditions in the patient or device (malfunction), imminent danger to the patient, and imminent device malfunction. Diagnostic functions include identification of pathophysiologic conditions and alerting caregivers to conditions that can worsen and become life-threatening [11].

Ideally, a combined monitor and therapeutic device will detect an evolving condition, alarm to notify nearby providers, and initiate the correct therapeutic intervention. This scenario requires accurate detection of physiologic decline and appropriate alarm activation. However, current alarm systems are nonspecific and lack context sensitivity. False alarms are common because in most high-acuity settings, alarms are programmed to decrease the likelihood of a false-negative alarm (a positive condition that does not result in an alarm) in order to prevent an unsafe condition [11, 12].

In an attempt to avoid false-negative alarms, false-positive alarms occur frequently due to monitor data variability [13], alarm thresholds, and artifact filter settings [11]. False-positive alarms, also referred to as "nuisance alarms" [14], have been reported as high as 90 % in ICU environments with one study demonstrating a negative predictive value of 99 % and sensitivity of 97 % [11]. These false-positive alarms, while technically correct, are clinically irrelevant and have been reported to change management less than 1 % of the time [14]. As a result, the staff in ICUs and other acute care settings have been demonstrated to experience significant "alarm fatigue" [13]. Once desensitized to an alarm, clinicians have been observed to tolerate an alarm for up to 10 min and false-positive alarms have been noted to be a distraction as well as disruptive to patients' sleep quality [12, 15]. Furthermore, clinicians have been noted to use extremely wide alarm limits to quiet them. Those adjustments, however, often set alarms to levels that are inadequate to provide an early warning to a potentially life-threatening situation [11, 15].

Monitor alarm false positives could be mitigated by graded alarms to reflect alarm priority and severity, but no standards exist and few manufacturers have implemented such alarm systems. There are also no auditory standards among different medical devices and devices from various manufacturers often have dissimilar alarm sounds for the same condition [15].

Monitor alarms can be univariate or multivariate in nature, measuring one or more than one variable, respectively. Independent of the alarm, the patient's problem might be univariate but the ideal algorithm solution may be either univariate or multivariate. Univariate approaches do not reflect patient complexity as injury severity increases. Multivariate monitoring is thought to be ideal in many cases, but there are few tools to accomplish the collection, integration, and processing of the data [16]. Currently, the most commonly implemented algorithm solutions are univariate [11], based on simple event identification that results in an alarm [16]. However, in the future, it is likely that computational and quantitative methods to analyze physiologic data will be used to drive decision support that can predict, diagnose, and treat using multimodal information [16].

Data

Resolution

Data resolution describes the frequency with which data is measured, recorded, and stored. At one extreme, continuous monitor data is used to present waveforms to providers at the point of care. At the other extreme, discrete data are intermittently collected from monitor feeds or from recorded values in an electronic medical record or on paper with far less resolution. In spite of technological advances, most current data recording, archiving, and analysis methods are relatively primitive and underutilized, especially with the continued prevalence of paper charts

[17]. Overall, the quantity of real-time data we are now able to collect is far greater than what we currently record, process, or integrate into the patient care process [16].

Integrity/Artifact

Data integrity problems most commonly arise due to challenges associated with timing and artifact. Without a "master clock," asynchrony can make high-resolution data interpretation difficult or impossible [17]. In addition, data may simply be missing. Network connectivity problems, disconnected cables, and a variety of other technical issues may cause spurious data and missing values. When using data for real time or subsequent analysis, algorithms must be trained to deal with artifact and/or missing values [16]. Data may also be recorded too late for it to be useful, which was the case in one study that examined criteria to develop an early-warning alert system for deterioration in acute care patients [6].

Even if the data are complete, in sync, and timely, artifacts may be presented to providers as real [13, 17]. More granular data collection complicates data interpretation because of common ICU artifacts, such as flushing and zeroing of arterial lines, and turning patients, that are clinically appropriate and necessary [16]. Artifact filters are needed to eliminate noise, preferably before the data analysis that may lead to an alarm. Dual median filters have been shown to fulfill that role, increasing true positives [11]. Statistical control charts are a technique that can identify processes that are "out of control" and have shown some promise with simulated physiologic data. The method is limited, however, requiring a target value where one may not exist or may not be easily determined either within a patient (intraindividual) or between patients (interindividual). Process control methods are also limited by temporal data dependencies and an inability to use outliers, level shifts, and trends to discriminate between relevant clinical patterns [11].

One study in which investigators used physiologic data to develop an Early Warning Score (EWS) reported both high noise in monitor data and missing manually recorded data. In order to accomplish their objectives, data summarization was performed on the "noisy" ICU physiologic data and variance in observation frequency. Manually recorded data was missing at such a high rate in that study that it was deemed unreliable and excluded entirely [6].

Other statistical algorithms developed in response to data integrity challenges include pattern detection with time-series analysis, dynamic linear models and Kalman filters, autoregressive models and self-adjusting thresholds, phase-space embedding, trend detection and curve fitting, and multivariate statistical methods. Artificial intelligence (AI) methods include knowledge-based approaches, knowledge discovery based on machine learning, neural networks, fuzzy logic, and Bayesian networks. Each has its own strengths and weaknesses depending on the patient population and environment in which they are applied. In general, most AI methods are not deterministic and are therefore unpredictable in behavior. For instance, neural networks cannot be used when a patient is unstable in the learning phase. This is problematic clinically as well as a regulatory obstacle, and none of the methods have moved to the forefront of patient monitoring [11]. Advanced alarm algorithms based on these types of approaches are not in use today primarily due to the regulatory environment which has forced manufacturers to apply the most sensitive of algorithms. Additionally, there is little commercial incentive for manufacturers to try to develop and sell monitors that use advanced alarm algorithms, given the risks and associated additional liability [11].

Interoperability, Integration, and Multimodal Monitoring

Monitor technologies are a flexible, viable way to complement provider observations, shedding light on nuances often with greater precision and timing [8]. Multimodal monitoring may present the patient's condition in a coherent manner to allow clinicians to more quickly and

easily formulate and test hypotheses that hopefully lead to timely and effective patient care and improved outcomes [17]. But monitoring alone cannot improve outcomes. Instead monitoring must lead to correct interpretation, and an effective goal-directed intervention must be available and implemented to ameliorate outcomes [18].

However, critical care environments continue to have problems with accurate and consistent data exchange [17]. Ideally, systems should automatically extract routinely recorded data to eliminate unnecessary manual work [12]. But heterogeneous data generated from continuous monitoring originating from different monitors and intermittently recorded variables such as laboratory values, fluid balances, pharmacologic interventions, and respiratory parameters makes integrating historical data and current data difficult and time-consuming [12].

Even when data exchange obstacles are overcome, monitoring of multiple parameters assuming "one size fits all" generally does not deliver the desired tools for assessment, diagnosis, or treatment. Current unimodal (univariate) monitor alarm systems cannot identify complex physiologic syndromes, such as sepsis, since monitor value integration with intermittent values and applying proven detection algorithms must follow a specific process for each condition [12]. Barriers include data capture reliability and information overload, which diminishes providers' ability to interpret the data in a meaningful way [12]. In summary, the obstacles to presenting high-resolution data from several sources captured by several devices, synchronously, and without artifact in a meaningful fashion must still be overcome [17].

Data Utilization

High-resolution data collection may be a source of rich data, but often the signal-to-noise ratio is quite high. Eliminating the noise can be accomplished by data-driven or model-based methods, which can then be used to drive successful diagnoses and treatment, improving patient outcomes.

Data-driven methods to predict an "outcome of interest" may be a useful method if future event prediction using physiologic parameters is desired [17]. Existing data is analyzed either with known outcomes or in an exploratory fashion to find unexpected relationships [17]. Other exploration techniques such as regression analysis, decision tree analysis, neural networks, and cluster analysis can also be employed.

In contrast, model-based methods view patients in physiologic/pathophysiologic states and provide guidance to move these patients towards more "favorable" states versus "fixing" physiologic values. Mathematical techniques for these models include dynamical system models that describe how systems evolve over time, and dynamic Bayesian networks using Bayesian inference which describes uncertainty through probabilities [17].

Standardization Versus Predictable Variability

Standardization and elimination of variability are goals to improve quality in healthcare. However, application of these concepts to acutely ill patients is challenging, since there is often more than one problem that is changing. This complexity does not easily lend itself to simple yes/no answers [19], and many consider these environments to be nonlinear systems. An excellent example of this complexity and variability is acute respiratory distress syndrome (ARDS), where severity, temporal considerations, and data integration have resulted in different interventions that have unproven benefits and may potentially harm if misapplied [19].

Complex systems analysis can be used with nonlinear systems and is currently used to measure variation in physiologic parameters such as heart rate, QRS complexes, and intracranial pressure. Included in these analyses is approximate entropy, measuring the degree of randomness within a data series [19]. Low entropy can make it easier to predict patterns, and high entropy makes predicting patterns more difficult, suggesting a more complex system.

Applied at a patient level, decision support tools may identify deterioration risk over time in either a predictive fashion when factors do not rapidly change (low variability), or in a detective fashion when factor variability over time is high [20]. Detective decision support may be more desirable, but with greater contemporaneous data recording and data resolution requirements, tool creation can be challenging [20].

One successful implementation of these monitoring techniques occurred recently among surgical intensive care unit patients. Text messages were sent from an alerting engine in the surgical intensive care unit to alert caregivers of physiologic condition, laboratory data, blood gases, drug allergies, and toxic drug levels. These alerts were found to be predictive, since the patients in question were 49.4 times more likely to die in the ICU, more likely to stay in the ICU longer, and 5.7 times more likely to die in the hospital even if they were discharged from the ICU to the floor [21].

Data Delivery

Care environment complexity is dynamic, interactive, interdependent, nonlinear, and often emergent in nature [8], with the timing of work activities increasing the possibility of errors. The combination of unpredictability in patients' conditions and clinician work patterns, a sizable decision space, and using incomplete evidence complicate decision-making. Predicting complex system behavior cannot be accomplished by the study of components in isolation, and conversely, component study reveals little, if anything, of the system as a whole. This applies both to workflow and decision-making, since predicting the available information, knowledge, and expertise at each point of clinical decision-making is not possible [8].

When developing systems that can process data to eliminate or mitigate errors and predict events, adjustments must be made for patient complexity and the nature of the workforce [3]. If these factors are not recognized and adjusted for, patients' needs may not be met and the potential for deterioration increases, especially as complexity, variability, and criticality (acuity) of the patients' physiologic state increases.

The same nonlinear dynamics, specifically entropy, can be applied to issues around provider mobility when delivering results to mobile clinicians. For instance, in one emergency department, the entropy of physician mobility was less (more stable) than that of nurses, making physician mobility easier to predict [8], which in turn could be used to learn how to deliver patient information in a more effective manner. There can be pitfalls however, with the shifting of responsibilities and workloads among provider types. One example occurred during a computerized physician order entry (CPOE) implementation, in which shifts in responsibility between nurses and physicians were evident. While nurses believed their decreased responsibilities made the process of patient care more efficient, physicians countered that the redesign led to a cumbersome system with excessive prompting for unnecessary information [22].

The communication of important data to the right provider, at the right place, at the right time, is defined as augmented vigilance [23]. One common method of communication is text alerts. Text alerts have been useful in delivering decision support in a variety of settings with variable results such as with an acute kidney injury "sniffer" [24], an alert for acute stroke patients [25], and notifications around implementation of tighter glucose control protocols in the ICU [26].

Text alerts also demonstrate an important concept where "pushing" information to a provider's mobile device supported by fail-safe delivery would be ideal. In contrast, providers who query a system to receive a result is a "pull" delivery method that is inefficient due to logins with no guarantee that the data will present at the time of the request [27].

Moving beyond text messages, computerized user interfaces are now being used to deliver representations of patient conditions with images. Some use advanced user interface concepts, but

care must be taken. While the concepts can be used to more rapidly understand an unwell patient's state, flawed user interfaces may lead to cognitive errors and data misinterpretation, resulting in substandard care [22].

To combat misinterpretation, work has been done to develop single scores that summarize a patient's condition, progress, or trend into one number. The scope of the score could be limited to a calculation such as fever burden or deliver greater analytical complexity related to a particular system (e.g., pressure reactivity index measuring cerebrovascular autoregulation) [17]. Of course, these scores are commonly predictive and can confer a one-size-fits-all mentality that may not be scalable even within a particular patient population and may require episodic data making analysis difficult.

An example of a single score is an aggregate weighted track and trigger system (AWTTS), VitalPAC early-warning system (ViEWS). AWTTS-ViEWS is a paper-based system [28] that uses objective physiologic data that could be delivered in real time, except for the neurologic assessment portion of the score, which is episodic and somewhat subjective. The episodic nature of the scoring system limits its use as a patient deterioration detector. However, some scores, like the Early Warning Score (EWS), can be more successful. EWS is used with patients diagnosed with acute pancreatitis and in several other environments. It detects many "unwell" conditions and can be used to identify those patients with SIRS response. It outperforms other scoring systems, with less temporal constraint and requiring fewer, mostly discrete, data points [29]. In contrast, the Patient At Risk (PAR) score fails to identify the majority of patients needing ICU admission, and the Modified Early Warning Score (MEWS) may identify those at an increased risk of death and ICU admission with higher scores, but there was no effect on outcome. Some have suggested that increasing the number of variables measured and the number of rules for scores leads to a failure to detect failing patients and increased false positive alarms who do not need the attention of emergency response teams [6].

Acceptance and Use

Acceptance and use of health information technology (HIT) is an important consideration given the large number of failed implementations and associated negative economic impact and inability to build an electronic evidence base for studies [30].

There is a growing need to use HIT to deliver decision support for nurses while keeping them part of the care process. Nursing to patient ratios have increased, as has patient complexity. The overall quality of care will decline and suboptimal care may be more likely, if information delivery is not improved. It will be essential to facilitate communication to allow nurses to seek advice and communicate deterioration and care transitions effectively, while compensating for staff shortages and inadequate medical team structures that contain hierarchies [3].

Presenting clinical decision support as a tool to augment nursing care without the implication of "Big Brother" will be a challenge in some environments. A focus on "filling the gaps" in knowledge, assessment skills, and the action to take based on the data collected would aid in identification and intervention of deteriorating patients during times of heavy workload and at times when patients observation frequency is commonly low [3].

Other environments may welcome such changes when it is used to overcome communication barriers. Nurses may be anxious when calling for emergency assistance from physicians possibly from an inability to articulate worried feelings, fear of being wrong, and negative past experiences [31]. Nurse-led teams may alleviate this anxiety. An evaluation conducted in 2006 showed that an early-warning indicator combined with a nurse-based ICU liaison team serving as a backup for nursing increased support and confidence and empowered them to discuss and troubleshoot issues. Patient assessment and decision-making confidence also improved [31].

This highlights that HIT implementations may be more successful when the specific workplace culture is taken into account. A periodic review of the systems in use is necessary to understand

how they are being used and how environmental changes may have an impact [32].

Outcomes

Monitoring is used to compensate for bedside clinical observation, which when used alone can lead to therapies based on subjective criteria, resulting in inadequate or harmful interventions or omission of therapies that may be helpful or lifesaving [33].

There is some doubt that monitoring systems can improve outcomes in the ICU and other acute care environments. With so many physiologic variables being monitored, one would assume that a large, strong body of evidence demonstrating which monitoring applications lead to positive outcomes should exist [33]. However, 67 randomized, controlled trials looking at hemodynamic, respiratory, and neurologic monitoring concluded that broad evidence of any form of monitoring that improves outcomes does not exist, including the most commonly used devices [33].

Obstacles include monitoring needs that are so obvious that they have not been tested or would be unethical to test, like vital signs. Heterogeneous populations may require multiple interventions, producing too much noise to determine a monitor's value. The use of a monitor system and its data accuracy, collection, interpretation, and intervention timing may also influence results. In other words, how a monitor system is used may significantly impact an outcome, while simply using a monitoring system may not improve outcomes [33].

Conclusion

Caring for the unwell in high-acuity units requires the reliable collection and utilization of high-resolution data in real time. Meaningful, filtered, artifact-free data using algorithms that utilize a variety of statistical methods applicable to a patient's condition and environment will be necessary to minimize "nuisance alarms" and alert fatigue in an effort to increase patient safety [13]. The alarms should detect and alarm for all life-threatening situations, warn before life-threatening conditions occur, and provide diagnostic information related to the alarm [11] in a time-sensitive fashion [12].

Identifying relationships between physiologic and clinical data will require methodological advances to produce new algorithms and statistical analysis methods in order to lead to improved outcomes [16]. This will require analyses to be delivered in an appropriate timeframe and displayed to the correct staff in an intuitive, meaningful way [16]. Timely and intuitive analyses of physiologic and clinical data will necessitate a better understanding of clinical decision-making and the interaction between clinicians and decision support to determine what makes data clinically valuable so that clinically relevant, useful data can be delivered [32]. The development of new algorithms will require trust between researchers and industry to create algorithms using extensive amounts of reliable, real-world data and to assure their safety and efficacy in improving outcomes [11].

This cycle of timely collection, filtering, analysis, delivery and display, treatment, and outcome improvement will require frequent reevaluation. The majority of the most common monitoring has not been well evaluated. Of those studied, the negative or "no benefit" results have been observed where benefit is commonly recognized [33].

Proving monitor-use outcome benefits may be even more challenging as new monitor technology enters the marketplace, seeking to displace older technologies. Often, the reliability of these technologies is difficult and artificial methods are often employed, which will make their impact on outcomes more difficult to prove [34].

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Introduction to Signals

3

Justin P. Henneman and Jesse M. Ehrenfeld

Introduction

In order to understand how monitors work, it is important to have a grasp of the fundamental principles of signal detection, acquisition, processing, and analysis. This allows a clinician to truly understand not only what the numbers, graphs, and tracings on a clinical monitor represent, but also how the signal was obtained. Each parameter we choose to monitor in medicine has its roots in physics, from pressure waves to electrical impulses; yet in the modern era, all these signals simply end up displayed on a digital screen and recorded in an electronic record. The raw information that many medical devices collect, however, is utterly meaningless at first glance. In this brief chapter, we will discuss how information is transformed from raw signal into digital output from the eyes of an engineer.

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Sound to Sensors to Signal to Screen

In honor of one of the first attempts to monitor a patient, the stethoscope, we will use sound to draw an example. A textbook is shut in frustration, generating a pressure wave in the air. A microphone nearby is struck by this pressure wave, displacing a thin membrane, which in turns moves a coil of wire back and forth. This produces a current that shoots down towards a computer. The computer measures the current and applies a numerical value to it, storing this number on a hard drive, then another and another until a list of numbers is generated. Software decides which numbers have meaning, and which do not. It may even insert numbers of its own. The computer then generates an image whereby each value is shaped into a dot, some high and some low. Thousands of dots spew out onto the white background of your monitor until a waveform is born. Should enough dots be above a line, the beeping begins. So what really happened? There are four basic actions:

1. *Physical change:* The pressure wave created a physical motion of a sensor, namely, a device designed to capture information of one type (sound) and produce another (current).
2. *Signal acquisition:* That current was measured by another device, which was able to record it in a meaningful way so that it can be used later.
3. *Signal processing:* The set of values is changed from raw data into a more meaningful set; that

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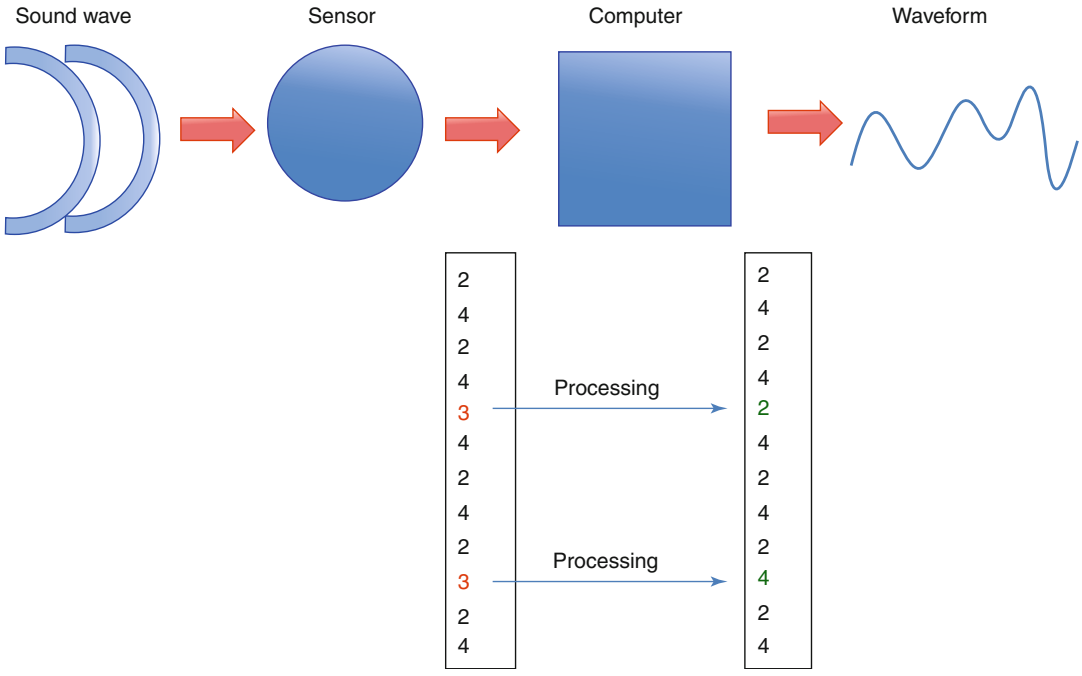

Fig. 3.1 Generation and modification of a signal

is to say, it's given properties that make it more reflective of what actually happened.

4. *Signal transduction/transmission:* This new set of information is saved or shared in a meaningful way. It can be converted into pixels on a screen or ink drops on a page to produce information we can readily interpret (a waveform on the screen or sound played back) (Fig. 3.1).

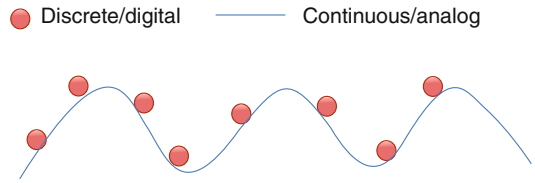

Fig. 3.2 A comparison of discrete versus continuous signals

Discrete Versus Continuous Signals

Information can be read as discrete bits, which means "in pieces," or continuously. Discrete data is like gathering up a collection of stones from a river, perhaps to size or count. In general, it's analogous to saying "digital." Meanwhile, continuous (analog) signals provide information without fail. It's more like the river itself. You can always take water from it. There is no separation of one drop to the next. Many physiological parameters can be read in both forms, as both discrete points in time (blood pressure at the start of a surgery and every 10 min thereafter) and continuously (as pressure always exists). The constraints of digital space and circuitry prevent us from capturing every blood pressure reading, but it's still always there, able to be measured. Most physiological properties of the human body don't change fast enough for us to need a continuous signal, so, in general, discrete information will suffice (Fig. 3.2).

Data Collection and Sampling

Once a data source is identified, we must capture it. Important questions such as "how much we need," "how often we need it," and "how close to

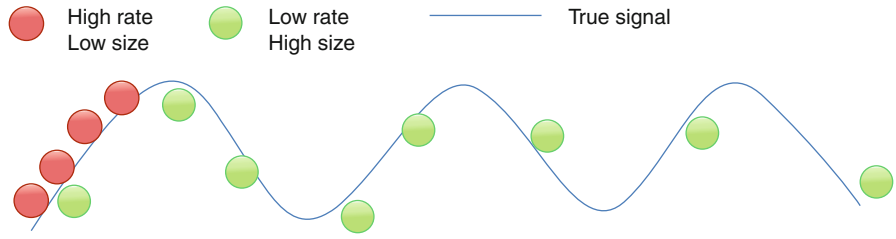

Fig. 3.3 Signal capture characteristics

the real thing it has to be" must all be answered. These questions are typically answered in the form of three concepts: sample size, sampling rate, and error.

Sample size is the total number of discrete data points captured.

Sampling rate is the number of data points captured per unit time.

Error is how different from the true value a captured data point is.

Very rarely do we obsess over a single characteristic. Instead, it's far more important to decide what sort of story one needs to tell. If we want to hear a patient's lung sounds, we can't exactly get a noise every minute and call it breath sounds. Nor do I need high-definition surround sound to tell if a patient is wheezing. Sample rate and size are often balanced to a point where we have enough information to give a signal meaning. Too much size or rate and we may run out of memory space; too little and we may miss important information. A good rule of thumb is to collect data twice as often as we expect it to change, giving yourself room to adjust for errors and noise. However, as always, more data is better data. Compare the two sets of measurements made in Fig. 3.3: the first is driven to a high sampling rate and a low sampling size, with the other doing the opposite.

Notice that neither tells a great story and neither can tell us the whole story. However, the second measurement may give a better representation of what actually happened. The error between what actually happens and what the sensor picks up is often a characteristic of the sensor itself and is generally corrected for later on in the story when we modify the signal. It is, however, important to know how much error there is, in what direction it goes (underestimates/overestimates), and does the error change. Is it random enough that half sit above a true value and half sit below, and with some tweaking we can average out the truth? Lastly, one must consider if the error is enough to change the meaning of the signal. With good planning and processing, most signals can be salvaged to tell us a great story that's close enough to make the right point. In the clinical setting, it's paramount to find out how accurate we need to be to make the right call. A blood pressure change of 5 % could signal simple dehydration, and yet the same change in temperature may imply imminent disaster. Monitoring is only effective if it can guide us towards the right action.

Signal Processing

The scope of signal processing is in and of itself a complex topic, but the basic concept is simple: take a story and edit it enough to still tell the truth. We have a few tools that essentially use simple mathematical techniques to change a series of numbers: resampling, windowing, and filtering.

- *Resampling* implies changing our own data, by reexamining the numbers we collected. For example, if you captured 1,000 numbers, I may choose to only look at every fourth value (down-sampling). This is useful if you collected far too much data to manage, but you'll still have plenty to tell the story even after cutting down. On the other hand, I could up-sample by adding in extra numbers in between all the ones I already had, by say, using the average of the two numbers

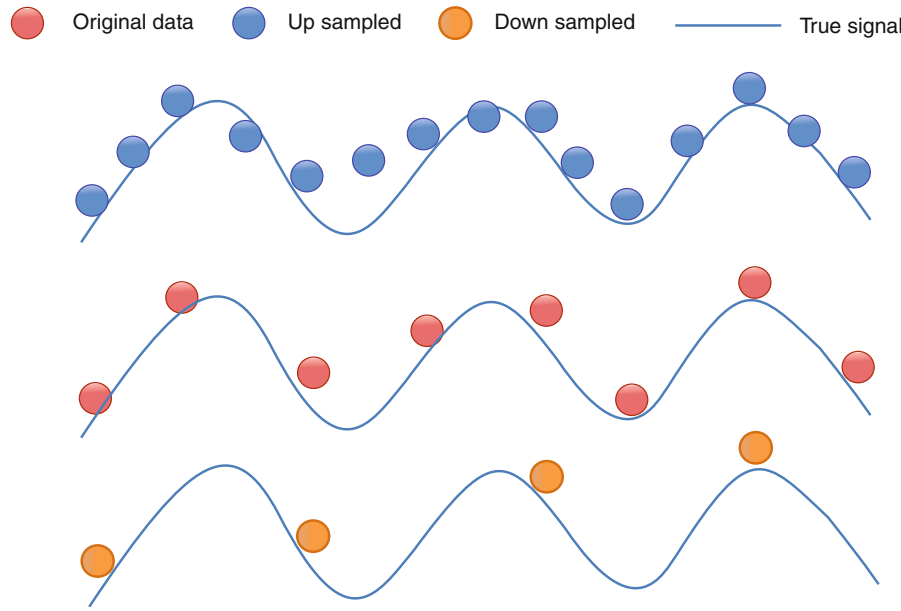

Fig. 3.4 Signal processing concepts: resampling

(1,3,5,7,9 becomes 1,2,3,4,5,6,7,8,9). This makes a series of dots look more like a line and helps us to interpolate (guess) at what was happening when no one was looking.

- *Windowing* implies examining/changing small subsets of data, for example creating a running average, so that we can change our data to demonstrate slow changes over time. This removes the drastic effect of sudden changes in your data, like a dampener. For example, given a set of numbers—1,1,1,5,3,3,3,11—I could window every four samples and make them all the same (the average of their own set), making it into 2,2,2,2,5,5,5,5. Every value becomes less true, but the error is spread out.
- *Filtering* implies changing how we weigh parts of the data. For example, if we want to filter out high-frequency noise, we can reduce the value of changes that happen often (shrink data points that vary wildly from sample to sample, while relatively neglecting changes that occur slowly). This is, of course, fixed to how quickly we collected the data (i.e., our sampling rate). We have to collect data quickly to see information that changes as such (i.e., we have to have seen it changing, to then ignore it). This is very often a fundamental signal processing step in medicine, as huge amounts of information are distorted by the environment, often in predicable ways (light from ceiling distorts a pulse oximeter, or the 60-Hz current in the AC wall socket changes an EKG reading) (Figs. 3.4 and 3.5).

Example Applications of Signal Processing in Clinical Monitoring

In order to tell the right story, we have to present the information we collected in the proper light. Clinical monitoring is the summation of the signal (is the patient moving enough air in their lungs to make noise?), the sensor (is the electronic stethoscope damaged?), the noise/error (is the patient moving around?), the processing (are we filtering out the ambient noise?), and finally the transduction (are we playing back an accurate enough sound?).

A Few Signal Processing Examples

- Pulse oximetry and windowing: These monitors are fed a steady stream of values, and yet only a singular value is presented on our

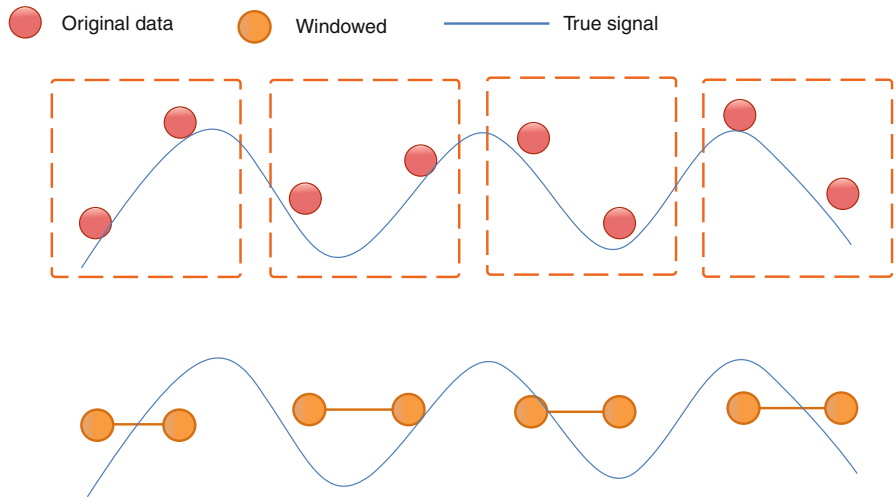

Fig. 3.5 Signal processing concepts: windowing

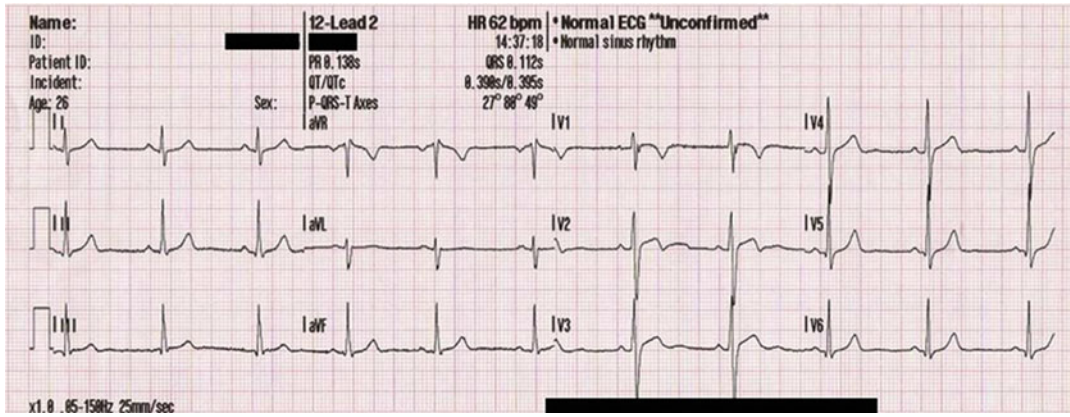

Fig. 3.6 A standard EKG

screen. They automatically window/average their values, so as to reduce the variability of changes to provide a more sturdy approximation of the true value. If the display flickered between 99 and 100, we'd feel comforted by the presence of a device that updates every quarter of a second; but should the patient sneeze, and the monitor drop off to 40 from a sudden error, we might grow weary of any one number. So taking the running average of every 100 values is not only more clinically accurate at any one time, it's more practical to watch.

- EKGs and filters: Noise always seems to finds its way into our data, through either electrical noise or an anxious and moving patient. To get to the true meaning, we have to filter out the things we know aren't useful. Take a look at the EKG in Fig. 3.6. You don't even need to know what it means clinically to recognize that it doesn't really change all that quickly. It takes a second or so to repeat itself. A common source of noise that likes to sneak its way into systems is that of the standard AC current and its 60-Hz cycling (the wall outlet); because of this, most circuits and computers toss it out with the use of a filter. In short they reduce the amplitude of changes that occur every 1/60th of a second (60 Hz) to get rid of most the error, without dramatically affecting the true signal that changes much slower (Figs. 3.6 and 3.7).

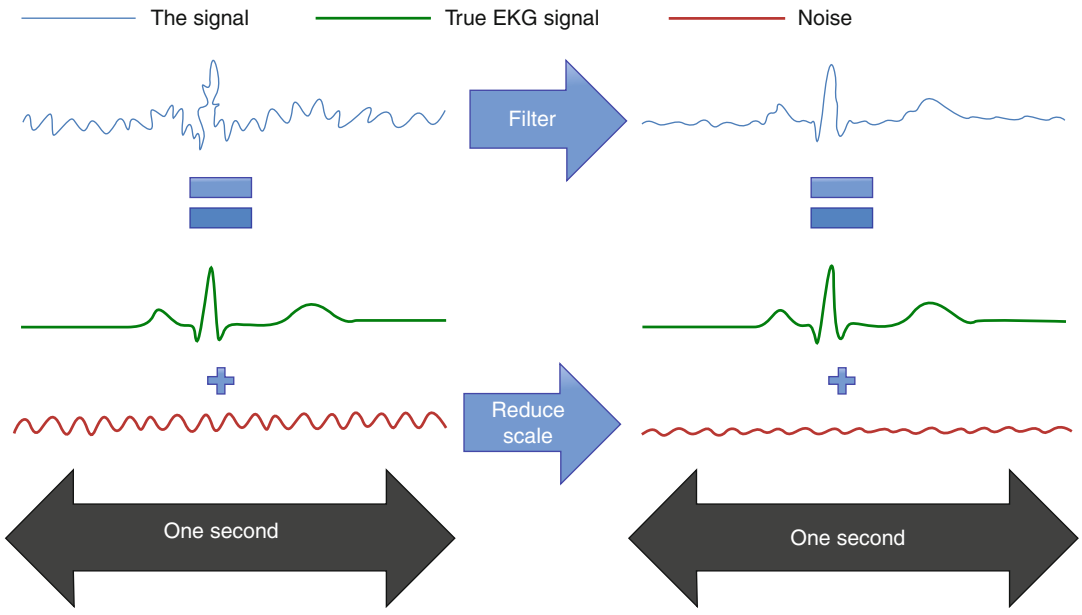

Fig. 3.7 Filtering an EKG

Conclusion

The numbers, lines, and digitized output that define clinical monitoring are nothing more than signals that have survived trial and error long enough to become accepted truths. It is up to us to flesh out their meaning for a patient. Be wary of perfect numbers and graphs that fit too well, and never assume that scribbles contain nothing of worth. Data points are only information; they can be right or wrong, largely based on how we measure, modify, and record them. Don't forget where they came from, lest we be fooled into thinking we've figured the human body just yet.

Signal Analysis: Acquisition, Storage, and Analysis of Physiological Signals

4

Christine Kim Lee

Introduction

We live in an increasingly digital world. Within the last decade there has been an exponential increase in data and information available to health professionals. With the push to implement more electronic medical records, the advance of clinical decision support systems, and the increasing number of clinical measurements and devices, the requirement for appropriate physiological signal databases and analysis is becoming widespread and important not only for research purposes but also for the quality and efficiency of modern healthcare. There is a need to manage physiological signal data in order to keep up with the pace of medical technology, but the data needs to be not only easily accessible but also meaningful.

Signal Acquisition and Storage

There are many different measured physiological signals available to a clinician, such as ECG, blood pressure, ventilation, and pulse oximetry. Through each device, there are also several different clinical values that can be collected for future analysis. For example, within just blood pressure, there are invasive blood pressure values and noninvasive values, and diastolic, mean, and systolic pressures can be collected for each. This makes a total of six blood pressure values that can be acquired and put into an electronic medical database.

In addition, every physiological signal is usually encoded in a proprietary format, and one of the greatest challenges of data acquisition from several different clinical measurement devices is the extensive number of interfaces to take into account and organize. Encoded data can be taken from different devices via hardware or the cloud and then needs to be processed into data that makes sense. Hardware includes hardwired interfaces like RS232 and USB or device-specific data acquisition cards that can be inserted into a PC bus. Cloud data collection is a much newer idea and means wireless data collection into a database.

There are also several other considerations for data acquisition and storage to ensure meaningful data. The signal acquisition and storage can be periodic or continuous, the decision of which can impact future analysis. A device may be capable of measuring and outputting a value every second, but the values could be recorded and stored every 5 min into an electronic medical database. Considerations for periodic versus continuous monitoring and acquisition include effects of drugs, physiological abnormalities, and patient position effects. Any of these changes in the environment and their effects on a patient can be missed by deciding on the wrong timing of data

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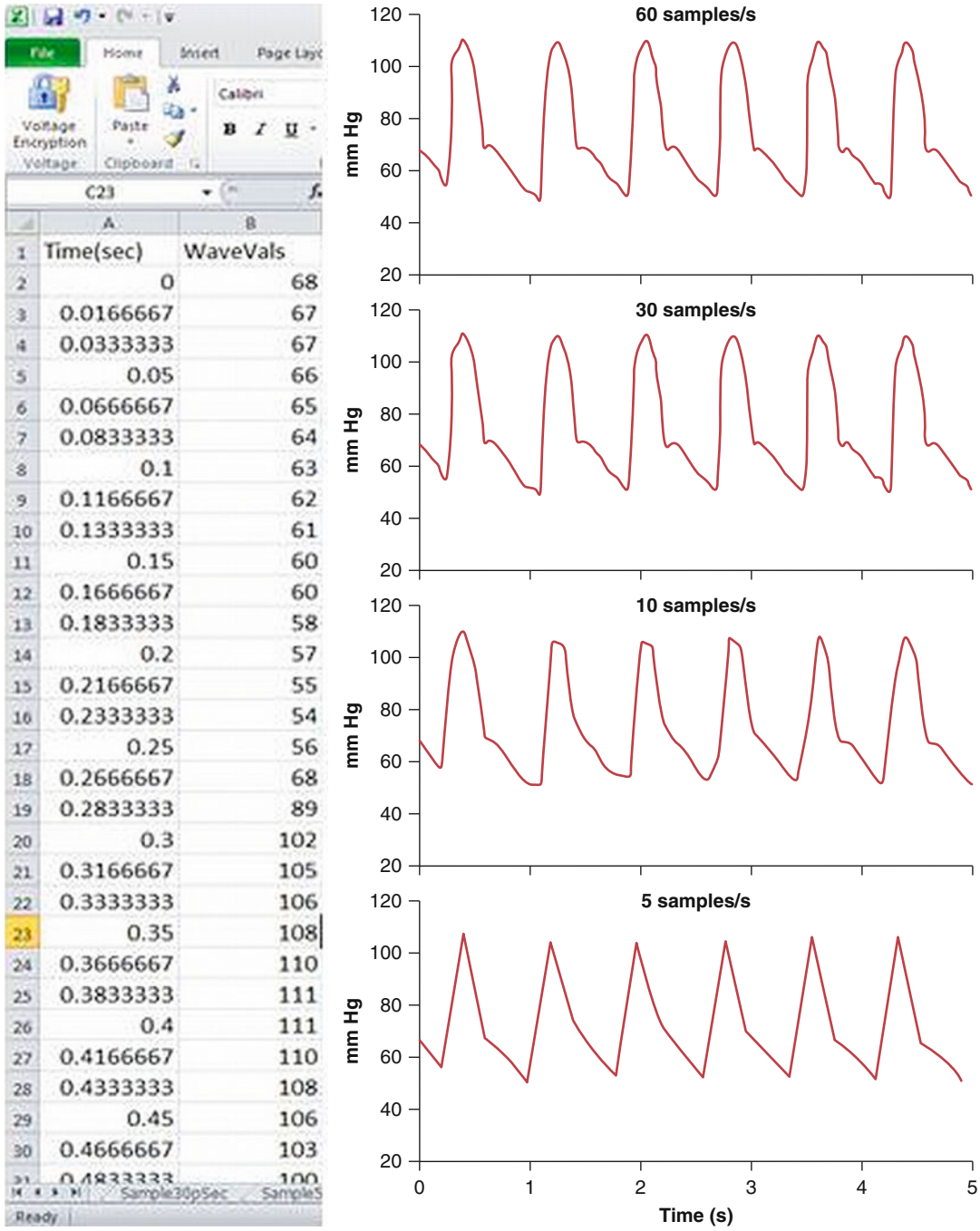

Fig. 4.1 Arterial pressure waveforms digitalized and graphed from 60 samples of data collected every second, 30 samples/s, 10 samples/s, and 5 samples/s

acquisition. For example, any pressure instabilities can be minute changes in a waveform reading, and recording arterial blood pressure waveform data sampled at a rate of 60 samples per second is more meaningful for future analysis than every 10 per second or 1 per second (Fig. 4.1). In addition, physiological signal data can come in a variety of forms: absolute values, device-calculated indices, and waveforms are a few of the more common types of signals measured.

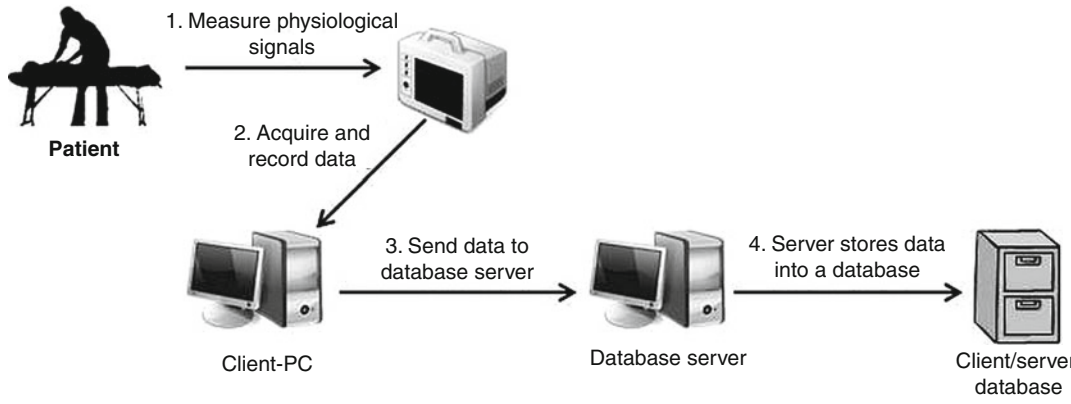

Fig. 4.2 Simplified system designs for data acquisition and storage of physiological signals

Databases

The next question then is the form of data to store. Figure 4.2 illustrates a simplification of the flow of physiological signal from patient to device to a database. Encoded physiological signal data can be transformed into useful clinical values that can be easily stored in databases, while waveforms can be digitalized and stored for future retrieval. Depending on the use of the data in the future, one must also decide between "data dumps" versus real-time processing, in other words, taking the measured signal values or encoded data as is and "dumping" the data into an output file for later versus analyzing and processing them in real time and storing the results (calculated values, trends, variability). An example of real-time processing is pulse pressure variation (PPV) which is calculated from analysis of the arterial pressure waveform. A "data dump" would be just storing all the digitalized waveform values, while real-time processing would be calculating PPV values and storing those. In addition, within the computer, or client PC, collecting the data, there can be the option of text-based free responses and automated tracking of specific trends (e.g., a sudden decrease of systolic blood pressure by 10 %) that can make the physiological signals recorded more meaningful in the context of clinical environment.

Once all of the decisions on data acquisition have been made, the next step is how to store the data for easy access and retrieval. As discussed previously, every physiological signal measurement device will have "data dumps," raw output files that can be stored for future analysis. On the other hand, one can pick and choose what specific values are to be stored. In either case, a database management system is needed to organize and securely store the data. Database management can be divided into two main types: shared-file based and client/server. Shared-file databases are typically stored and accessed on a local computer. A disadvantage of a shared-file database, however, is that it can be difficult to access the data from multiple remote locations. In other words, several clinicians couldn't look at the data of one patient simultaneously. Client/server databases such as Microsoft SQL Server and Oracle offer a centralized database with server-side processing, which eliminates the difficulty of sharing between multiple users seen with shared-file databases. However, these types of databases are much more difficult to design and maintain and require a well-trained team of technicians and information system analysts dedicated to the database.

Data Retrieval and Query

Physiological signal data are controlled and organized for the ease of future retrieval and analysis. Client-side retrieval and query (in other words querying your own data records) must be easy or else the stored data is useless. However, database queries are complex and require knowledge of query language syntax such as SQL. In a complex database, the process of database retrieval begins

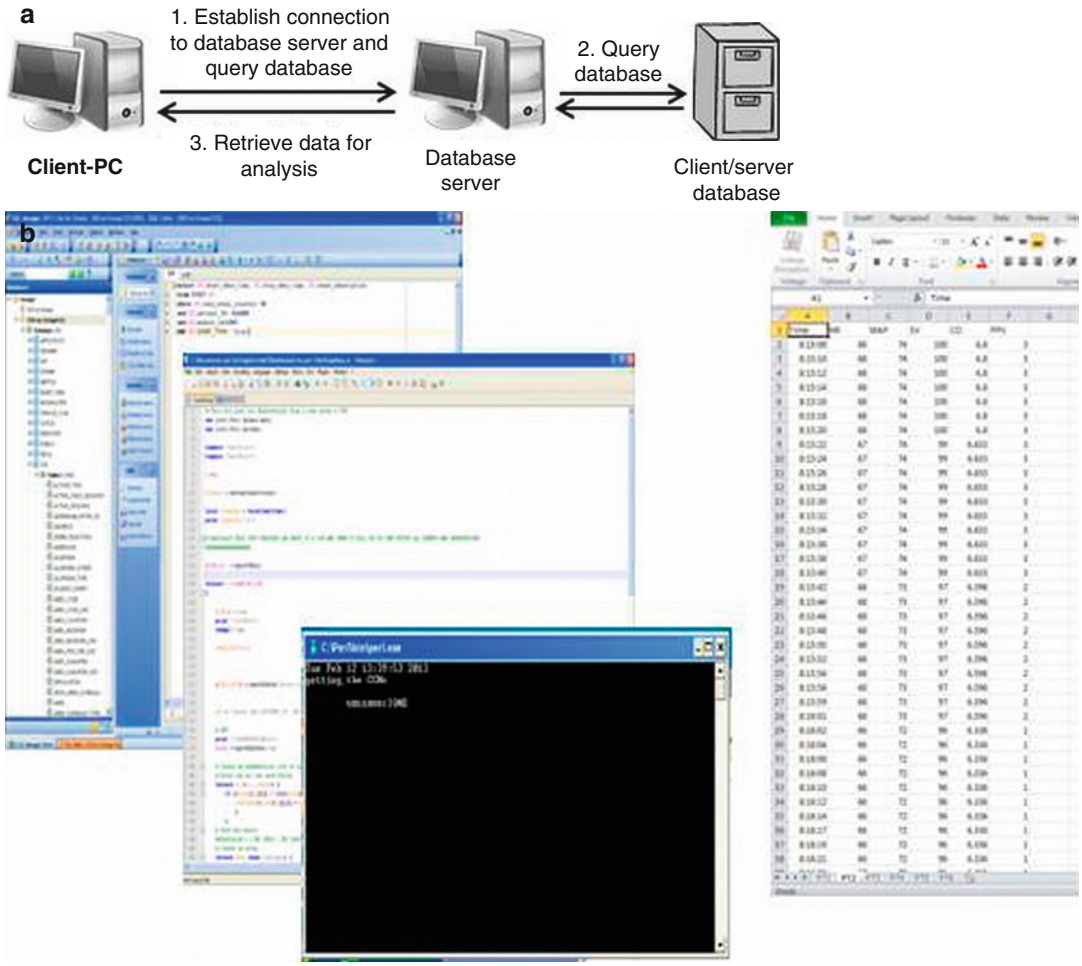

Fig. 4.3 (**a**) Simplified system designs for data query and retrieval. (**b**) Screen images from a client-initiated SQL query. The *top screen* illustrates the SQL Manager Lite for Oracle application utilized for database management. The *middle screen* illustrates a written Perl code query of physiological signals of interest to access the database and retrieve data. The *bottom screen* illustrates a command prompt execution of the code. The *right screen* shows the output file of data queried

with a client request to the server for a specific piece of information (Fig. 4.3a). The server then connects to the database and transforms the data per defined in the request before giving it back to the client. Figure 4.3b illustrates the construction of a database query in which a programming code is written with SQL syntax to query for patient-specific intraoperative clinical values, with the organized data output. Within a programming code, one can also analyze/process queried data (i.e., average over time), which makes the query more valuable. Although, not everyone knows how to create such queries, which is why a well-trained team built around the database is so important, but there are existing interfaces that allow queries without the knowledge of query language. For example, Reporting Servers in SQL Server[1] enables the developers on your database team to create automated data analysis reports at your request. In addition, ColdFusion[2] is a web-interface application originally developed to connect web pages to databases. This type of technology could then be used to provide

[1] http://msdn.microsoft.com/en-us/library/ms159106.aspx
[2] http://www.adobe.com/products/coldfusion-family.html

easy database accessibility, query, and retrieval to multiple users. An example of such an interface is PubMed or GenBank; these are large databases that allow users to query and retrieve data on a web interface without knowing the behind-the-scenes database language, and users can use natural language.

Data Analysis

Once all data has been retrieved and organized, the analysis can begin. Physiological signal data can be split into quantitative and qualitative data (i.e., absolute heart rate values and heart rate value increase/decrease trends). In either case, the most clinically significant data analysis looks at longitudinal trends and functional statuses. For example, over time the way that arterial pressure changes and the range of change and whether there was any hemodynamic instability are the types of analysis most clinically relevant to a physician. In reality, any types of analysis, graphing, tables, statistical, etc., can be done as long as the data obtained is organized in a meaningful way. This goes back to robust data acquisition, storage, and queries, which determine meaningful physiological signal data analysis.

Conclusion

Healthcare information and data is becoming a part of the "big data" world. Electronic medical records and advances in not only clinical technology but also information technology mean more opportunities for advance in the understanding of medicine and personalized medicine. With a better understanding of the acquisition, storage, and analysis of physiological signal data, the medical field can truly appreciate the data it is capable of collecting.

Information Displays and Ergonomics

5

B. Samaiya Mushtaq, Judith W. Dexheimer, and Shilo Anders

Introduction

Within the hospital, the acute care environment treats the most severely injured and sickest patients. Infusing new technologies to decrease the patient's length of stay and mortality is of particular interest. Increases in healthcare costs coupled with an aging population increasingly stress hospitals, making it even more vital to discover promising future technological applications to aid in the efficacy and stabilization of the healthcare field. The use of informational displays to convey patient data and status in acute care environments is instrumental in facilitating and monitoring patients. This chapter explores monitoring technology from the prospective of human factors and ergonomics. Human factors engineering focuses on the development and application of knowledge about human physiology and behavior in the context of display design. This chapter will illustrate the principles of human factors in information display design with respect to monitoring technologies in acute care.

Human factors aspects of monitoring technologies are an essential consideration in acute care environments where the most complex patients reside. Monitoring technologies present information that is available and can be automated (e.g., capturing a patient's blood pressure at regular intervals) while leaving the remaining parts of work to a human [1]. As a consequence, the task of a human becomes a vigilance task and may, in fact, camouflage developing patient issues.

A summary of the types and unique aspects of information display design for bedside monitoring is presented. Then this chapter explores the more recent remote monitoring in acute care environments and associated information displays. The chapter concludes with a discussion about the ergonomic or more physical environment and layout of monitoring displays in these environments.

Bedside Monitoring

In the acute care environment, the number and variety of monitoring displays at the bedside varies depending on a patient's condition. Patients are often dependent upon life-sustaining supportive therapy that utilizes this technology (see

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Table 5.1 Examples of bedside monitoring technologies with information displays

Monitoring technologies	
Anesthesia information system in the OR	Electronic medical record
Vital signs monitor	Glucose monitor
Neuromonitoring technologies [2]	EEG monitoring
Electrocardiographic monitoring [3]	Ventilator system

Table 5.1 for a list of example technologies). A practitioner's ability to detect and assess changes in patient physiology in a timely manner is a key component to protecting against adverse outcomes.

Information display format can influence a practitioner's ability to identify potentially adverse changes in a patient's state at the bedside [4]. Ash et al. found that medical displays are often incompatible with practitioners' workflow and unnecessarily fragment patient information [5]. Critical information is often spread across different types of monitoring technologies, including ventilator displays and patient physiological monitors that may be located on a multiplicity of information displays, thus requiring information search and acquisition. This may confound practitioner's ability to detect evolving changes, make it more difficult to attain a holistic view of a patient's state, lead to care inefficiencies, and frustrate clinicians.

Information displays that integrated patient information in physiologically meaningful ways better supported ICU nurses' ability to detect changed parameters [6]. Similar effects have been found in integrated graphical displays with anesthesiologists monitoring for physiological changes during a simulated patient event [4, 7–10]. In these studies, the design goals were decreased response time, improved situational awareness, and better adverse event detection in anesthetized patients. In a scenario involving heavy fluid loss, anesthesiologists responded faster when using the integrated graphical display rather than a traditional waveform display [7]. In contrast, there were no differences between displays in a transfusion reaction scenario.

In a study assessing ICU nurses' abilities to detect abnormal patient variables using a novel graphical bedside monitoring display compared against a conventional tabular information display, reporting of important physiological information was superior with the novel graphical monitoring display. This display was also perceived as more usable [11].

Rather than displaying more information at once, some monitoring displays are useful in their ability to filter out irrelevant information and display clinically significant information. Decision support systems are designed to process large quantities of data and display the useful information for a specific point of time. Compared to standard bedside monitors, enhanced monitors used in decision support showed quicker identification of sepsis and subsequent onset of treatment [12]. Critical care nurses with a varying range of experience participated in a simulated scenario of a monitor displaying for signs in a patient sepsis. The time latency between the physiological changes displayed on the monitor and until the nurse verbally identified the onset of sepsis was measured, as well as the time the nurse took to begin treatment of sepsis. Using enhanced beside monitors shortened all of these times, suggesting that the displays designed to support the decision support presented the information in a more functional way.

Information displays developed specifically for monitoring technologies should accommodate the full diversity of the intended user population across use sites and be carefully integrated with existing technologies to minimize any unintended consequences. There is ample evidence that properly designed, contextually relevant information displays could be beneficial in a range of acute care environments [13, 14].

Remote Monitoring

Practitioners currently monitor patients at the bedside, however, recent technological advances have led to the development of remote patient monitoring. The information displays of these types of technologies present unique challenges,

especially given that they may be accessed on various platforms. The following two examples highlight the challenges of such information displays.

The tele-ICU is a remotely located facility designed to supplement ICU care at the bedside by providing remote, instantaneous, 24-h access to experienced physicians (e.g., intensivists) and nurses with specialized ICU expertise [15–17]. Individuals in the tele-ICU monitor patients via a control center, which has access to patient physiological data, treatment plans, and medical records. Tele-ICU personnel use a combination of approximately six computer screens configured to each user's specific needs to monitor between 25 and 35 patients depending on the tele-ICU. Specifically, the physicians and nurses in the tele-ICU have access to real-time vitals (e.g., blood pressure, heart rate), tracking vitals over time, remote two-way audio and one-way video feeds, and the electronic patient record, which includes history, labs, and notes. In addition to the patient data, the system has "smart alerts" that are patient-specific alarms based on changes in the vitals over time. Finally, the tele-ICU software allows users and managers to create reports about outcomes, practice patterns, resource utilization, and clinical operations [18].

This type of remote monitoring technology is unique in that an individual, usually a remotely located nurse, is utilizing the information display, including automated alerts to enhance and intervene when warranted [19]. Rather than the bedside nurse providing care and constantly monitoring the various displays, the tele-ICU is able to assist in this process. Additionally, the tele-ICU has its own monitoring technologies that exceed those available in at the bedside. Studies have shown positive improvements in patient outcomes including mortality and length of stay after the implementation of this type of monitoring technology [20–22].

Mobile technology has the potential to bring data and contextually appropriate support to monitoring information displays in ways never before possible as long as they are efficient, effective, and easy to use. VigiVU, a wireless, remote monitoring smartphone application implemented in the operating room (OR) is meant to improve clinical communications, attending physicians' situational awareness, and patient safety outcomes [23]. It is a smartphone extension of the Vanderbilt Department of Anesthesiology's computer-based vigilance system.

VigiVu provides its users with real-time monitoring data for patients under their care and more broadly the current status of all ORs in the system. It displays data feeds from OR physiological monitors, streaming video of OR, and the information from the Anesthesia Information Management System. Anesthesiologists currently use the VigiVU system to complement their standard monitoring practices. This system is unique in its ability to provide access to the expertise of a physician who has a known understanding of the patient anesthetic practice. Additionally, through automated push notifications, the constant monitoring of information displays is not a requirement for use.

Summary: Information Displays

With the increasing popularity of remote monitoring technologies, new issues have arisen, involving the accuracy of the medical advice and the user interaction with the system. The design of the information displays for both bedside and remote monitoring technologies in acute environments is critical to understanding a complex patient's status. The design of information displays in this environment impacts their effectiveness and usefulness in both remote and bedside monitoring technologies. Clarity surrounding the patient's condition should be enhanced through the information display and graphical representations including any deviations that signal deterioration in status.

The design of information displays should promote coordination among practitioners including the monitoring technologies, especially when decision support systems are present, because machine agents are literal-minded and potentially behave in unexpected ways [24]. Coordinated systems also promote a common understanding by those involved in patient treatment and help

to quickly diagnose status changes, which is essential to remote and bedside monitoring [25]. Remote monitoring technologies provide the unique capability to access expertise that might not otherwise be available in a timely manner. Information displays are limited in that providers may be overwhelmed by the sheer amount of information available to them through monitoring technologies. When the provider does not know what information in the display would be useful to attend to, benefits of this technology are diminished [26]. Careful consideration to data integration, effects of information display on workload, and navigation among displays will help to overcome these issues [26, 27].

Ergonomics of Monitoring Displays

Due to the wide variety of monitoring displays, there are many ergonomic factors to consider in acute care environments. Often the location, display size, and ease of use of these displays can become significant concerns for the health providers interacting with them.

The location and positioning of monitor displays can have significant impact on performance outcomes [28, 29]. One study explored the ergonomic impact of three monitor locations for a simulated in laparoscopic surgery task. The ergonomic setup, which was a neutral position, was preferred to the other setups. Positioning the monitor at hand level, 20° from the eyes, decreased task time significantly and led to no significant change in perceived workload, but was not as ergonomic. Despite improved performance with position C, the subjective preference in laparoscopy is typically neutral position, which limits flexion of the neck [28].

The ergonomic effectiveness and efficiency in the utilization of monitoring displays depends on its key features that promote ease of use. A study on ventilator display ergonomics in Queen Elizabeth Hospital in the United Kingdom compared two ventilator interfaces, the Drager Evita 4 and the Drager V500 [29]. Both ventilators had a button on the interface to activate capnography to confirm endotracheal tube position prior to intubation. However, the Evita display had the activation button within a section off the main screen, whereas the button was moved onto the main screen of the configurable Drager. In a randomized crossover controlled trial, the study found that of 31 ICU staff, only one was unable to activate capnography within 2 min of using the Drager, compared to almost half ($N = 14$) who were unable to do so using Evita. The ergonomic layout of interactions for display use is integral to monitoring technologies, and such considerations can lead to significant changes in outcomes, especially in acute care where time is of the essence.

Additional considerations should be taken into account when considering the use of alternative platforms (e.g., iPad) as information displays and their appropriate use in care delivery. In comparison to fixed LCD monitors, the iPad has a considerably smaller screen size (9.7 in., most monitors are upwards of 15 in.) but with only slightly less resolution. As long as they do not compromise image quality through resolution or features, mobile displays may be used in lieu of traditional fixed displays. Recent studies have found no significant decrements in image interpretation using mobile tablets, as long as a zoom function was made easily accessable [30, 31].

Several of the aforementioned studies have shown statistical significance in outcomes in simulated settings, but they are limited in their generalizability by other real-time factors (e.g., monitoring multiple displays during a surgical procedure). Other ergonomic considerations include muscle fatigue over longer and continued use of monitor displays in certain positions and the learning curve of healthcare professionals unaccustomed to using newer displays. Further research in clinical environments is warranted to gain more understanding of these influences.

Conclusion

Information display design for monitoring technologies and their associated ergonomic qualities when added to an acute care environment impact physicians, staff, and patients in positive ways while being potentially limiting. The numerous studies described here have focused on the development of information displays and ergonomic considerations for

monitoring technologies in acute care settings. Current challenges associated with the design and ergonomic features include data overload, lack of integration, and poor ergonomic design. Critical to facilitating the ability to overcome the challenges associated with improved patient care is supporting the recognition of potentially dangerous operating conditions. Also, effective information displays must make available potentially relevant material as well as highlighting this information within the display [32]. In the future, improvements in remote monitoring information display capabilities have the potential to further enhance patient care in the acute care environment, especially as sensing technologies become more sophisticated.

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Decision Support and Closed-Loop Systems

6

Guy A. Dumont

Introduction

Today's critical care environment, with its myriad of monitors and sophisticated equipment, poses a major challenge to critical care clinicians who need to make quick decisions, while being literally bombarded with data. As a result, anesthesiologists in the operating room may suffer serious information overload. This is particularly true in the event of a crisis, at which time the anesthesiologist needs to devote their attention to the patient rather than to the monitors. While the monitors continue to present streams of data, they might actually get in the way, as they do not necessarily present information in a clinically relevant and context-sensitive fashion to help the clinician in their decision-making. Obviously, doing away with the monitors is not an option and perhaps paradoxically, a potential solution is offered by yet more technology: decision support systems, expert systems, and automation of some tasks. Indeed such technology has been shown to significantly improve safety in the aerospace and airline industry as well as in the nuclear energy industry. Well-designed decision support and automation systems could potentially have the same impact in healthcare, and particularly in critical care. However, a major challenge in this sector comes from the significant inter-patient variability and from the lack of fundamental knowledge and first-principle models for many interventions. Indeed despite approximately a million general anesthetics being delivered daily in the world, the fundamental mechanisms of action of anesthetics are still not well understood.

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Decision Support Systems

Decision support systems are computer-based information systems that support decision-making. Although the SAGE North America air defense system completed in 1962 is probably the first data-driven decision support system (DSS) [1], DSSs first appeared in earnest during the 1960s and 1970s primarily in the business world to help organizations manage, operate, and plan production in manufacturing plants. Today, decision support systems are used in a variety of industries and activity sectors such as manufacturing, agriculture, transportation, marketing, banking and finance, and to a much lesser extent medicine and healthcare. In the mid to late 1970s, decision support systems became a topic of academic research, and the development of a theory of DSS started. A major characteristic of DSSs is that they support rather than automate the decision-making process, leaving the human ultimately in charge. A generally accepted taxonomy of DSSs is the one suggested by Power [2], who classes them in five

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categories: communication-driven, data-driven, document-driven, knowledge-driven, and model-driven DSS:

- A *communication-driven* DSS uses communication and collaboration tools between decision-makers who share documents, desktops, etc., to support a group decision. Tools such as Microsoft's NetMeeting or SharePoint are good examples of such DSSs. In this age of globalization, such tools are essential to provide virtual teams geographically dispersed over several time zones support for shared decision-making.
- A *data-driven* DSS supports the analysis of usually large databases of structured data (either historical or real time) and provides a high level of functionality in terms of data/time-series analysis [2]. Such DSSs are used extensively in financial decision-making. To be most effective, these systems generally require data of high quality and thus often their implementation has to be preceded by the development of an adequate data collection system to ensure data quality.
- A *document-driven* DSS is used when analysis of large amounts of unstructured data (financial statements, meeting minutes, images, videos, etc.) is required to reach a decision. This is relatively new technology, made necessary by the large amount of diverse and unstructured data, the so-called big data one can find on the web. The development of analysis tools for rich media (audio, video) is a rapidly evolving field.
- A *knowledge-driven* DSS is used when highly specialized knowledge or skills are required to support decision-making. For instance, a knowledge-driven medical diagnostic system would contain knowledge about symptoms about a given class of pathologies to suggest a diagnostic and a treatment to a physician. In some instances, in the absence of fundamental knowledge, data mining is used to discover relationships and patterns hidden in data to build the knowledge base.
- A *model-driven* DSS is based on a quantitative model of the system at hand and is rarely data intensive. When either static or dynamic (i.e., using temporal relationships) modeling is possible, models can be manipulated by users, for instance, in a what-if scenario, or can be used to reach goals via some optimization technique. Such DSSs are used extensively in the financial and economic sectors.

Most DSSs are built around three or four basic components [3], a database component, a set of models and analytical tools, a communications component, and a user interface (Fig. 6.1). The database component needs to be tailored to the type of DSS and will be different whether it is data-driven, document-driven, or knowledge-driven DSS. Given the computing power available on today's computers, a model-driven DSS can be based on a very sophisticated simulation or optimization model. However, such a DSS tends to be more work to maintain, as the parameters within the model have to be kept up to date.

The opportunities for DSS applications in healthcare are numerous [4]. As in any enterprise, a DSS could be used to increase efficiency of administrative and clinical operations in order to reduce costs and maximize use of expensive facilities and personnel. Obviously in delivering healthcare, the first priority should be quality of care and patient satisfaction, and DSSs have a large role to play, particularly to ensure compliance with protocols. DSSs have been used to monitor drug interactions, tailor interventions to patients, and reduce communication and handoff errors. In the future, we will see DSS integrated with the hospital information system, fed with data from radio-frequency identification sensors (RFID), wearable sensors, and mobile devices via wireless technology, turning data into real-time, clinically relevant information.

Automation

Automation is defined as "the creation and application of technology to monitor and control the production and delivery of products and services" [5]. A control system that performs such automation typically consists of sensors that feed information to a computer. On that computer, software implements algorithms that decide how

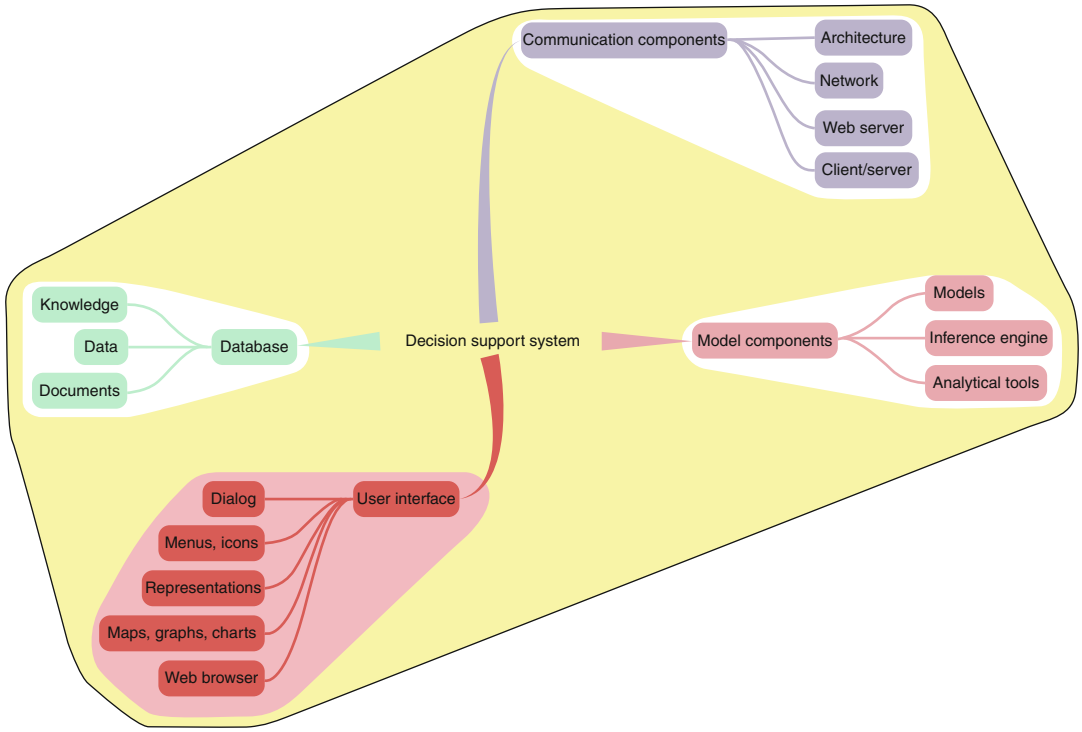

Fig. 6.1 Components of a typical decision support system. Depending on the type of DSS, some components may be more prominent than others

to actuate on the process under control. Changes to the process being controlled are achieved by sending commands to a set of actuators connected to the computer. Although those control systems mostly use closed-loop control based on the concept of feedback, sometimes they operate in open-loop mode, using model-based feedforward theory.

Open-Loop Control

An open-loop control system uses a mathematical model of the system it is controlling to compute and implement the value of the manipulated variable (input) that will set the output of the model (controlled variable) at a desired target value (set-point). Whether the output of the actual system reaches that value depends (1) on the accuracy of the model and (2) on the absence on unmeasured disturbances. Indeed, in the absence of feedback from the actual measured output, an open-loop controller has no means of compensating for disturbances. In anesthesia, target-controlled infusion (TCI) represents the archetypical open-loop control system. In TCI, a population-based pharmacokinetic (PK) or pharmacokinetic-pharmacodynamic (PKPD) model is used to compute the plasma or effect-site concentration in response to a given infusion rate profile. The first commercially available open TCI system for use in anesthesia is shown in Fig. 6.2. The idea of open-loop based TCI is essentially to invert the model to compute the required infusion rate to achieve a desired plasma or effect-site concentration. In order to improve the accuracy of TCI, the models used typically use covariates such as age, weight, and gender, to name a few. Typically, the PK models are compartmental models. A major drawback of open-loop control is the lack of verification that the target is actually achieved on the real system. Open-loop control is thus very sensitive to model uncertainty and disturbances. Indeed, because it is not reactive, open-loop

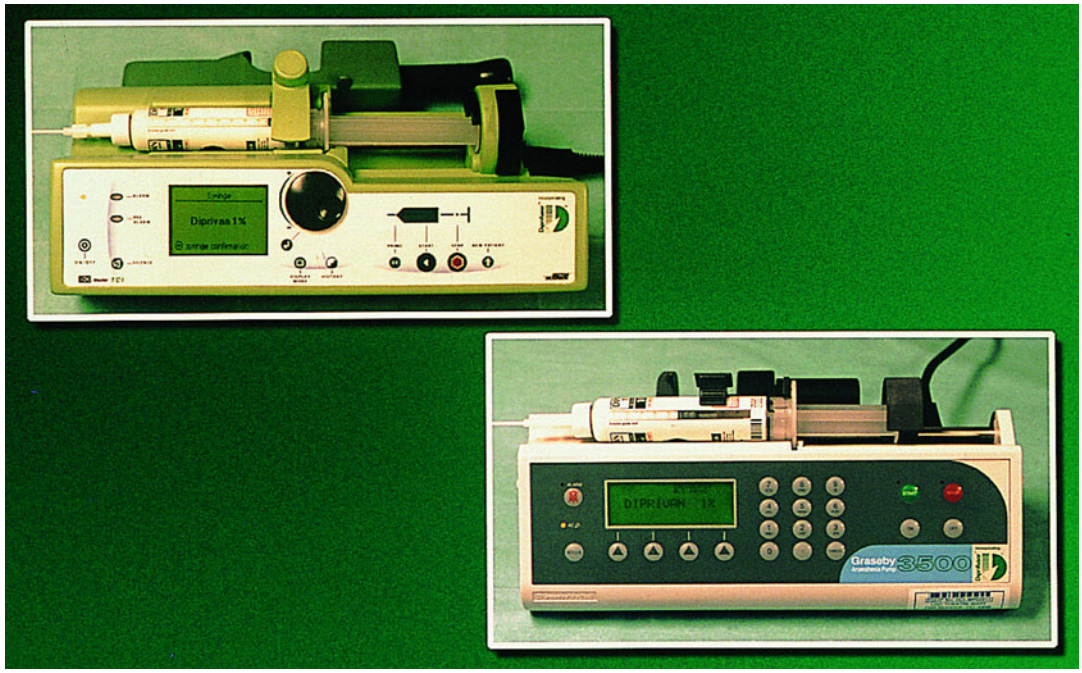

Fig. 6.2 The first commercially approved target-controlled infusion system incorporating a Diprifusor module into a syringe pump (Reproduced from Glass et al. [6]; kind permission from Springer Science+Business Media B.V.)

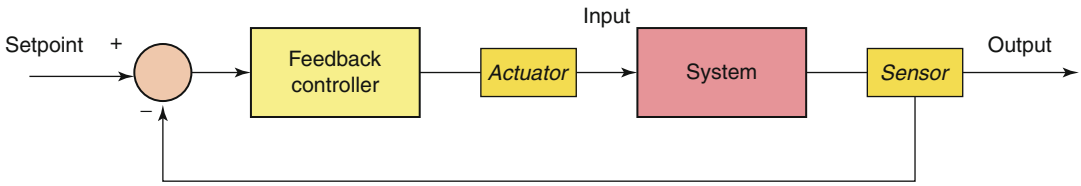

Fig. 6.3 The components of a typical feedback loop. The output of the system under control is measurement obtained via a sensor compared with the setpoint. The difference, called the error, is then used by the feedback controller to generate a control action, which is used, via an actuator, to change the input to the process

control cannot reject disturbances. However, an advantage of open-loop control is that it cannot affect the stability of the system it operates on. Consequently, when using TCI, the anesthesiologist will typically adjust the target manually to reflect the actual patient response, in essence acting as a human feedback controller [7].

Closed-Loop Control

Although used since antiquity, closed-loop or feedback control has only been formulated as a rigorous theory for less than a century. For a brief review of feedback control, see the recent article by Dumont [8]; for a more in-depth introduction, see the excellent book by Albertos and Mareels [9]. Harold Black articulated the modern concept of feedback in 1934, when he introduced the feedback amplifier to the world of telecommunication. In those days, amplifiers were built from tubes with nonlinear and uncertain characteristics. As a result, the properties of amplifiers built from similar components were highly variable. Black proposed a feedback amplifier with spectacular results, showing that feedback allows the design of good systems from not so good components. Black's invention would lead to a revolution in telecommunication. Figure 6.3 shows a typical feedback loop. The principle is deceivingly

simple: the measurement of the system output obtained using a sensor (controlled variable) is compared with the desired target value (setpoint), the difference being used to compute the value of the system input (manipulated variable) which is applied to the system using an actuator. As has been shown by Black and many others since, feedback has some amazing properties. A fundamental property of feedback is that is reduces the effect of uncertainties, and thus does not require perfect models or perfect components to work satisfactorily. This is a significant difference between open-loop and closed-loop control. Feedback thus outperforms open-loop control when there is a significant uncertainty about the system to be controlled and when unknown disturbances are present. However, a significant possible problem with feedback control is that if poorly designed or tuned too aggressively, it can lead to instability, obviously a disastrous consequence. The design of a feedback controller is then always an exercise in finding the appropriate compromise between performance and robustness (i.e., the guarantee of stability and a minimum level of performance despite the expected uncertainty). For this, control engineers have at their disposal a number of formal techniques based on rigorous theory. No feedback controller should be used unless its design can be verified and robust stability and performance can be guaranteed against a specified uncertainty. This is especially true for safety-critical applications such as in aerospace and in automatic drug delivery (e.g., in closed-loop anesthesia).

Feedback control is ubiquitous and, although often not visible, is essential to many of today's appliances and devices. Because of its ubiquity and yet lack of visibility, feedback control has been called a "hidden technology" [10]. In anesthesia it is only starting to be considered seriously in various research circles, but it has yet to have a significant impact on the practice of anesthesia, although it is bound to eventually revolutionize the field, particularly for total intravenous anesthesia. A property of feedback is that it transfers the variability from the output to the input. It is best seen by an example comparing TCI versus closed-loop control of depth of hypnosis. Assume two patients of the same age, weight, and gender. Under TCI, assuming that the clinician chooses the same target concentration for both, the infusion rates for these two patients will be identical. Given inter-patient variability due, for example, to different medical conditions and genetics, these two patients, although receiving exactly the same drug regimen, will likely respond differently to the drug and may have very different depths of hypnosis evolution. Closing the loop will result in maintaining the same depth of hypnosis for both patients at the "cost" of now having different infusion regimens. Thus, in effect, the variability will have been transferred from the output (depth of hypnosis) to the input (infusion rate), ensuring that each patient receives the right amount of drug, nothing less, nothing more.

DSS or Closed Loop?

Most DSSs provide support to the user for making a decision, but will not themselves make any decision, leaving that to the user. In effect, they help by digesting the information and presenting it in a form more amenable to decision-making. On the other hand, a closed-loop system automatically makes a decision and acts on it and can do that repeatedly, rapidly, and with great accuracy. A closed-loop system is thus very appealing for repetitive, very frequent tasks, such as adjusting the infusion rate of a drug to maintain a given clinical effect. With a closed-loop system, an anesthetist might be able to better concentrate on the patient, rather than on an infusion pump. A decision support system will be most useful when making the right decision relies on complex, unstructured information and expert knowledge, and the process does not have to be repeated frequently. Taking hemodynamic management as an example, F. Michard states that "closed-loop systems are the ultimate solution to ensure therapies are delivered" [11]. However, many therapies may be too complex and necessitate the integration of too many variables for a closed-loop system. For example, although closed-loop control of blood pressure by vasopressors is feasible, it is not the right therapeutic intervention in case of hypovolemia. Michard thus argues that decision

support system tools such as innovative displays of information may actually provide a more practical solution and would reserve closed-loop control for simple and repetitive tasks where workload and human attention are a concern.

Conflict of Interest GA Dumont is coinventor of the NeuroSENSE monitor (NeuroWave Systems Inc., Cleveland, OH). He has consulted for NeuroWave Systems Inc and GE Healthcare.

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Part II

Hemodynamic Monitoring

Introduction to Hemodynamic Monitoring

7

Azriel Perel

All important decisions must be made on the basis of insufficient data. Yet we are responsible for everything we do. No excuses will be accepted.

Sheldon Kopp

The hottest places in hell are reserved for those who, in times of great crisis, do nothing.

Dante

Introduction

Accurate assessment of the hemodynamic status is vital for making correct decisions in the acute care environment. Since hemodynamic impairment is one of the major hallmarks of acutely ill patients, these decisions, made and acted upon in a timely manner, may have an immediate impact on patient outcome. And yet, hemodynamic assessment may pose a considerable, often underestimated, challenge. This is due to the fact that an impending hemodynamic deterioration may not always be easily identified, the "diagnosis" (e.g., septic shock, cardiogenic shock) does not always tell us what the main physiological disturbance is, and the hemodynamic status may be complex (e.g., hypovolemia *and* myocardial depression) and may be further confounded by preexisting comorbidities. The challenge of making an accurate hemodynamic assessment is made even more critical since, very often, each of the potential decisions (e.g., fluid administration, vasoactive drug therapy) is associated with its own significant risks.

In view of this daily challenge, it is no wonder that physicians who practice in the acute care environment have always searched for more physiological information that would help them to better choose and better titrate suitable therapies. This quest has been fueled by the realization that clinical examination alone, though being a most important initial step in hemodynamic assessment [1], may often be inadequate for this purpose. Additionally, the monitoring of vital signs alone, which has become the standard of care in the acute care environment, has also been shown to frequently provide unreliable indication of the adequacy of tissue oxygen delivery and to be unable to serve as an end point of resuscitation. As a result, and in order to reduce the considerable uncertainty that characterizes the acute care environment, we employ a variety of monitoring modalities that improve our ability to make informed and correct therapeutic decisions. In the following chapters of this new book on monitoring technologies in acute care environments, the readers will find valuable information about some of these new technologies and how to should they be correctly used.

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Considerations When Interpreting Hemodynamic Monitors

Although the concept of hemodynamic monitoring, and monitoring in general, as a way of reducing uncertainty may seem quite straightforward, the correct selection and application of specific monitoring modalities and the correct *interpretation* of the monitored variables are often the subject of hot debate. A necessary first step in understanding this debate is the realization that each and every hemodynamic variable that we measure has limitations and confounding factors and that knowing the limitations of these parameters is as important as knowing their potential value. Hence, a correct application of the information that is provided by our monitors necessitates a thorough understanding of the monitored variable and its underlying physiology. A noncritical acceptance of a numerical value may too often lead to erroneous therapeutic decision, especially in view of our tendency to normalize abnormal values. Although the extent to which physiological variables differ from normal values indicates how ill the patient is and what is the prognosis, "automatic" normalization of any derangement may lead us to ignore the underlying problem and/or to induce harm [2].

Using Hemodynamic Monitors to Set Targets and Goals

The overreliance on specific values of monitored parameters is often seen in "goal-directed" approaches, which recommend the achievement of specific "target" physiological values for all patients. Such approaches often disregard the large interindividual range of these parameters and their inherent limitations in reflecting the adequacy of the hemodynamic status [3]. A good example of the potential pitfalls of such an approach can best be seen in the Surviving Sepsis Campaign guidelines, where the initial hemodynamic resuscitation protocol recommends the achievement of central venous pressure (CVP) above 8 mmHg and central venous oxygen saturation ($ScvO_2$) of 70 %, although the CVP is a poor measure of preload and although a "normal" $ScvO_2$ value may be due to decreased oxygen extraction and not due to successful resuscitation [4]. Similarly, recommending a "supranormal" value of oxygen delivery in *all* surgical patients as part of an "optimization" process may be inappropriate at least in the frail and elderly.

Hemodynamic Monitor Accuracy

Another factor that has to be taken into account when interpreting the specific values of measured hemodynamic parameters is the inherent inaccuracy of the measurement process itself. Such potential inaccuracies may often be due to a faulty measurement technique, as in the common case of an uncalibrated pressure transducer. They may also be due to the inherent inaccuracy of the monitoring technology itself. The influx of new, less-invasive, uncalibrated means of monitoring cardiac output (CO) continuously has indeed been associated with much debate about their accuracy [5]. This debate presents the clinician with a considerable dilemma and may partially explain, for example, why clinical practice remains out of sync with the current evidence base with regard to perioperative goal-directed therapy [6]. On the other hand, when evaluating the role of new CO devices in clinical care, the fundamental question is whether the new device can replace thermodilution CO measurement as a guide to clinical decisions [7] and whether a measurement obtained by a less-invasive technique may be preferable if it can be obtained more rapidly and easily, even if it is slightly less accurate [3].

Static Versus Continuous Measurements

There are a number of approaches that may help us overcome the inherent inaccuracy in hemodynamic monitoring. The first one is maximizing the clinical value of real-time continuous measurements. The best and most common example is the vast amount of information that is offered

by the continuous analog signal of the blood pressure waveform in comparison with its digital readout. The *continuity* of our measurement offers a powerful tool especially in the assessment of the response to therapeutic or diagnostic events with short time constants, such as a mechanical breath (which generates dynamic parameters like the systolic, pulse pressure, and stroke volume variations), fluid loading, passive leg raising, or the immediate response to inotropes. In these circumstances a continuous real-time CO is more useful and informative than CO measured by intermittent bolus thermodilution which has a precision of ±10–20 %.

Multiparameter Hemodynamic Assessment

The integration of various variables from multiple sources is another useful approach that may be helpful in overcoming the inherent inaccuracy of hemodynamic monitoring [3]. Since any variable on its own provides limited information and is just one piece of a large puzzle, therapeutic decisions have to rely on a multiparametric approach [3]. Relevant examples of this approach include the simultaneous observation of the blood pressure and the end-tidal CO_2 (in order to elucidate the nature of hypotension), the combination of CO and dynamic parameters (to determine fluid responsiveness), or the combination of CO and $ScvO_2$ (which complement each other especially in septic patients). Last but not least, we have to adopt decision-making strategies that take into account the uncertainty of our measurements. The "gray zone" approach for the prediction of fluid responsiveness is an example of such a strategy, recommending that higher-than-normal pulse pressure variation (PPV) values should serve as an indication for fluid administration where fluid overload may be particularly deleterious [8]. Such approach is indeed of special value during "therapeutic conflicts" (i.e., when each of the possible therapeutic decisions carries some potential harm). The successful management of such situations necessitates a priori assessment of the possible harm that each of the respective potential decisions may cause (when found to be wrong), as well as the highest expertise in the correct application and interpretation of hemodynamic monitoring.

Evidence Base for Hemodynamic Monitoring

The readers of the following chapters will note that even though hemodynamic monitors have become more sophisticated and more informative, there is little or no evidence that they do indeed improve patient outcome and that only few monitoring systems, except for the pulmonary artery catheter, have been evaluated by a randomized controlled trial (RCT) [9]. The main reason for this apparent lack of evidence is that outcome is determined by our clinical decisions and not by the monitor we use, and, as a result, an excessively large number of patients need to be included in such RCT [10]. In addition, more information is not always better, and monitoring will only benefit the patient if the data are interpreted or applied correctly and if there is indeed an effective treatment for the underlying cause [3, 11].

Conclusion

Doubt about the evidence base, worry about inaccuracies in monitoring techniques, and a lack of energy and motivation needed to adopt new monitoring technologies may all have contributed to the fact that many clinicians still base their clinical decisions on clinical examination and conventional monitoring alone. Such practice is still prevalent even though it has been repeatedly shown that without additional monitoring, our ability to correctly assess the hemodynamic status is very limited, especially in severely ill patients. It is clear that management decisions, when based on inaccurate clinical assessment, may be detrimental to patients. It is unfortunate that evidence-based medicine (EBM), which has become such a dominant paradigm in our current practice, is rarely of help in guiding individualized management at the bedside [12]. This major limitation of EBM, and its declared

de-emphasis of reasoning based on pathophysiological rationale, leaves the physician at the acute care environment no choice but to guide individual hemodynamic management according to basic physiological principles, which are indeed the foundation of medicine [13]. Only the skilled interpretation of relevant and timely information about key hemodynamic variables may induce significant beneficial changes in patient management and outcome. The following chapters describe some of the technologies that are available for this purpose and will be of great value to those of us who bear the responsibility of individual patient care.

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Pulmonary Artery Catheterization

8

Olufunmilayo Ogundele, Eliezer Bose,
and Michael R. Pinsky

Introduction

Although the first right heart catheterization of humans was performed in the 1920s, the first bedside pulmonary artery catheterization was not performed until 1964 following decades of technologic advancements in catheter design and pressure monitoring [1]. Cardiac output thermodilution techniques were introduced in 1968 and Swan and Ganz reported the use of a flexible balloon tip catheter to pass into the pulmonary artery without need for radiographic guidance [2]. In the two decades following this discovery, the pulmonary artery catheter (PAC) became the gold standard for hemodynamic monitoring of critically ill patients in the intensive care unit (ICU). The PAC is unique in its ability as a single catheter to monitor continuously mixed venous O_2 saturation (SvO_2), cardiac output (CO), right atrial pressure (Pra), pulmonary arterial pressure (Ppa), right ventricular ejection fraction (RVef), and, by mathematical derivation, right ventricular end-diastolic volume (EDV) and, by intermittent distal balloon occlusion, pulmonary artery occlusion pressure (Ppao). No other cardiovascular monitoring device shares this pluripotential presence.

Controversy

While the PAC was widely accepted as an excellent hemodynamic monitoring tool, it was never studied directly as to its utility and direct benefit to patient care. In fact, when studies specifically addressed the benefit of PAC-guided therapies, the resultant data suggested it was harmful. In 1996, an observational study of 5,735 patients concluded that PAC use was associated with an increased mortality and use of resources [3]. This led to several studies consistently reporting that the PAC use did not improve survival and in some cases actually increased mortality [3–12]. Subsequent editorials called for a moratorium on PAC use in the ICU. To date, there is no consensus on whether the PAC is beneficial or harmful for hemodynamic monitoring of critically ill patients in the ICU. At best, well-designed studies show its use of marginal effect on outcomes. Since no monitoring device, no matter how insightful its data will improve outcome, unless coupled to a treatment which itself improves outcome, PAC use may not be the issue. In fact, as will be discussed below, when used to guide therapies of proven efficacy, the PAC has demonstrated clear benefit.

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Although there are mixed reviews on the benefit of PAC use in the hemodynamic monitoring of patients, some recent publications have advocated for their continued use in specific situations and patient populations. A recent meta-analysis by Hamilton et al. examined postoperative outcomes in 29 trials involving 4,805 patients who underwent moderate- and high-risk surgery. They reported a significant reduction in overall mortality of 7.6 % (OR 0.48 [0.33–0.78]; $P=0.0002$) [13]. The ongoing ESCAPE trial assessed the application of PAC use in non-acute and non-shock decompensated heart failure. Though the results showed a neutral impact of PAC-guided therapy over therapy guided by clinical judgment alone, PAC was still recommended for management of refractory heart failure, pulmonary hypertension, and transplant evaluation [14]. Furthermore, a study survey of cardiac anesthesiologist showed an overall support for continued PAC use in cardiac surgery with the caveat that the usefulness of PAC as a monitoring tool is only as good as the user interpreting the data [15].

Despite a >50 % reduction of PAC use in the last 5 years, there continues to be advocacy for selective PAC use in as far as its benefit outweighs the risk and a reliable hemodynamic monitoring alternative does not exist [16, 17]. Although less invasive monitoring alternatives such as the ultrasound and arterial pressure-derived estimates of cardiac output are increasingly being used, studies still advocate the PAC use in situations where knowledge of pulmonary pressures, Ppao, and SvO_2 are needed if coupled to the appropriate interventions [18–20]. Newer monitoring modalities such as arterial waveform monitoring and algorithm-based monitors have been cited to lack reliability outside of narrow ventilation and rhythm parameters, thus giving further support for continued PAC use. Manoach et al. recently examined the evolution and current use of invasive hemodynamic monitoring resuscitation in perioperative critical care. They advocate for continued PAC use in patients with complex cardiac disease such as pulmonary hypertension because these patients were excluded from key PAC efficacy trials, and such patients may benefit from the PAC's ability to differentiate precapillary from postcapillary pulmonary hypertension [21].

However, more recent literature continues to question continued PAC use and benefit. A recently published FACCT trial was a prospective comparison of costs and long-term outcomes of care in of ICU patients with acute lung injury who had a PAC versus central venous catheter-directed therapy once initial resuscitation resulted in hemodynamic stabilization concluded that use of PAC increased cost without long-term benefit. They concluded that PAC use is unjustified in the routine care of acute lung injury [22]. The FACCT trial needs to be interpreted with caution, however, because patients were only enrolled 24–36 h after being diagnosed with acute lung injury and, thus, long after the initial acute resuscitation had been delivered. Furthermore, more patients who would otherwise have been eligible to be enrolled into this randomized study were excluded because they already had a PAC. Thus, we can conclude form the FACCT trial that in patients in whom a critical care physician does not deem that the use of a PAC is warranted and after such patients have been stabilized, PAC use for the longer-term management of patient with acute lung injury is unjustified. Barmparas et al. examined the changing pattern of PAC use in trauma care to determine its effect on several outcomes. Results on the matched population concluded that PAC is invasive and associated with multiple complications and increased health care cost. While the authors recognized PAC use in selected populations, they discouraged its widespread routine use with an emphasis on alternative monitoring approaches [23]. In contrast to some studies reporting a reduced mortality with PAC use [13], Schwann et al. compared increased risk of poor outcomes in cardiac surgery patients with and without PAC placement. PAC use was associated with increased risk of all cause mortality (21.3 % vs. 15.4 %, OR 1.68 [1.24–2.26; $P<0.001$), as well as increased risk of poor cardiac, cerebral, and morbidity outcomes. The group with the PAC also received more inotropic drugs, larger postoperative positive fluid balance, longer time to tracheal extubation, and longer ICU stay [24].

Still, a primary caveat of all these studies is that they did not use the PAC to guide specific therapies known to improve outcome. They used it merely to sustain specific hemodynamic values. Prior to placing a PAC, clinicians should ensure that the hemodynamic data they seek is not available by less invasive monitoring modalities. In the situation where other modalities are not available or cannot provide this information, it is reasonable to insert a PAC. It has been demonstrated that that PAC use in goal-directed therapies can improve patient outcomes. Several studies have documented improved mortality outcomes and decreased hospital length of stay when resuscitation decisions were guided by PAC measures of SvO_2 and CO [25–34]. In postoperative patients, resuscitation protocols guided by oxygen delivery (DO_2) were shown to decrease postoperative complications and increase patient survival [25–33]. Furthermore, when PAC was coupled to specific treatment endpoints using algorithms, PAC showed survival benefits thus emphasizing the fact that the benefit of PAC is more related to patient selection, use of known beneficial therapy, and clinical situation. The FACCT trial mentioned above is a case in point where Ppao was compared to CVP to predict volume responsiveness; a benefit of PAC was not observed because neither Ppao nor CVP measures reliably predict preload. Other studies illustrating the suboptimal choice to use PAC have been documented in patients with preexisting organ failure and high mortality risk [35–38]. Despite studies showing lack of improved patient outcomes with PAC use in ICU patients, other alternative monitoring devices have also not demonstrated utility either [25, 39].

Indications

Etiology of shock has traditionally been categorized as hypovolemic, cardiogenic, obstructive, and distributive. The PAC measures CO and SvO_2, and Ppao can be readily used to characterize these different shock states. Such hemodynamic profile analysis is central to the initial enthusiasm for PAC use. The decision to place a PAC in patients should be guided by the information one seeks to obtain which cannot be obtained from less invasive means. Furthermore, one must have an experienced practitioner that cannot only perform the procedure accurately and safely but who can also interpret the data accurately in order to use it to guide appropriate therapy. Clinical practice guidelines published by the Society of Critical Care Medicine and the American College of Cardiology recommended the use of PAC in various disease processes if its insertion will alter the course of therapy.

The decision to forego inserting a PAC is made when other means are available to obtain the same hemodynamic data. If one needs only to measure CO, then other less invasive technologies are routinely available, notably analysis of arterial pulse pressure contour. There are many commercially available devices ranging from those requiring central venous and arterial catheterization (e.g., LIDCOplus and PICCO) to those requiring only arterial catheterization (e.g., FloTrac-Vigileo and LiDCOrapid) [40–44]. Other noninvasive technologies for continuous CO measurements include esophageal Doppler monitoring [44, 45] and NICOM-based thoracic bioreactance [46]. However, only the PAC provides direct monitoring of intrathoracic intravascular pressures (Pra, Ppa, Ppao). While a central venous access will allow measures of Pra and a surrogate of SvO_2, namely, central venous O_2 saturation ($ScvO_2$), it still cannot measure CO, Ppa, or Ppao. Since numerous studies have documented that neither Pra, Ppao, nor their changes in response to fluid challenge predict volume responsiveness, PAC insertion to predict volume responsiveness is not indicated. But using the PAC to note how resuscitation efforts impact CO, SvO_2, Pra, and Ppao are not only appropriate but often required for effective titration of cardiovascular therapy. For example, Ppao measures can separate out primary (acute lung injury) from secondary (cardiogenic) pulmonary edema. The third measurement obtained from PAC is SvO_2 which has been used as a surrogate for effective global tissue perfusion. In critically ill patients, both SvO_2 and $ScvO_2$ have been used to titrate to resuscitation goals with improved outcomes, despite differences in the absolute O_2 saturation values for the

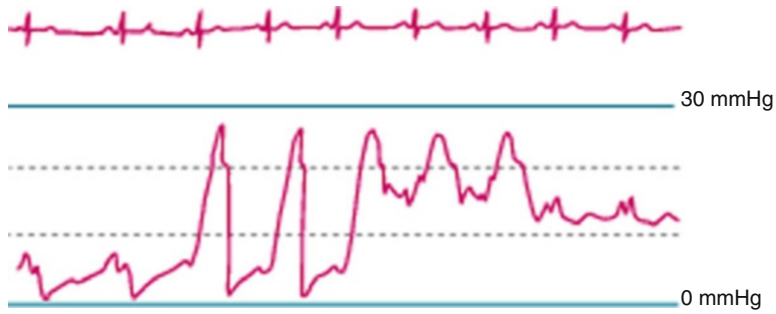

Fig. 8.1 Floating the pulmonary artery catheter (PAC). Transduction of the pulmonary artery port as the PAC initially reveals a normal central venous pressure (CVP) tracing until it passes through the tricuspid valve into the right ventricle. Right ventricular systole then results in relatively high systolic peaks on the waveform, but diastolic pressure remains similar to right atrial filling pressures. As the PAC passes through the pulmonic valve, the diastolic pressure increases to that of the pulmonary artery diastolic pressure. When the catheter wedges into a smaller pulmonary artery, the waveform begins to reflect pulmonary vein and left atrial pressures, with wave morphology (a, c, and v waves) similar to a CVP waveform. With normal lungs, the left atrial filling pressures are normally 3–4 mmHg less than the pulmonary artery diastolic pressures (Reproduced from Field [71]; kind permission from Springer Science+Business Media BV)

two measures [47]. While both SvO_2 and $ScvO_2$ change in parallel during shock states, exceptions to this correlation exists with reduced flow to the lower extremities causing an overestimation of $Scvo_2$ relative to SvO_2. Therefore, while $ScvO_2$ is a reasonable approach to estimate a low SvO_2, it is not appropriate to place a PAC for the sole purpose of using SvO_2 to determine resuscitation goals [48, 49].

Insertion Method

Prior to inserting a PAC, several patient-specific data must be checked to ensure there's no contraindication to PAC insertion. A 12-lead EKG should be obtained to rule out a left bundle branch block. Inserting a PAC under this condition can cause a complete heart block. A coagulation profile should be obtained, and if a coagulopathy is present, these should be corrected prior to PAC insertion. Electrolyte abnormalities such as low potassium and magnesium should be corrected as well. Finally, a consideration should be made to use radiographic guidance for patients with a pacemaker, as a potential exists for dislodgement during PAC insertion.

Next, the PAC is visually inspected to ensure there is no physical defect precluding its use. The latex balloon at the tip should be inflated and deflated to check for symmetrical expansion without leaks. Balloon deflation should always be done by passive deflation having removed the inflation air syringe. Never manually suck air out of the balloon because this may cause the balloon to rupture causing air embolism upon reinflation. The distal lumen should be connected to the pressure monitoring system and all lumens flushed to remove air and ensure good flow. The pressure transducer should be zeroed and a fast flush done to assure a frequency response and appropriate damping.

Adhering to standard sterile conditions, the PAC is passed through a 7.5- to 9-Fr gauge introducer with a hemostatic valve on its proximal end for prevention of air embolism. Using Seldinger technique, the introducer is inserted into a central vein usually the internal jugular or subclavian vein. While femoral and antecubital routes can be used, they are associated with more insertion difficulties. Next, the operator passes the catheter tip through the introducer and pushes it down past the introducer for about 15 cm then slowly inflates the PAC balloon. If using the internal jugular or subclavian route, a Pra waveform should appear after the catheter tip has advanced about 15–20 cm from the skin surface (Fig. 8.1). The catheter is then advanced farther, usually

about 10 cm, and the right ventricular waveform should appear on the monitor. Often a sensitive touch will feel the tug of the tricuspid value on the PAC balloon as it passes from the right atrium into the right ventricular cavity. Once in the right ventricle, the catheter is advanced another 10 cm or until PA waveforms are evident. Arrhythmias due to the position of the PAC balloon next to the intraventricular septum commonly occur at this time. From the PA tracings, advancement of catheter for another 10 cm usually reveals a dampened and decrease signal consistent to Ppao waveforms. Once Ppao is obtained, the balloon should be allowed to deflate and the PA waveform should return. Lastly, the proximal protective sleeve should be locked onto the catheter while the distal protective sleeve is locked onto the hemostatic valve of the introducer.

After placement of the PAC, a chest radiograph should be obtained to ensure the catheter tip is within 2 cm of the cardiac shadow. All pressures from the PAC should be measured at end expiration.

Hemodynamic Data

Measuring Ppao

Ppao is obtained only intermittently during a balloon inflation maneuver. Such balloon inflation transiently migrates the PAC distal tip into a medium-sized pulmonary artery and caused a flow in that vessel to cease creating a column of blood from that point to the point where flow resumes in the large pulmonary veins about 1.5 cm from the left atrium, also called the J-1 point of the pulmonary veins [2]. Often Ppao values are often used to drive resuscitation therapies, although their usefulness in doing so in patients with acute respiratory distress syndrome has been challenged.

Airway Pressure and Ppao

The lung vasculature can be considered existing on one of the three perfusion pressure states as popularized by West, as Zones 1, 2, and 3, based on the relative differences in pulmonary artery pressure, pulmonary airway pressure, and pulmonary venous pressure. Arterial and venous pressure decreases as vessels lie above the level of the heart, such that the higher up the lung, the vascular pressures decreases progressively while alveolar pressures remain constant throughout the lung. If alveolar pressure exceeds pulmonary artery pressure, no flow occurs. This is called Zone 1 conditions. If both pulmonary artery pressure and pulmonary venous pressure exceed alveolar pressure, then flow is solely determined by vasomotor tone and perfusion pressure. This is called Zone 3 conditions. However, if alveolar pressure is greater than pulmonary venous pressure but less than pulmonary arterial pressure, then the driving pressure for blood flow is the difference between pulmonary arterial pressure and alveolar pressure and changes in pulmonary venous pressure do not influence this flow. This is called Zone 2 conditions. If the PAC tip is in Zone 1 or 2 conditions, then Ppao will reflect alveolar pressure during occlusion, not pulmonary venous pressure. How can you identify that the Ppao value actually reflects alveolar pressure and not pulmonary venous pressure. This can be accomplished by noting the dynamic changes in both pulmonary artery diastolic pressure and Ppao during a positive-pressure breath. Pulmonary vasculature senses pleural pressure (Ppl) as its surrounding pressure, while alveoli sense Paw as their pressure. Thus, pulmonary artery diastolic pressure fluctuations will always be influenced by changes in pleural pressure. In Zone 2 and 3 conditions, Ppao will also vary with pleural pressure. However, in Zone 1 and 2 conditions, alveolar pressure rises which are always greater than pleural pressure rises will document that the sensed Ppao is invalid [50].

Pleural Pressure, PEEP, and Ppao

Ventilation causes significant swings in Ppl and, conventionally, Ppao values are measured at end expiration, where pleural pressures variations with respect to ventilation are minimal. During

quite spontaneous respirations and as described elsewhere, end expiration occurs at the highest vascular pressures values, and during positive-pressure breathing, end expiration occurs at the lowest vascular pressure. With forceful ventilatory efforts, it is often difficult to define end expiration, and it is much difficult in a patient who is not sedated and tachypneic with high respiratory drive, making end expiration unreliable for measuring values. Even if Ppao is measured at the end expiration, these values may overestimate Ppao if Ppl is elevated at end expiration. Hyperinflation, due to either extrinsic PEEP or dynamic hyperinflation (intrinsic PEEP), will cause pleural pressure to remain elevated at end expiration, that making Ppao reading overestimate actual Ppao values. Importantly, if PEEP is <10 cmH_2O in patients with acute lung injury, Ppao values are not significantly influenced by the PEEP. However, at levels >10 cmH_2O, measured Ppao values increased by 2–3 cmH_2O with every 5 cmH_2O PEEP increase [51, 52]. Due to differences in the lung and chest compliance, one cannot assume a fixed relationship between increases in Paw and Ppl [53]. The Ppao measurement is subject to many errors due to dynamic changes in intrathoracic pressure (i.e., not identifying end expiration correctly), hyperinflation (i.e., increased intrathoracic pressure even at end expiration), and improper direct measures of a variable pressure waveform.

In a setting of hyperinflation, even accurate measures of Ppao in Zone 3 conditions and end expiration will still overestimate pulmonary venous pressure. Two techniques have been proposed to compensate for the unaccounted for increase in pleural pressure. These techniques are the nadir wedge pressure measurement and the lung compliance estimation methods. The first technique assumed that with sudden airway disconnection at end expiration, airway pressure and lung volume will rapidly decrease to normal functional residual capacity before any fluid and blood shifts alter cardiovascular function. One observes the associated Ppao behavior during the airway release maneuver. The nadir Ppao value reached within <3 s of disconnection from the ventilator reflects the on-PEEP pulmonary venous pressure. The nadir wedge measurement is not recommended for two reasons. First, with transient airway disconnection, airway derecruitment can also occur rapidly and result in hypoxemia that may not reverse quickly. The other indirect technique for measuring Ppao during hyperinflation is by calculating transmural value of end-expiratory Ppao as a ratio of airway to pleural pressure changes during a breath. Ppao depends on pleural (Ppl) and airway pressures (Paw); the proportional transmission of pressure from the airway to the pleural surface, referred to as the index of transmission (IT), equals the ration of the differences between changes in Ppao and Paw during a breath. Thus, transmural Ppao = end-expiratory Ppao − (IT · total PEEP), where IT is an index of transmission of Palv to Ppao calculated as IT = (end-inspiratory Ppao-end-expiratory Ppao)/(plateau pressure − total PEEP). Total PEEP is combined intrinsic and extrinsic PEEP. Although this formula appears to be complex, it can be easily derived at the bedside and does not require airway disconnection from the patient. In practice, performing the nadir wedge maneuver is not recommended because of the potential derecruitment that the sudden loss of airway pressure may include in patients with acute lung injury.

Clinical Significance of Ppao

Ppao is useful at bedside in the assessment of (1) pulmonary edema, (2) pulmonary vascular tone, (3) intravascular volume status and left ventricular (LV) preload, and (4) LV performance [54]. The uses and limitations of Ppao for assessing these conditions follow.

Acute pulmonary edema is a life-threatening emergency, and alveolar flooding occurs if the pulmonary capillary pressure is more than 18–20 mmHg. Pulmonary edema can be classified into primary (Ppao is less than 18–20 mmHg), where along with increased pulmonary capillary pressure, alveolar epithelial permeability contributes to the edema and secondary or hydrostatic pulmonary edema (Ppao more than 18–20 mmHg), where pulmonary capillary pressure is predominantly contributing to the lung

edema. If pulmonary capillary pressure increases above 18–20 mmHg, alveolar flooding occurs.

However, the numbers can be misleading. For example, one can have a secondary of hydrostatic pulmonary edema with a Ppao less than 18–20 mmHg. Here, the contributing factors may be on one hand transient elevation of Ppao and resolves or if pulmonary capillary pressure significantly overrides Ppao. The former situations can be encountered in transient acute LV dysfunction like acute coronary syndromes (myocardial ischemia), cardiac arrhythmias, inspiratory stridor, and obstructive sleep apnea. The later can occur in clinical situations like in increased pulmonary capillary pressure due to rapid swings of massive sympathetic discharges like cocaine overdose or acute intracerebral hemorrhage.

Pulmonary circulation is normally a low resistance circuit, and increases in pulmonary artery pressure can be due to either increase in pulmonary vascular tone or due to passive increases in Ppao secondary to LV failure acute or chronic. Based on this, pulmonary hypertension can be classified as primary or secondary. Normally, pulmonary artery diastolic is slightly higher than the Ppao. Normal pulmonary vascular resistance is 150–250 dyn/s/cm^{-5}. By measuring pulmonary artery pressure, Ppao, and cardiac output in patients with pulmonary hypertension, one can differentiate if increase in Ppa is due to increased pulmonary vascular resistance (looking for causes in the lung) or secondary to passive buildup of pressure (looking for LV dysfunction as a contributing factor).

Intravascular volume status and LV preload: In the setting of circulatory shock, maintaining an adequate LV preload is central to management. Aggressive fluid challenges are often performed and with a premise that fluid resuscitation increases LV end-diastolic volume, and this in turn increases CO. Commonly used bedside targets for achieving such goals of resuscitation are by targeting a CVP of 8–12 mmHg, and Ppao of 12–15 mmHg has been proposed in recent international guidelines on management of severe sepsis. However, numerous studies have shown that neither Ppao nor Pra is valuable for guidance of fluid resuscitation in patients with circulatory failure [55–57]. In their study, based on the evidence, using Ppao to predict response to fluid resuscitation is not recommended, except at the extremes of Ppao values.

A major use of PAC is to assess LV performance. As stated above, Ppao serves as a surrogate of LV end-diastolic volume (EDV), which itself is a fundamental determinant of stroke volume and LV stroke work (LV stroke volume × developed pressure). Bedside assessment of LV performance has important clinical implications, like in determining the etiology of cardiovascular insufficiency and tailoring the appropriate therapeutic strategies. The key factors determining the LV stroke volume are preload (LV EDV), afterload (LV wall stress, which in turn is the product of LV EDV and diastolic arterial pressure), heart rate, and contractility. Based on the Frank-Starling curves obtained by plotting Ppao and LV stroke work, patients with heart failure can be classified into four categories using Ppao and cardiac index cutoff values of 18 mmHg and 2.2 L/min/m^2, respectively. Patients with low cardiac indices and high Ppao are presumed to have primary heart failure and low cardiac indices and low Ppao hypovolemia. Those with high indices and high Ppao have volume overloaded, and those with high indices and low Ppao are deemed to have increased sympathetic tone. This simplistic classification works with uncomplicated heart failure patients but fall apart in the setting of sepsis and acute respiratory distress syndrome.

Cardiac Output

The standard method for CO estimation is thermodilution which is based on the indicator dilution principle that when an indicator substance is added to flowing blood, the flow rate is inversely proportional to the mean concentration of the indicator downstream. In this case, temperature is used as the indicator and can be cold or warm. In cold thermodilution, a 10 mL bolus of cold saline or 5 % dextrose is injected as a bolus through the proximal port of the PAC and mixes with blood in the right ventricle. A thermistor proximal to the balloon records the temperature

change in the pulmonary artery displayed as a temperature time curve. The area under the curve is inversely proportional to the flow rate in the pulmonary artery which estimates CO from the Stewart-Hamilton equation. Several derived parameters can also be calculated from CO, namely, cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular index, right and left ventricle stroke work index, oxygen delivery, and oxygen uptake.

In the warm thermodilution method, a thermal filament is attached to the PAC about 14–25 cm from the tip. The filament generates heat pulses intermittently, and the temperature change is recorded by the thermistor in the pulmonary artery. The heat pulses are generated at random to minimize other causes of heat generation such as respiratory changes and infusions. The cardiac output is averaged over the previous 3–6 min and is updated every 30 s to a minute. The continuous CO method is commonly used and during steady state conditions is very accurate. However, because it integrates measures of many minutes, sudden CO changes will not be rapidly identified.

The most important feature of PAC is its ability to measure cardiac output because it is a global assessment of circulation or blood flow to tissues. Cardiac output is the product of stroke volume and heart rate. Stroke volume is determined by preload, afterload, and myocardial contractility. While cardiac output allows blood flow to tissues, there are other factors for considering in assessing if tissues have adequate oxygenation. Oxygen transport to tissues involves gas exchange in the pulmonary system, interaction of oxygen with hemoglobin, oxygen delivery (DO_2) to organs, and oxygen consumption (VO_2) at the tissue level.

Oxygen delivery is determined by central and peripheral factors. Central factors rely on convection or bulk blood flow and are the product of cardiac output and arterial oxygen content (CaO_2) [58]. Factors that determine CaO_2 are arterial oxygen saturation of oxygen (SaO_2) and hemoglobin concentration. Among central factors, cardiac output is the major determinant of DO_2 because a fall in PaO_2 and Hgb can be compensated by an increase in CO; however, the reverse is not true. The oxyhemoglobin dissociation curve dictates that increases in PaO_2 beyond the level that ensures SaO_2 above 90 % produce relatively small additional increases in CaO_2. Furthermore, hemoglobin concentrations do not change acutely, and while blood transfusions can be given, it can inadvertently decrease DO_2 as a result of increased blood viscosity. Therefore, under ideal physiologic conditions, cardiac output constantly adapts to the oxygen needs of the patient. Peripheral factors involve the redistribution of cardiac output to different organs and his regulation of the microcirculation [58]. These are determined by the autonomic control of vascular tone, local microvascular and local microvascular responses, and the degree of hemoglobin's affinity for oxygen. In critically ill patients, such as those with sepsis, local vascular tone is often altered causing microthrombi which constrict some capillaries therefore altering local distribution of blood flow. Therefore, a normal cardiac output reading via PAC in critically ill patients does not mean that the patient has adequate blood flow. Regional and microcirculatory distribution of cardiac output is determined by a complex interaction of endothelial, neural, metabolic, and pharmacological factors. The oxygen extraction capability of the tissues is determined by matching microvascular blood flow to microregional oxygen demand.

In ill patients there is heterogeneity in capillary perfusion which results in a mismatch between DO_2 and VO_2. The amount of oxygen consumed as a fraction of oxygen delivery defines the oxygen extraction ratio (OER). The maximum OER in most tissues is 60–70 %, beyond this point, further increase in VO_2 or decline in DO_2 results in tissue hypoxia. For example, in sepsis, the slope of the OER decreases but the curve does not plateau and oxygen consumption continues to increase even at supra normal level of oxygen delivery. Intensivists have adopted this concept and often give aggressive volume resuscitation and inotropes to augment cardiac output, and hence, DO_2 trials have demonstrated that this approach has no benefit after patient develops organ failure [6, 35, 59]. Increasing global DO_2 may improve blood flow to regionally hypoxic

tissue by raising blood flow through all capillary beds. This is an inefficient process and, if achieved via vasoactive drugs such as noradrenalin, may adversely affect regional distribution especially in the kidney or splanchnic beds. Patients in late shock have increased endothelial permeability and myocardial dysfunction; therefore, aggressive fluid resuscitation would result in widespread tissue edema impairing pulmonary gas exchange and tissue oxygen diffusion. Therefore, the reported increase in mortality associated with the use of PAC likely reflects the adverse effects of attempting to achieve supranormal levels of DO_2 [60].

Complications

Complications related to the use of the pulmonary artery catheter (PAC) in a clinical setting can classified into three different categories: (1) complications related to insertion of the introducer or the PAC, (2) complications related to the use and maintenance of the PAC, and (3) complications related to the interpretation of hemodynamic data.

Complications Related to Insertion

Problems associated with passage of the PAC are caused by trauma to the vessels and heart, potentially leading to vascular inflammation or rupture, valvular damage, and arrhythmias. Atrial and ventricular arrhythmias are the most commonly occurring complications during passage of the catheter through the cardiac chambers. While temporary ectopy arises from the catheter irritating the endocardium of the right ventricle, severe arrhythmias have also been noted. Adjusting patients in the head-up and right lateral position while passing the PAC can reduce the incidence of severe arrhythmias [61]. The phenomenon of significant ventricular tachycardia or ventricular fibrillation usually occurs in those patients with concurrent cardiac ischemia and does not require intervention with IV lidocaine prior to the placement [62]. However, it is recommended that to decrease incidence of these arrhythmias, the operator should move quickly through the right ventricle while advancing the catheter, with the balloon inflated.

Right bundle branch blocks have also been reported in few patients placing patients with preexisting left bundle branch blocks at greater risk of developing complete heart blocks [63, 64]. Thus, in many centers, pulmonary artery insertion in the presence of a left bundle branch block is usually performed under fluoroscopic guidance to expedite passage thru the right ventricle and decrease the incidence of developing a complete heart block. During insertion, if loops are allowed to form within one of the cardiac chambers, knotting of the catheter can occur [65, 66]. In order to prevent occurrence of knotting, the balloon should be deflated and the catheter pulled back if characteristic waveforms do not appear at the expected length.

Complications Related to Maintenance

The main complications associated with use and maintenance of the PAC includes pulmonary artery rupture, migration, thromboembolic events, and catheter-related infections. While rupture of the pulmonary artery requires emergent thoracotomy for management [67], the treatment is largely supportive such as intubation of the unaffected lung, use of PEEP, and fluid replacement. While migration of the PA catheter most often occurs due to over-wedging or increased number of balloon inflations, they can be prevented by the use of the pulmonary artery diastolic pressure to approximate Ppao when appropriate. Although the incidence of thromboembolic events has been decreased by the use of heparin-based catheters [68], mural thrombi induced by inflammation or infection can propagate or embolize acting as a nidus for infection. While the PAC-related infections remain common complications, if infection is suspected, the patient should be cultured, treated with broad-spectrum antibiotics, and the catheters removed or replaced if possible.

Complications Related to Interpretation of Hemodynamic Data

Misinterpretation of the hemodynamic data is another complication related to the use of PAC. Under ideal conditions, the tip of the catheter sits in Zone 3 of the lung, where the arterial pressure exceeds the venous pressure and the venous pressure exceeds the alveolar pressure. In this position, the left atrial pressure is similar to LV end-diastolic pressure, which reflects LV EDV. If these conditions do not apply, it can result in inaccurate data leading to potential mismanagement of the patient. Other sources of error leading to data misinterpretation include improperly calibrated or leveled pressure monitors and overestimation of Ppao because of incomplete pulmonary artery branch occlusion [69]. Several studies have documented a wide interobserver variability in the interpretation of hemodynamic data from PAC among intensivists and anesthesiologists [70].

Conclusion

Despite the controversy surrounding the benefit of PAC in critically ill patients, it is still a useful hemodynamic monitoring device in selected patients. The decision to place this invasive device should be based on the specific information one is seeking that cannot be obtained by less invasive means. The fact that PAC use has decreased in the last few years indicates that there's ongoing dialogue and careful selection process prior to inserting this device. This is also partially due to increasing availability of less invasive devices. Most central to PAC use is that it is only as good as the operator and interpreter of the information whose role is further enhanced by understanding its benefit and limitations.

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Noninvasive Cardiac Output Monitoring

9

Robert H. Thiele, Karsten Bartels,
and Tong J. Gan

> When I first gave my mind to vivisection, as a means of discovering the motions and uses of the heart, and sought to discover these from actual inspection, and not from the writing of others, I found the task so truly arduous, so full of difficulties, that I was almost tempted to think, with Fracastorius, that the motion of the heart was only to be comprehended by God.
>
> Ernest Henry Starling, Cambridge, 1915

Introduction

The description of a catheter, floated into the right heart of a man by Jeremy (H.J.C.) Swan in 1970, suddenly allowed measurements of intracardiac and pulmonary artery pressures in the acute care environment. Although initially tremendously popular, the pulmonary artery catheter failed to show beneficial effects on clinically relevant patient outcomes. Pulmonary artery catheterization is prone to complications, such as arrhythmia, vascular injury, infection, and pneumothorax, and the untoward consequences of catheter use have been implicated for canceling out the potentially beneficial effects of adding a more sophisticated level of hemodynamic monitoring. In an attempt to preserve the potential benefits of improved monitoring without exposing patients to the risks of an invasive device, a multitude of minimally invasive or noninvasive cardiac output monitoring (NICOM) technologies have evolved.

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Ultrasound-Based Techniques

Physical Basis

The velocity of any moving object can be estimated by analyzing the frequency difference between incident and reflected ultrasound waves. The Doppler equation defines this relationship more precisely:

$$v = \cos(\theta)\, c\Delta f / (2 f_0) \quad (\text{Doppler equation})$$

with (v) the velocity of the target, (θ) the incident angle, (c) speed of sound in the medium, Δf indicating the frequency difference, and (f_0) the frequency of the originally emitted ultrasound beam.

In order to derive stroke volume, the velocity time integral (VTI, average distance that a red blood cell travels during one heartbeat) has to be multiplied by the cross-sectional area of the

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structure where the Doppler measurement was taken. While in theory (and in some in vitro studies) Doppler-based techniques can be highly accurate, several potential sources of error must be kept in mind. Inaccurate measurement of the area of interest (e.g., by assuming the left ventricular outflow tract is a circular structure and deriving its area from a single diameter measurement) impairs assessment of stroke volume and hence cardiac output. This method also assumes that the cross-sectional area of the interrogated structure (e.g., aorta) remains constant throughout systole. Lastly, the velocity profile of blood flow is assumed to cover the entire cross section, which is not the case in either laminar or turbulent flow settings.

Doppler-based cardiac output measurements are noninvasive, and results can be obtained and interpreted in real time. In addition to allowing assessment of cardiac output, they permit quantification of stroke volume as well as stroke volume variation. Stroke volume variation is becoming a more widely used index to predict a patient's hemodynamic response to a fluid challenge and has been incorporated into goal-directed fluid management strategies.

Clinical Applications

Esophageal Doppler

Utilizing a small, flexible ultrasound probe, blood flow velocity in the descending thoracic aorta can be measured as shown in Fig. 9.1. While some probes have the ability to determine the diameter, and thereby estimate the area of the descending thoracic aorta, others use nomograms of aortic cross-sectional arrears based on age, weight, and height. In addition, esophageal Doppler cannot directly measure cardiac output, as some of the blood is diverted to the innominate, left common carotid, and subclavian arteries proximal to the measurement point in the descending thoracic aorta. It is assumed that flow in the thoracic descending aorta resembles approximately 70 % of total cardiac output. That said, Doppler measurement of the descending thoracic aortic blood flow was shown to estimate cardiac output well when compared to both the Fick method and electromagnetic flowmeters.

Esophageal Doppler monitoring (EDM) has been incorporated into fluid resuscitation regimens demonstrating utility of different approaches of goal-directed therapy. In 2007, the US Department of Health and Human Services Agency for Healthcare Research and Quality reviewed the available technology and reported that "*The addition of esophageal Doppler monitoring for guided fluid replacement to a protocol using CVP and conventional clinical assessment during surgery leads to a clinically significant reduction in the rate of major complications and total complications in surgical patients compared to CVP plus conventional clinical assessment. The strength of evidence supporting this finding is strong*." On the basis of the increased evidence that EDM reduces length of stay, surgical complications, and hospital costs, in March of 2011 the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom stated that EDM "*should be considered for use in patients undergoing major or high risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring*."

Surface Doppler

Surface Doppler probes are used to obtain suprasternal and apical transthoracic windows to measure the velocity of blood flow in the ascending aorta. Although most ultrasound systems in clinical use can be utilized to make these measurements, most clinicians are not familiar with this approach. In addition, standard transthoracic probes generally have large faceplates designed to optimize two-dimensional imaging. They are not optimized for the acquisition of Doppler signals. The USCOM 1A probe (www.uscom.com.au) is a suprasternal Doppler probe that estimates aortic cross-sectional area using a nomogram. It was designed specifically to measure stroke volume and stroke volume variation and simplifies this measurement as compared to using a full-featured echocardiography workstation.

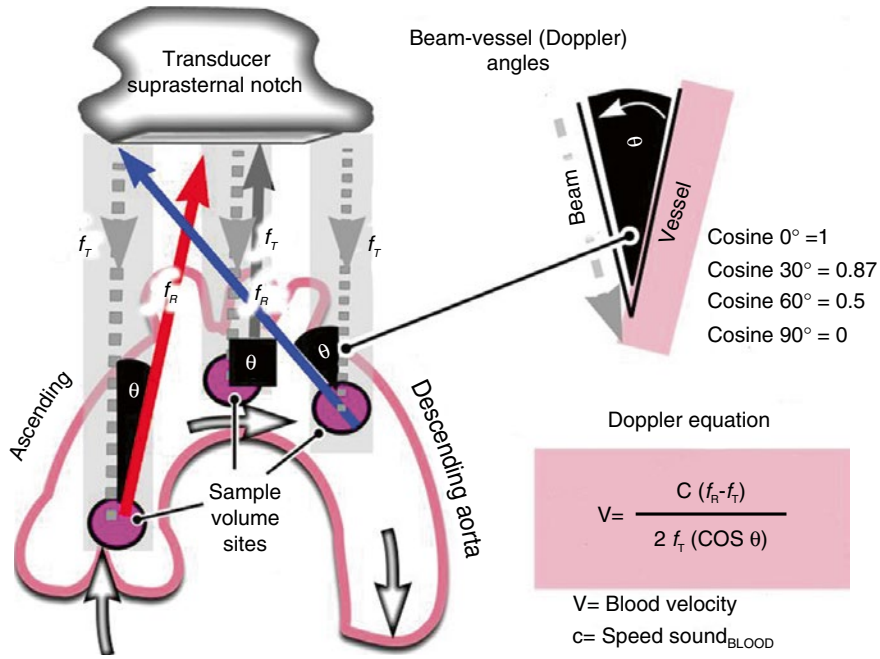

Fig. 9.1 Doppler equation in echocardiography. The Doppler equation is used to convert Doppler frequency shifts into blood flow velocities. However, the accuracy of the Doppler frequency shift is directly influenced by the beam-vessel alignment or the Doppler angle. The smaller the Doppler angle, the more accurate the measurement. Although the actual angle can be used in the equation to correct Doppler beams that are not exactly parallel to the interrogated flow (most ultrasound equipment has the capability to do this), the further this angle is from 0°, the less accurate the measurement will be (Reproduced from Bulwer B, Rivero J, Solomon S. Basic principles of echocardiography and tomographic anatomy. In: Atlas of echocardiography. vol. 1. New York: Current Medicine; 2008; kind permission from Springer Science + Business Media BV)

Bioimpedance and Bioreactance

Physical Basis

Bioimpedance

Bioimpedance-derived measurements of cardiac output are made by measuring changes in thoracic impedance (Z) and determining flow (I) based on its relationship to electrical potential difference (E) that are defined by Ohm's law:

$$I = E/Z$$

Another representation of Ohm's law is shown in Fig. 9.2. To more closely approximate the conditions encountered in human physiology, additional variables, such as shape, volume (V), length (L), area (A) of the conducting material, and the resistivity of blood (ρ) have to be taken into account. Peak ascending aortic blood flow (dV/dt_{max}) can be calculated through the following relationship:

$$dV/dt_{max} = \rho \times L^2/Z_0 \; 2dZ/dt_{max}$$

Additional modifications for determining cardiac output from bioimpedance attempt to incorporate variables to reflect the non-cylindrical shape of the thorax, body mass index, and gender. Contemporary devices use estimates for the ventricular ejection time, the volume of the electrically participating tissues, and for fluid conductivity.

Given that bioimpedance-derived cardiac output measurements are based on multiple assumptions that are subject to interindividual variations, several limitations apply:

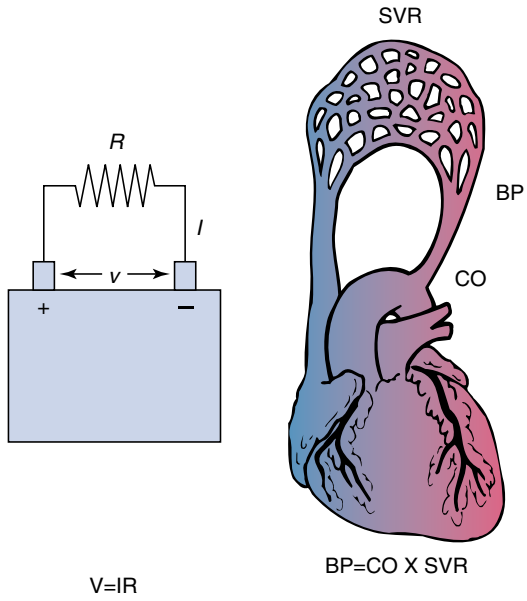

Fig. 9.2 Ohm's law. In the physics of electricity, Ohm's law states that the potential difference across a circuit (*V*) is directly proportional to the current (*I*) and the resistance (*R*). In a directly analogous way this can be applied to the human body: The potential difference across the circulation is the blood pressure (BP), the current of flow through the body is the cardiac output (CO), and the resistance is the systemic vascular resistance (SVR). It can be seen that a decrease in blood pressure can be caused by a decrease in cardiac output (e.g., hypovolemia or cardiogenic shock) or a decrease in SVR (e.g., anaphylaxis or sepsis) (Reproduced from Woodcock B, Tremper K, Miller R. Hemodynamic emergencies. In: Atlas of anesthesia. vol. 4. New York: Current Medicine; 2008; kind permission from Springer Science + Business Media BV)

1. Peak aortic flow rate may not be proportional to mean aortic flow rate.
2. Thoracic impedance changes are not only dependent on intrathoracic blood volume.
3. Ventricular ejection time cannot accurately be determined from an EKG signal.

Bioreactance

The practical limitations encountered during clinical use of the bioimpedance technique led to the development of bioreactance technology for cardiac output monitoring. In this approach cardiac output is determined from intrathoracic blood volume acting as an electrical capacitor or inductor. Stroke volume (SV) can be determined by the relationship of a constant (c), the ventricular ejection time (VET_x), and the maximum slope of the phase shift between the applied and the received electrical signals as a function of time ($d\phi/dt_{max}$).

$$SV = c\left[VET_x\left(d\phi/dt_{max}\right)\right]$$

Clinical Applications

Clinical devices for measurement of bioimpedance-derived cardiac output are available from several different manufacturers (SonoSite, Bothell, WA, www.sonosite.com), ICG (Philips Medical, Andover, MA, www.philips.com), TEBCO (Homo Sapiens Inc., Bucharest, Romania, www.hemosapiens.com), CircMon (JR Medical, Estonia, www.online.ee/~medical), and ECOM (ConMed Co., Utica, NY, http://www.conmed.com/products_ECOM.php), which provides some additional features of arterial pressure waveform analysis. Correlations between bioimpedance and other cardiac output monitors vary significantly depending on which device was evaluated and the technology to which it was compared to. Potential sources for erroneous measurements include patient movement, variations in ECG electrode placement, changes in lung fluid content, and irregular heart rhythm. Given that multiple factors that impact accuracy of this technology vary significantly in *real* clinical practice, it has not been adopted widely at this time.

Pulse Contour Analysis

Physical Basis and Application

Pulse contour analysis is one of the most commonly used noninvasive modalities to measure cardiac output. To use the pulse pressure waveform for estimation of stroke volume according to the *Windkessel* model for blood flow, several assumptions are made. During systole, blood ejected into the aorta distends the aortic wall. The proximal large vessels then form a capacitor for the energy generated by the left ventricle, whereas the peripheral arteries form a resistor.

Both systolic (Q_S) and diastolic flow (Q_D) contribute to stroke volume. Flow in diastole is dependent on blood pressure (P) and a constant (c) that is dependent on vascular resistance and compliance:

$$Q_D = c \times P$$

Assuming that resistance and compliance remain relatively constant over the course of a cardiac cycle, flow is proportional to the area (A) under the pulse contour or the blood pressure:

$$Q_S / A_S = Q_D / A_D \text{ or } Q_S = Q_D * A_S / A_D$$

Stroke volume (SV) can then be defined as follows:

$$\begin{aligned} SV &= Q_D + Q_S = Q_D + Q_D * A_S / A_D \\ &= Q_D * (A_S / A_D + 1) = k \times P (A_S / A_D + 1) \end{aligned}$$

Once k has been determined by another technique, SV can be measured continuously, assuming k stays constant.

Building on the two-element *Windkessel* approach described above, the three-element *Windkessel* approach recognizes the presence of pulsatile forces that are characterized in a vascular system by their impedance.

Yet another approach to arterial waveform analysis is to estimate cardiac output based on empirically derived data in conjunction with measured parameters. These include heart rate, body surface area, blood pressure, and other mathematical characteristics of the arterial pressure wave. This is approach is the basis for the *Flo Trac*.

Partial Rebreathing

Physical Basis and Application

Partial rebreathing technology essentially relies on the physical principle of preservation of mass. The Fick equation applies this principle so that the product of cardiac output (CO) and the difference between the systemic arterial and mixed venous O_2 saturations ($CsaO_2 - CmvO_2$) equals the body's oxygen consumption (VO_2):

$$CO \times \begin{pmatrix} CsaO_2 - CmvO_2) = VO_2 \\ \text{or } CO = VO_2 / (CsaO_2 - CmvO_2 \end{pmatrix}$$

Measurement of the cardiac output using the above Fick equation requires continuous measurement of the mixed venous oxygen saturation as well as oxygen consumption. When carbon dioxide is used to derive cardiac output based the Fick principle (Fig. 9.3), the same principle of preservation of mass applies to the production of carbon dioxide (CO_2):

$$CO \times \begin{pmatrix} CmvCO_2 - CsaCO_2) = VCO_2 \\ \text{or } CO = VCO_2 / (CmvCO_2 \times CsaCO_2 \end{pmatrix}$$

For the partial rebreathing technique, CO_2 is measured once under conditions with minimal dead space breathing and then with intentional partial rebreathing of exhaled gases. Assuming cardiac output and mixed venous oxygen content are unchanged between measurements, cardiac output can then be calculated from the systemic arterial CO_2 and the exhaled CO_2 in the breathing circuit; each measured once under minimal and then under partial rebreathing conditions.

Limitations of this approach include the assumption that alveolar partial pressure of CO_2 can be used to accurately estimate systemic arterial CO_2 content. High levels of intrapulmonary shunt lead to higher levels of systemic arterial CO_2 and subsequently decrease the denominator in the equation for CO_2-derived cardiac output measurements above. This would then lead to falsely elevated estimates of cardiac output. This source of error is partially negated by the use of Nunn iso-shunt graphs that predict arterial CO_2 content based upon an assumed shunt fraction.

The NICO device (NICO Sensor, Respironics, Wallingford, CT, www.nico.respironics.com) assumes the difference between end tidal CO_2 and systemic arterial CO_2 partial pressure to be 6 mmHg. While it is this that negates the need for obtaining arterial blood samples, another potential source of error is introduced.

Photoplethysmographic

Physical Basis and Application

The *volume clamp* technique is the basis for measuring blood pressure through analysis of beat-to-beat variations in finger blood volume.

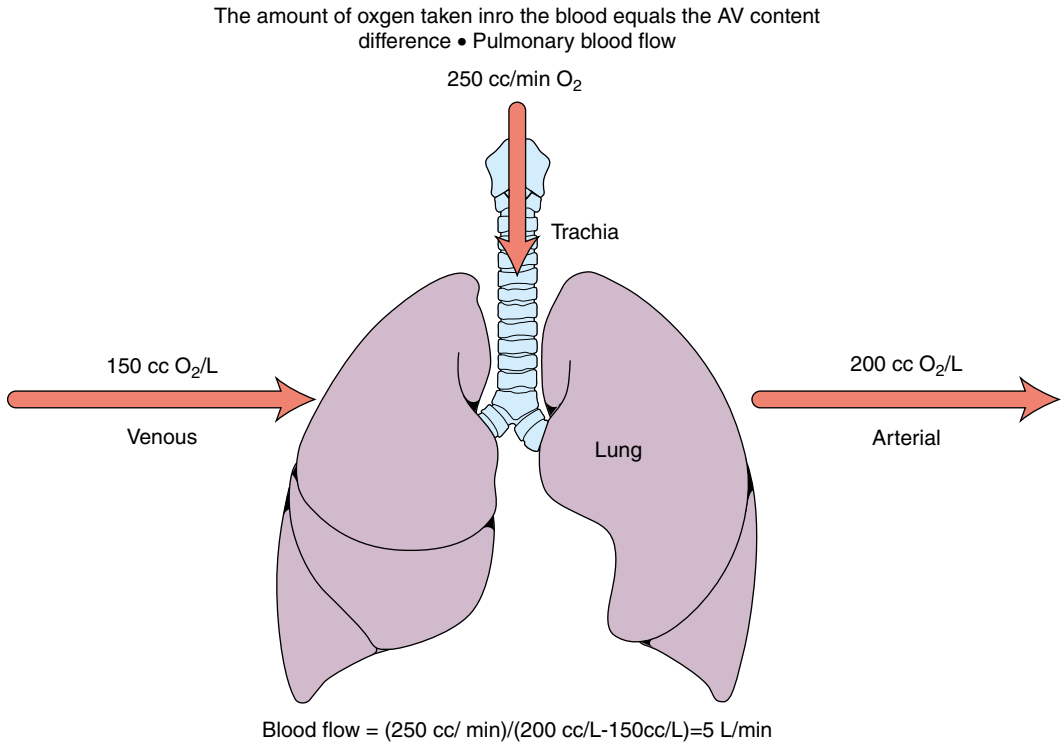

Fig. 9.3 The Fick principle. It is inconvenient to directly measure blood flow in vivo. One can, however, apply physical principles to make indirect or noninvasive estimates of blood flow. An early example is the Fick method of calculating cardiac output, which is shown in this figure. The method relies on the principle of conservation of mass: One assumes that the quantity of an indicator substance in blood can be completely accounted for by a simple mass balance equation and that blood flow into an organ is the same as the blood flow out. If the content per unit of blood of an indicator substance such as oxygen (O_2) can be measured on both the inflow and outflow sides of the lungs, and the whole body oxygen consumption can also be determined, then one can write an equation stating that the rate of oxygen flowing out of the lungs (via blood in the pulmonary veins) equals oxygen flowing in through the pulmonary arteries plus that flowing in through the trachea (Reproduced from Rampil I, Schwinn D, Miller R. Physics principles important in anesthesiology. In: Atlas of anesthesia. vol. 2. New York: Current Medicine; 2002; kind permission from Springer Science + Business Media BV)

This is accomplished through an inflatable finger cuff in conjunction with an infrared transmitter/sensor. Changes in finger blood volume are detected by the altered infrared signal. Rising volumes lead to inflation of the cuff and decreasing volumes lead to deflation of the cuff. This keeps the artery "unstretched" and permits continuous measurement of finger pressure that is assumed to correlate with systemic arterial blood pressure. Further refinements of this technique aim at better maintaining the artery in an "unstretched" position, which is a critical component for the accuracy of the obtained measurements.

A device in clinical use is the Nexfin (BMEYE B.V., Amsterdam, Netherlands). A second-generation application (^{CC}Nexfin) estimates brachial artery pressure from the peripheral tracing and uses this information to approximate left ventricular stroke volume.

Pulse Wave Velocity

Physical Basis and Application

Measurement of cardiac output based on pulse wave velocity through an elastic tube relies on the relationship of the velocity (V) and a constant (k), the tube's elasticity (E), wall thickness (h), diameter (D), and the fluid density (ρ):

$$V = k\left(Eh/rD\right)^{1/2}\ \left(\text{Moens} - \text{Korteweg Equation}\right)$$

In order to derive cardiac output measurements from the pulse wave velocity principle, it is assumed that stroke volume (SV) is related to pulse pressure (PP) as defined by

$$\text{SV} = k \times \text{PP}$$

In addition, pulse pressure is proportional to pulse wave transit time (PWTT) or pulse wave velocity as defined by

$$\text{PP} = \alpha \times \text{PWTT} + \beta$$

The assumed relationship of stroke volume, pulse pressure, and pulse wave transit time is the basic devices that estimate cardiac output from pulse wave velocity measurements. The esCCO monitor by Nihon Kohden (Tokyo, Japan, www.nihonkohden.com) is available in Japan but currently not approved by the US Food and Drug Administration.

Conclusion

Less invasive means of measuring cardiac output have become popular in clinical use after invasive cardiac output measurements using a pulmonary artery catheter failed to demonstrate improved clinical outcomes. This recognition led to the development of multiple alternatives to measure cardiac output, such as Doppler-based methods, bioimpedance and bioreactance, pulse contour analysis, partial rebreathing, and pulse wave velocity. While their less invasive nature makes these devices appealing for clinical use, further studies are needed to determine their ability to positively impact patient outcomes.

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Transpulmonary Thermodilution

10

Olfa Hamzaoui, Xavier Monnet,
and Jean-Louis Teboul

Introduction

The use of the pulmonary artery catheter has declined during the past decade [1], partly in relation to the absence of demonstration of outcome benefits [2] and to the emergence of less invasive hemodynamic monitoring methods such as the transpulmonary thermodilution. Two commercially available devices can provide transpulmonary thermodilution-derived parameters. For more than 10 years, the PiCCO monitor (Pulsion Medical Systems, Germany) has been subjected to numerous validation studies and safety evaluations and has been used in many clinical studies in different patient populations [3, 4]. Recently, TPTD became available in the VolumeView/EV1000 monitor (Edwards, USA); clinical experience with this new monitor is very limited at this stage, but preliminary validation studies seem promising [5, 6].

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General Principle

The transpulmonary thermodilution method applies the indicator dilution principles using temperature change as an indicator. A known amount of cold solution with a known temperature is injected rapidly into the circulation through a central venous catheter (superior vena cava territory). This cold solution mixes with the surrounding blood, and the temperature is measured downstream at the level of the femoral artery through a thermistor-tipped arterial catheter (Fig. 10.1). The mathematical analysis of the thermodilution curve (blood temperature vs. time) recorded by the device allows calculation of cardiac output (CO) and of other relevant hemodynamic variables.

Measurement of CO by Transpulmonary Thermodilution

After rapid injection of a fixed volume (in general, 15 mL) of the cold indicator (saline solution at <8 °C), the blood temperature first decreases and after reaching a nadir value returns to its initial value (Fig. 10.2). Similarly to the intermittent bolus pulmonary artery thermodilution (using pulmonary artery catheter), the area above the transpulmonary thermodilution curve is inversely related to CO according to the Stewart-Hamilton principle. However, because the thermistor is placed in the femoral artery, and not in the pulmonary artery, the thermodilution curve has a

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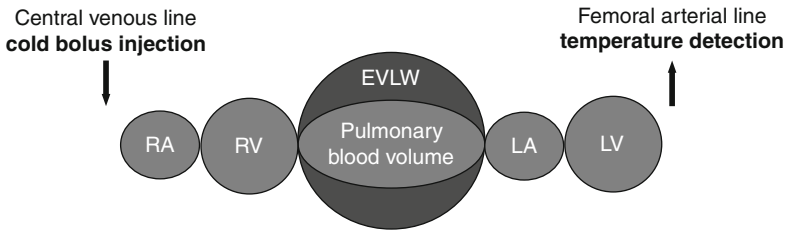

Fig. 10.1 Principle of transpulmonary thermodilution. The cold bolus injected into a central vein of the superior vena cava territory mixes with the surrounding blood in the right atrium (*RA*), right ventricle (*RV*), intrathoracic blood volume (sum of pulmonary blood volume and extravascular lung water), left atrium (*LA*), and left ventricle (*LV*). The decrease in the blood temperature is detected at the level of the femoral artery through a thermistor-tipped artery catheter

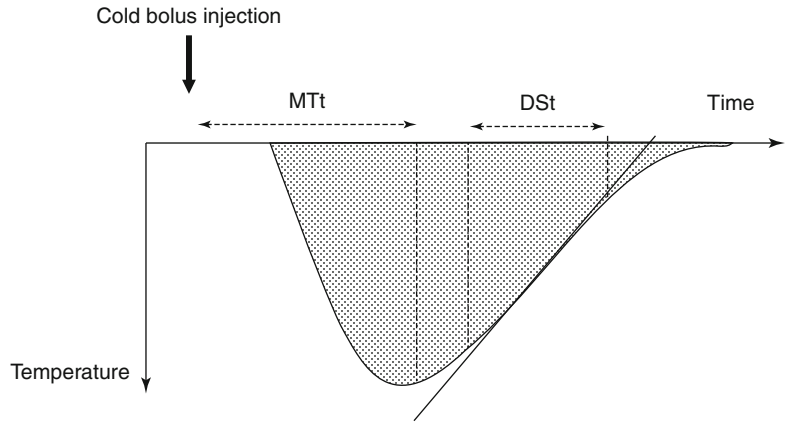

Fig. 10.2 Transpulmonary thermodilution obtained after cold bolus injection into a central vein of the superior vena cava territory. The area under the thermodilution curve, the mean transit time, and the downslope time are automatically measured by the transpulmonary thermodilution monitor. These parameters are used to calculate cardiac output and global end-diastolic volume

longer appearance time, a less negative nadir value, and a longer return time to baseline temperature compared with the pulmonary artery thermodilution curve. Nevertheless, the values of areas above the two curves should be almost identical. In this regard, studies in critically ill patients comparing CO measured with transpulmonary thermodilution and intermittent bolus pulmonary artery thermodilution showed a good agreement between both methods [7, 8]. Although theoretically the conventional thermodilution method should provide more accurate measurements of CO (less indicator loss between the injection and the sampling sites), the transpulmonary thermodilution method has the advantages to be less influenced by the respiration. This is particularly advantageous in case of application of positive pressure ventilation in preload-dependent patients, in whom the respiratory variations of stroke volume are marked [9].

It is generally recommended to average measurements obtained after three consecutive cold bolus injections. By doing so, the precision is acceptable (<10 %), and the least significant change in cardiac ouput is below the 15 % cutoff that is usually considered as clinically relevant [10]. Transpulmonary thermodilution also provides acceptable measurements of CO in pediatric intensive care patients [11], in patients receiving continuous veno-venous hemofiltration even at high pump flow [12], in hypothermic patients after cardiac arrest [13], after one-lung ventilation [14], and even during prone positioning [15].

It is also important to notify that in adults, normally 15 mL of cooled saline (<8 °C) is injected through a central venous catheter for the measurement of CO; however, a lower amount of indicator (10 mL) and a room temperature injectate also allow correct measurements of cardiac ouput [16]. A femoral thermistor-tipped arterial

Table 10.1 Normal ranges for the main transpulmonary thermodilution variables

CI	3.5 L/min/m^2
GEDVI	600–800 mL/m^2
CFI	>4
EVLWI	3–10 mL/kg
PVPI	<2.8

Abbreviations: *CI* cardiac index, *GEDVI* global end-diastolic volume index, *CFI* cardiac function index, *EVLWI* extravascular lung water index, *PVPI* pulmonary vascular permeability index

catheter is most often used, but the axillary, brachial, and radial (long catheter) arteries may also be used [17].

Transpulmonary Thermodilution-Derived Variables

In addition to CO, transpulmonary thermodilution provides physicians with numerous hemodynamic variables that give relevant information on cardiac preload and systolic function and on the degree and nature of pulmonary edema. The normal ranges of the main thermodilution-derived variables are presented in the Table 10.1.

Global End-Diastolic Volume (GEDV)

In addition to the area under the curve, two characteristics of the transpulmonary thermodilution curve, i.e., the mean transit time and the downslope time, can be automatically calculated by the transpulmonary thermodilution device (see Fig. 10.2). The product of CO by the mean transit time equals the volume of distribution of the thermal indicator, which is named intrathoracic thermal volume (sum of intrathoracic blood volume and EVLW). The product of CO by the downslope time equals the pulmonary thermal volume (sum of pulmonary blood volume and EVLW). In the PiCCO2 device, the GEDV is the difference between intrathoracic thermal volume and pulmonary thermal volume and equals the product of CO by the difference between mean transit time and downslope time. In the VolumeView device, the GEDV is calculated with a slightly different formula, which does not take into account the downslope time but the ratio of the maximal ascending and descending slopes of the thermodilution curve [5]. A good agreement between GEDV values obtained with the PiCCO2 and the VolumeView was demonstrated in animals [3] and in humans [6]. For both systems, the GEDV is assumed to reflect the sum of the maximal values of the four cardiac chambers.

It is difficult to define normal indexed GEDV (GEDVi) values. In surgical non-critically ill patients, the average values of GEDVi (obtained with the PiCCO2 monitor) are around 700 mL/m^2 [3]. This volume is greater than the real cardiac blood volume but is very dependent on the ventricular blood volumes. Accordingly, the GEDV has been shown to behave as a marker of global cardiac preload: it increases with volume expansion and does not change with dobutamine [18], and its changes during fluid administration are correlated with changes in left ventricular end-diastolic area (an echocardiographic index of left ventricular preload) [19]. It is noteworthy that although GEDV and CO are derived from the same thermodilution curve, they do not necessarily vary in the same direction [18].

The major limitation of GEDV is that it cannot differentiate right ventricular volume and left ventricular volume. The GEDV can be in the normal range in cases of isolated right ventricular dysfunction and thus cannot give valuable information on the influence of pulmonary hypertension on the size of the right ventricle. Abnormally high values of GEDVi can be observed in some conditions such as aortic aneurism or atrial dilatation because the GEDV depends on the blood volume contained between the site of injection (central venous catheter) and the site of detection (femoral artery catheter) of the cold bolus. It is recommended not to inject the cold bolus into a femoral vein because of the risk of overestimation of GEDV [20].

Cardiac Function Index (CFI)

This parameter is the ratio of CO over the GEDV. It is automatically calculated by the transpulmonary thermodilution monitor after cold bolus

injection. It is considered as a marker of the global systolic function of the heart. Accordingly, the CFI has been shown to behave as a marker of systolic function: it increases with dobutamine volume expansion and does not change with dobutamine [21], and its changes with cardiovascular therapies are correlated with changes in echocardiographic left ventricular ejection fraction [21] or left ventricular fractional area contraction [22]. A CFI value lower than 3.2/min is able to identify a left ventricular ejection fraction <35 % with acceptable accuracy. However, as for GEDV, CFI provides information on global cardiac performance and cannot differentiate between left ventricular function and right ventricular function. A low value must encourage the clinician to perform an echocardiographic examination to confirm and to determine the mechanism of cardiac insufficiency.

Extravascular Lung Water (EVLW)

The EVLW is equal to the difference between the intrathoracic thermal volume and the intrathoracic blood volume. The intrathoracic thermal volume is directly calculated by the monitor from the thermodilution curve as the product of CO by mean transit time. The intrathoracic blood volume can only be estimated from the product of 1.25 by GEDV. The EVLW obtained with the PiCCO system is well correlated with the EVLW measured by gravimetry, the method of reference in animals [23] and to the postmortem lung weight in humans [24]. The EVLW values measured by the PiCCO2 and the VolumeView monitors agree in animals [5] and in humans [6]. The normal range of indexed EVLW (EVLWi) values is between 3 and 7 mL/kg. Because of the potential errors in measurements, it is generally assumed that EVLWi is abnormally high (pulmonary edema) when it is above 10 mL/kg. In cases of cardiogenic pulmonary edema or acute respiratory distress syndrome (ARDS), values greater than 35 mL/kg can be measured [25].

The main potential limitation of EVLW estimated by transpulmonary thermodilution is the poor distribution of the cold indicator in poorly perfused lung areas (e.g., hypoxic areas) as it is the case in some forms of ARDS. In this regard, EVLW assessed by double dilution (cold and colored indicator) may underestimate the amount of pulmonary edema measured by the gravimetric method during experimental ARDS, especially in cases of heterogeneous lung injuries [26]. However, this limitation is probably of minor importance in case of clinical ARDS where an excellent agreement between EVLW and lung edema assessed using quantitative computed tomography was reported [27]. The relevant value of EVLW during clinical ARDS has been emphasized by results of a large study (200 patients), in which EVLW was reported to be an independent risk factor associated with 28-day mortality (cutoff EVLWi, 21 mL/kg) [25].

The clinical interest of measuring EVLW in critically ill patients is multiple. The EVLW is helpful to establish the diagnostic of certainty of pulmonary edema in cases of doubtful diagnosis. It also can be used as a "safety" parameter for fluid infusion in patients at risk of pulmonary edema.

Pulmonary Vascular Permeability Index (PVPI)

This parameter is automatically calculated by the transpulmonary thermodilution as the ratio of EVLW over pulmonary blood volume. It is assumed to reflect the permeability of the lung capillary membrane. This was confirmed in an animal study where PVPI increased when pulmonary edema was created by lung instillation of oleic acid but did not change when it was created by balloon inflation in the left atrium [23]. The clinical diagnostic value of PVPI was demonstrated in two clinical studies showing that a PVI greater than 2.85 [28] or than 3 [29] could diagnose increased permeability edema with good accuracy. The PVPI can also be used to characterize the degree of lung inflammation during ARDS. It must be taken into account in the decision-making process concerning fluid administration. High values of EVLW and PVPI may discourage clinicians to give fluids even in case

of hemodynamic instability with patent signs of preload dependency. It must also be stressed that PVPI is an independent risk factor of mortality in ARDS patients [25].

Transpulmonary Thermodilution and Right-to-Left Intracardiac Shunt

A right-to-left intracardiac shunt related to an atrial septal defect can be diagnosed by using the transpulmonary thermodilution curve [30]. In this setting, one part of the cold indicator passes through the atrial septal defect and rapidly reaches the arterial thermistor, with a curve appearing biphasic due to the premature hump related to the early thermal indicator shunt [30]. In the case of recirculation of thermal indicator, an overestimation of the EVLW could be observed. Accordingly, Michard et al. [30] emphasized the value of transpulmonary thermodilution as a simple tool to diagnose and monitor right-to-left intracardiac shunting in ARDS patients. In presence of hypoxemia, therapeutic implications such as pulmonary vascular dilatation or PEEP removal can be immediately assessed using a single cold saline bolus.

Conclusion

The transpulmonary thermodilution method provides physicians with measurements of CO, GEDV, CFI, EVLW, and PVPI. Knowledge of these variables and of those obtained with the pulse contour analysis (a technology also included in the PiCCO and VolumeView devices) can help in the decision-making process in patients with acute circulatory failure and especially those with cardiac dysfunction and/or lung injury.

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Echocardiography in the Acute Care Setting

11

David W. Boldt and Aman Mahajan

Introduction

The rapidity, portability, and safety of ultrasound make it an ideal diagnostic aid in the acute care setting. Ultrasound images of the thorax and abdomen can quickly and noninvasively be obtained and used to guide further diagnostic or therapeutic decisions. Once a tool of the cardiologists and obstetricians, the ultrasound has since found its way into emergency departments (ED), intensive care units (ICU), postanesthesia care units (PACU), and even hospital floors and outpatient clinics around the world. The so-called FAST exam (focused assessment with sonography for trauma) is now part of the routine examination performed by trauma surgeons when assessing trauma patients in the emergency department for such critical conditions as pericardial tamponade and intraperitoneal hemorrhage. Intensivists in the ICU have quickly advanced their sonographic skills and are now able to skillfully assess for global cardiac function, the presence and significance of pericardial effusions, gross valvular pathology, intravascular volume status, hemothorax, pneumothorax, and ascites, to name a few. Furthermore, the ultrasound can then be used to safely guide procedures such as thoracentesis or paracentesis, much as is done by the interventional radiologist. In the world of anesthesiology, the ultrasound has become the standard of care to safely place internal jugular central venous catheters, it is increasingly used in the PACU to assess for many of the same conditions as in the ICU, and it remains invaluable in the world of cardiac anesthesiology, where transesophageal echo is used to guide patient care both before and after cardiopulmonary bypass and to assess the adequacy of the surgical repair. These examples are only the beginning of what has led the past couple of decades to bring about "the age of the ultrasound."

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Echocardiography and Ultrasound in the Emergency Department

As mentioned above, the FAST exam is now a standard part of the Advanced Trauma Life Support (ATLS) initial assessment of any trauma patient that presents to the ED, particularly when blunt thoracoabdominal trauma is the mechanism. According to a major trauma website, "The use of focused ultrasonography has now become an extension of the physical examination of the trauma patient" [1]. When screening the trauma patient with sonography for pericardial

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hemorrhage and hemoperitoneum, attention is paid to four major areas: (1) the pericardium via a subxiphoid/subcostal view; (2) the hepatorenal recess, which is the space between the liver and right kidney, also known as Morison's pouch; (3) the perisplenic space between the spleen and the left kidney; and (4) the pelvic space, or cul-de-sac, also known as the pouch of Douglas in females. Any fluid seen in these spaces in the setting of significant thoracoabdominal trauma is presumed to be blood. The trace amount of pericardial fluid and intra-abdominal fluid that is normally present in our bodies is too small to be seen on ultrasound, so if fluid is noticeable on exam, it is deemed abnormal. The presence or absence of fluid in these areas helps to guide further diagnostic and therapeutic decisions in the care of these trauma patients. The development and widespread use of the FAST exam has made the once standard DPL, or diagnostic peritoneal lavage, a rare necessity in the diagnosis of intraperitoneal hemorrhage. Although a DPL is fast and accurate, it is invasive and carries a risk of complications, mainly viscus perforation and hemorrhage. An alternative noninvasive means of detecting intraperitoneal hemorrhage is with abdominal CT scan. Although also accurate, it requires stabilization of the patient for transport to the CT scanner, which is not always possible or safe. This brings us back to the FAST exam as the quickest, safest, and most reliable means by which the diagnosis of intraperitoneal hemorrhage can be made.

The question of how well the FAST exam compares to DPL and abdominal CT scan in the detection of intraperitoneal hemorrhage has been answered by several studies, which suggest that the sensitivity of the test is quite high, up to 100 %. Several studies have evaluated the decision of a trauma surgeon to take an unstable patient to the operating room for exploratory laparotomy for suspected intra-abdominal injury vs to continue to evaluate for an alternative source of hypotension. Data from these studies suggest that FAST exam might be most helpful in the evaluation of a hypotensive trauma patient (defined as a systolic blood pressure <90 mmHg) following blunt abdominal trauma. In this setting, the FAST exam has both a sensitivity and a negative predictive value of 100 % [2–4]. The specificity of the FAST exam is slightly less, although as high as 96 % [2]. The reason for this lies partly in the inability of the ultrasound to differentiate between fluid which appears hemorrhagic and that which does not (e.g., ascitic fluid). In these cases, CT scan would likely be better to characterize the density of the fluid based on the Hounsfield units. The other areas that ultrasound is unable to compare with CT scan are in the detection of retroperitoneal hemorrhage and either contained solid organ injuries or hollow viscus injuries. Of those patients studied who had negative FAST exams and then went on to be diagnosed with intra-abdominal injuries by CT scan or laparotomy, many of them had either contained splenic or liver lacerations, and a few had bowel injuries [4]. Therefore, when properly applied in the right setting, namely, in the hypotensive patient following blunt abdominal trauma, and with recognized limitations in the detection of retroperitoneal and contained solid organ injuries, the sensitivity of the FAST exam for the detection of intraperitoneal hemorrhage is very high, likely equal to that of either DPL or CT scan, and with a lower rate of complications and less risk to the patient.

To sum up the role for echocardiography and ultrasound in the trauma patient, it should be used as an initial screening tool in all patients with blunt thoracoabdominal trauma. In addition, with recognized limitations, it should also be used as a decision-making tool in those patients who are too unstable to be transported to the CT scanner and in whom the decision needs to be made urgently whether or not to take them to the operating room for an exploratory laparotomy. Lastly, it is worthwhile noting that many trauma centers have added two additional views of the right and left hemithorax to the standard FAST exam, creating what is now referred to as the extended FAST, or EFAST, exam. The purpose of these two views is to look for the presence of hemothorax and pneumothorax, and the sensitivity of ultrasound in this regard has been shown to rival that of chest radiography [5] (Fig. 11.1).

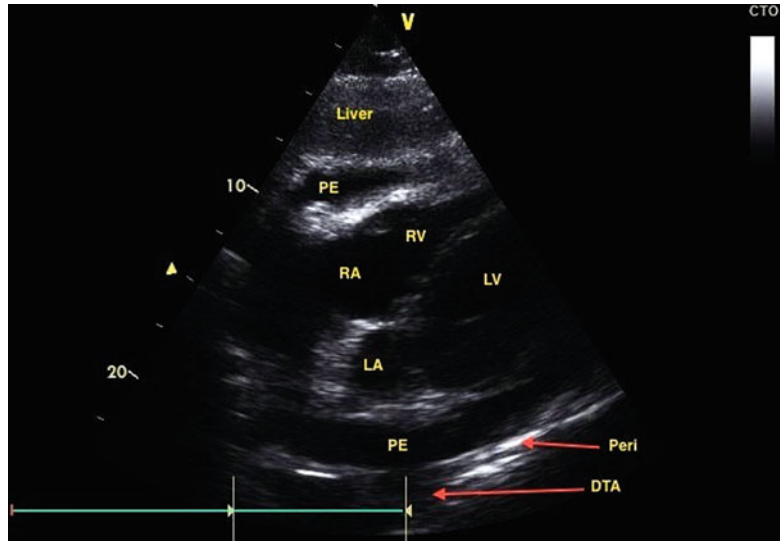

Fig. 11.1 Subcostal view of the heart revealing a moderately sized pericardial effusion (*PE*). Note that all four chambers of the heart can be seen well from this view: the left atrium (*LA*), left ventricle (*LV*), right atrium (*RA*), and right ventricle (*RV*). The pericardium (*Peri*) can be easily identified as the white hyperechoic stripe surrounding the heart, in this case outside of the effusion. The location of the effusion in relation to the pericardium and the descending thoracic aorta (*DTA*) is an important distinction, as pleural effusions can be seen on echo and are often mistaken for pericardial effusions. In relation to the DTA, pericardial effusions are usually anterior to this structure, while pleural effusions are posterior to it

Echocardiography and Ultrasound in the Intensive Care Unit

In a recent review article on the topic of bedside echocardiography in a major critical care journal several years ago, the statement was made that "The role of ultrasound and bedside limited echocardiography in the critical care setting is likely to expand in the future and become a part of daily care in every surgical intensive care unit" [6]. Indeed, this is what we have seen in the last several years. The intensive care unit has become a place where the availability of a portable bedside ultrasound could now be considered the standard of care. In only a few minutes, a quick transthoracic echocardiogram can be performed on hemodynamically unstable patients, providing an overall assessment of global cardiac function, scanning for significant valvular abnormalities, determining intravascular volume status, and ruling out the presence of a pericardial effusion and possible tamponade. In addition, ultrasonography of the chest can assess for the presence and significance of pneumothoraces and pleural effusions and also be used to guide their drainage via thoracentesis. Intensivists skilled in vascular ultrasound use the technology to place central lines, peripherally inserted central venous catheters, or PICCs, and scan for deep venous thrombosis of the upper and lower extremities. Abdominal ultrasonography can be used to assess for free fluid in the same way it is used in the emergency department, and in addition it is helpful in the assessment and drainage of ascites via paracentesis. These skills can quickly be acquired with limited training, even in intensivists who have not received prior formal training in bedside ultrasound. This was demonstrated by Benjamin et al. in a study in 1998 published in the Journal of Cardiothoracic and Vascular Anesthesia [7]. Five surgical intensivists, each with no prior training in ultrasound, were trained to perform limited cardiac echocardiography and interpret the exams by two senior cardiologists. A total of 100 exams were performed and interpreted by each intensivist. The data gathered

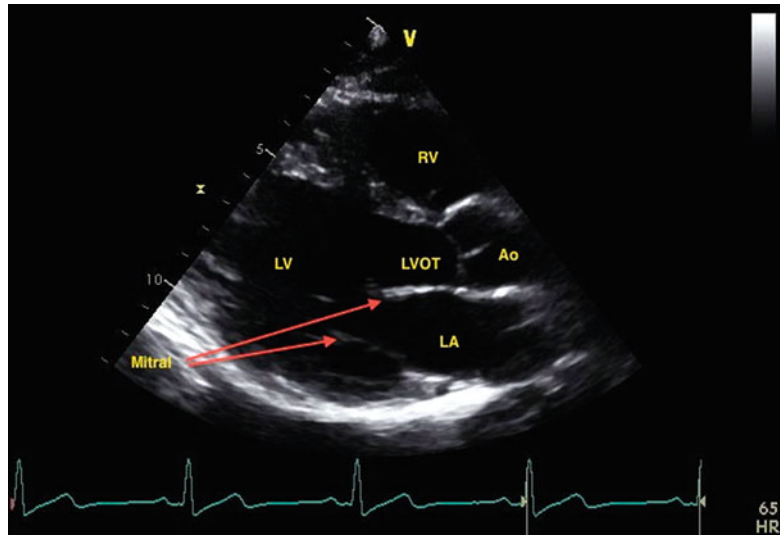

Fig. 11.2 The standard parasternal long-axis view of the heart revealing the right ventricle (*RV*), left ventricle (*LV*), left atrium (*LA*), left ventricular outflow tract (*LVOT*), and aortic root (*Ao*). Note the closed position of the aortic valve and the wide open position of the mitral valve (the anterior and posterior leaflets are labeled), indicating the period of the cardiac cycle immediately following atrial systole and prior to ventricular systole. This corresponds to the interval just before the QRS complex on the EKG strip, seen at the bottom of the image

and its interpretation led to valuable and accurate information that greatly affected the treatment of critically ill patients.

A comprehensive transthoracic echocardiographic exam includes imaging of the heart from three different areas on the body: (1) The parasternal windows, revealing the parasternal long- and short-axis views, which are obtained with the probe placed just to the left of the sternum and roughly about the level of the third or fourth intercostal space. (2) The apical windows, revealing the apical 4-chamber, 2-chamber, 3-chamber, and 5-chamber views. These are obtained with the probe overlying the apex of the heart, which corresponds to the point of maximal impulse on physical examination of the chest. (3) The subxiphoid or subcostal windows, which are obtained by placing the probe just below the xiphoid and angling up towards the left shoulder, using the left lobe of the liver as an acoustic window. These windows can be used to obtain an excellent view of the inferior vena cava as it enters the right atrium. Measurements taken at this junction are useful for assessing volume status. Further focused views can be obtained at each window, analyzing segmental wall motion and specific valvular anatomy and function. Discussion of these detailed views is beyond the scope of this chapter (Figs. 11.2, 11.3, 11.4, 11.5, and 11.6).

Echocardiography and Ultrasound in the Postanesthesia Care Unit

The postanesthesia care unit (PACU) is becoming a place where ultrasound technology, particularly transthoracic echocardiography, is finding a niche in the rapid assessment of postoperative patients. Much like in the ICU, a quick bedside TTE can reveal much about the status of postsurgical patients. Volume status, global cardiac function, new wall motion abnormalities, and the presence of pericardial effusions can provide a clue as to the underlying etiology in hemodynamically unstable patients. At centers like the University of California Los Angeles and Vanderbilt University Medical Center, anesthesiologists in the main operating room PACU are being trained in focused bedside transthoracic echo to aid in the postoperative care of our surgical patients. With a little practice, the basic exam is easy to learn and most physicians find the

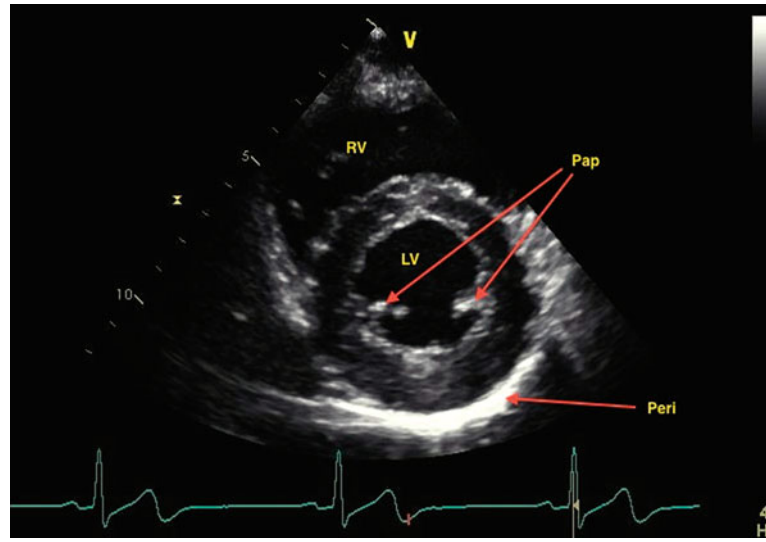

Fig. 11.3 A normal parasternal short-axis view, revealing the right (*RV*) and left (*LV*) ventricles. The papillary muscles (*Pap*) are noted, indicating that we are roughly at the mid-section of the LV. Again, note the hyperechoic white stripe indicating the pericardium (*Peri*). In the parasternal long axis, the RV typically holds a 9–12 o'clock position in relation to the LV. Note the thicker-walled LV in comparison to the RV

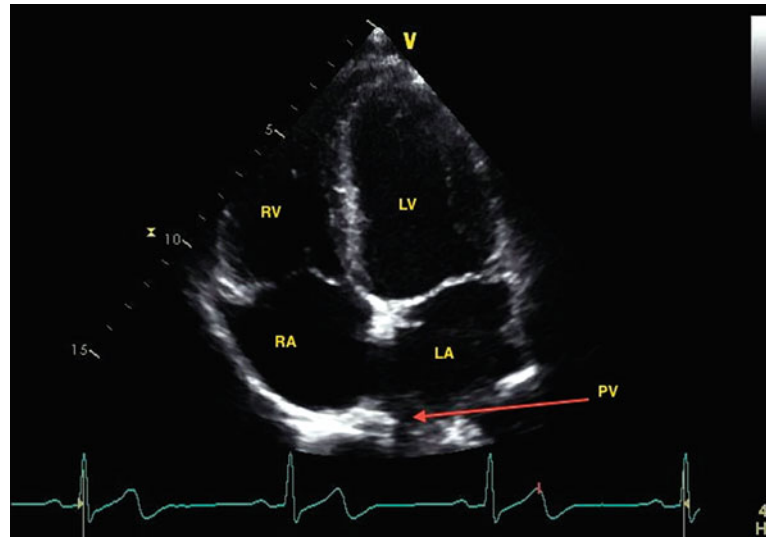

Fig. 11.4 The apical 4-chamber view. The mitral and tricuspid valves can be seen, along with one of the pulmonary veins (*PV*) as it enters the left atrium. Note the relatively smaller chamber size of the RV when compared to the LV. Counterclockwise rotation and slight angular manipulation of the probe from the apical 4-chamber view reveals the apical 2-, 3-, and 5-chamber views

information gathered extremely helpful in dealing with a variety of postsurgical patients. In the near future, ultrasound and echocardiography will likely be the standard of care in most PACU's, just as it has become in the ED and ICU.

The images below were recently acquired in on a PACU patient who was suffering from unexplained postoperative hypotension and low urine output. The operation was relatively unremarkable except for moderate blood loss and subsequent resuscitation with crystalloid and colloid solutions. Bedside transthoracic echo revealed right ventricular volume overload and failure. The patient was admitted to the ICU and started on inotropic therapy for RV support. She was gradually diuresed over the next few days and was discharged to the floor uneventfully. Were it not for the information gathered from bedside TTE, the patient would likely have received further volume resuscitation in the PACU in response to her hypotension and low urine output, with subsequent worsening of her RV failure. This is an excellent example of the utility and importance of bedside TTE in the evaluation of patients in the PACU (Figs. 11.7 and 11.8).

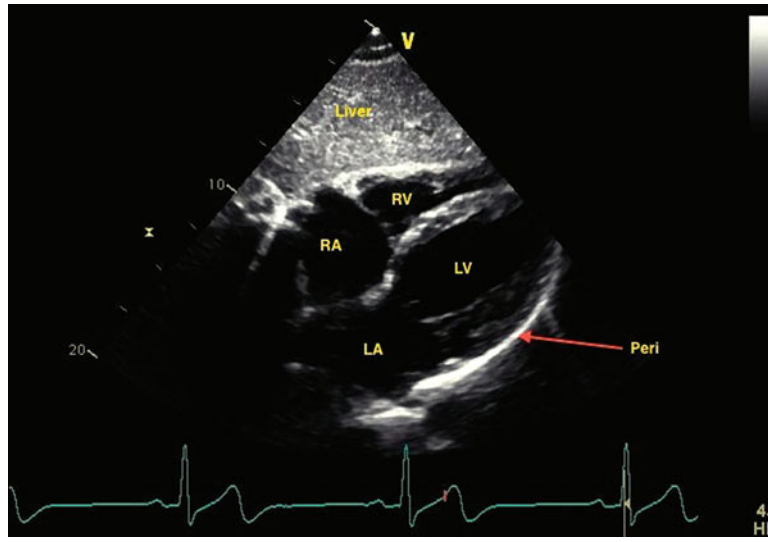

Fig. 11.5 The standard subcostal, or subxiphoid, view. All four chambers of the heart are easily seen along with the mitral and tricuspid valves. Again note the relatively small chamber size of the RV when compared to the LV as well as the appearance of the pericardium (*Peri*), which is closely adherent to the LV and is not separated by a layer of pericardial effusion, as in Fig. 11.1. The left lobe of the liver can be seen anterior to the right heart and is used as an acoustic window when acquiring images in this view

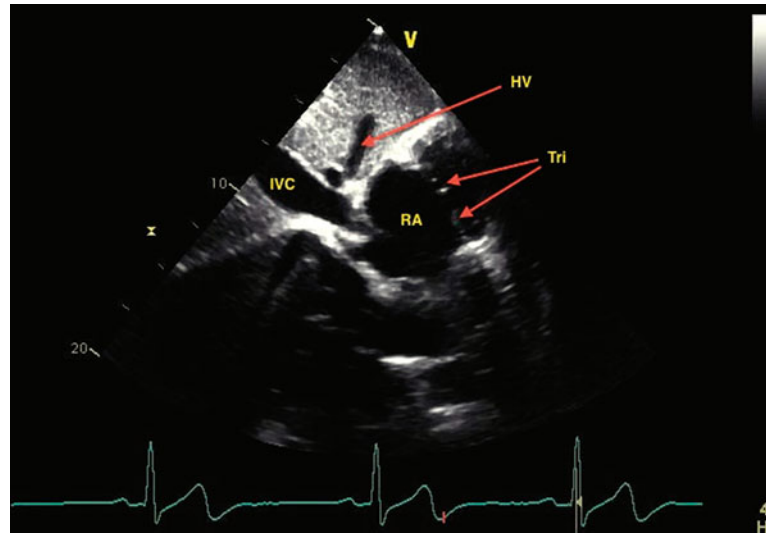

Fig. 11.6 A subcostal inferior vena cava (*IVC*) view, showing the junction of the IVC and RA. Measurements taken of the IVC at this location looking at its diameter as well as its collapsibility with forced inspiration can be used to estimate central venous pressure as an indicator of volume status. The hepatic vein (*HV*) and its junction with the IVC can also be seen, along with the tricuspid valve (*Tri*) between the RA and RV

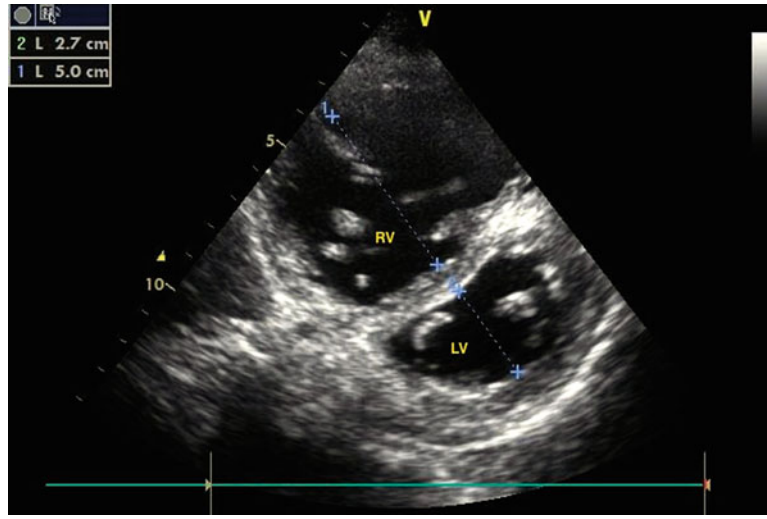

Fig. 11.7 A parasternal short-axis view of a patient in right ventricular failure. Measurements have been taken of the mid cavitary RV and LV diameters, 5.0 and 2.7 cm, respectively. Recall that normally the RV diameter in this view is smaller than the LV (see Fig. 11.3), demonstrating the severely overloaded state of the RV in this patient. Also note the "D shape" of the left ventricle, as opposed to its normally circular shape (again referring to Fig. 11.3) when compared to the RV, which is a result of its relatively thick, muscular wall. In the setting of severe RV volume overload, the interventricular septum is pushed towards the LV, diminishing its chamber size and further impairing LV filling

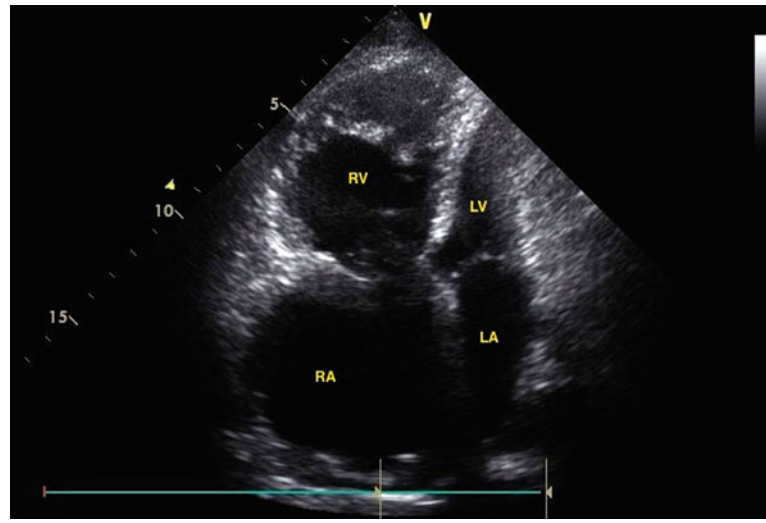

Fig. 11.8 An apical 4-chamber view of the same patient, again demonstrating the relatively large, volume-overloaded right atrium and right ventricle in comparison to the left side of the heart. Reference can be made to Fig. 11.4 for the normal appearance from this view

Acknowledgment I would like to thank Einat Mazor, RDCS, dedicated sonographer and echo lab coordinator here in our Department of Acute Care Medicine, for the generous donation of her time and skills in acquiring the ultrasound images included in this chapter.

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Noninvasive Arterial Pressure Monitoring

12

Jos J. Settels

Why Arterial Pressure Monitoring?

The circulation is a system consisting of an arterial part, a venous part, and a capillary bed in between. Each of the conduit parts has different elasticity (or compliance) and resistance to flow.

When we start filling the total system with blood, the elastic parts can first be filled with blood without stressing their walls: the volume that is stored without stress is called the unstressed volume. If we then continue filling with blood beyond this volume, the walls of each segment will be stressed or loaded, and pressure will start building up depending on the pressure-volume relationship – or compliance – of the segment. If there is no flow, all pressures will equalize to what is called mean filling pressure [1]. Filling the circulation with about 5 L of blood will create a mean filling pressure of about 11 mmHg.

Adding a pump – the heart – to the circulation will create flow, and because of the resistance to flow in the arterioles and capillaries, the total volume of blood will redistribute between the segments before the resistance and with a relatively small compliance – high pressure and low volume, the *arterial pressure* side – and the segments after the resistance with a relatively high compliance – low pressure and high volume, the venous pressure side [1, 2].

The main function of the circulation is to provide adequate oxygen to all tissues. This goal requires two physiological objectives: adequate perfusion pressure to force blood into the capillaries of all organs and adequate cardiac output to deliver the oxygen. So a hemodynamic profile of a patient should contain information on both arterial pressure and cardiac output [1]. Two vital organs are especially arterial pressure dependent: the brain and the heart. Our body therefore monitors arterial pressure at the output side of the pump (the left heart, with sensors in the aortic arch) and at the input side of its most important customer (the brain, with sensors in the carotid body).

Arterial pressure is measured clinically at the start of virtually every medical examination or treatment. It is also measured routinely throughout the course of most illnesses. The clinician usually measures the arterial pressure at different places than the body does: in the upper arm, in the wrist, or in the finger. In other words, we measure it in places where we have access, in an extremity, with superficial and accessible conduit arteries.

The history of the registration of the human pressure pulse wave in an absolute, calibrated way goes back more than a century. During that time, the understanding of the physics and physiology of the registration of pulse waves proceeded hand in hand with the development of the

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DOI 10.1007/978-1-4614-8557-5_12,

technology of the equipment. For more historic background, we refer to articles by Wesseling and Chung [3, 4].

Measurement Principles to Monitor Arterial Pressure

Arterial pressure is defined as the force per unit of surface that the cells in the blood exert on the arterial wall when the artery is filled to beyond its unstressed or unloaded volume.

Any measurement of the arterial pressure pulse wave, with all its dynamics, therefore requires some sort of transducer, which typically has a membrane (to keep the blood from flowing out freely) and which needs to fulfill a number of requirements:

1. The membrane needs to "see" the blood, which means that it needs direct contact.
2. It needs to be able to transfer the intra-arterial pulse to an outside pickup without loss of energy, distortion, or attenuation; therefore the membrane should have no hysteresis and should be stiff in order to achieve a bandwidth of at least 25 Hz [2].
3. It needs a recording system to measure the membrane deflections, with adequate bandwidth.
4. It needs a calibration method to translate membrane deflections into mmHg.

Direct Principle: Replace Part of Arterial Wall

A first and direct principle to achieve all of the above requirements is to replace a small part of arterial wall by an artificial membrane, connected by an artificial artery – a short tube – to a conduit artery (Fig. 12.1).

Because we can technically control the properties of the membrane and the recording system, it can be made to fulfill the aforementioned requirements:

1. The membrane is in direct contact and "sees" the blood.
2. The membrane can be made stiff, with practically no energy loss from inside (artery) to outside (transducer).
3. The stiff membrane will have a small excursion, and a high-fidelity pickup – such as a strain gauge – can be added.
4. The combination of membrane + strain gauge can be factory calibrated.

In practical applications, the total bandwidth properties will be determined not so much by the transducer membrane, but mostly by the artificial connecting artery – the connecting tube –and should be at least 25 Hz or preferably more [2].

The main advantage of this approach is that it provides a direct and calibrated measurement of the arterial pressure pulse wave. The main disadvantage is, of course, that it requires the puncture

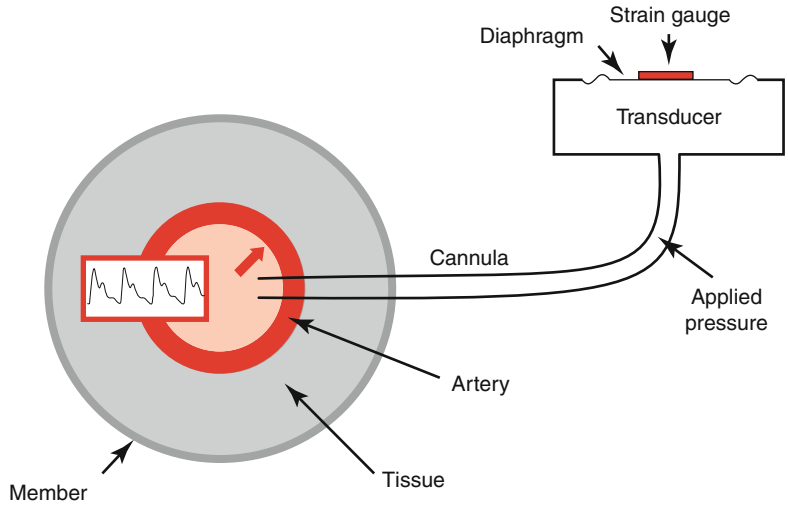

Fig. 12.1 Schematic diagram of the principle of an invasive A-line transducer. Member: typically the wrist or arm. Tissue: tissue, bone, tendons. The cannula punctures the arterial wall, and connects the blood and its pressure to the transducer membrane which replaces a small part of the arterial wall

of the arterial wall. Since this chapter focuses on *noninvasive* methods to measure arterial pressure, we will not discuss this first principle further here, but we will use similar requirement descriptions for the noninvasive principles.

Indirect Principle: Apply Counter Pressure to Unload the Arterial Wall

An alternative principle to achieve the requirements mentioned is:

- To use the arterial wall as the transducer membrane
- To apply a counter pressure to the outside of the arterial wall to unload the arterial wall
- To use a criterion to determine when the arterial pulse is transferred to the counter pressure without distortion and attenuation
- To measure this counter pressure

Schematically (Fig. 12.2), an artery (inner red circle) with a pulsating intra-arterial pressure is surrounded by the tissue in a member (middle grey circle); the total is enclosed by a medium (typically a cuff, outer black circle), which can exert a counter pressure on the tissue that is transferred to the outside of the arterial wall.

We owe this principle to Marey, who from 1860 onwards applied the concept of using counter pressure and unloading the arterial wall to measure arterial pressure noninvasively in humans and who developed various ingenious instruments to do so [3, 5].

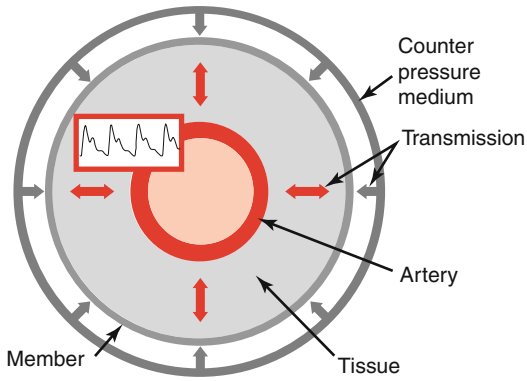

Fig. 12.2 Schematic diagram of the counter pressure principle. An artery with a pulsating intra-arterial pressure is surrounded by tissue (including bone, tendons) inside a member (arm, wrist, finger). The member is enclosed by a medium (typically a cuff) that can exert a counter pressure onto the tissue. This pressure then is transferred to the outside of the arterial wall

Using a second counter pressure makes it an indirect system; we therefore need to slightly adapt the system requirements accordingly:

1. The arterial wall as membrane is in direct contact and "sees" the blood; this requirement is fulfilled in this concept. In addition, the other side of the membrane needs to "see" the counter pressure, which can only be indirect because there is always tissue in between. This is a limitation.
2. The arterial wall needs to "see" the counter pressure without distortion or loss of energy. If the counter pressure and the unloading are quasi-static, this is relatively easy. However, if the counter pressure and unloading are dynamic, the counter-pressure system needs to have an adequate bandwidth of at least 25 Hz.
3. The principle requires a recording system to measure the arterial wall excursions or membrane deflections as transferred to the secondary counter-pressure system, with adequate bandwidth of at least 25 Hz. The arterial wall as membrane is not stiff but viscoelastic. If it is pulsating, the arterial pulse is transferred from inside (artery) to outside (pickup) with considerable distortion and energy loss or attenuation caused by the distending arterial wall. This is a formidable issue in practice.
4. The principle needs a calibration method to translate membrane deflections into mmHg. The calibration will depend on the criterion to decide when the arterial wall is unloaded: the pressure on the inside of the membrane – the intra-arterial pressure – and then equals the pressure on the outside of the membrane, the counter pressure. This criterion will highly dependent on local physiology of the arterial wall and cannot be factory calibrated. Calibration is also a formidable issue.

The main advantage of this approach is that it can provide a *noninvasive measurement* of the arterial pressure pulse wave. The main disadvantage is that its measurement, via the measurement

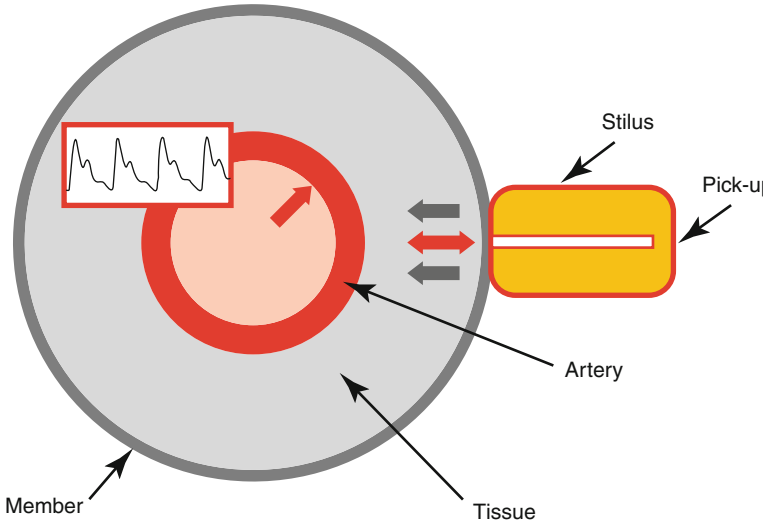

Fig. 12.3 Schematic diagram of the tonometric principle. Counter pressure is exerted locally by the stylus to part of a superficial artery – usually the radial or carotid. Sphygmograms are measured by a small pickup probe against the skin inside the counter-pressure stylus

of counter pressure, is indirect and depends on a criterion of complete unloading of the arterial wall, depending on many physiological factors which we cannot always control.

We will further focus on four different noninvasive methods using the counter-pressure unloading principle to indirectly measure arterial pressure, in historic order. The methods differ in their use of different modes of applying counter pressure (local, from one side or uniform, from all sides), in applying the counter pressure and thus unloading the arterial wall quasi-statically or dynamically, and in using different criteria of determining equal pressures on either side of the arterial wall as membrane. Quasi-static is defined as changing only slowly, from second to second, while dynamically is defined as changing fast, from millisecond to millisecond.

Local, Quasi-Static Counter Pressure: The Tonometric Method

Counter-Pressure and Recording System

In this mode, a superficial artery – radial, carotid, or temporal – is used that is supported at its rear side by a bone and/or tendons. The front side is sensed by a small pickup probe on the skin inside a counter-pressure stylus (Fig. 12.3).

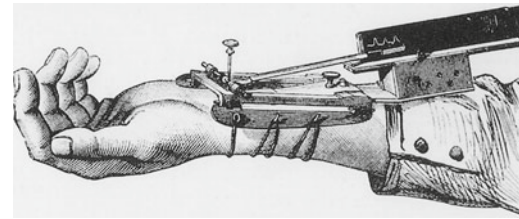

Fig. 12.4 Marey's radial sphygmograph from 1860

If the stylus is applied with sufficient force – the counter pressure – then a floating area on part of the artery is created and a so-called sphygmogram can be made and measured by the pickup probe, giving an uncalibrated arterial pulse. Without counter pressure, if a partial unloaded or floating area is not achieved, an arterial plethysmogram is inscribed, recording normal arterial pulsations.

Criterion

The counter pressure is increased from low values to supra-systolic pressure levels to find the counter pressure at which the observed oscillations by the pickup are maximal.

Probably the first instrument to record sphygmograms was designed by Vierordt in 1853. Much improved devices were later developed by Marey [3, 5] (see Fig. 12.4 for Marey's radial tonometer from 1860). The method is sometimes also referred to as applanation tonometry.

Fig. 12.5 (**a**) Manually operated tonometric device (SphygmoCor, AtCor Medical, Sydney, Australia) placed over the radial artery. (**b**) Automatic tonometric device (T-line, Tensys Medical, San Diego, USA) placed over the radial artery

Since devices using this principle are rather sensitive to correct placement and motion artifacts, much attention has to be paid to fixating the part of the body investigated to the instrument. Modern developments include stylus-like manual probes that can be manually placed over the radial or carotid artery [2] (SphygmoCor by AtCor, see Fig. 12.5a.) and ring like circumferential wrist systems where the pickup probes are automatically placed over the radial artery [4] (T-line by Tensys, see Fig. 12.5b).

Reviewing the requirements for adequate arterial pressure measurement:

1. The arterial wall as membrane is in direct contact and "sees" the blood. However, only an unknown and small part of the arterial wall is unloaded by the counter pressure.
2. The counter pressure and unloading are only local and quasi-static.
3. The counter pressure is not actually measured but rather increased until the arterial oscillations measured by the pickup are maximal. As a result, the artery is pulsating and the arterial pulse is transferred to the pickup with distortion, energy loss and attenuation.
4. The criterion of maximal arterial oscillations measured by the pickup is not very reliable because the sphygmograms are distorted and attenuated. In the modern devices, therefore, an empirical algorithm using calibration values from another measurement (like NIBP) is used to transform the attenuated sphygmograms into a "calibrated" pressure pulse wave.

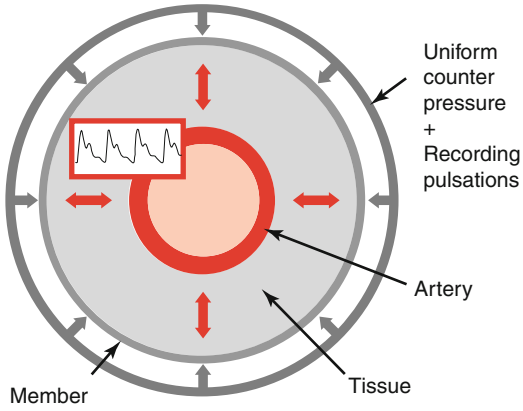

Fig. 12.6 Schematic diagram of the oscillometric principle. An artery inside a member – upper arm, wrist, finger – is unloaded uniformly and circumferentially by applying a counter pressure. The counter pressure system is also used to record the sphygmograms

Uniform, Quasi-Static Counter Pressure: The Oscillometric Method

Counter Pressure

In this mode, an artery inside an extremity – such as upper arm, wrist, or finger – now is unloaded uniformly and circumferentially from all sides by enclosing the part of the body containing the artery by a cuff or container with incompressible fluid or air (Fig. 12.6). The counter-pressure system still only exerts quasi-static counter pressure or unloading.

Recording System

The same system is also used to record the membrane deflections as they are transferred to the counter-pressure system as oscillations superimposed on the counter pressure.

Criterion

The uniform counter pressure is measured and quasi-statically varied from low to supra-systolic pressure levels. Without counter pressure or unloading, an arterial plethysmogram is recorded. If the artery is unloaded, the plethysmogram is turning into a sphygmogram. When the counter pressure is increased, the oscillation amplitude in the sphygmogram increases, reaches a maximum or plateau, and then decreases again (Fig. 12.7).

Marey proposed the pressure at which the oscillations were maximal to equate with the blood pressure [5]. This later became the criterion for measuring mean arterial pressure [6] that has been generally adopted in many oscillometric NIBP instruments.

Marey soon after designing his first tonometric devices realized that he needed uniform counter pressures and developed ingenious fluid-filled systems to apply this principle, using the entire forearm and recording the sphygmograms [5] (Fig. 12.8).

He also constructed a much simpler and smaller apparatus consisting of a water-filled finger cuff, a bulb to change the water pressure in the system, and a mercury manometer. Vendrik and Vierhout [7] showed the fingers to provide us with the more favorable physiological circumstances.

Reviewing the requirements for adequate arterial pressure measurement:

1. The arterial wall as membrane is in direct contact and "sees" the blood. The arterial wall is now unloaded uniformly by the counter pressure.
2. The counter pressure and unloading are quasi-static.
3. The recording system to measure the arterial pulsations superimposed on the counter pressure – a large cuff with long connecting tubing – has only a very low and basically inadequate bandwidth to faithfully record the sphygmograms.
4. Like with tonometry, the criterion of maximal arterial oscillations is unreliable. The correctness of this criterion has been criticized, suggesting that there is no direct relationship between the mean blood pressure and the maximum amplitude algorithm (MAA) estimate and that multiple variables may affect the accuracy of the MAA estimates of mean blood pressure, most notably the nonlinear, viscoelastic behavior of the pulsating arterial wall when being unloaded only quasi-statically [8–12].

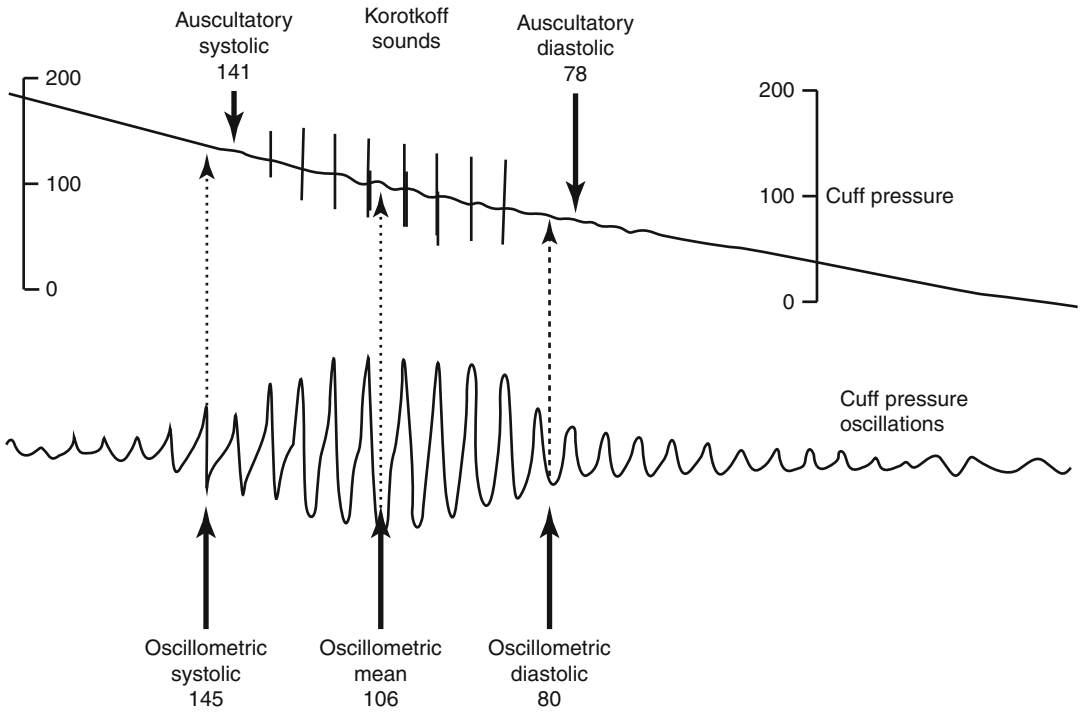

Fig. 12.7 Oscillometric principle – maximum amplitude criteria. When the counter (cuff) pressure system is increased and then quasi-statically decreased, the oscillation amplitude in the sphygmogram increases, reaches a maximum or plateau, and then decreases again. The counter pressure at which the oscillations are maximal is taken as measure of mean arterial pressure. The increase and decrease of oscillations amplitude is taken as measure of systolic and diastolic pressure, respectively. Auscultatory principle – Korotkoff sounds criteria. A stethoscope is placed over the brachial artery just distal to the upper arm cuff, to monitor the Korotkoff sounds. When the counter (cuff) pressure is increased to supra-systolic levels and then quasi-statically decreased, the first sound is taken as systolic and the muffling of the sounds is taken as diastolic pressure (Adapted from Geddes [41])

Later implementations of this principle use a pneumatic cuff as counter-pressure system (Fig. 12.9). Observe that this is the origin of the oscillometric method that today is accepted as the standard NIBP modality in most clinical circumstances.

Automatic, easy-to-use systems using this principle (Dinamap by Critikon, Tampa, USA) were introduced by Ramsey [13] using algorithms to determine the pressure at maximal oscillations – equated with mean arterial pressure – and also using various algorithms for the identification of systolic and diastolic pressure from the decay of the pulsations recorded in the counter pressure [14].

Uniform, Quasi-Static Counter Pressure: The Auscultatory Method

Counter Pressure

Soon after Marey's hydraulic counter-pressure experiments, pneumatic member-encircling (upper arm, forearm, finger) counter-pressure devices appeared. The prototypes of our present-day blood pressure cuffs were those described by Riva Rocci [15] and Hill and Barnard [16].

Recording System

A major improvement was the introduction of a completely independent measurement system

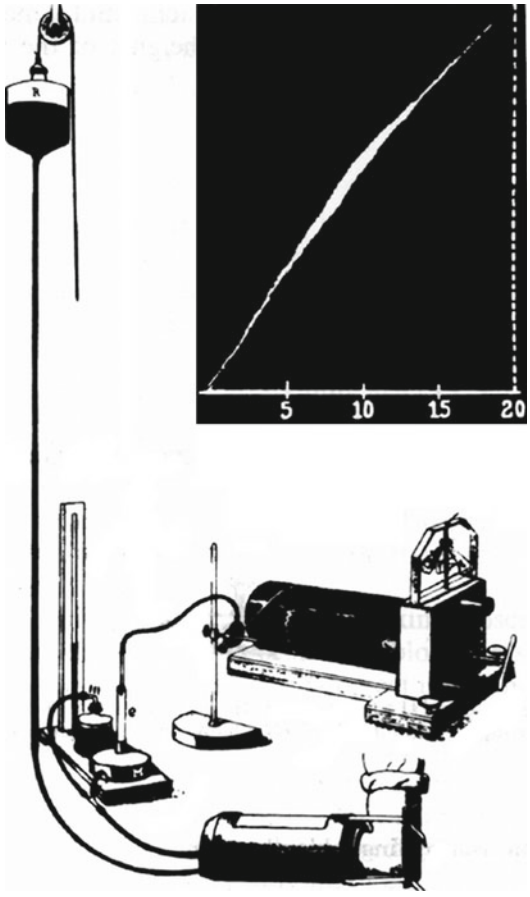

Fig. 12.8 Marey's fluid-filled forearm oscillometric device from 1881

for the membrane deflections: Korotkoff [17] introduced the auscultatory method, in which a stethoscope is placed over the brachial artery just distal to the cuff, to monitor the sounds as the counter pressure is reduced slowly (Fig. 12.10).

Criterion

Cuff pressure at the appearance of the first sound is taken as systolic pressure, while the criterion for diastolic pressure, most used, is the muffling of the sounds (see Fig. 12.7).

Reviewing the requirements for adequate arterial pressure measurement:

1. The arterial wall as membrane is in direct contact and "sees" the blood. The arterial wall is unloaded uniformly by the counter pressure.
2. The counter pressure and unloading are quasi-static.
3. The recording system to measure the effects of the arterial pulsations during unloading is separated from the counter-pressure system and can be optimized independently.
4. The cause of the Korotkoff phase IV muffling and phase V disappearance of sounds, in fact the very reason for sound generation under an unloading cuff, are not known with certainty [18].

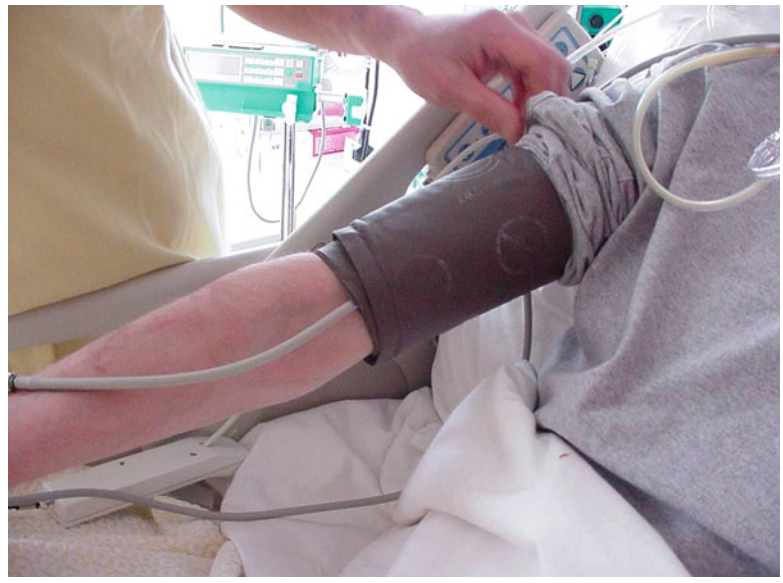

Fig. 12.9 Oscillometric principle using a pneumatic cuff as counter-pressure system: the upper arm NIBP cuff of today

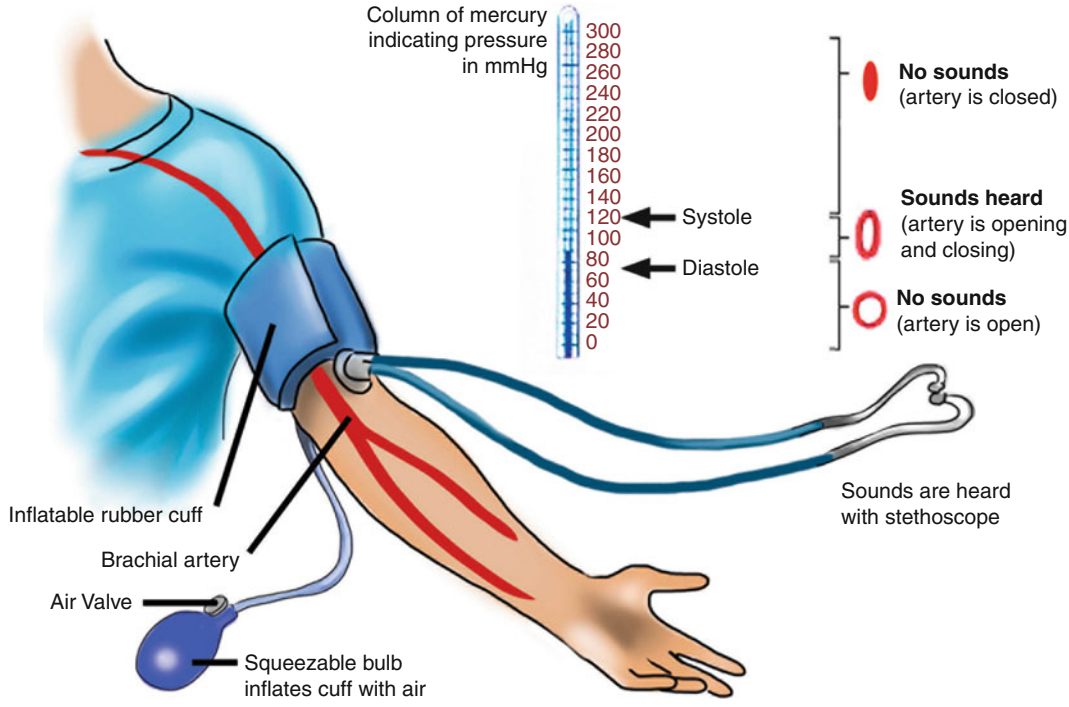

Fig. 12.10 Auscultatory principle: A stethoscope is placed over the brachial artery just distal to the upper arm cuff, to monitor the Korotkoff sounds as the counter pressure is first increased to supra-systolic and then quasi-statically reduced. See also Fig. 12.7

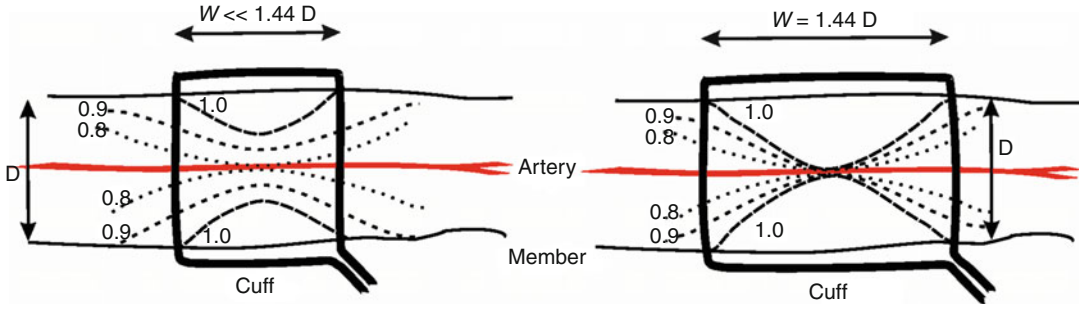

Fig. 12.11 Appropriate cuff width assuring that the counter pressure in the cuff that is applied to the outside of the member is transferred 1:1 to the outside of the artery inside the member (*right panel*). Appropriate cuff width is 1.44 * Diameter or 0.46 * Circumference of the member. If the cuff width is taken too small, the pressure measured will be erroneously high, since the pressure transmission to the artery is not reaching 1:1 (*left panel*)

Cuff Width: Important Factor

Studies on the importance of the counter-pressure system, the length of the compressed region of the arm or the cuff width, were being undertaken already by Von Recklinghausen [19] who found that the Riva Rocci and Hill and Barnard cuffs were too narrow and gave falsely high pressures. Here was the beginning of the recognition that the appropriate cuff width should be used for the size of the member being compressed [20–22] in order to reasonably assume that the counter pressure applied to the outside of the member is transferred more or less 1:1 to the outside of the artery inside the member (Fig. 12.11).

The errors made by the wrong cuff size in clinical practice are not negligible [23, 24] Today, the correct cuff width is 46 % of the member circumference [21]. This important principle holds for any member, including upper arm, wrist, and finger.

Uniform, Dynamic Counter Pressure: The Volume Clamp Method

Counter Pressure

In all previous modes, major causes for inaccuracies are twofold. First, the arterial wall is only unloaded quasi-statically, and thus it still pulsates and as a membrane it is not stiff but viscoelastic. Therefore the arterial pulse is transferred from inside (artery) to outside (pickup) with considerable distortion and energy loss or attenuation. Second, and related to the first cause, all criteria used are unreliable.

We owe the fundamental solution to these issues to Peňáz [25] and Wesseling [26, 27], who developed three major breakthroughs.

Counter Pressure

Peňáz created a counter-pressure system to for the first time dynamically unload the finger arterial wall using an electropneumatic servo feedback system (Fig. 12.12).

In all earlier implementations, the arteries cycled between open and collapsed against the residual compliances in the system. In the *Peňáz volume clamp* method, the volume of just the arteries is held constant by dynamically varying the counter – cuff – pressure, guided by the volume signal from the optical plethysmograph (see below) [25]. The total liquid volume under the cuff, however, may vary freely and has no impact any more. The step from quasi-static to dynamic unloading is breakthrough number 1.

When the volume signal from the plethysmograph in Fig. 12.12 would increase by the arterial volume increasing through rising intra-arterial pressure, the differential amplifier would immediately sense this deviation from the setpoint volume and force the control valve to sufficiently increase cuff pressure such that the arterial volume is kept at the preset setpoint value. A fast servo feedback system is required to achieve this in practice.

Recording System

Peňáz also separated the recording system to observe the unloading of the arterial wall from

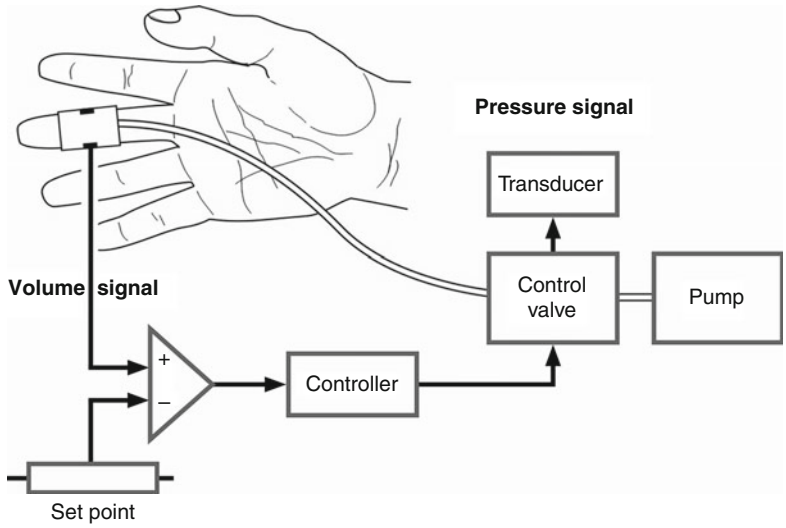

Fig. 12.12 Volume clamp principle applying dynamic counter pressure using a fast servo feedback system. The volume of the arteries under the cuff is held constant by dynamically varying the counter – cuff – pressure, guided by the volume signal from the optical plethysmograph. When the volume signal from the plethysmograph would increase, the differential amplifier would immediately sense this deviation from the setpoint volume and force the control valve to sufficiently increase cuff pressure such that the arterial volume is kept at the preset setpoint value

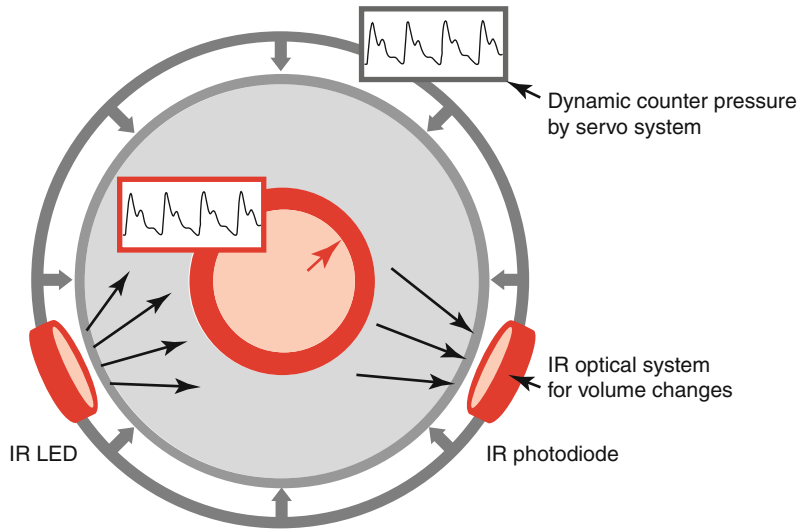

Fig. 12.13 Volume clamp principle observing the dynamic unloading of the arterial wall by using an infrared optical plethysmograph built in the cuff

the counter-pressure system, using an infrared optical plethysmograph built in the cuff (Fig. 12.13) [25].

The infrared plethysmograph can thus be made to respond almost exclusively to changes in blood volume within its field of view, not to the total tissue and liquid compartment under the cuff as in earlier implementations. Once the venous system under the cuff is collapsed and capillary flow blocked, only arterial volume changes are monitored with the plethysmograph. This optical system is breakthrough number 2.

Criterion

Peňáz did not have a solution for the setpoint value at which to clamp the arteries under the cuff to. Wesseling [26, 27] developed a breakthrough strategy to automatically determine the setpoint. The arterial wall under the cuff is only fully unloaded if it is kept constant – clamped – by the servo system at its unloaded volume. In the *Wesseling Physiocal criteria*, a strategy was designed to determine this unloaded volume from the pressure-volume pulsations over a limited number of heartbeats when the counter pressure is gradually varied from zero to supra-systolic (Fig. 12.14). He called this strategy *Physiocal*, which is short for physiological calibration; it calibrates the physiology of the finger arteries under the cuff [27]. The Physiocal setpoint strategy is breakthrough number 3. Together, they solve the fundamental issues of the previous modes.

The start-up of the volume clamp method and the computation of the first setpoint volume are shown in Fig. 12.14. In the left panel we see intra-arterial pressure, the counter pressure generated in the cuff by the servo system, and the volume signal from the plethysmograph for 15 beats. In the right panel, we see the same signals but now shown as volume pulsations versus transmural pressure over the arterial wall. When cuff pressure is increased, the plethysmogram becomes a sphygmogram when the artery cycles between open and collapsed and finally is fully closed. The setpoint determined by the Physiocal algorithm at which the volume is clamped after these first 15 beats by the servo system is indicated by the dark-blue dot and is located at zero transmural pressure, indicating that the arteries indeed are fully and dynamically unloaded. The pressure generated in the cuff to achieve this is directly measured by a standard transducer and is shown as the blue pressure waveform.

Reviewing the requirements for adequate arterial pressure measurement:

1. The arterial wall as membrane is in direct contact and "sees" the blood. The arterial wall is unloaded uniformly by the counter pressure.
2. The counter pressure and unloading are now dynamic. Therefore, the counter-pressure system needs to have an adequate bandwidth of at

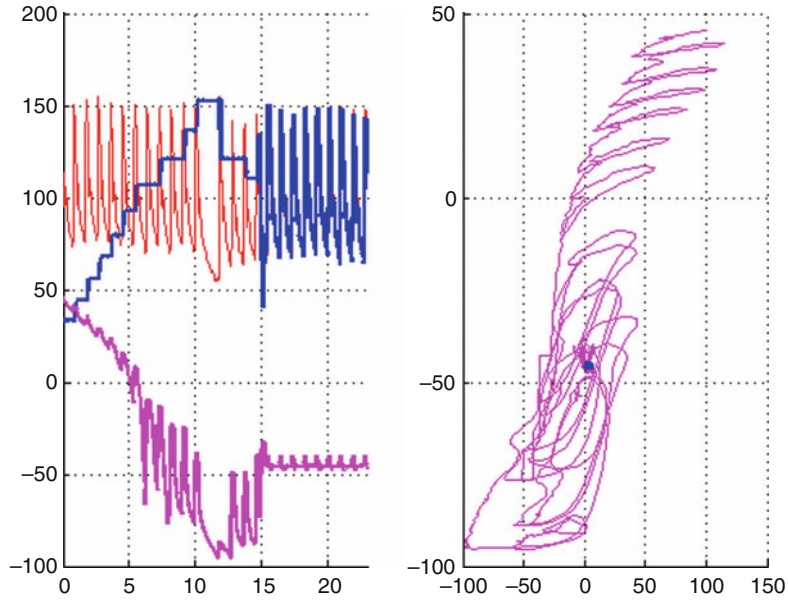

Fig. 12.14 Volume clamp setpoint by Physiocal: determine the unloaded volume setpoint from the pressure volume pulsations over a limited number of heartbeats when the counter pressure is gradually varied from zero to supra-systolic. *Left panel*: intra-arterial pressure (*red*), counter pressure generated in the cuff (*blue*) and the volume signal from the plethysmograph (*purple*) for 15 beats. *Right panel*: same signals, shown as volume pulsations (*y*-axis, arbitrary units) versus transmural pressure (*x*-axis, in mmHg). Setpoint determined by Physiocal initially is indicated by the *dark-blue dot*, located at zero transmural pressure

least 25 Hz, preferably higher. This poses challenges to the cuff design (keep the volume small), the valve (fast dynamic performance), and the servo controller.

3. The infrared plethysmographic recording system to observe the unloading of the arterial wall now observes only arterial volume changes under the cuff and can be made fast by using appropriate optical components.
4. Clamping the arterial volume to its unloaded value virtually turns the arterial wall into the membrane of a differential manometer which is dynamically stiffened, transforming it into an ideal manometer membrane. The viscoelastic properties of the arterial wall finally are taken out of the equation since the wall practically does not move any more. The Physiocal algorithm, however, does have to deal with the viscoelastic hysteresis type of pressure-volume relationships and is based on a combination of physiological studies and empirical findings [27, 30].

Tracking Setpoint Over Time

Because the setpoint in this principle is based on a physiological pressure-volume relationship of the finger arteries which change over time considerably by vasoconstriction, vasodilatation, temperature, hematocrit, and many other factors, the correct setpoint needs tracking over time. Therefore, the Physiocal procedure is repeated, requiring a few beats of recalibration (see Fig. 12.15).

The initial setpoint volume (light-blue dot in right panel) is adjusted by Physiocal, using the 3-heartbeat pulsation information, to the new setpoint volume (dark-blue dot in the right panel). Note that arrhythmia, even during a Physiocal, is not an issue.

Physiocal includes a fully automatic algorithm that determines the interval in between calibrations based on the observed dynamics of the finger arterial physiology: if more dynamic, the interval automatically becomes smaller, if stable, the interval increases to 70 beats in between recalibrations (Fig. 12.16) [27].

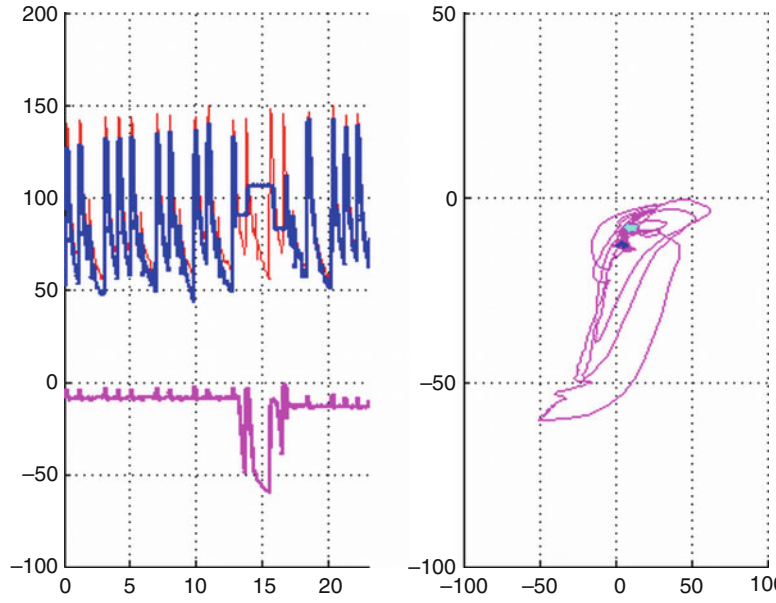

Fig. 12.15 Physiocal principle. *Left panel*: intra-arterial pressure (*red*), counter pressure generated in the cuff (*blue*) and the volume signal from the plethysmograph (*purple*) for 15 beats. *Right panel*: same signals, shown as volume pulsations (*y*-axis, arbitrary units) versus transmural pressure (*x*-axis, in mmHg). At $t = 13$ s., the servo loop is opened and cuff pressure is kept constant at different levels between systolic and diastolic, to record the sphygmogram pulsations for two, three (this case), or more beats and redetermine the correct unloaded volume setpoint and recalibrate the finger physiology. *Right panel*: the initial setpoint volume (*light-blue dot*) is adjusted by Physiocal, using the three-heartbeat pulsation information, to the new setpoint volume (*dark-blue dot*). Note that arrhythmia, even during a Physiocal, is not an issue

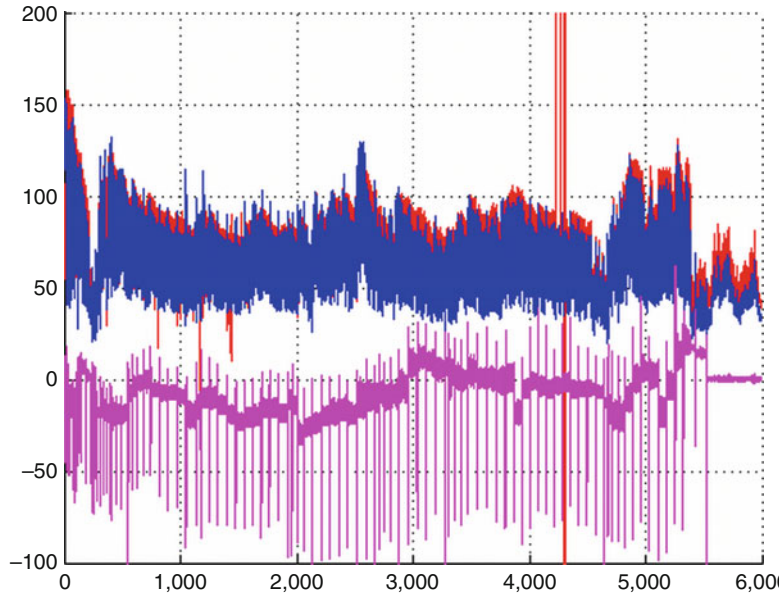

Fig. 12.16 Physiocal tracking. Interval in between calibrations set fully automatic based on the observed dynamics in the finger arterial physiology. Intra-arterial pressure (*red*), noninvasive arterial pressure (Nexfin) (*blue*), and volume signal from the plethysmograph (*purple*) with Physiocal recalibrations shown as the vertical down-spikes. Recording taken from a cardiac surgery OR case, period before cardiopulmonary bypass shown, patient on bypass at about 5,500 s. Note the dynamics in the interval between recalibrations and the dynamics in the actual setpoint during this phase of the OR case (*thick purple line*). Note the excellent tracking of invasive and noninvasive arterial pressures

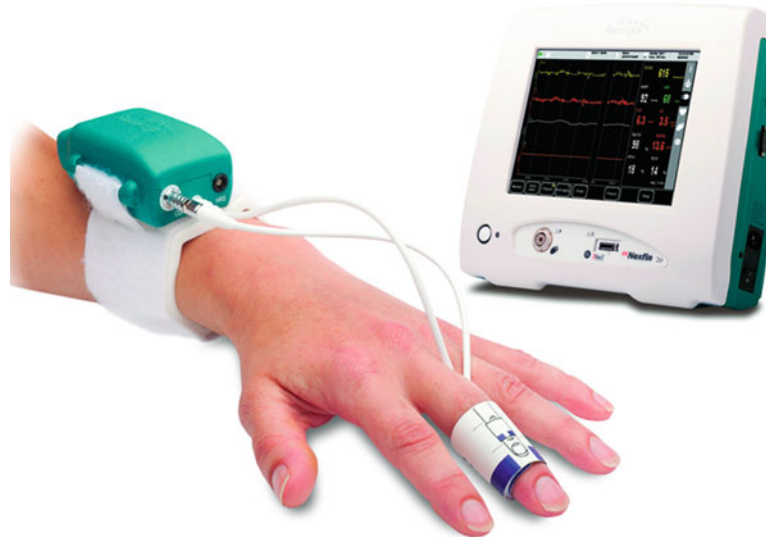

Fig. 12.17 Nexfin monitor (Edwards Lifesciences BMEYE, Amsterdam, Netherlands)

The combination of the volume clamp principle, requiring a setpoint at which volume to clamp the artery as provided by Physiocal, is also known as the *Peňáz-Wesseling method*.

The first clinical research device that used the Peňáz-Wesseling method was the Finapres [26, 28, 29, 31, 32]; the first clinical patient monitor using the method is the Nexfin monitor (Fig. 12.17), which was introduced in 2007 [34, 35]

Unique Features

The servo feedback loop principle of volume clamp at the correct unloaded volume will generate in the cuff pressure a copy of whatever the heart generates inside the finger arteries. Normally, that will be a pulsating pressure. The principle has no problems with arrhythmia, no matter how strong, because they will be tracked (Fig. 12.18).

Even stronger, there is no real need for a pulsating intra-arterial pressure: even a reduced pulsatile (see Fig. 12.18) or even non-pulsatile blood pressure such as during asystole or when using a left ventricular assist device (LVAD) will be measured reliably [33].

Another device using the volume clamp method of Peňáz is the CNAP monitor by CNSystems (Fig. 12.19). Although it uses the volume clamp principle, it does not use Physiocal and its way of obtaining a volume clamp setpoint is unclear and undocumented and requires an upper arm NIBP calibration. A setpoint not determined from the finger physiology reintroduces partial quasistatic loading of the arterial wall with the associated problems energy loss and distortion.

The CNAP calibration with an oscillometric NIBP, which can be repeated at intervals between 5 and 60 min, is much less frequent than the Nexfin Physiocal and is unlikely to track the changes in finger physiology. It introduces the errors associated with the NIBP principle as explained earlier and further elucidated in the later paragraph on accuracy. In combination, the CNAP approach takes an important step back in the developments of arterial pressure measurements using counter pressure principles.

Importance of Reference Level

Hydrostatic Pressure

In any body of fluid, the pressure at the surface of the fluid is equal to atmospheric pressure, but the pressure increases by 10 mmHg for every 13.6 cm of distance of the measurement point below the fluid surface, resulting from the weight of the fluid column. This is called the gravitational or hydrostatic pressure. Gravitational pressure also occurs in the human vascular system because of the weight of the blood in the vessels. The effects are greatly dependent on the body position: in the upright position, the gravitational weight of the blood between the vessels in the foot and the heart can be as large as 90 mmHg [1].

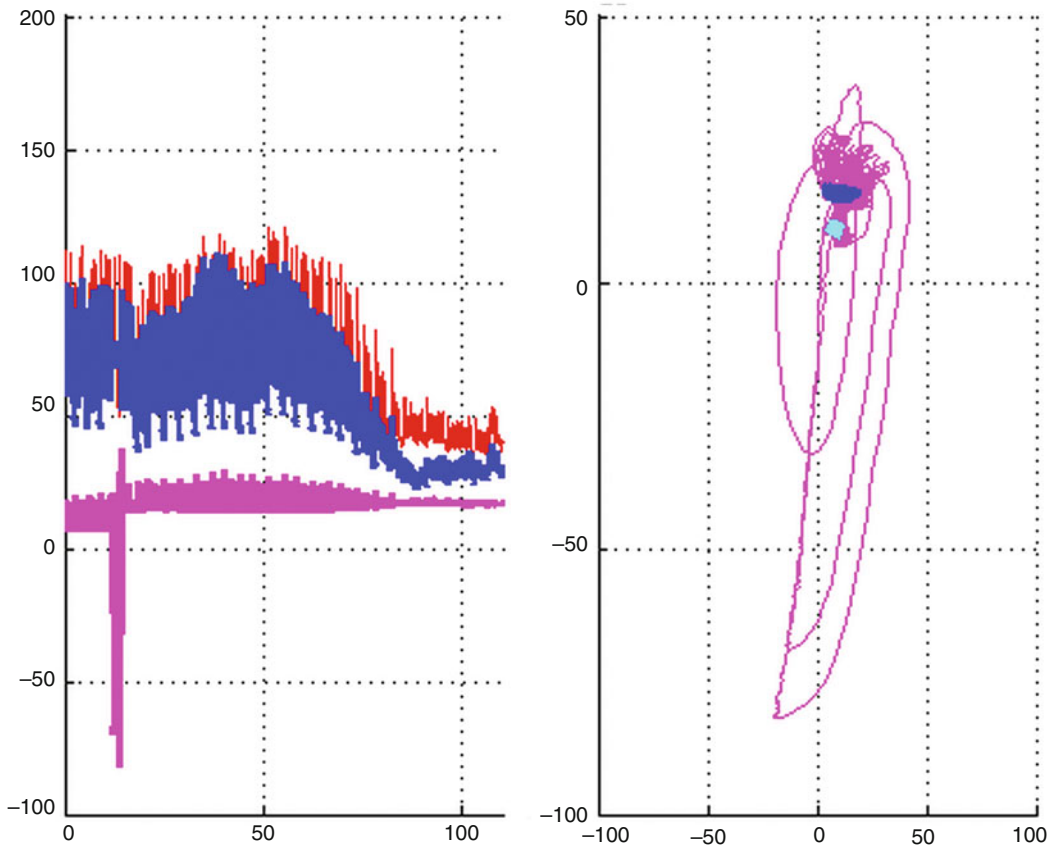

Fig. 12.18 Arrhythmia and reduced pulsatility. *Left panel*: intra-arterial pressure (*red*), noninvasive arterial pressure (Nexfin) (*blue*), and volume signal from the plethysmograph (*purple*) with a three-beat Physiocal recalibration scheduled at about 10 s. *Right panel*: the initial setpoint volume (*light-blue dot*) is adjusted by Physiocal, using the three-heartbeat pulsation information, to the new setpoint volume (*dark-blue dot*). Note the frequent arrhythmia before the patient is going on bypass at about 80 s. Cardiac pulsations disappear; the small pulsations are then caused by the bypass pump

Because of this hydrostatic effect, it is crucial for any pressure measured in the circulation to first state the gravitational or hydrostatic level in the circulatory system to which this pressure is referred. This is true for an invasive pressure transducer, for a noninvasive (NIBP) upper arm cuff, and also for a noninvasive finger arterial pressure.

Location of the Reference Level

There is one point in the circulation at which hydrostatic pressure factors caused by changes in body position do not affect the pressure measurement: this the *level of the tricuspid valve* in the right atrium, which therefore is used as the *reference level* for pressure measurements in the circulatory system [1]. The level of the right atrium is situated approximately at the level of the fourth intercostal space. In the supine position this is approximately halfway between the bed surface and the sternum. Figure 12.20 shows the correct use of a supporting pillow, lifting the upper arm to the correct reference level.

In clinical practice, however, this pillow is often not used, causing a hydrostatic error in the order of 10–15 mmHg depending on the size of the patient.

Important

The membrane of the transducer of any arterial pressure measurement system should be at the reference level. Alternatively, an automatic compensation system (e.g., the Heart Reference System (HRS) in the Nexfin monitor [34, 35]) should be used to correct for the hydrostatic differences.

Location of Measurement: Arm, Wrist, or Finger

Our body monitors arterial pressure at the output side of the pump (the left heart) and at the input side of its most important customer (the brain). Clinically, arterial pressure is measured as discussed at different places than the body does: in the upper arm, in the wrist or in the finger.

The standard location for blood pressure measurement according to the American Heart Association is the upper arm [36]. The brachial artery, the radial artery and the finger artery all are conduit arteries, with inner diameters of approximately 4, 2 and 1 mm respectively. The finger artery is a more muscular artery than the radial and brachial. Because all three sites are well before the location where the resistance to flow takes place (the arterioles and capillaries), mean arterial pressure at these sites is practically the same, with some pressure gradient (about 10 mmHg on average) from brachial to finger [1, 2]. Because of reflections at the arteriolar site, the waveform shapes change from more rounded at the brachial, more central site to more peaked at the finger, more peripheral site [2] (Fig. 12.21).

The waveform reflection and pressure gradient effects in the finger arterial pressure measurement with the Nexfin device are automatically compensated for by reconstructing the brachial pressure waveform from the finger pressure using a physiological transfer function algorithm [34].

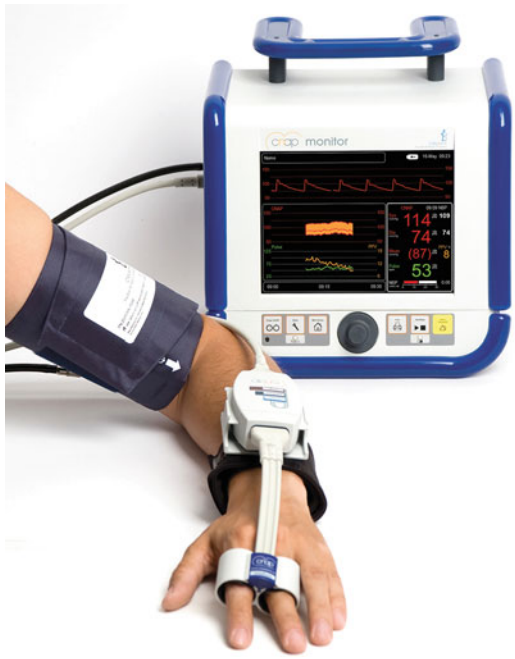

Fig. 12.19 CNAP monitor (CNSystems, Graz, Austria)

Accuracy and Comparisons

All monitors available for clinical use should be validated and tested for accuracy. The two protocols most widely accepted for this were developed by the Association for the Advancement of Medical Instrumentation (AAMI) [37] and the British Hypertension Society (BHS) [38]. The AAMI protocol sets limits for the difference between a reference (usually the intra-arterial line) and a noninvasive device of 5 mmHg (bias) and 8 mmHg (1 SD).

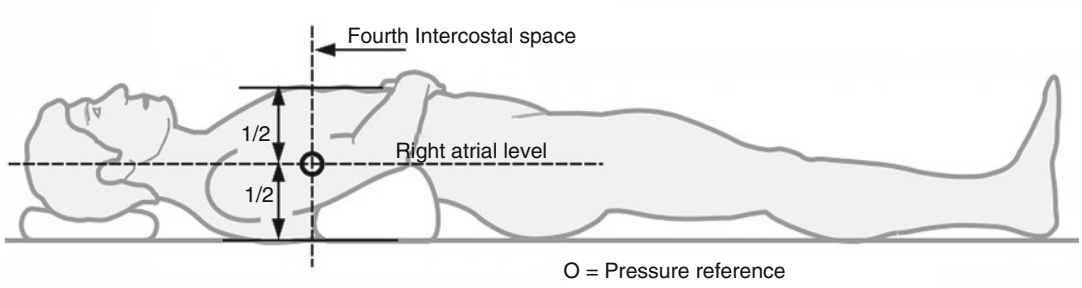

Fig. 12.20 Reference level: level of the tricuspid valve in the right atrium, situated at the level of the fourth intercostal space. In supine position this is approximately halfway between the bed surface and the sternum. For upper arm cuff, a supporting pillow lifts the upper arm to the correct reference level

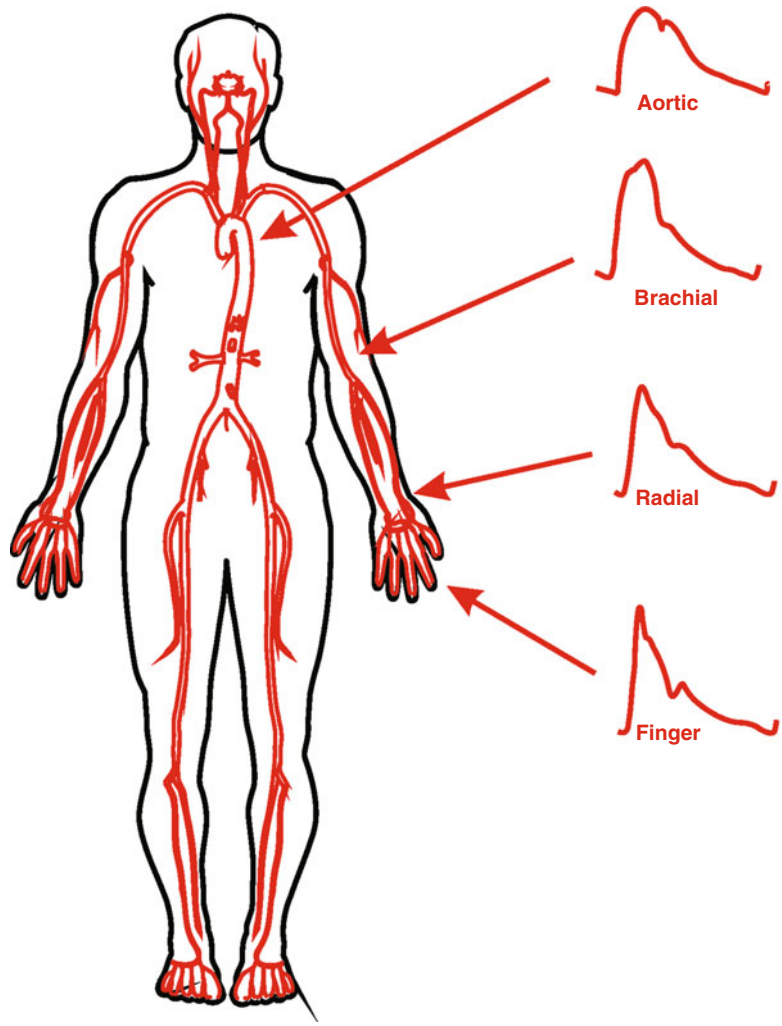

Fig. 12.21 Site of pressure measurement: because of reflections at the periphery (arterioles, capillaries), the arterial pressure waveform shapes change from rounded at the aortic sites to slightly peaked at the brachial site to more peaked at the more peripheral radial and finger artery sites

The auscultatory method is the clinical "gold standard" for NIBP. The two other principles most widely accepted, tested, and validated over the last decades are the oscillometric intermittent NIBP and the volume clamp and Physiocal or Peňáz-Wesseling continuous NIBP methods.

Rather than reviewing a large number of clinical validation papers (for reviews, see references [4, 39]), we focus here on the oscillometric principle as the de facto accepted current standard NIBP modality in most clinical circumstances and use for this goal a very interesting recent meta analysis study performed by Wax et al. [40]. Simultaneous measurements of invasive radial artery pressure (ABP) and simultaneous noninvasive oscillometric blood pressure (NIBP) in 24,225 adult patients during non cardiac cases were extracted from electronic anesthesia records, and the differences were subjected to regression analysis.

The overall statistics of the differences were reasonably close to (but not meeting) the AAMI limits of 5 ± 8 mmHg – for systolic, −1 ±16 mmHg; for diastolic +5 ±11 mmHg; and for mean, +3 ±10 mmHg. However, when looking at the distribution of the differences over the pressure ranges, it is clear that the actual individual differences showed a much larger scatter with a significant bias distribution as a function of pressure (Fig. 12.22), leading to their conclusion: "Our data showed a significant difference between intra-operative blood pressures when

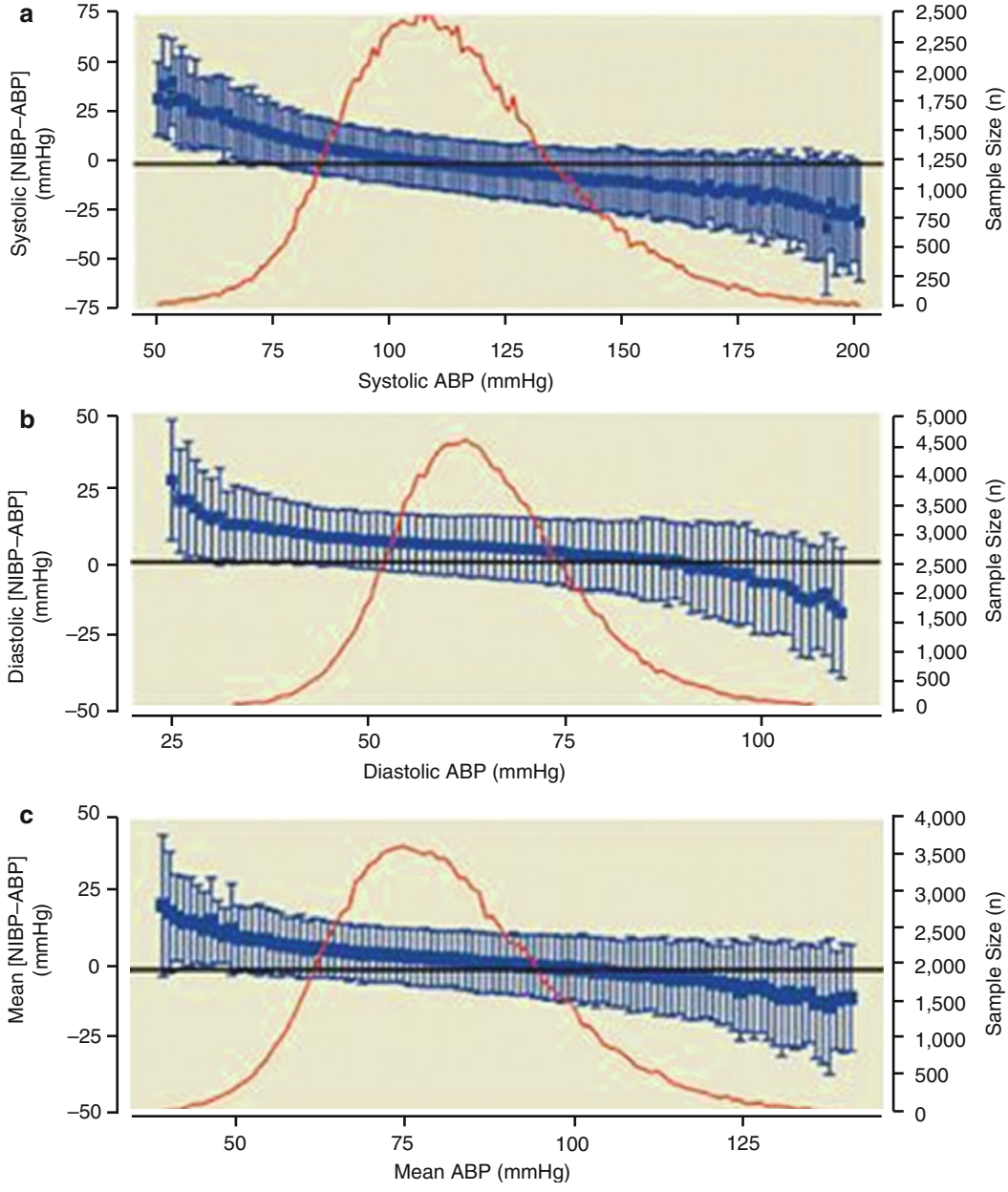

Fig. 12.22 Errors in clinical NIBP measurements. Differences between oscillometric cuff and radial artery catheter measurements of blood pressure. Average differences (±1 SD) between simultaneous noninvasive (*NIBP*) and invasive radial artery (*ABP*) systolic (**a**), diastolic (**b**), and mean (**c**) blood pressure measurements are shown in 24,225 adult patients during noncardiac surgery and anesthesia. Note the considerable positive and negative biases and the significant standard deviations of the errors. Total sample size of data pairs for each ABP value is also shown in the bell-shaped curves and right-side *y*-axis (Reproduced with permission from Wax et al. [40])

Table 12.1 Additional analysis of data published by Wax et al. [40]

Analysis data Wax	*P* [mmHg]	Bias [mmHg]	SD [mmHg]	Percent error [%]	PE_{ABP} [%]	PE_{NIBP} [%]
Systolic	60	27	19	60	10	59
	105	−1	14	26	10	24
	185	−20	23	24	10	22
Diastolic	30	14	15	98	10	97
	65	5	11	32	10	30
	100	−9	18	34	10	32
MAP	45	15	14	61	10	60
	75	5	9	24	10	22
	130	−10	18	26	10	24

The mean bias between the two methods ranged from −20 to +27 mmHg (systolic) with lower values (−1- to +15 mmHg) for diastolic and mean pressures. The combined Percent Error ranged from 24 to 98 %; when allocating 10 % error to the gold standard ABP, the Percent Error for NIBP ranged from 22 to 97 %, with the lower values (22–30 %) for the blood pressures in the middle ranges

NIBP was compared with ABP. NIBP was likely to be higher than ABP at lower pressures, and NIBP was likely to be lower than ABP at higher pressures."

Figure 12.21 shows the differences between oscillometric cuff and radial artery catheter measurements of blood pressure. Average differences (±1 SD) between simultaneous noninvasive (NIBP) and invasive radial artery (ABP) systolic (*A*), diastolic (*B*), and mean (*C*) blood pressure measurements are shown in 24,225 adult patients during non-cardiac surgery and anesthesia. Total sample size of data pairs for each ABP value is also shown in the bell-shaped curves and right-side *y*-axis. The bias, standard deviation, and combined percent error for both methods (defined as 1.96 * sd/mean) as computed from their data (using DataThief III, www.datathief.org) for the pressures at the lower end, the higher end and the middle of bell-shaped curves is summarized in Table 12.1.

The combined Percent Error (as $\sqrt{(PE^2_{ABP} + PE^2_{NIBP})}$ is divided up into an assumed PE_{ABP} of 10 % and a resulting PE_{NIBP}.

This meta-analysis highlights several important aspects: First, differences between an invasive reference method and a concomitant noninvasive arm cuff NIBP measurement in clinical practice are much larger than the AAMI standards suggest and may contain significant systematic deviations and random scatter errors. Second, when comparing arterial pressure values obtained simultaneously by arm cuff NIBP and a second method, one can easily expect to find differences in the order of several tens of mmHg.

Conclusion

The principle of counter pressure and arterial wall unloading has been crucial and instrumental in the development of methods to measure arterial pressure non-invasively. In several fundamental steps, the main limitations have been subsequently resolved. In Table 12.2, the most important aspects of the four principles as discussed are summarized, including a short overview of advantages and limitations. We stand on the shoulders of giants like Marey, Riva Rocci, Korotkoff, Peňáz and Wesseling in our current endeavors to further improve the technologies and develop the monitors to continuously and non-invasively monitor arterial pressure.

Table 12.2 Principles of noninvasive arterial pressure monitoring

Principle	Method of measurement	Advantages	Limitations
Tonometric (Marey)	Local, quasi-static unloading of arterial wall	Continuous monitoring, waveform	Positioning of tonometer over superficial artery can be difficult and is motion sensitive
	Measurement of sphygmograms at counter pressure with maximal amplitude of sphygmograms. Translation of sphygmogram into pressure pulse	Can be placed on the carotid artery to measure a central waveform	Sphygmograms distorted by viscoelastic nonlinear behavior arterial wall Translation needs calibration with other method
Oscillometric (Marey)	Uniform, quasi-static unloading of arterial wall	Automated devices	Criterion for MAP debated, criteria for SYS and DIA unclear
	Measurement of sphygmograms with gradual change of counter pressure Criterion for MAP at pressure of maximal sphygmogram amplitude	Easy to use Accepted as the standard NIBP modality in most clinical circumstances	Overestimates lower BP, underestimates higher BP values Only intermittent data Cuff size error Problems with arrhythmia, obese patients, motion artifacts
Auscultatory (Riva Rocci, Korotkoff)	Uniform, quasi-static unloading of arterial wall	Clinical "gold standard" of NIBP	Requires trained operator
	Measurement of Korotkoff sounds when cuff is inflated and slowly deflated. SYS at first sound, DIA at muffling of sounds		Criteria for DIA debated Only intermittent data Cuff size error Problems with arrhythmia, obese patients, motion artifacts
Volume clamp and Physiocal (Peňáz-Wesseling)	Uniform, dynamic unloading of the finger arterial wall by volume clamp	Continuous monitoring, calibrated waveform	Requires flow in a finger artery, Raynaud patients and patients in shock that shut down peripheral arteries excluded
	Physiocal criteria for unloading at the correct volume setpoint	Automated device	Cuff size error.
	Tracking by Physiocal of changes in arterial wall physiology due to vasoconstriction, temperature	Easy to use First data within 30 s. Insensitive to arrhythmia, motion artifacts. High-fidelity finger pressure waveform allows reconstruction to brachial pressure waveform.	

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Heart Rate Variability

13

Benoît Tavernier and Mathieu Jeanne

Introduction

Heart rate variability (HRV) can be measured at the bedside, noninvasively, and using standard equipment. It provides information on autonomic nervous system (ANS) activity and more specifically on the so-called sympathetic-parasympathetic balance, which plays an important role in human physiology. Although management of the intensive care patient is generally considered best optimized when clinical decisions are based on analysis of multiple physiological variables, HRV monitoring is far from being considered a standard of monitoring in acute care environments. HRV is in fact frequently perceived by clinicians as an esoteric research tool, whose results are expressed in nonintuitive units (typically, power spectrum at various frequencies obtained by Fourier analysis), with no clear clinical relevance. This is not totally false! To appreciate whether a significant improvement could be expected in the near future, it is necessary to understand what HRV is, how it is measured, and the kind of information it provides about a patient's ANS status in the acute care environment.

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What Is Heart Rate Variability?

Basically, HRV is a very simple phenomenon: during normal sinus rhythm, heart rate actually slightly varies from beat to beat despite its apparent regularity. Importantly, HRV physiologically occurs at different frequencies, classified into (1) ultralow frequencies (ULF; > 5-h cycle length), (2) very low frequencies (VLF; > 25-s cycle length), (3) low frequencies (LF; > 6-s cycle length), and (4) high frequencies (HF; 2.5- to 6-s cycle length) in humans [1, 2]. The most important oscillation in the ULF band is the circadian rhythm. VLF are affected by thermoregulatory processes and humoral systems. The LF power is primarily under the influence of sympathetic and parasympathetic tones activities, whereas the HF domain is under parasympathetic influence only. The HF power is actually closely related to the respiratory sinus arrhythmia (RSA), which is the oscillation of HR caused by ventilation (either spontaneous or mechanical). This comes from the direct relationship between cyclic distension of pulmonary stretch receptors by ventilation and the sinus node via the vagus node in the brain stem. A tachogram, which is the representation of consecutive R-R intervals over time, usually easily depicts the RSA, as shown in Fig. 13.1. Finally, the LF/HF ratio has been proposed as a measure of the sympatho-vagal balance [1, 2]. However, methodological caveats have early cast a doubt on the clinical interpretation of this measure, and LF and HF spectral components of HRV may actually not be very reliable markers

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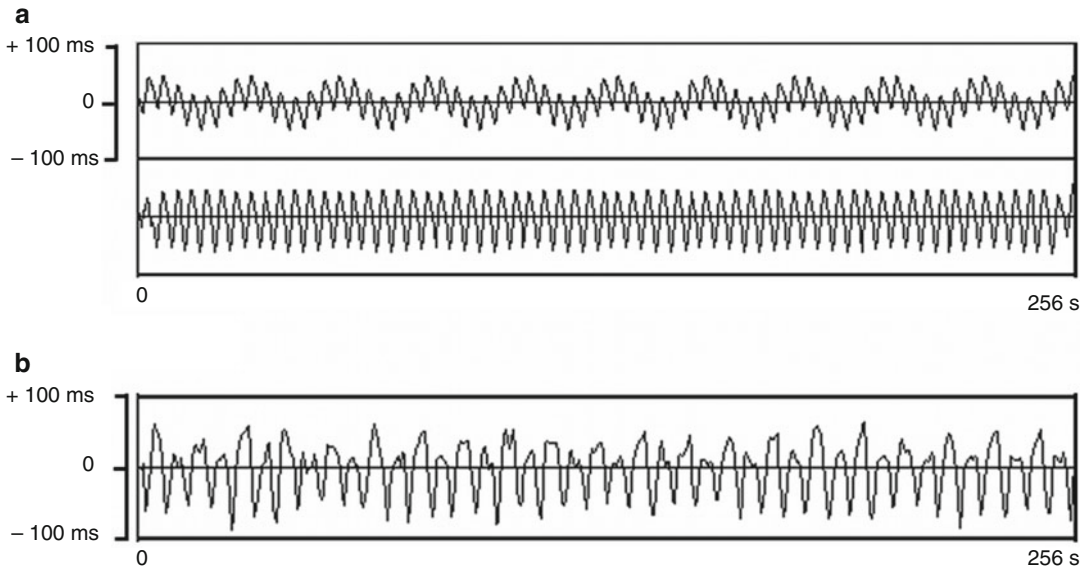

Fig. 13.1 (**a**) *Upper panel*: simulated R-R series over a 256-s period with respiratory rate at 15 cycles/min (= 0.25 Hz, i.e., HF compound) and LF compound at 0.04 Hz. The *y*-axis is centered on the mean R-R length (equivalent to mean heart rate) and quantifies the instantaneous changes in R-R length. *Lower panel*: the series has been band-pass filtered so that only the HF compound (i.e., the respiratory sinus arrhythmia) appears in the tachogram. (**b**) Filtered (in the HF range) R-R series over a 256-s period in a real case under general anesthesia (respiratory rate = 12 cycles/min; 0.20 Hz). The respiratory sinus arrhythmia clearly appears in the tachogram

for quantification of cardiac sympatho-vagal balance either in health or disease [1, 3], especially at the individual level. Nevertheless, trends of the LF/HF ratio in a given subject or group of patients allowed coherent interpretation in most studies performed in the critical care setting, provided that conditions of measurement were adequately controlled.

Measurement of Heart Rate Variability

More and more sophisticated methods have been proposed for HRV measurement, but in every case, three fundamental principles must be respected: (1) instantaneous heart rate (i.e., consecutive R-R intervals) must be precisely measured; (2) mean heart rate must be constant over the analyzing window (HRV cannot be correctly measured during an acute increase or decrease of heart rate); and (3) the minimum length of ECG recording necessary for adequate measurement of a given HRV component depends on its frequency (or cycle length). Accordingly, ULF and most VLF cycles cannot be measured on "short-term" (1–5 min) ECG recordings. On the contrary, HF fluctuation may theoretically be quantified correctly from a 30-s recording. In practice, the objective of HRV measurement in an acute care environment is to correctly assess both HF and LF dimensions, which requires at least 1-min recording. Moreover, it can be intuitively understood that within the 1- to 5-min range, the longer the recording, the more reliable the measure, but the risk of a change in mean heart rate or of ectopic heartbeat or other artifacts also increases.

Ectopic heartbeats are critical to detect, as their "abnormal place" in the course of the R-R series, usually followed by a longer "compensatory" period of time until the next normal R wave, can strongly affect HRV analysis measurements. Various correcting methods have been proposed to eradicate this "noise," such as exclusion of the parts of ECG recordings that present with ectopic heartbeats or electric noise; another possibility consists in replacing the abnormal

Table 13.1 Various time domain measurements

SDNN	Standard deviation of N-N intervals
SDANN	Average over 5 min of standard deviation of N-N intervals
ASDNN (index)	Average over 24 h of SDANN
rMSSD	Root mean square of successive N-N intervals
NN50	Number of N-N intervals by 50 ms longer than the previous one
pNN50	Percentage of NN50 intervals in the whole R-R series

N-N normal-to-normal intervals (see text)

non-sinus R wave by a theoretically "good" one, respecting the mean and standard deviation of R-R intervals measured before the ectopic heartbeat.

Once all R waves on the ECG have been detected and validated, the R-R series can be analyzed. All HRV analysis techniques that have been described have their own requirements and caveats, in particular when mean heart rate is not constant over the analyzing window. This situation is most likely to occur in the critically ill patient. Kleiger et al. reviewed the various existing HRV analysis techniques [4].

Time Domain Measurements

These measurements are simple statistics about successive R-R intervals, which are noted as normal-to-normal intervals (N-N). Table 13.1 presents the various time domain measurements. rMSSD, NN50, and pNN50 are strongly correlated and have been mainly associated with respiratory sinus arrhythmia.

Spectral Techniques

Various spectral techniques can be used to assess HRV. They provide information about the power spectrum in three to four spectral ranges, depending on the length of the analyzed R-R series (see above). The relatively simple use of *Fourier transform* for HRV spectral analysis is probably one reason for the abundant literature on the subject, even if specific caveats can probably account for divergent findings in similar situations, such as stationarity, which must be checked before proceeding with Fourier transform. Power spectral results are presented in absolute values (ms^2), but LF and HF should also be measured in normalized units (n.u.), which represent the relative value of each power component in proportion to the total power minus the VLF component [2]. The representation of LF and HF in normalized units emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system [1, 2] and can also be illustrated on a tachogram (Fig. 13.2). *Wavelet transform*, a more recent spectral technique, is better adapted to nonstationary signal analysis and can be used for filtering as well as for spectral analysis of R-R series. A further advantage of wavelets over Fourier transform is that where Fourier cannot detect the time of a particular frequency shift, the periodogram obtained with wavelet transform shows the actual change of frequency at precisely the time when it takes place. Table 13.2 shows the relation between time domain and spectral measurements.

Parametric Measurements

Parametric measurements such as autoregressive moving average (ARMA) can be used on short-time R-R series and provide information about various frequency compounds of R-R series without the need for power spectrum measurement. The main limitation comes from the use of a model with predetermined coefficients in a possibly changing situation for the ANS, so that the model validity needs to be checked accordingly.

Normalized Graphical Measurements

Jeanne et al. developed a graphical, original HRV measuring technique, leading to a normalized index: the analgesia nociception index (ANI) [5]. The ANI, which is strongly correlated with the normalized HF content, was shown to be related to the analgesia/nociception

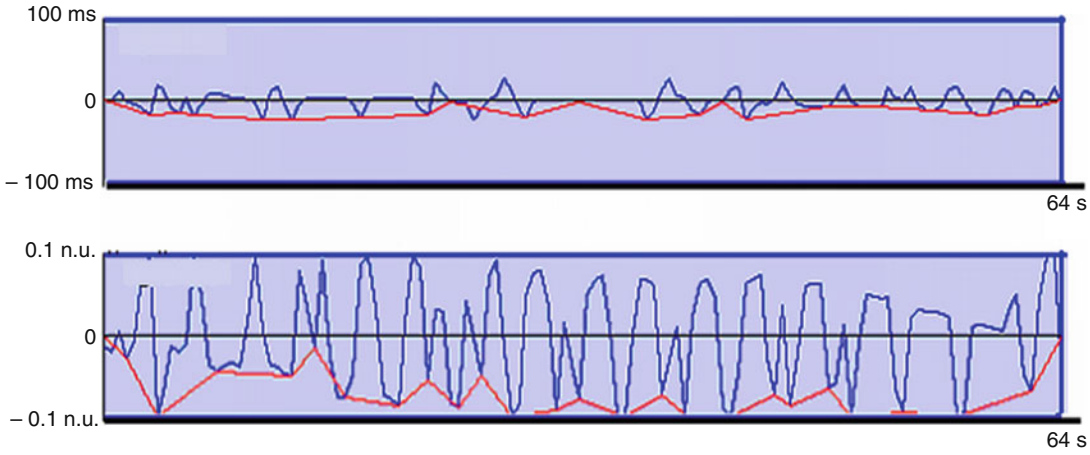

Fig. 13.2 Tachograms illustrating the different and complementary informations provided by absolute and normalized units. *Upper panel*: filtered (in the HF range) R-R series showing the absolute changes in R-R length with respiration (i.e., the respiratory sinus arrhythmia), expressed in ms. As compared with Fig. 13.1b, variability appears reduced in this example. *Lower panel*: the same R-R series has been normalized over its vectorial norm, so that the *y*-axis (from −0.1 to +0.1 n.u.) arbitrary represents the total (~ HF + LF) power of HRV. This representation allows illustrating the respiratory sinus arrhythmia "graphically normalized" to total power. It appears high in this example, which immediately suggests, in this case where absolute HF is low (*upper panel*), that LF power is still more reduced than HF power

Table 13.2 Time domain measurements and the related spectral ones

Time domain	Spectral domain
SDNN	Total power
SDANN	ULF
ASDNN	VLF
PNN50, rMSSD	HF

balance during general anesthesia [6]. Its usefulness in intensive care patients, however, has not yet been evaluated.

Measurements in Clinical Practice

Even using standard spectral analysis in normal subjects, normal ranges are difficult to establish when quantifying absolute values, as large interindividual variability is observed, due to technical as well as true physiological considerations [1, 2]. Normalized values (including the LF/HF ratio) seem more useful for comparisons between patients. Interpretation must take into account the many factors known to interact with HRV in patients in acute conditions, especially sedation and analgesia (see below), ventilator settings, nursing maneuvers, environment, and multidrug therapy that can interfere with ANS function [7].

Experience in the Acute Care Environment

Sedation and Analgesia

Sedation and analgesia are required in many acute care patients. All hypnotic drugs have been reported to have significant effect on HRV. In practice, the main change induced by these agents consists in attenuation of total spectral power, with a decrease in the LF/HF ratio (i.e., a predominant reduction of the sympathetic activity as compared to parasympathetic activity). These effects are more or less concentration dependents and are thus typically evident at anesthetic (vs. sedative) concentrations. In

addition, at a given level of hypnosis, HRV varies with nociceptive stimuli and analgesia. More specifically, the normalized HF content (or its equivalents using other techniques) was shown to be related with the analgesia/nociception balance during general anesthesia. This can be monitored using specific devices such the ANI monitor [5, 6]. Preliminary experiments in the intensive care unit suggest that the ANI monitor may be used to adjust analgesia during painful procedures, but clinical validation remains very limited in this setting.

Hemorrhage

Experimental models of hemorrhage in animals as well as in humans have shown that compensatory autonomic response to progressive hypovolemia as assessed by HRV (decrease in normalized HF and increase in LF/HF) occurs in direct relation to decreased central volume and may track early these changes in autonomic function [8, 9]. However, at the individual level, there is no clear correlation between HRV changes and those in stroke volume [10]. In clinical practice, movement artifacts or electrically noisy ECG recordings may limit the applicability of these data during the early stages of hemorrhage, for example, in the prehospital setting or in the emergency department. In addition, controlled experimental conditions do not reproduce the many factors, such as pain, anxiety, transport conditions, and caregiver interventions, that may influence HRV in patients. In the operating room, because of anesthesia, this compensatory autonomic response to reduced blood volume is likely to be blunted.

Septic Shock

Human studies have convincingly shown that autonomic control of the cardiovascular system is impaired in septic shock [11–13]. Global HRV is reduced, especially its LF component, which results in a decreased LF/HF. A reduced LF/HF ratio <1.0 has even been proposed as a diagnostic test for sepsis in critically ill adults [14]. The reduction of HRV on ICU admission was also found associated with hypercytokinemia [15], APACHE II score (negatively), the development of multiple organ dysfunction [16], and poor outcome. This reduced LF/HF ratio is consistent with an impaired sympathetic modulation of the heart. This may appear in contradiction with the marked tachycardia present in almost any septic shock patient and strong evidences that sympathetic outflow to both heart and peripheral vessels is increased during septic shock. Many factors have been proposed to account for theses discrepancies, including anesthesia, severity of illness, and experimental conditions. However, the most likely explanation is at the cardiomyocyte level. The inward current of Na^+ (I_f), which determines the rate of the slow diastolic depolarization resulting in spontaneous activity in cardiac pacemaker cells, is altered in experimental sepsis [17, 18]. It was shown in human atrial cardiomyocytes that endotoxin interacts with cardiac hyperpolarization-activated cyclic nucleotide-gated ion channels, which mediate I_f and play an important role in transmitting sympathetic and vagal signals on heart rate and HRV [17, 18]. This altered cardiomyocyte response is likely secondary to myocardial inflammation and/or the high sympathetic drive and elevated concentrations of circulating catecholamines at the early stage of sepsis.

Brain-Damaged Patients

A relation between a decreased HRV spectral content and the severity of brain injury as well as neurological outcome has been shown in patient with acute brain injury, including children [19–23]. A negative relationship between HRV and intracranial pressure was suggested in at least one study [21]. Kahraman et al. showed that an "autonomic index" combining HRV and pulse pressure variability was related

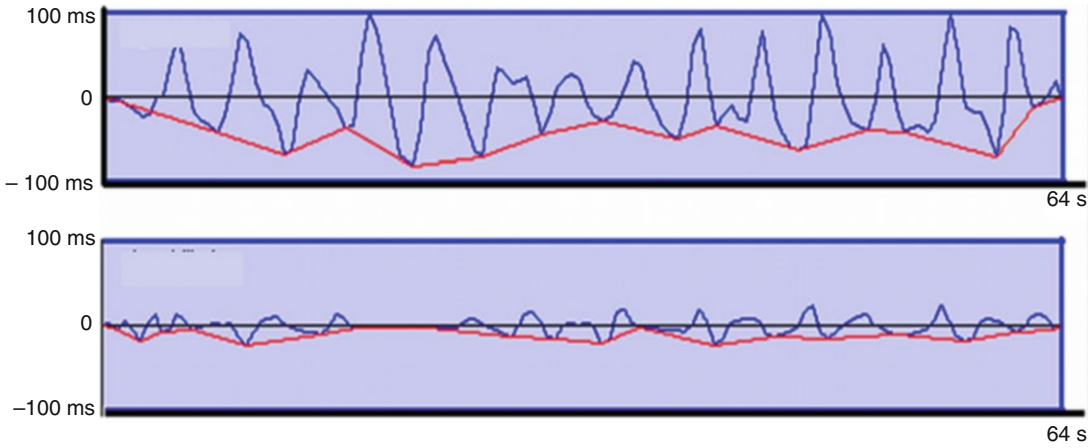

Fig. 13.3 R-R series over a 64-s period in a patient with severe brain injury (upper tachogram) and then at the time of brain death (lower tachogram). Respiratory rate = 15 cycle/min. The series has been band-pass filtered so that the HF compound only appears on the figure. The absolute reduction in HF power is clearly apparent between the two tachograms

to intracranial pressure and cerebral perfusion pressure in traumatic brain-injured patients and could provide useful prognostic information [23]. Finally, brain death is associated with a dramatic reduction of the global spectral power of HRV [20, 24], as shown in Fig. 13.3. This effect seems to predominate on the LF component, thus resulting in a reduction in the LF/HF ratio.

Conclusion

Heart rate variability analysis is feasible in the acute care environment. Acceptance of online monitoring by clinicians may be improved by using more intuitive expression of results, including graphical expression via tachograms. HRV provides reliable information on autonomic nervous system regulation of cardiac activity. By testing autonomic dysfunction, HRV analysis may provide useful information on pathophysiology, disease severity, response to treatment, and early prognosis in the acute care environment [7]. It remains, however, to establish how these techniques are applicable to a particular treated patient.

Conflict of Interest Drs. Tavernier and Jeanne are inventors and the University Hospital of Lille (France) is proprietary in the following patent: "Method for processing a series of cardiac rhythm signals (RR) and the use thereof for analyzing cardiac rhythm variability, in particular for assessing a patient's pain or stress". PCT/FR2005/002056. Dr. Jeanne is a scientific adviser to MetroDoloris (Lille, France) and owns shares of MetroDoloris.

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Preload-Dependent Monitoring

14

Olufunmilayo Ogundele and Michael R. Pinsky

Background

Cardiac preload is the maximum degree of myocardial fiber stretch or tension prior to ventricular contraction and on a cellular level reflects the mean sarcomere length at the end of diastole [1]. Since left ventricular (LV) end-diastolic volume (EDV) approximates this maximal stress, LV EDV is presumed to be synonymous with LV preload. Increases in preload result in a greater force of contraction and thus a larger stroke volume than lower levels of preload, if all else remains constant. This proportional relation between LV EDV and force of contraction is referred to as the Frank-Starling relationship, in deference to the two clinicians who first described this phenomenon over 100 years ago. Although both right ventricular (RV) and LV EDV actually reflect their respective preload, usually LV EDV is presumed to be the primary determinant of cardiac preload. Since LV filling occurs along a diastolic compliance relation, as LV volumes increase, LV distending pressure also increases. Thus, intracardiac pressure is often substituted for EDV as an estimate of cardiac preload. However, the relation between LV volume and distending pressure is not linear even under normal conditions but curvilinear. LV compliance decreases markedly as the LV distends, whereas compliance is high at the start of filling. Furthermore, LV distending pressure is the difference between the pressure inside the LV lumen and pericardial pressure. Since pericardial pressure can independently increase during cardiac tamponade or with marked RV dilation and passively increase if intrathoracic pressure (ITP) increases, knowing intraluminal LV pressure alone makes the estimate of LV EDV and thus preload difficult to measure. Still, from a pragmatic perspective, since LV intraluminal pressure can be estimates as pulmonary artery occlusion pressure (Ppao), Ppao is often taken to reflect LV preload. Accordingly, measures of ventricular filling pressures estimate ventricular EDV which is presumed to reflect ventricular preload.

In the management of patients with cardiovascular insufficiency and circulatory shock, a primary treatment is to increase intravascular volume by fluid resuscitation with the aim of increasing cardiac output by increasing LV preload. Although volume expansion is often the first-line treatment in hemodynamically unstable patients, only 50 % of all patients presenting with circulatory shock respond to fluid administration, as judged by an increase in systolic pressure and/or cardiac output [2]. These data suggest that many hemodynamically unstable patients are not preload responsive. Although the intended goal of fluid resuscitation is to augment cardiac output through the Frank-Starling mechanism, the increase in extravascular volume appears to be effectively only half the time and may also carry with it adverse effects, such as venous pressure

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overload promoting pulmonary and peripheral edema, acute cor pulmonale, and cerebral edema. Therefore, using clinically reliable parameters that identify patients who will respond to volume expansion helps to avoid potential harm to nonresponders.

Traditional static hemodynamic measures, such as central venous pressure (CVP) as an estimate of right ventricular (RV) filling and Ppao as an estimate of LV filling status, have been used for many years to predict a patient's response to fluid administration. However, the robustness of these pressure measures to predict individual patient responses to fluid challenge were never rigorously validated. Recent clinical trials and large meta-analyses of pooled studies clearly document that static measures of either RV or LV preload do not accurately identify those patients who will increase their cardiac output in response to fluid loading [3–7].

Recent technological advances have created bedside monitoring devices that can accurately measure arterial pressure, pulse pressure, and by inference LV stroke volume (SV) on a beat-to-beat basis from arterial waveform analysis. Because these monitors allow beat-to-beat measures of arterial pulse pressure and LV stroke volume, new hemodynamic parameters have evolved, and as will be described below, these new parameters more accurately predict preload responsiveness and can be used to guide fluid therapy in the critically ill. Many studies have shown these arterial pulse pressure and stroke volume variation dynamic parameters to be better predictors of volume response than do static parameters [3–7]. This chapter will cover concepts of preload and preload dependency along with various static and dynamic methods used to determine fluid response.

Preload Dependence

The curvilinear Frank-Starling relationship between preload and SV defines that LV SV increases as LV EDV increases (Fig. 14.1). Under normal conditions as the left ventricle fills at the start of diastole, LV diastolic compliance is low such that LV filling occurs for a minimal increase in LV distending pressure. However, toward the end of normal LV filling, the left ventricle becomes progressively stiffer, such that markedly greater increases in distending pressure are required to induce a lesser increase in EDV. According to the Frank-Starling relationship, the greater the ventricular EDV or cardiac muscle stretch, the greater the force of contraction. However, this relationship too is not linear but curvilinear. With greater distention past a given point, force of contraction

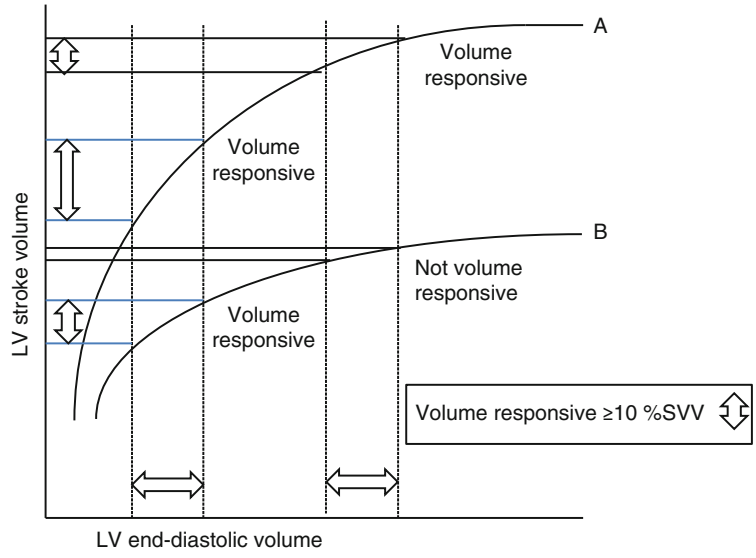

Fig. 14.1 The curvilinear Frank-Starling relationship between preload and SV defines that LV SV increases as LV EDV increases

remains constant. Thus, not only the relation between LV intraluminal pressure and LV EDV is not constant, but the relation between LV EDV and force of contraction is not constant. Once a maximum preload has been reached, further preload increase does not result in significant additional increase in stroke volume. Finally, in disease states and with hypertrophy, the relations between LV EDV and force of contraction vary widely from that seen in normal conditions. Thus, it is not surprising that there is little to no relationship between estimates of filling, such as CVP and Ppao, and ventricular output, such as LV SV and cardiac output.

The relationship between preload and stroke volume depends on the shape and slope of the Frank-Starling curve, which itself is a function of the heart's contractility; ejection pressure and structural issues such as scar and aneurysm dilatations of the LV free wall will increase LV volumes independent of wall stress. Thus, preload dependency describes the heart's capacity to modify stroke volume in response to changes in preload, not the absolute LV volume [8]. Although the force of contraction may increase as LV EDV increases, if the left ventricle is ejecting into a higher arterial pressure, then the LV stroke volume will be less, whereas in a vasodilated state wherein the arterial pressure is lower, LV stroke volume will be higher for the same preload and intrinsic contractility. Thus, analysis of preload responsiveness using only LV stroke volume as the read out may be very misleading, if arterial pressure also changes. For example, phenylephrine decreases cardiac output in non-preload-dependent heart, while it increases cardiac output in preload-dependent hearts despite increasing arterial pressure equally in both patient subsets [9]. A critical analysis performed by Michard et al. revealed that 40–72 % of critically ill patients respond to volume expansion judged by a change in stroke volume. This wide variation suggested that better methods are needed to predict which patients will respond to volume expansion [10].

However, it is important for the bedside clinician to also understand that under normal conditions LV stroke volume and cardiac output usually covary with whole body metabolic demands over a relatively constant preload. This non-preload-dependent cardiac performance is referred to as audiometric autoregulation, or the Anrep effect. Thus, if a patient is given a fluid bolus and they are volume responsive, cardiac output will increase and LV EDV will also transiently increase. But after a few heartbeats, LV EDV will return to its original baseline value, while both stroke volume and cardiac output remain elevated owing to an increased intrinsic contractility. Indeed, the definition of heart failure is that the subject can only increase cardiac output through the Frank-Starling relationship.

Static Parameters

Mechanically Ventilated Patients

Mechanical ventilation has a significant effect on cardiovascular function, which depends on the baseline contractility and intravascular volume status. Importantly, positive-pressure breathing cyclically increases in ITP by forcing the expanding lungs to passively expand the chest wall. This causes CVP to increase proportionally. Since CVP is the back pressure to systemic venous return to the heart, these cyclic increases in CVP cause reciprocal changes in venous return. However, as a static end-expiratory value, CVP is often taken as an estimate of the intravascular state. A low CVP is felt to reflect a low circulating blood volume and a high CVP an expanded blood volume [10–12]. But is that true?

The most commonly used static measure of preload is CVP, usually estimated clinically by transduction of a central venous catheter [13]. However, neither CVP nor Ppao predict a patient's response to fluid challenges [14–16]. A recent meta-analysis examined CVP as a predictor of fluid response, showing a poor correlation ($r=0.18$) with a receiver-operator characteristic (ROC) of 0.56, indicating no discrimitive benefit. That review concluded that CVP should not be used to guide clinical decisions for volume resuscitation [17]. For all the physiological reasons listed above, these findings are not surprising [18].

Both CVP and pulmonary artery pressure can also be estimated using cardiac ultrasound to assess inferior vena caval (IVC) diameter and tricuspid regurgitant jets, respectively. Recent studies suggest that respiratory changes in IVC diameter may be helpful in predicting fluid response in mechanically ventilated patients [19–21]. By exploiting the relationship between CVP and IVC diameter changes during respiration, the CVP can be estimated. In a study of septic patients, IVC diameter decreases of >50 % during inspiration correlated with a CVP <8 mmHg (r=0.74) [22]. The sonographic IVC diameter changes approximate CVP if tricuspid regurgitant flow is minimal [23, 24] and is more accurate than jugular venous distension in assessing CVP [25].

Static volumetric measures are another way to assess preload in mechanically ventilated patients. Transthoracic thermodilution techniques can be used to obtain estimates of global biventricular end-diastolic volume index (GEDVi), which is an evaluation of the biventricular preload. Michard et al. demonstrated that 80 % of preload responders have GEDVi I <600 mL/ m^2, while the percentage of responders with values >800 mL/m^2 is 30 % [26]. GEDVi in the intermediate range does not distinguish volume responders from nonresponders. Computed tomography (CT) methods of estimating GEDVi have not been accurate in estimating preload in a retrospective analysis of critically ill patients [27]. Another static measure obtained from thermodilution technique is the RV EDV index, which is obtained from a pulmonary artery catheter. Values <90 mL/m^2 predict volume response, while values >140 mL/m^2 predict lack of response. However, intermediate values between 90 to 140 mL/m^2 do not distinguish preload responders from nonresponders [28, 29].

Transthoracic and transesophageal echocardiography are reliable ways to measure ventricular end-diastolic area. However, measures of end-diastolic area are poor predictors of volume response. A low LV end-diastolic area (<5 cm^2/m^2) has been identified to be specific for low preload; however, the sensitivity is poor. In the case of RV dilatation or RV impairment, the ratio of RV end-diastolic area/LV end-diastolic area ≥1 identifies cor pulmonale and is a contraindication to volume expansion as a means to increase cardiac output [30].

Spontaneous Breathing Patients

Static parameters have also been shown to be poor predictors of volume response in spontaneously breathing patients mainly related to the general lack of agreement in basal cutoff values for volume responders. Few studies exist that examine CVP measures before and after volume resuscitation in patients breathing spontaneously. Two studies by Schneider et al. and Wagner et al. included a subset of non-ventilated patients reporting a lower baseline CVP value in responders than in nonresponders where individuals with spontaneous breathing represented 33 and 6 %, respectively, of the study population [31, 32]. Though the CVP measures in these studies varied, a very low value (<5 mmHg) effectively predicted volume response in both studies. In the case of Ppao, most studies examining this measure in spontaneously breathing patients have not reported a lower baseline value among fluid responders [33–39]. However, the study by Wegner et al., where 6 % of the study population were spontaneously breathing patients, reported a low baseline Ppao and fluid response [31]. While it is generally accepted that Ppao <7 mmHg is a predictor of preload response to fluids, there is no standard accepted cutoff for the upper limit of nonresponders due to a limited applicability of volume expansion in patients with high filling pressures [10].

Ventricular volume and echocardiographically measured ventricular area have also been examined as estimates of preload in non-ventilated patients. Two studies examined RV end-diastolic index (RVEDVi) in spontaneous breathing patients: an absence of preload response was observed in patients with RVEDVi >140 mL/m^2 and response observed in patients with RVEDVi <90 mL/m^2 [28, 29]. Lamia et al. demonstrated that the LV end-diastolic area calculated from

transthoracic echocardiography cannot discriminate between fluid responders and non-responders. Other measures such as the IVC diameter at the sub-xiphoid window have been examined in spontaneous breathing patients, and values <12 mm was predictive of fluid response while values >20 mm predicted an absence of volume response [2].

Dynamic Parameters

Dynamic measures of fluid responsiveness created by positive-pressure ventilation can predict preload response and are better than static parameters even in patients with different disease conditions [10, 40]. This accuracy of dynamic parameters is made possible by the respiratory cycle's impact on systemic venous return. These small variations in flow that occur with every breath phasically alter RV EDV while in turn phasically alters RV stroke volume if the RV is volume responsive, which then phasically alters LV EDV which in turn alters LV stroke volume if the LV is volume responsive. Thus, measures of LV stroke volume variation (SVV) or the resultant arterial pulse pressure variation (PPV) will identify global volume responsiveness. However, this dynamic phasic interaction creating the SVV and PPV signals can only be used to predict volume responsiveness during positive-pressure breathing and not during spontaneous breathing. This is because spontaneous inspiration by decreasing CVP markedly increases venous return to the right ventricle simultaneously decreasing LV diastolic compliance by the process of ventricular interdependence. Thus, the changes in LV EDV that occur during spontaneous inspiration do so independent of changes in LV wall stress, as actual LV preload remains constant despite changing LV EDV. Such inspiration-associated decreases in LV stroke volume and arterial pulse pressure are referred to as pulsus paradoxus. They identify marked negative swings in ITP, cor pulmonale, and tamponade, but not volume responsiveness [2, 8].

Mechanically Ventilated Patients

The positive pressure generated by mechanical ventilation causes cyclic changes in venous return as described above. After a few beats, this decreased flow reaches the left ventricle decreasing its EDV. If both the right and left ventricles are preload responsive, then positive-pressure breaths will induce dynamic SVV and PPV, the magnitude of which will be proportional to the subject's volume responsiveness and size of the positive-pressure breath. Since beat-to-beat recording of LV stroke volumes is difficult to achieve at the bedside, different stroke volume surrogates that change with the respiratory cycles have been used such as PPV to quantify these beat-to-beat variations. Newer arterial waveform monitoring devices estimate LV stroke volume on a beat-to-beat basis allowing continuous reporting of both PPV and SVV. Commercially available devices include PiCCO (Pulsion Ltd), LiDCO (LiDCO Ltd), Vigileo (Edwards Lifesciences), and MostCare. Most studies using these devices show that a SVV >10 % in a subject being ventilated with a tidal volume of >8 mL/kg is predictive of preload response to volume expansion [40, 41]. Furthermore, since arterial pulse pressure is caused by LV stroke volume, measures of PPV are also predictive of volume responsiveness. Pulse pressure variation >13 % or SVV >10 % in mechanically ventilated patients have been documented to be excellent predictors of volume responsiveness in a wide variety of clinical situations [10, 40, 42–44]. When PPV was examined in patients undergoing acute normovolemic hemodilution, the change in PPV was superior to changes in CVP or Ppao in tracking the changes in blood volume [3]. Another method of assessing volume responsiveness which does not require calculation of PPV is to observe the increase in arterial pulse pressure seen during a 15-s end-expiratory pause maneuver. Monnet et al. examined 34 patients during mechanical ventilatory support in which a 15-s end-expiratory pause was applied. They documented that a 15 ± 15 % increase in arterial pulse pressure predicted a 12 ± 11 % increase in cardiac

index in response to volume loading with a sensitivity of 87 % and a specificity of 100 % [45]. While PPV has a strong predictive value, a recent study has demonstrated that values between 9 to 13 % are inconclusive in patients undergoing general anesthesia [46]. Although SVV, if accurately measured, should be an accurate predictor of preload responsiveness, it is actually estimated from the arterial pulse, thus its accuracy be less. Heijman et al. reevaluated the accuracy of this measure in ICU patients after undergoing cardiac surgery. They reported that SVV was a better functional marker of fluid responsiveness compared to CVP and Ppao [7]. The accuracy of PPV and SVV also seems to be related to the underlying cardiac function of the patients. Both PPV and SVV were examined in patients with RV failure. While increases of CVP, SVV, and PPV were suggestive of RV failure, SVV and PPV failed to predict volume responsiveness in these patients. This suggests that in patients with RV failure, these dynamic measures can assess volume response but do not necessarily predict well in this setting [47].

Ultrasound measures of respiratory variations of IVC diameter also predict volume responsiveness in ventilated patients in shock. During the inspiratory phase of mechanical ventilation, the increased ITP transmits to the right atrium reducing venous return causing IVC dilation. However, during expiration, the decreased ITP increases venous return and decreases IVC diameter which is more pronounced in hypovolemic patients. Several studies in septic patients demonstrated that changes in IVC diameter >12 % or IVC collapsibility index ≥18 % differentiated volume responders from nonresponders [19, 20]. Studies have also looked at the SVC collapsibility index >36 % to have similar sensitivity and sensitivity in identifying volume responders [48, 49].

Besides SVV, PPV, and IVC collapsibility index measures, there are other dynamic parameters based on the same physiologic mechanisms. However, these other indirect measures are less predictive than SVV and PPV. These other parameters derived from arterial pressure analysis include systolic pressure variation (SPV), aortic blood flow velocity recorded via esophageal Doppler ultrasound [50, 51], pressure wave variation by pulse oximetry, aortic flow velocity time [52, 53], and brachial flow variation time [37].

Spontaneous Breathing Patients

Most of the dynamic parameters derived from arterial pressure such as PPV have been validated in mechanically ventilated patients in sinus rhythm. In the last decade, several noninvasive maneuvers have been explored that allow us to adapt these parameters to the non-ventilated patient. These maneuvers have also been explored in spontaneous breathing patients with arrhythmias.

Pulse pressure variation during a Valsalva maneuver has also been examined in non-ventilated patients with reported sensitivities >90 % and specificity of 95 % [37]. The physiology of this test lies in the fact that in spontaneous breathing patients, forced expiration against an occluded airway (i.e., Valsalva maneuver) causes an increase in ITP, which causes a reduction in venous return. These changes translate to a decrease of the arterial pulse pressure. The Valsalva PPV is the difference between the higher pulse pressure during the initial strain phase of Valsalva maneuver and the lowest pulse pressure during release. In a study of 30 patients, Monge et al. reported that a Valsalva PPV >52 % predicted a positive response to fluid administration with a 91 % sensitivity and 95 % decrement, respectively [37].

Another maneuver to increase the sensitivity of dynamic parameters to predict volume responsiveness in spontaneous breathing patients is the increase in arterial pulse pressure with end-expiratory occlusion. Monnet et al. examined this maneuver on 23 spontaneous breathing patients and found that it predicted fluid responsiveness significantly better than respiratory PPV. The reported receiver operating characteristics (ROC) for the effect of occlusion maneuver on PPV and cardiac index, respectively (0.99; 95 % CI, 0.827–1 and 0.971; 95 % CI, 0.796–0.98), were significantly greater than those obtained with

the respiratory variation of pulse pressure and systolic volume (0.679; 95 % CI, 0.45–0.88, and 0.571; 95 % CI, 0.34–0.781) [45].

Both Mechanically Ventilated and Spontaneous Breathing

There are several noninvasive methods of assessing preload response in both mechanically ventilated patients and non-ventilated patients. One simple and reliable method useful in both setting is the hydrostatic challenge induced by a passive leg raising (PLR) maneuver. This maneuver is performed by passively raising both legs to an angle of 45° with respect to the bed for at least 1 min while continuously measuring cardiac output. The PLR maneuver is equivalent to giving a 70-kg patient a transient volume bolus of 300 mL. This maneuver essentially transfers blood from the lower extremities to the intrathoracic vessels causing an increase in intrathoracic blood volume. If the subject is volume responsive, then the PLR will increase cardiac output by at least 10 % [54]. Since this PLR maneuver is temporary, it only identifies those subjects who are volume responsive; it is not a therapy into itself.

Plethysmography wave via pulse oximetry (Pplet) is a noninvasive dynamic parameter that has been studied in ventilated and spontaneous breathing patients. In mechanically ventilated patients, two studies have shown a correlation between PPV and Pplet with sensitivities of 87–100 % and specificities 70–100 %. However, in the setting of spontaneously breathing patients, there's a lack of agreement on Pplet's ability to predict volume response. Delarmee et al. initially reported that Pplet predicted fluid response in patients' in the emergency room in relation to a PLR maneuver [39]. However, their follow-up study 2 years later, using the same PLR maneuver, found no correlation between changes in Pplet during the PLR maneuver and subsequent changes in cardiac index in response to fluid challenge [38]. Further studies are needed to fully characterize the use of Pplet as a predictor of fluid response.

Limitations of Predicting Volume Responsiveness

Volume responsiveness has been defined as ≥15 % increase in cardiac output as a response to a 500-mL fluid challenge. Although, the presence of fluid responsiveness does not necessarily mean that the patient needs fluid nor does it guarantee that it fluids are given cardiac output will increase [55]. In mechanically ventilated patients, the major limitations are the inherent dependence on ventilator-induced changes in intrathoracic pressure great enough to change CVP. Therefore, tidal volumes <6 mL/kg or irregular spontaneous respirations will give false-positive PPV and SVV. Furthermore, these dynamic measures rely on heart rate regularity; therefore, arrhythmias such as atrial fibrillation can render these measures inaccurate. However, the cardiac output response to passive leg raising will perform well in the setting of arrhythmias [56].

While studies have reported high sensitivities and specificities with the PLR maneuver, there are patient specific factors that can limit its usefulness [35]. For example, the PLR maneuver should not simultaneously drop the height of the head below the supine plane or it will raise intracranial pressure. Thus, the use of the PLR may be contraindicated in patients at risk for intracranial hypertension [56, 57]. Other conditions showing reduced efficacy of the PLR maneuver include intra-abdominal compartment syndrome [56, 57], preexisting use of compression stockings, and low-flow states such as hemorrhagic and cardiogenic shock [56, 58, 59].

Lastly, clinicians have empirically given fluid bolus challenges to evaluate a patient's response to volume expansion. However, these boluses are not fluid resuscitation, merely tests to document volume responsiveness. There is solid evidence behind aggressive fluid resuscitation in volume-responsive patients in shock [13, 60]. Volume administration guidelines have been proposed to evaluate early response to fluid therapy in the first 10–20 min of resuscitation based on mean blood pressure and CVP target values [39]. While this has been applied clinically especially in patients where static and dynamic parameters are

non-predictive, the limitation of using probing blind volume challenges is the potential for volume overload in patients with suboptimal cardiac function. Therefore, it may be more efficient to use endpoints of fluid therapy based on the disappearance of preload responsiveness rather than static values of preload in guiding fluid therapy in critically ill patients in shock [61].

Conclusion

Preload-dependent monitoring is an essential part of the resuscitation of critically ill hospitalized patients. Assessment of volume responsiveness coupled to appropriate therapies dramatically improves the care of patients with hemodynamic compromise. However, while both static and dynamic parameters can be useful in mechanically ventilated and spontaneously breathing patients, clinicians must understand the limitations of both methods when used to make clinical resuscitation decisions.

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Monitoring the Microcirculation in Critically Ill Patients

15

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Introduction

Microcirculatory disruptions are one of the main characteristics observed in critically ill patients, especially in patients with severe sepsis. These alterations are characterized by an increase in microvascular perfusion heterogeneity. Handheld video microscopy has been extensively used to clinically monitor and quantify perfusion abnormalities associated with the microcirculation. However, despite growing evidence of the association between microcirculatory perfusion abnormalities and poor outcomes [1–3], guiding resuscitation using these techniques remains a major challenge. It is anticipated that more complete and personalized treatments based on resuscitation of the microcirculation will improve patient outcomes in the near future as technology related to bedside microcirculatory monitoring progresses.

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Historical Background

Much has been achieved since William Harvey (1578–1657) did pioneering work on blood circulation in the 1600s. After almost a century, Stephen Hales (1677–1761) was able to measure blood pressure from a horse blood vessel by connecting a pipe to a long glass tube and measuring the height at which the animal's blood moved up into the tube. Thereafter, Vierordt described the principles of the sphygmograph, and more than 25 years later, Samuel Siegfried Karl Ritter von Basch invented the sphygmomanometer which was modernized and perfected by Riva-Rocci and became the apparatus we know today. It was not widely used in clinical practice until the twentieth century, when Harvey Cushing popularized its use [4].

Despite the value of patient hemodynamic monitoring, it is most important to understand the underlying pathophysiology related to the causative disease so that affective therapy can be initiated. There has been much discussion about the respective value offered by different hemodynamic modalities ranging from peripheral temperature monitoring to the effects of Swan-Ganz catheter utilization on mortality. There is some progress in this area, as demonstrated by the implementation of treatment bundles driven

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by the surviving sepsis campaign, in which monitoring response to treatment strategies in severe sepsis and septic shock has shown dramatically improved survival rates. However, despite achieving stable macrohemodynamic conditions, many critically ill patients still die from (multi-) organ failure. Several mechanisms may contribute to this phenomenon, among which is the persistent disturbance of the microcirculation and thus perfusion of tissues. This dissociation between the macro- and microcirculation has been demonstrated especially in sepsis by several authors [5, 6] and remains a subject of intense investigation.

Different techniques have been used to assess the microcirculation of critically ill patients at the bedside. These include nailfold video capillaroscopy, orthogonal polarization spectral (OPS) imaging [7], near-infrared spectroscopy (NIRS) [8], and sidestream dark-field (SDF) imaging [9]. In this chapter, we will discuss several techniques for evaluating the microcirculation and how translational data obtained from clinical studies using these techniques have advanced our knowledge concerning the pathophysiology of critical illness at the bedside.

Tools for the Assessment of the Microcirculation

Patient physical examinations have always been the first and most important method for identifying changes in regional perfusion as clinical signs such as a difference between core and toe temperature or the cold knee tactile approach (Marik's sign) [10–12] have historically been associated with these alterations. However, since the skin is an organ with independent mechanisms of regulation, it is not always a good indicator of the function of more vital organs [13]. Thus, the development of handheld video microscopes with which the microcirculation of clinically more relevant locations has provided clinicians with the ability to study changes in the microcirculation in humans with great detail.

Perfusion and Hypoxia Measurement Techniques

Laser Doppler Imaging

Laser Doppler flow measurements provide a two-dimensional visualization of microcirculation flow status by means of the analysis of reflected changes in laser light traveling into a tissue. Laser Doppler flowmetry (LDF) is a noninvasive method to measure blood flow on tissue surface. The technique is based on measuring the Doppler shift induced by moving red blood cells (RBCs) with respect to the illuminating coherent light. Single-point LDF (or laser Doppler perfusion monitor) is limited to small areas reflecting single-point measurements and usually requires multiple measurements in the same region of interest (ROI). This technique has been shown to identify blunted hyperemic response in septic patients [14]. Other existing techniques based on the laser Doppler principle are laser Doppler perfusion imaging, which can measure flow in a large tissue area by scanning the laser beam over the desired ROI. This type of technique has been used in areas such as in ophthalmology, dermatology, neurosurgery, and also in critically ill patients. This technique, however, lacks temporal sensitivity making its use for assessing reactive hyperemia limited. In the critical care setting, LDF was used to assess cutaneous perfusion of the foot during arterial cannulation in critically ill patients treated with adrenergic agents, demonstrating that, despite the vasoactive drugs, the presence of the femoral catheter did not appear to reduce blood supply to the skin. Other applications of this technique have included the assessment of anastomotic perfusion during colonic surgery [15, 16]. More recently laser speckle imaging (LSI) has been validated to reflect capillary blood flow and has a higher temporal sensitivity than laser Doppler imaging [17, 18] systems. However, similar to nailfold capillaroscopy, these techniques are sensitive to subtle changes in skin perfusion due to temperature variations. Laser speckle imaging allows more rapid evaluation of perfusion images of organ surfaces [18].

Near-Infrared Spectroscopy

Introduced in the 1970s, the NIRS technique uses the near-infrared region of the electromagnetic spectrum ranging between 700 and 2,500 nm (in clinical practice, 700–850 nm) to determine local tissue oxygen saturation [8]. The principle of clinical NIRS is to noninvasively measure the attenuation of light by hemoglobin differentiating between oxy- and deoxyhemoglobin [19] utilizing a narrower spectrum of wavelengths than pulse oximetry (which penetrates deeper into the tissue and is not dependent on pulsatile wave). The NIRS system consists of a probe that is placed on the skin of a determined area of interest (i.e., abdomen for mesentery, forehead for cerebral, and lower back for renal) and a monitor with electronic hardware to read the signals relayed by the probe and tissue (see Chap. 28). Each probe consists of a light source and, usually, two photodetectors to measure tissue oxygen levels at superficial and deeper tissue depths. The emitted photons, not absorbed by tissues, are returned to the photodetector following Lambert-Beer law. By measuring the difference between deep and surface path of returned light, NIRS values represent the amount of spectral absorption that occurs in the tissue vascular bed. This measurement represents the average of arterial, venous, and capillary oxygenation at the tissue level.

NIRS has been tested in different anatomical locations and has generated a substantial amount of clinical information in the intensive care setting through its application on the thenar eminence. This location has relatively thin fat tissue over the muscle, providing the best possible target for muscle tissue oxygen saturation (StO_2) measurements even in obese and critically ill patients [20]. However, the StO_2 value represents an average of tissue oxygenation, with approximately 75–80 % of the signal originating from venous return in the microcirculatory network [21]. Provided this given information and the limited utility of continuous StO_2 that could be very stable during very different microcirculatory and clinical conditions, measurements occluding the arterial blood flow to the thenar eminence are performed to assess oxygen tissue dynamics. A vascular occlusion test (VOT) is of special interest in septic shock [22, 23] patients as the rate of desaturation and re-saturation of the StO_2 in thenar eminence has revealed possible prognostic implications [24].

Optical Methods for Microcirculation Assessment

Intravital Microscopy (IVM)

By the end of the sixteenth century, Zacharias Jansen invented the compound microscope, which led to intravital microscopy. Marcello Malpighi was the first to apply physiological imaging of capillaries in the lung in 1661, thereby identifying the vascular conduits linking arterial and venous blood vessels that eluded William Harvey. However, despite many discoveries and technique improvements, eighteenth-century researchers considered these microscopes unreliable since the lenses were primitive creating artifacts and distortions. It was not until compound achromatic lenses were introduced in the 1830s that microscopy became widely adopted as a research tool. In 1839 R. Wagner reported, by means of IVM, leukocyte rolling and actual tissue microcirculation for the first time [25, 26]. In the early 1900s, the technique of nailfold capillaroscopy was developed and used to monitor the nailfold capillary bed. In 1971 Sherman et al. introduced incident dark-field (IDF) illumination technique for IVM that allowed the observation of the microcirculation in tissue surfaces without the need to transilluminate the preparation [27]. Slaaf and coworkers later implemented a different approach by applying cross-polarization for filtering out surface reflections of incident illumination, allowing observation of the microcirculation of tissue surfaces [28]. These techniques were utilized later on and incorporated into handheld microscopes for bedside vital microscopy [29].

Orthogonal Polarization Spectral (OPS) Imaging

Based on the technique of Slaaf and coworkers [28], in 1999, the first-generation handheld

bedside imaging instruments based on OPS imaging were introduced for clinical applications. OPS imaging operates by epi-illuminating the tissue with polarized green light (548 nm wavelength) that is absorbed by the (de-) oxyhemoglobin-containing RBCs in the capillaries [7, 28]. Backscattered depolarized light is captured by a CCD camera after it passes an analyzer oriented in a plane precisely orthogonal to the illumination light path, blocking the not depolarized light reflected by tissue surface. Eliminating the reflected surface light and imaging only the backscattered light, subsurface microcirculatory structures can be observed in great detail (RBCs are visualized as dark circulating bodies on a light background). These optical systems were incorporated into portable handheld video microscopes and enabled imaging of the microcirculation of the brain during surgery for the first time in humans [30]. OPS imaging was later validated against conventional capillaroscopy, the gold standard in microcirculation assessment techniques [31].

Sidestream Dark-Field (SDF) Imaging

The second-generation of bedside imaging modalities utilized dark-field imaging introduced earlier by Sherman and Cook and was referred to as SDF imaging [32]. The SDF imaging instrument employs a central probe equipped with green light-emitting diodes (LEDs) at the outer circumference of its probe tip. This allows for an independent passage for light through the lens system while optically isolated from the illuminating outer ring, preventing tissue surface reflections. Light from the illuminating outer core of the SDF imaging probe also uses green light as the other devices used previously and was chosen to correspond to an isosbestic point in the absorption spectra of (de-) oxyhemoglobin. SDF imaging has led to many new studies being performed and has the added benefit of low-power LED illumination [33], enabling portable operation for ambulatory and onsite applications, where high mobility is of great necessity.

Microcirculatory Image Acquisition Technique Using OPS and SDF Imaging

The SDF and OPS imaging probes are fitted with a ×5 objective lens system. The OPS system requires an external power source, whereas the SDF device is powered by battery. Both are based on analogue video cameras and can be directly connected to a television monitor. For computer imaging however the output has to be digitalized to give a suitable output for computers. Focus of these devices is accomplished by hand by adjusting a dial situated in extension of the microscope body. A protective sterile disposable plastic cap is securely attached around the probe prior to imaging in patients. For the acquisition of images, illumination intensity must be adjusted by the user and can be a source of variation between users and introduce user-dependent errors [34]. For measurements, the probe must be positioned exactly perpendicularly on the tissue surface, while alterations in microcirculation must be avoided by eliminating pressure-induced artifacts due to the weight of the devices and/or by active pressure exerted by the user. Pressure on the microvasculature impedes the flow of RBCs and is referred to as a pressure artifact. While recording data, gently pulling the probe back until contact is lost and then slowly advancing to the point at which contact is regained with the microcirculation in proper focus is the best methodology to achieve pressure-free measurements.

Main Concepts of Microcirculation Assessment

The perfusion of a given tissue is dependent on the number and distribution of the capillaries and the blood flow. There are two main principles that summarize how oxygen reaches the tissues from the microcirculation and define the main microcirculatory functional parameters obtained from microcirculatory images. One is convection, based on RBC flow, and the other is diffusion, the distance O_2 must travel from the red blood cells in the capillaries to the parenchymal cells. Convection is

quantified by measurement of flow in the different size microvessels, and diffusion quantifies density of perfused microvessels, referred to as perfused vessel density (PVD). In the absence of online quantitative analysis, convection has been quantified by the so-called microvascular flow index (MFI), introduced by Boerma and coworkers. The score is based on determination of the average or the predominant flow type in four quadrants in the field of view and is defined as either being absent (0), intermittent (1), sluggish (2), or normal (3) [35] and total or perfused vessel densities (TVD or PVD, expressed as mm/mm^2), respectively. To determine the MFI, microcirculatory videos are divided into four quadrants in which blood flow assessments are categorized based on vessel diameters: small (10–25 μm), medium (26–50 μm), and large (51–100 μm). Subsequently, the flow properties of each vessel type are scored to represent information about each vessel type separately in a quadrant defined by two grid line crossings exactly at the *x*- and *y*-axis. PVD is defined as the total length of perfused capillaries per area and is usually performed using offline computer-assisted video analysis software. In other tissues where outer layers of epithelium are thicker and the microvasculature are composed of hairpin-shaped capillary loop patterns (e.g., buccal, labial, gingival mucosa, and nailfold), capillary density (i.e., total capillary density [TCD] and functional capillary density [FCD] expressed as cpll/mm^2) can be quantified as the number of repetitive structures per observation area, thus facilitating quantification of vascular densities without specialized software.

Measuring the total length of vascular networks (i.e., TVD and PVD) in the area of interest is time-consuming, even with the aid of software; for this reason, a semiquantitative method of measuring a proportion of perfused vessels was devised by De Backer and coworkers [5]. The De Backer scoring method is based on the principle that the density of the vessels in a given area is proportional to the total number of vessels crossing an arbitrary grid with three equidistant horizontal and vertical lines. The currently available software package (AVA version 3.02) [33] draws and superimposes a size-adapted grid onto stabilized video sequence (can also be performed manually); a computation of microvascular density is then calculated as the number of vessels crossing the lines divided by the total length of the grid lines [5]. Although software helps in these analyses, it is time-consuming, and attempts have been made to develop automated software [33]. The newly introduced computer-controlled imaging sensor devices based on incident dark-field imaging [27, 29, 36] should allow more automated analysis.

Using vessel density and flow characteristics, a proportion of perfused vessels (PPV [%]) can be calculated using the following formula: 100 • (total number of vessels − [no flow + intermittent flow])/total number of vessels. The perfusion heterogeneity of tissues is another parameter for identifying the oxygen-extracting capabilities of the tissue embedding the microcirculation [37] and is increased in humans during septic shock [5]. For that reason, a flow heterogeneity index (Het Index) – derived from previous calculated MFI – was introduced and defined as the highest site flow velocity minus the lowest site flow velocity and divided by the mean flow velocity across five sublingual sites [6]. To summarize the above defined parameters, PVD accounts for the most variables involved in tissue perfusion; defined in practical sense as the functional vascular density parameter, it is essential in computing the PPV in any tissue, which gives a general impression of microvascular density and its functionality. A drawback, however, is that RBC velocities cannot be accounted for in continuously perfused capillaries and still relies on visual (subjective) evaluation. MFI scoring is relatively simple to perform but does not provide any information on the vessel density and is a discontinuous variable (i.e., that a change from 1 to 0 might have different implications than say a change from 2 to 1); this complicates the interpretation of the MFI score. In 2007, a unified consensus for the assessment of microcirculation was published [38].

Microcirculatory Alterations in Critically Ill Patients

In 2002, De Backer et al. demonstrated a decreased capillary density and a reduced

proportion of perfused capillaries in 50 patients with severe sepsis and septic shock compared to healthy volunteers or ICU control patients using OPS imaging [5]. In the septic patients' group, heterogeneity of blood flow was also increased, a key characteristic of sepsis as was shown in many subsequent studies of the septic microcirculation. All these changes were unrelated to conventional hemodynamic or oxygenation parameters and were more severe in non-survivors than in survivors [1]. These data have been confirmed by Trzeciak et al. [6] and also were demonstrated at early stages of sepsis using SDF imaging by Spanos et al. [39], recently by De Backer et al. in a large cohort of patients [1], as well as by us in pediatric intensive care patients [2].

Trzeciak et al. investigated early sublingual microcirculatory perfusion derangements in patients with severe sepsis and septic shock. They semi-quantified the MFI in five imaged sites and calculated flow Het Index. Septic patients had more heterogeneous blood flow when compared to a control group. The results from that study showed that non-surviving patients had a more heterogeneous flow distribution than surviving patients. In another study, Sakr et al. [40] reported that the persistence of microcirculatory disturbances even in resuscitated shock was a determinant of mortality (i.e., quantified microcirculatory parameters improved rapidly in septic shock survivors but not in non-survivors). Moreover, multi-organ failure (MOF) and death were higher in patients with enduring microcirculatory disruption, despite similarities in all macrohemodynamic and oxygenation variables between their patient groups. The authors concluded that improvement in microvascular perfusion, as early as 24 h after the onset of shock, can be a good predictor of ICU mortality.

Next to sepsis and septic shock, microcirculatory derangements have also been reported in cardiogenic shock and cardiac surgery patients. In 2004 De Backer and coworkers described the derangements that take place in patients with heart failure. They found that the proportion of perfused vessels was significantly lower in heart failure patients and also that these alterations were poorest in patients that did not survive [41]. More recently, a reduction in MFI was also demonstrated in acute decompensated chronic heart failure patients [42]. Microcirculatory alterations also appear in patients undergoing cardiac surgery. Bauer et al. [43] reported that FCD (in this case, equal to PVD as assessed by OPS imaging) was marginally reduced during cardiopulmonary bypass (CPB) in cardiac surgery and returned to baseline after discontinuation of extracorporeal circulatory support. These reported changes are thought to correlate with temperature and hemoglobin concentration. Similarly, using SDF imaging, den Uil et al. [44] performed sublingual measurements during elective coronary artery bypass grafting with CPB and reported that decreases in MFI occurred irrespective of changes in macrohemodynamics, and as previously described, these changes returned to normal once the CPB was discontinued.

So far, research and clinical findings suggest a role of the microcirculation in predicting patient outcome and monitoring of therapeutic interventions. Many studies have been conducted relating to this issue, including the study of the effects of vasopressors, fluids, and blood transfusion in critically ill patients [45–47]. In patients with severe sepsis undergoing early goal-directed therapy, vascular expansion either by fluid administration or passive leg rising within the first 24 h of sepsis is associated with increased sublingual microvascular perfusion [48, 49]. For example, norepinephrine is used in the treatment strategies for septic patients. In one study, increasing the dose of norepinephrine revealed no significant changes in preexisting abnormalities of sublingual microvascular flow, despite an increase in global oxygen delivery, cutaneous microvascular flow by means of LDF, and tissue oxygenation [50]. Similarly, Dubin et al. reported a trend towards a decreased in vessel density with unchanged MFI or percentage of perfused vessels in different vessel types as mean arterial pressure (MAP) values were raised by

means of norepinephrine in septic shock patients. They described an inverse correlation between the baseline level of the sublingual microcirculation state and the microcirculatory response to the increase in MAP [51]. Furthermore, Dubin and coworkers reported a high heterogeneity with respect to the underlying state of the microcirculation, depicting improvements in patients with worst microcirculatory pattern at baseline or lack of change or even worsening of the microcirculation in patients with an initially better preserved microcirculation when MAP was increased. In another investigation, restoring MAP with norepinephrine demonstrated that ileal microcirculation and mucosal acidosis remained unchanged in a study performed in sheep [52]. Another vasoconstrictor commonly used is phenylephrine. A study demonstrated that phenylephrine may decrease microcirculatory blood flow in the sublingual microcirculation due to microvascular blood flow shunting [53].

When oxygen transport and oxygen consumption are distorted in septic patients, blood transfusion is also one of the strategies that helps in the reversal of this imbalance. However, in one study in septic patients, blood transfusions only changed microcirculatory parameters in patients with already disrupted capillary perfusion prior to the transfusion [47]. Weinberg et al. found similar findings in trauma patients following RBC transfusion [54]. Importantly, blood transfusion demonstrated beneficial effects in cardiac surgery improving FCD (i.e., PVD) and tissue oxygenation but without changing MFI [55]. Similar to RBC transfusion, dobutamine has improved, but not restored, microcirculatory parameters irrespective of macrohemodynamics. This may have been due to a direct effect given that results showed no correlation with cardiac output [56]. Interestingly, despite the beliefs that vasodilatory drugs could be used to improve the microcirculation, negligible to no effects have been found. Although preliminary research showed that the use of vasodilating drugs, such as nitroglycerine, could be beneficial in septic shock [57], in a randomized, controlled trial with 70 septic shock patients, nitroglycerin after standard resuscitation had no effect on the microcirculation [58].

Future Perspectives for Clinical Utilization of Bedside Microcirculatory Diagnostics and Guiding of Therapy

Although OPS and SDF imaging have provided important insights into the microcirculation, several technical limitations, the main one of which is the inability to online analyze microcirculatory images for immediate diagnosis and titrating therapy, which have hampered the integration of microcirculatory microscopy into the routine clinical monitoring environment [59]. Current OPS and SDF imaging devices can be regarded as first- and second-generation devices, respectively, employing relatively low-resolution analogue camera technology and requiring recording and offline analysis for image quantification limiting the use of these devices for guiding therapy and clinical utility.

At present, a novel lightweight third-generation computer-controlled imaging sensor-based handheld microscope, the CytoCam, incorporating incident dark-field imaging [27] has been clinically introduced [29, 36]. Due to the high resolution of the imaging sensor and new optics, it provides superior imaging modality and over twice the size of the field of view for more comprehensive clinical observation of the microcirculation (Fig. 15.1). Its short-pulse illumination and exposure times and computer control allow immediate analysis of the flow pattern of the microcirculatory images. The new device further features motorized focusing with a depth control and measurement at the micrometer level [36]. This allows, once the focus depth of the patient has been determined, repeated measurements to be made without the need to adjust focus in subsequent measurements reducing the measurement time significantly.

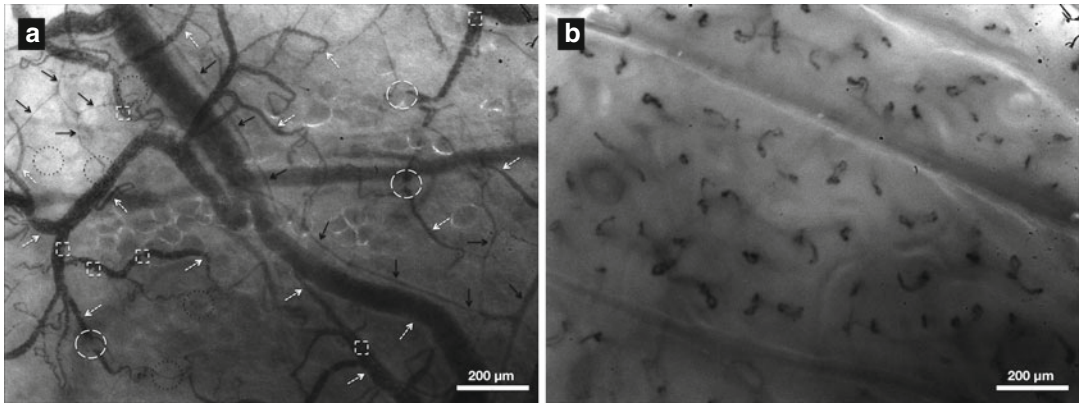

Fig. 15.1 The CytoCam. With a field of view over twice the size of previous vital imaging instruments, enhanced high-resolution images with new optics provide superior quality for a more comprehensive clinical observation and identification of microcirculatory elements. Panel (**a**) illustrates a typical image of sublingual mucosa (i.e., floor of the mouth) microcirculation in a healthy volunteer, detailed observation of arterioles (*black arrows*), capillaries (*black dotted circles*), venules (*white dashed circles*), leukocytes (*small white dashed squares*), and plasma gaps (*white dashed circles*) can easily be identified. Panel (**b**) illustrates for the first time high-resolution images of the cutaneous microcirculation

Conclusion

An increasing body of evidence exists emphasizing that microcirculatory alterations are associated with morbidity and mortality in a wide array of clinical scenarios. This includes patients in whom high mortality rates still persist, even after optimization of macrohemodynamics. Consequently, rather than limiting therapy to macrocirculatory targets exclusively, microcirculatory targets might be incorporated to potentially reduce mortality rates in critically ill patients. At present, clinical studies do not yet exist due to the unavailability of bedside technology for scoring microvascular density and perfusion in real time. Recent technological advances in microcirculatory image acquisition and analysis should provide a platform enabling microcirculation-targeted resuscitation by providing instant clinical feedback on the efficacy of the applied therapeutic strategies at the microcirculatory level.

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Hemodynamic Monitoring During Cardiopulmonary Bypass

16

Jason D. Kennedy, Robert J. Deegan, and Julian S. Bick

Introduction

Cardiopulmonary bypass (CPB) involves diverting the blood flow from the right atrium thru an oxygenator and then to the aorta bypassing the heart and lungs in order to provide for a bloodless surgical field as shown in Fig. 16.1 [1]. Monitoring the hemodynamics during CPB seems a simple task, but since normal parameters may not apply to these patients, who usually have non-pulsatile flow or minimally pulsatile flow, ensuring optimal hemodynamics can in fact be very challenging.

Principles of Cardiopulmonary Bypass

When monitoring hemodynamics during CPB, there are some key issues that need to be considered. First, the purpose of hemodynamic monitoring is to ensure adequate end-organ perfusion during the period of CPB. It is common practice in medicine to measure pressures and assume flows. During CPB, the perfusionist starts the pump at a given flow dependent upon patient body surface area and the current temperature. The vast majority of CPB in the United States is instituted utilizing non-pulsatile flow with either a roller pump or a centrifugal pump (Table 16.1) [1]. Regardless of the type of pump used, adequate flow is primarily dependent upon venous drainage (i.e., pump preload). If there is inadequate venous drainage, the CPB pump will have an inadequate volume to reach the set flow rate. Full CPB is dependent upon fully diverting blood from the heart and not allowing it to eject blood from either the right or left side. It is also important to remember that flow from centrifugal pumps is also very afterload dependent. Therefore, with excessive afterload, flows will be difficult to achieve without an excessively high ABP and line pressure. Understanding these principals is the key to implementing and understanding monitoring issues during CPB.

Arterial Pressure Monitoring During CPB

The most frequently utilized monitor during CPB is the arterial blood pressure. During CPB the use of invasive arterial blood pressure (ABP) monitoring is mandatory because noninvasive blood pressure monitoring is not accurate [1–5].

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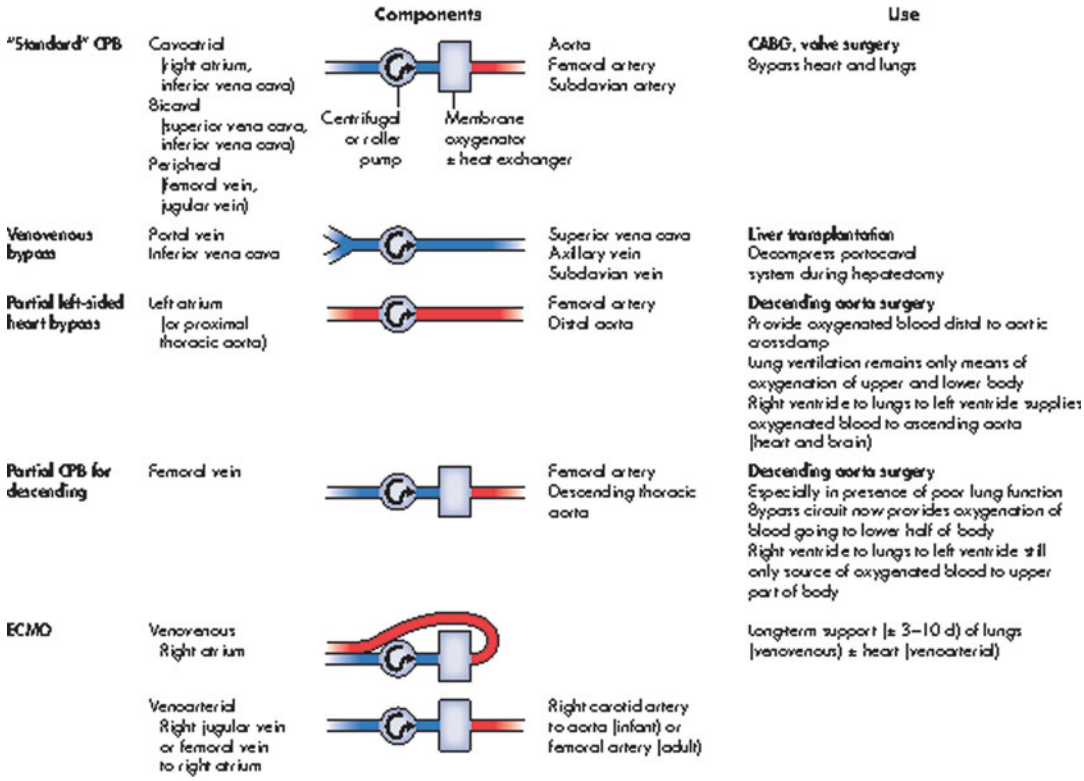

Fig. 16.1 Cardiopulmonary bypass: types of extracorporeal circulation. Venovenous bypass is used to decompress the portocaval system during hepatectomy in liver transplantation surgery. Blood from the portal vein and inferior vena cava (IVC) is moved by a centrifugal pump to a vein in the upper body that drains into the superior vena cava (SVC). Partial left heart bypass may be used during descending aorta surgery to provide oxygenated blood distal to the aortic cross-clamp. Oxygenated blood from the left atrium (LA) is moved by a centrifugal pump to the femoral artery. Partial cardiopulmonary bypass (*CPB*) for descending aorta surgery may use the femoral vein and either the femoral artery or descending thoracic aorta as sites of cannulation and a centrifugal pump and oxygenator. Extracorporeal membrane oxygenation (*ECMO*) may be used for long-term support of the lungs and heart. In venovenous ECMO, blood is moved thru a centrifugal pump and an oxygenator then back to the patient. Deoxygenated blood is removed from the SVC/right atrium (RA), oxygenated, and then pumped back into the SVC/RA. In venoarterial ECMO, blood is moved thru a centrifugal pump and an oxygenator and back to the patient. Deoxygenated blood is removed from the SVC/RA, oxygenated, and then pumped via the carotid (infants), femoral (adults), or ascending aorta (during thoracotomy). *CABG* coronary artery bypass graft (Reproduced from Schell et al. [63]; kind permission from Springer Science + Business Media B.V.)

Several considerations regarding ABP merit attention during CPB. These include optimal site of measurement, discrepancy in MAP at different sites, optimal MAP during CPB, and relationship between MAP and flows.

Radial Artery Monitoring

The most commonly used site for ABP is the radial artery [6, 7]. The radial artery is easily cannulated with a low rate of complication. The hand has collateral blood flow via the ulnar artery, and this allows for continued blood flow in instances of radial occlusion [10, 11]. In the past, the Allen test was performed to ensure adequate collateralization prior to cannulation; however, several studies have shown that the Allen test has poor positive and negative predictability in regard to ischemic complications [8, 9]. Hence, the practice of performing the Allen test has been abandoned. Alternative and routinely used sites

Table 16.1 Cardiopulmonary bypass: centrifugal versus roller pumps

Factors	Centrifugal pump	Roller pump
Afterload	Dependent	Independent
Occlusive	No	Yes
Risk of air embolism	↑	↓
Expense	$$	$
Priming volume	Greater	Less
Generate pulsatile flow	Poor	Better
Excessive arterial line pressure	Not possible	Possible
Reverse flow possible	Yes	No
Can hand crank	Yes	Yes
Trauma to bypass tubing	Less	Greater
Trauma to blood	?Less	?Greater
Superior outcome	?Better	?
Inflammatory response	More (controversial)	

Adapted from Schell et al. [63]

for arterial blood pressure monitoring include the axillary, brachial, and femoral arteries.

It is well described after CPB, especially when hypothermia has been induced, that there is a substantial discordance between MAP measured at the radial artery compared to more central sites such as the aorta and femoral artery [11–16]. This discrepancy can last for several hours after the return to euthermia. This can lead to erroneous treatment with vasoconstrictors or fluids. Therefore, due to this discrepancy, many centers choose to monitor more central locations such as femoral, brachial, and the axillary arteries.

Femoral Artery Monitoring

Femoral arterial blood pressure is a very accurate surrogate of central aortic blood pressure after CPB [17]. Considerations unique to femoral ABP monitoring include infection, mobility limitation after extubation, and retroperitoneal hematoma. Given these issues, alternative sites for ABP monitoring may be desirable.

Brachial Artery Monitoring

In order to overcome some of the concerns for inaccurate measurements from the radial site and limitations of the femoral site, some centers routinely cannulate the brachial artery for ABP during CPB. Given that the brachial artery is an end artery without significant collaterals, there has been concern that cannulation for ABP may entail an unacceptable risk for forearm ischemic complications [20, 21]. However, multiple studies have demonstrated a complication rate similar to radial arterial cannulation after percutaneous brachial cannulation [18, 19, 22–24]. Other than thrombosis of the artery, consideration for median nerve praxia should be considered. This is usually transient and manifests as dysesthesia and not loss of motor or sensory function. Brachial arterial cannulation is routine practice at several large cardiac centers as the primary site of cannulation for any patient undergoing CPB [18, 19].

Axillary Artery Monitoring

Use of the axillary artery is considered as a safer site of cannulation for ABP monitoring by some as compared to the brachial artery due to the anatomic collaterals present around this site. Several studies have shown complication rates to be comparable between radial, axillary, and radial sites [18, 19]. Some of the limitations and concerns when monitoring an ABP is that with adduction and tucking of the arms, the tracings and measured pressures can be dampened and may not reflect the blood pressure accurately. Another significant concern is that especially from the right side, the tip of the catheter lies immediately

adjacent to the takeoff of the vertebral arteries and that flushing of the arterial line can lead to embolization to the posterior circulation. Resulting neurologic defects would be subtle and may not be picked up on most standard neurologic exams. The incidence of neurologic complications from axillary arterial lines has not been studied, though there are studies that demonstrate that there is demonstrable retrograde flow in the carotids from excessively vigorous flushing of a radial arterial line.

Mean Arterial Pressure Goals During CPB

Optimal mean arterial blood pressure (MAP) during CPB is a very contentious and highly debated subject. Even with over 50 years of experience with CPB, and multiple studies, there is still not a consensus as to what constitutes ideal blood pressure management during CPB [25]. During CPB, flow is the control, or independent variable, and blood pressure is dependent upon flow and resistance of the vascular system.

Based upon older data and the notion that all patients maintain cerebral autoregulation and blood flow down to mean arterial pressures (MAPs) of 50 mmHg [61, 62], many centers have traditionally maintained MAPs of 50 mmHg. More recent data from Gold and Hartman have demonstrated that MAPs of at least 70 mmHg were associated with improved outcomes as compared to when MAPs were maintained at 50 mmHg (average of 52 mmHg) [26, 27]. This may be due to microvascular disease that is prominent in the diabetic patient. More recently, a study comparing patients at high risk for renal injury demonstrated that at MAPs of less than 70 mmHg, there was significantly increased incidence of acute kidney injury. Kanji and colleagues demonstrated that when MAPs deviated by more than 26 mmHg, the incidence of acute kidney injury was almost threefold [29].

Despite advances in knowledge, there continues to be considerable debate and heterogeneity in practice regarding MAP management during CPB. In practice, in many low-risk patients without preexisting hypertension or significant cerebrovascular disease, MAPs as low as 50 are well tolerated. Patients who are chronically hypertensive have significant renal dysfunction and carotid vascular disease, and those over 70 may benefit from higher MAPs. With this in mind, the MAP and CPB flows should ideally be titrated to each patient dependent upon comorbidities and monitoring of end-organ oxygenation [25, 28].

Measuring Blood Flow During CPB

Blood flow during CPB is a variable that is controlled by the perfusionist but needs to be monitored by the anesthesiologist to ensure adequate flows as shown in Fig. 16.2. As stated above, CPB flows and MAPs have to be considered together when assessing adequacy of perfusion while on CPB. Modern CPB machines that use roller pumps calculate flows based upon RPM of the pump head and tubing diameter. Therefore flow is usually not directly measured using these pumps. Flow from centrifugal pumps is not only preload but also very afterload dependent. Therefore, at a given RPM, the flow can change dependent upon the resistance characteristics of the CPB tubing, cannulae, and patient's SVR. When using a centrifugal pump, the flows must be measured [32, 33].

There are currently two primary methods of doing this: *ultrasonic measurement* and *electromagnetic flow devices*. Electromagnetic devices rely on blood-contacting electrodes that serve as possible break points in the circuit (with the possibility of air entrainment). The ultrasonic technique is more common and uses Doppler to calculate flow velocity because they do not rely on contact with the fluid that is being measured but will instead wrap around the pump tubing. The velocity time integral (area under the curve when velocity is plotted against time) is used along with the tubing diameter to give a pump flow. This is the same method used to calculate cardiac output using esophageal Doppler or via cardiac ultrasound [31, 33]. Ultrasonic flow meters measure peak flows and will assume a parabolic

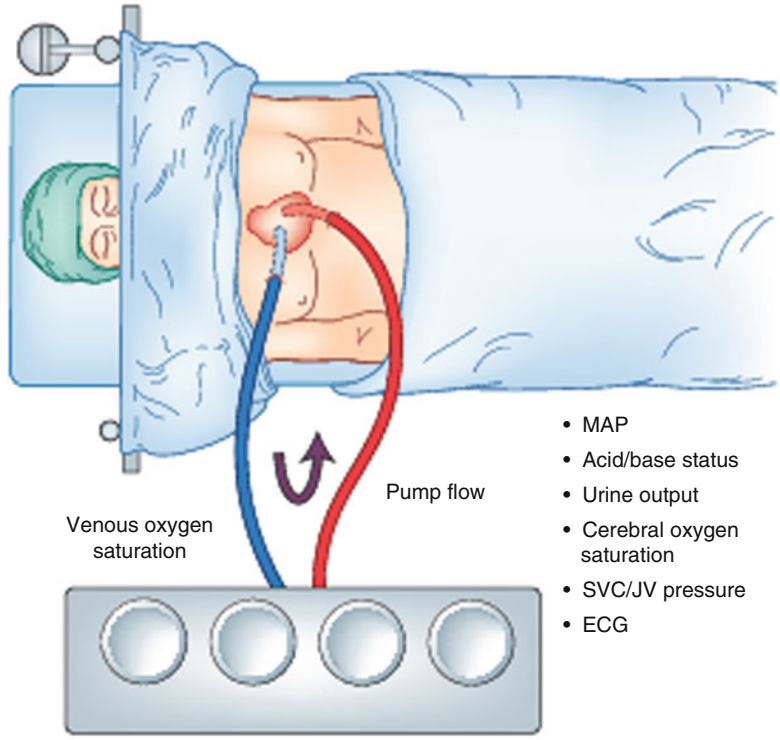

Fig. 16.2 Cardiopulmonary bypass: perfusion monitoring. Monitoring cardiopulmonary bypass (CPB) perfusion. The adequacy of CPB perfusion is globally assessed in the patient (by mean arterial pressure [*MAP*] and arterial blood gas [ABG] analysis) and the pump (by pump flow [L/min] and venous saturation on in-line blood gas monitor/ABG). Regional perfusion is estimated by urine output and possibly by cerebral oxygen saturation. However, urine output is a relatively unreliable method of monitoring regional organ perfusion during CPB. Superior vena cava (*SVC*)/jugular venous (*JV*) pressure should be monitored during CPB. An increase in JV pressure (i.e., impaired venous drainage) may negatively impact cerebral perfusion pressure (Reproduced from Schell et al. [63]; kind permission from Springer Science + Business Media B.V.)

flow pattern, which is not necessarily an accurate assumption. Furthermore, at low velocities, the Doppler flow return becomes noisy, causing inaccuracies in true flow at low pump speeds [30]. The use of transit time flow probes has overcome the issues with low flow ranges. The ultrasonic technology uses Doppler principals to determine the velocity of an ultrasound that is travailing in the same direction as the flow of blood and comparing this to an ultrasound pulse traveling in the opposite direction and comparing the slight velocity difference between these two flows to determine average flow velocity [34].

CPB pump flow reflects total system flow and does not reflect regional blood flow to critical organs such as the kidney and brain and splanchnic circulation. The optimal flow rate for CPB is altered by many different variables including hematocrit, body mass index (BMI), core body temperature, degree of neuromuscular blockade, and depth of anesthesia. Standard flows during CPB are institution dependent, but the most commonly used flows are about 2.2–2.5 L/min/m^2 [34]. There have been multiple tables and charts published that guide required CPB flows for any given BMI and patient temperature. The CPB flow ranges from about 2.0–2.5 L/m^2 at normal body temperature and decreases as core temperature decreases [35].

For each individual patient, this set flow may be adequate or may not be, dependent upon other factors such as preexisting hypertension, peripheral vascular disease, atherosclerotic disease, and individual variability [36]. Since the purpose of CPB

and monitoring during CPB is to ensure adequate organ flow, many centers use surrogates for adequate organ flow such as urine output, venous oximetry, and cerebral oximetry (see Chap. 28). Based upon this data, flows will be adjusted to improve a given variable, which should theoretically reflect improved end-organ oxygen delivery.

Mixed Venous and Central Venous Saturations

Mixed venous and central venous saturation, as measured in many other critical care environments, is not possible to measure in patients during the period of CPB. This is because the venous blood is usually bypassing the point of measurement for these variables and is returned to the CPB machine. Therefore, venous oximetry in CPB is usually measured by sampling the venous return line of the CPB circuit. It should be remembered that venous oximetry is a global surrogate for adequate blood flow and may not reflect individual organ hypoperfusion [37–40]. Venous oximetry is assumed to measure oxygen utilization and extraction, when oxygen delivery is inadequate, extraction increases, and venous oximetry decreases. Generally, venous saturations are considered adequate if they are above 60 %. Using this cutoff, nearly every patient who had low mixed venous saturations would have inadequate perfusion of some tissue beds, but many patients with normal mixed venous saturations can have malperfusion of specific organ beds. This effect is determined by flow out of the malperfused area and subsequent mixing with other vascular beds that might have a low oxygen extraction ratio.

Often, the perfusionist and anesthesiologist will manipulate certain parameters, such as the P_ACO_2, and hematocrit, which can modify the measured oxygen saturation, while having minimal, if any, effect on oxygen delivery and utilization. There are other issues to keep in mind when assessing the venous saturation. First it is a measure of global oxygen delivery and does not reflect individual organs at high risk for ischemia and malperfusion during CPB, such as the brain. An example of this being a problem occurs if an arterial cannula were misplaced and there was malperfusion to the cerebral circulation, there would be less venous return from the cerebral circulation, and the resulting hypoxemia might be masked by high venous saturations from other portions of the body thereby making the venous saturation an insensitive marker to focal ischemia or malperfusion. Additionally, interpretation of venous saturations assumes normal cellular ability to extract oxygen from the blood. This interpretation might be impaired in states such as sepsis or when high doses of sodium nitroprusside are used. Also transfused blood, which usually has depleted levels of 2,3 DPG, serves as an oxygen sink initially and will cause an elevation in measured oxygen content without a concomitant increase in oxygen delivery or oxygen utilization of the tissues. Finally, it should be remembered that venous oxygen saturation is monitored using technology similar to that used for pulse oximetry and that any type of dye, such as methylene blue, will dramatically affect the saturation measurement [41].

Cerebral Near-Infrared Spectroscopy (NIRS)

Cerebral near-infrared spectroscopy (NIRS) is theoretically an attractive opportunity to monitor an organ system that we are most concerned with in regard to adequacy of perfusion [45] (also see Chap. 28). The evidence for the utility of using cerebral NIRS during CPB is somewhat mixed. It is well described that blood is shunted centrally to the CNS and mesentery [47]. There is very strong evidence that low NIRS saturations predict increases in complications [49], mortality [44], neurologic deficits [42, 43, 49], and delirium [42, 48]. A study published in 2012 demonstrated the use of cerebral oximetry to detect the lower limits of cerebral autoregulation, and this might be the future of matching flows and pressures on pump to match end-organ oxygen demand [40].

A concern regarding the routine use of NIRS in all cardiac surgical patients is the associated expense. This is not without basis, since the costs of each disposable pad is about $100, with each patient usually requiring two pads. This

concern was addressed by an Irish cost analysis that demonstrated a savings of £114,000 per 100 patients treated using NIRS with a protocol-guided therapy [46]. This equals to about $183 US dollars saved per patient use. This is a preliminary study, and more data is needed to draw firm conclusions. However, a recent best evidence review would suggest that NIRS-guided protocols provide the most consistent, objective assessment of adequacy of cardiac output/pump flows for cardiac surgical patients [50].

Urine Output During CPB

Using the urine output (UOP) as a monitor for adequacy of perfusion during CPB is theoretically a simple and low-tech method to assess hemodynamics on bypass. A lack of UOP might be sensitive to a complete lack of renal blood flow, but it is not a sensitive to low medullary flow states nor is low UOP always indicative of low renal blood flow. UOP is frequently augmented by the use of mannitol or Lasix by the perfusionist; therefore, brisk or normal UOP is not necessarily indicative of adequate renal blood flow, only that there is some renal blood flow. Many patients do not necessarily produce urine in the absence of pulsatile pressure. This is especially true in the setting of metabolic and neurohormonal influences such as increased levels of AVP that are associated with surgery. In summary, UOP is neither sensitive nor specific to changes in the adequacy of blood flow other than in the absence of any renal blood flow, there is likely to be no urine output. There is no data that low intraoperative urine output or oliguria is predictive of postoperative renal function as there is no data that normal urine output is predictive of normal postoperative renal function [51–53].

Ventricular Drainage During CPB: Venting and Monitoring for Distention

The purpose of cardiopulmonary bypass is to have the patient's blood completely bypass the heart and lungs. To do this there must be adequate drainage of blood from the right atrium or SVC and IVC prior to entering the right ventricle. In essence, in its purest form, there should be an absence of cardiac ejection thru the pulmonic and aortic valves, though this is not always the case [54]. Lack of distention or adequate unloading of the ventricles is important to adequately rest the myocardium and maximize perfusion pressure to the myocardium. It is not uncommon to have some blood flowing thru the pulmonary vasculature during routine CPB operations, but care must be taken to ensure that the ventricles, especially the left, are not becoming distended. Left ventricular distention leads to ischemia and increased need for inotropes and vasopressors in the postoperative period. Adequate emptying of the left ventricle can be assessed by noting abrupt decrease to zero, or near zero, in CVP and pulmonary arterial line pressures and loss of pulsatile ejection from the PA catheter tracing and the ABP tracing.

When CPB is combined with aortic cross-clamping and cardioplegia with diastolic arrest of the heart, it is of the utmost importance to ensure that the heart, and especially the left ventricle, does not become distended. Distension of the left ventricle can occur thru return of bronchial blood flow thru the pulmonary and thebesian circulation and thru an incompetent aortic valve. If the left heart becomes distended, myocardial ischemia can develop from compromised cardiac myocyte protection [55]. It is important to monitor for evidence of left ventricular distention to prevent these complications. Some surgeons routinely place left ventricular vents to prevent this, while others do not do so or only do so selectively. Venting serves other purposes in patients undergoing CPB including other than just preventing distension of the ventricle and includes the reduction of myocardial rewarming, the prevention of cardiac ejection of air, and to facilitate surgical exposure.

Available methods used to monitor for distention of the heart include simple observation of the heart thru the open sternum. When visualized from a medium sternotomy, the right ventricle is the structure primarily visualized, and the ability to observe left ventricular distention

may be poor. Other more quantitative methods include using the pulmonary artery pressure as a means to monitor for left ventricular distention. Distention of the left ventricle would be noted by a rise in PAP or a PAP greater than 6–8 mmHg [56, 57]. TEE can also be used to assess for ventricular distention. When CPB is initiated with full bypass, there is usually a loss of good acoustic windows and normal cardiac architecture due to the loss of intracavitary blood as an acoustic medium. In the setting of ventricular distention, the heart's anatomy would be easily visualized, and flow from an incompetent aortic valve might also be seen [58].

Transesophageal Echocardiogram (TEE) During CPB

Other uses for a TEE in the patient who is undergoing CPB include assessment of valvular pathology, for presence of air in the systemic cardiac chambers, and for the presence of iatrogenic dissection [59, 60]. Blood or fluid in the pleural cavity can also frequently be seen, and this can be a cause of poor venous return and low pump flows. In some situations, the presence of new intraperitoneal fluid can be visualized with TEE and might alert the physician to presence of a vascular injury to the IVC. For a more complete discussion on the use of TEE, please see Chap. 11.

Conclusion

Due to the non-pulsatile nature of CPB, invasive hemodynamic monitoring during cardiac surgery might appear deceptively simple. In reality, monitoring these patients during this critical time of surgery has clearly not been perfected in the modern era. Arterial blood pressure measurement has to be interrupted very closely in relation to the CPB flows, the site of measurement, and other monitors of end-organ perfusion. There appears to be a reasonable amount of data to support the routine use of NIRS-guided protocols in cardiac surgery patients. Lastly and easily overlooked, adequate emptying of the ventricle should be assessed for to ensure that the myocardium is appropriately rested. This is especially true regarding adequate venting of the left ventricle to ensure organ protection and the avoidance of ischemia and myocardial infarction.

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Closed-Loop Fluid Management and Hemodynamic Optimization

17

Joseph B. Rinehart

General Principles of Fluid Therapy and Hemodynamic Optimization

Before a closed-loop system can be designed for any given task, there must be a clearly defined control objective. While this may seem obvious, in practice it can be a significant challenge. In the case of IV fluid administration, for example, there is no medical consensus on what constitutes optimal fluid therapy. It's clear that hypovolemia is undesirable and increases morbidity and mortality, and it's also clear that hypervolemia leads to complications as well. What constitutes "appropriate" resuscitation is not as clear. The first requirement for closed-loop fluid administration, therefore, is to define an endpoint of resuscitation.

The goal of IV fluid administration is to expand intravascular volume and in so doing improve blood flow to the tissues. Adequate tissue perfusion depends on both cardiac output and mean arterial pressure; the former ensures adequate oxygen and nutrient delivery and removal of waste while the latter ensures adequate driving pressure to force blood into capillaries and balance flow among the different tissues of the body which will have different needs and pressure requirements depending on the circumstances (Fig. 17.1). Fluid administration can increase cardiac output by increasing venous return. The increase in cardiac output may, in some cases, lead to an increase in mean arterial pressure as well, but this is not always the case. Because blood pressure arises from both cardiac output and systemic vascular resistance, the relationship between cardiac output and arterial pressure is not fixed. Despite this, standard practice in many clinical settings focuses fluid administration on arterial pressure alone, and flow monitoring (in the form of a cardiac output monitor of some kind) is overlooked.

The recent focus on cardiac output optimization/maximization in moderate- to high-risk surgery, however, has begun to change this trend in favor of administering fluid based on cardiac output endpoints instead of mean arterial pressure alone or generalized formulas. In this approach, fluid is administered until cardiac stroke volume no longer increases by some predetermined percentage in response to the bolus (e.g., a 10 % increase in stroke volume after 200 mL of fluid) [1]. Other approaches include dynamic predictors of fluid responsiveness like pulse pressure variation and stroke volume variation to reduce the number of unneeded fluid boluses. In appropriate patients (mechanically ventilated with 8 mL/kg tidal volumes, without arrhythmias, and without significant valvular or right ventricular pathophysiology) [2], these parameters can be used to predict whether the patient will increase stroke volume in response to fluid administration [3]. Fluid administration

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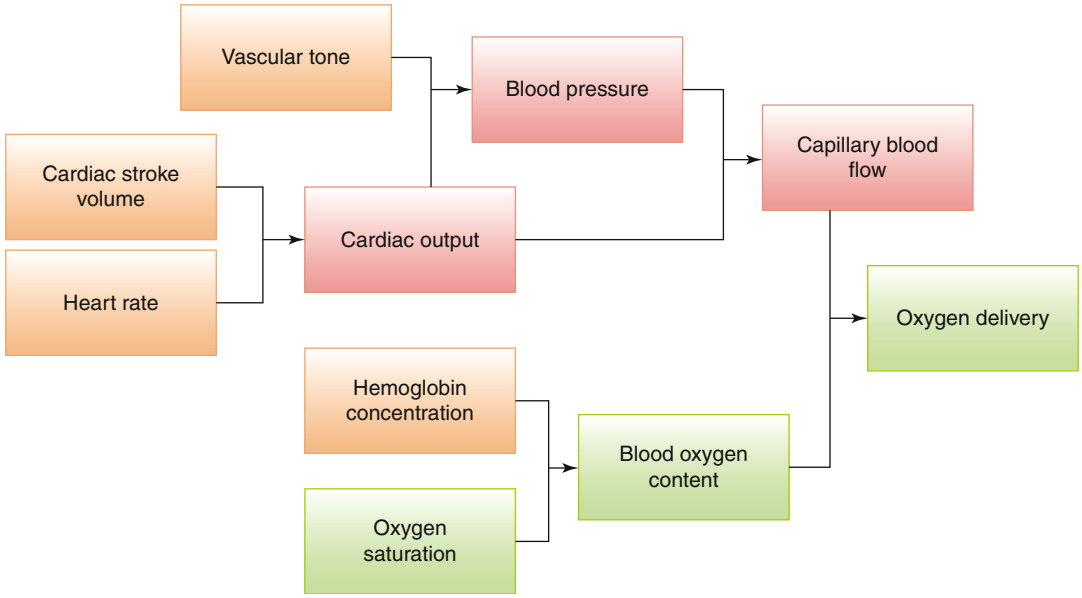

Fig. 17.1 Basic hemodynamic interrelationships. No element of hemodynamics can really be considered in isolation due to the interconnectedness of all of the components. Blood pressure, for example, arises from both vascular tone and cardiac output. Cardiac output, in turn, is dependent on both stroke volume and heart rate. To change any one of these components would alter the others as well. Thus, hemodynamic function must really be considered from a system standpoint as consideration of only individual elements will not provide a complete picture

protocols based on minimization of stroke volume variation, for example, have shown postoperative benefits [4], as have those based on pulse pressure variation [5] and plethysmograph variability [6].

Given the growing evidence supporting these approaches and the improved outcomes they are associated with, stroke volume and cardiac output maximization or optimization seems a natural target endpoint for closed-loop fluid administration. There is a subtle but important difference between the terms "optimization" and "maximization." Strictly speaking, stroke volume or cardiac output "maximization" would refer to the administration of IV fluid to drive the patient to the very top of the plateau phase of the Frank-Starling relationship (Fig. 17.2). While this would maximize oxygen delivery and blood flow, it may also lead to over-resuscitation because of the preload volumes required to achieve this result, especially in cardiovascularly fit patients who have high cardiac reserve [7]. "Optimization" would ideally mean matching cardiac output and oxygen delivery to oxygen consumption. At present, however, there is no convenient or reliable method to determine global oxygen consumption, nor would a global level guarantee that all individual tissues were adequately perfused because of regional differences in metabolic rate and blood flow. Thus, we more often use the term "optimization" to refer to the administration of fluid to bring the patient *near* the plateau phase of the Frank-Starling relationship, balancing the amount of fluid required to make further gains with the metabolic needs of the patient.

The best evidence we have at present, then, is that in moderate- to high-risk patients the goal of fluid administration should be cardiac output optimization. That means increasing the stroke volume and cardiac output to near (but not necessarily on) the plateau of the Starling curve, using as feedback either percentage change stroke volume/cardiac output, minimization of a dynamic predictor like pulse pressure variation or stroke volume variation, or some combination of both.

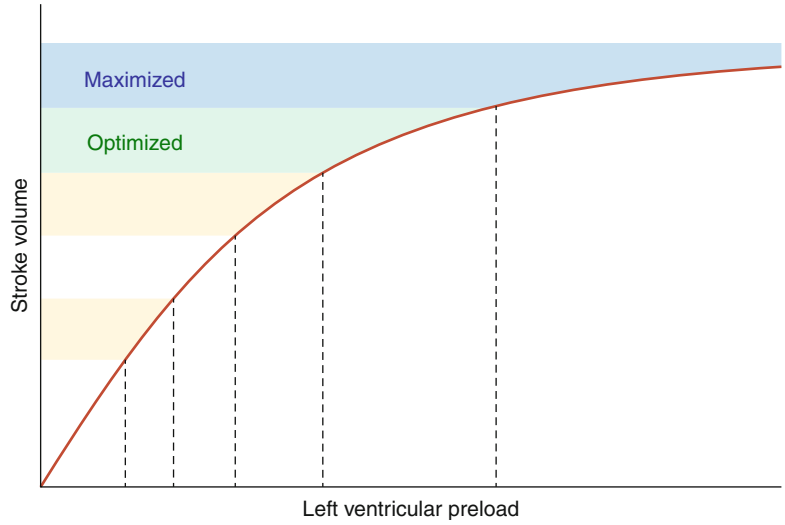

Fig. 17.2 Starling curve and cardiac output optimization. Because of the nonlinear response of the left ventricle to preload, the beneficial effects of fluid administration on stroke volume and cardiac output are subject to the law of diminishing returns. In the figure, it is easy to see that for a given fixed increase in stroke volume, increasingly larger preloads are required until at some point no further increase is even possible (the plateau phase). "Maximization" of cardiac output would require a relatively large volume of fluid to be given to drive the stroke volume to this maximal point. On the other hand, "optimization" of stroke volume could be considered achieved by merely approaching the plateau phase of the Starling curve. This could achieve 80–90 % of the maximal stroke volume with substantially less fluid loading required

Feedback Parameter Selection (and Historical Closed Loops)

Table 17.1 reviews some of the parameters that are relevant for fluid administration and might be used in a closed-loop resuscitation system. These parameters are discussed below along with studies that have been done using these parameters to guide automated resuscitation. Published studies on closed-loop fluid management are summarized in Table 17.2.

Urine Output

The very first closed-loop fluid administration system was developed in Utah in the early 1980s and was based on urine output [8]. This system was actually used clinically in intensive care for a time but was subsequently phased out of use when one of the developers left the university. Recent work in sheep using a proportional-integral-derivative (PID) controller to resuscitate after burn injuries showed more stable urine outputs than did manual adjustments [9]. This is typical of closed-loop control: frequently, there is no large difference in mean values between closed-loop control and manual control, but the closed-loop shows a much narrower range of deviations from the mean.

One challenge with urine output as a feedback parameter is that it is a late sign of hypovolemia, is relatively nonspecific, and is strongly affected by pharmacologic agents and blood pressure. In ICU conditions, it may be a reasonable target parameter for closed-loop fluid administration if the goal is to maintain net fluid balance. In more dynamic environments like the operating room or trauma settings, however, urine output would be of limited value as a feedback parameter.

Heart Rate

As a primary determinant of cardiac output and oxygen delivery, heart rate is intrinsically tied to

Table 17.1 Potential feedback parameters for use in a closed-loop fluid delivery system

Measurement	Utility	Limitations
Urine output	One of the principal routes of normal physiologic fluid loss. Trends with intravascular volume. Reassuring of adequate pressure and flow when normal	Late detector of hypovolemia and affected by many factors besides blood volume and arterial pressure
Heart rate	Easy to monitor, one of the primary determinants of cardiac output and oxygen delivery	Nonspecific and affected by many common pharmacologic agents
Central venous pressure and pulmonary capillary wedge pressure	Low values are indicative of hypovolemia	Invasive and difficult to monitor accurately, poor predictors of fluid responsiveness
Cardiac output	One of the primary determinants of oxygen delivery. Positive outcome studies. Minimally invasive and noninvasive measurement possible	Required cardiac output varies depending on metabolic need. Low-invasive monitoring techniques have their own intrinsic limitations
Mean arterial pressure (MAP)	Easily measurable and core determinant of tissue perfusion pressure	MAP may remain steady in the face of large changes in volume status due to normal compensatory mechanisms. Affected by many pharmacologic agents and anesthetics
Variation in pulse pressure or stroke volume	Highly predictive of fluid responsiveness, positive outcome studies, can be monitored from a single arterial pressure waveform	Requires mechanical ventilation, tidal volume at least 6 mL/kg, no arrhythmia, closed-chest conditions
Respiratory variations in the plethysmographic waveform	Good predictor of fluid responsiveness in patients with normal vasomotor tone, positive outcome study, easy to monitor, noninvasive	Sensitive to changes in vasomotor tone which limits utility in shock or when vasopressors are being used
Mixed venous oxygen saturation	Good indicator of global balance between oxygen delivery and uptake	Accurate measurement difficult due to venous mixing; global value may overlook regional flow deficiencies
Tissue oxygen saturation	Good indicator of adequate oxygen delivery	Difficult to measure presently. Single-site measurement may miss inadequate flows in other tissues

Table 17.2 Closed-loop fluid management studies

First author	Year	Control type	Controlled parameter	Intervention	Study type
Bowman R	1980	PID	Urine output	IV fluid	Animal and human
DeBey R	1987	Proportional	Urine output	IV fluid	Human
Blankenship H	1990	Proportional	Left atrial pressure	Autotransfusion	Human
Parkin G	1994	Proportional	Mean systemic filling pressure analog	IV fluid	Human
Chaisson N	2003	Nonlinear proportional	Cardiac output vs. tissue oxygenation	IV fluid	Animal
Hoskins S	2006	PID	Urine output	IV fluid	Animal
Vaid S	2006	Nonlinear proportional	Mean arterial pressure	IV fluid	Animal
Rinehart J	2011	Model and rule	Stroke volume	IV fluid	Simulation

volume status and resuscitation. Heart rate is obviously a very general guide to volume status, but there is little doubt that tachycardia is an expected response to hypovolemia. Like urine output, however, tachycardia is a late sign of hypovolemia and generally only appears when volume deficit is severe (15 % or more of total blood volume). Additionally, normocardia is not an assurance of adequate blood volume, especially in the presence of beta-blockade or cardiac

pathology. Moreover, heart rate is normally dynamic in healthy patients and is affected by pain, narcotics, sympathomimetics, and more. Perhaps because of this complexity, heart rate has never been used in closed-loop resuscitation as a control parameter.

The real utility and necessity of heart rate monitoring in closed-loop resuscitation is that heart rate is intrinsically tied to all other hemodynamic parameters and must be accounted for in any comprehensive resuscitation algorithm. For example, a computer algorithm based on cardiac output alone would not be able to differentiate between a stroke volume of 80 with a heart rate of 60 (CO = 4.8) and a stroke volume of 40 with a heart rate of 120 (CO = 4.8), even though these are obviously very different physiologic states in an adult. Note that using stroke volume instead of cardiac output does not entirely circumvent this problem, as heart rate still affects cardiac filling time and therefore influences stroke volume. Thus, heart rate is likely a required consideration in closed-loop fluid therapy and hemodynamic optimization. Additionally, changes in heart rate may provide valuable information about sympathetic outflow and pharmacologic interventions.

Mean Arterial Pressure

Mean arterial pressure is an easily measureable parameter and can be measured continuously, and now even noninvasive monitors are providing continuous waveform data. Since arterial pressure is required to drive blood into end-organ capillaries, a closed-loop hemodynamic controller would almost certainly want to include a continuous blood pressure measurement in the algorithm.

Anesthesiologists have traditionally focused resuscitation efforts towards management of blood pressure, and recent survey data has shown that this focus persists today. Blood pressure alone, however, is a poor predictor of preload dependency, and blood volume must be significantly reduced before arterial pressure begins to fall. Likewise, hypertension is not a specific indication of volume overload. Thus, as with heart rate, mean arterial pressure is unlikely to be useful as a lone endpoint but rather as a single parameter in a multi-input system.

Central Venous Pressure and Wedge Pressure

Central venous pressure and pulmonary capillary wedge pressure have historically been considered the best guides to resuscitation in intensive care and high-risk patients. Despite the common belief that these values accurately reflect left ventricular preload, however, these parameters are very inaccurate predictors of fluid responsiveness [10–12]. Even so, they have been used successfully to guide closed-loop resuscitation for postoperative autotransfusion [13] and for volume replacement during continuous hemofiltration [14]. It is conceivable that in otherwise stable patients who are not being subjected to changing pharmacologic therapies, surgical stimulation, anesthetic levels, or other dynamic forces, that these static parameters may generally trend with volume status and be adequate for guidance of resuscitation. Generally speaking, however, these static parameters are unreliable in most clinical conditions and are probably of limited value without other information.

Cardiac Output and Stroke Volume

Cardiac output and stroke volume are obvious choices for closed-loop control, primarily because they are principle determinants of oxygen delivery and have outcomes studies to support their use [15]. As noted above, cardiac output optimization cannot be performed without some consideration of heart rate. However, while increasing heart rate to improve cardiac output is a potentially useful strategy, it should be considered only when blood volume is already optimized, and tachycardia may be detrimental in patients with ischemic cardiac disease. Thus, most of the time when we speak of cardiac output optimization, we mean stroke volume optimization.

Either way, cardiac output and stroke volume are natural targets for closed-loop control, especially if the controller can account for the other components of hemodynamics (heart rate, arterial pressure, and vascular tone). The controller need not actually control these parameters as well, but an ability to utilize the additional information could add sophistication to the control algorithm. Stroke volume has been used as a primary control parameter in simulation studies on closed-loop control [16].

Dynamic Predictors

The dynamic predictors of fluid responsiveness – measurable parameters that arise from the interaction of the cardiovascular system and thorax during positive-pressure ventilation [17] – are the most accurate predictors of volume responsiveness yet described [18]. As such, they are invaluable for closed-loop resuscitation. The limiting factor for these parameters is that they are only accurate under specific conditions: tidal volume at least 8 mL/kg and positive-pressure ventilation, no arrhythmias, no valvular disease, closed-chest conditions, and normal right ventricular function. Furthermore, conditions like abdominal insufflation, prone positioning, and more have not been thoroughly studied and may reduce or invalidate the utility of these parameters. Any closed-loop designed for hemodynamic optimization should certainly be capable of using these predictors when the conditions are appropriate, but should also be able to function in their absence if it is not to be subject to the same set of limitations.

Mixed Venous Oxygen Saturation

Measurement of mixed venous oxygen provides a very sensitive indication of the balance between oxygen delivery and oxygen consumption in the body as a whole. Low values result from inadequate delivery and increased uptake in the periphery, while high values result from shunting and inadequate uptake. Alone this information would not indicate the cause of inadequate delivery (e.g., low cardiac output from hypovolemia versus heart failure) but if combined with cardiac output and other data could provide a very complete overall picture of hemodynamics. The challenge with mixed venous oxygen is that accurate measurement can be difficult due to differences in venous return from different parts of the body, and even if mixed venous oxygen is normal, it does not guarantee all tissues are adequately perfused. In septic shock supported with vasopressors, for example, global mixed oxygen may be in the normal range in the presence of some peripheral shunting (which would increase the value) combined with bowel ischemia (which would decrease the value).

Tissue SpO_2

Tissue oxygen levels are also closely related to cardiac output and have been used to guide closed-loop fluid resuscitation [19]. Of course, tissue oxygen levels will also be affected by hemoglobin concentration, arterial PaO_2, and tissue metabolism. Additionally, due to differences in regional blood flow, tissue oxygen levels in some tissues (muscle) may be adequate while other tissues (bowel) become ischemic, especially in the presence of sympathomimetic agents which cause redistributions in blood flow. Even given these limitations, ultimately our goal with resuscitation is to restore oxygen delivery and blood flow to capillary beds, so there is a strong intuitive rationale to incorporate tissue oxygenation in some form into a closed-loop control scheme for resuscitation if simultaneous measurement in many body tissues becomes feasible.

Specific Monitoring Considerations

In addition to the specific parameter or parameters used to guide fluid administration and resuscitation, some consideration must be given to the monitoring system used to provide that information. Some parameters, like heart rate and mean

arterial pressure, can be monitored very accurately from a variety of sources. Other parameters, like stroke volume and tissue SpO_2, may be dependent on the method and location of measurement. For example, disagreement between values obtained from esophageal Doppler measurements and thermodilution measurement techniques is up to 20 % [20], and larger disagreement has been found between thermodilution and measurements of cardiac output derived from arterial waveform analysis [21], especially in patients with disturbances in vascular tone.

Disagreements between measurement approaches do not mean that these measurements are not still potentially useful for guidance of resuscitation or closed-loop control. Noninvasive and minimally invasive systems can still provide good information with reduced risk to patients as compared with more invasive monitoring. We must be aware of their limitations, however, and include those limitations in our clinical decision-making. Thus, use of these systems in closed-loop control will require control schemes that include the possibility of error in measurement and protect the patient from adverse events as a result.

Certainly monitor accuracy will improve with time and at some point error will no longer be as large an issue. Until that time, however, the trade-offs between clinical utility and limitations of current monitors must be a design consideration in any closed-loop for hemodynamic management.

Controller Types

Based on the feedback parameters available for guidance of closed-loop resuscitation discussed above, it seems obvious that rather than an individual parameter, a multiple-parameter strategy makes the most sense for control. Figure 17.3 shows an example of why multiparameter feedback may be not just advisable but required for closed-loop fluid administration. Figure 17.3a shows a sample of cardiac stroke volume as recorded during an animal hemorrhage study [22]. Looking at only the stroke volume, it is very difficult to determine the causes of the changes seen at point 1 and point 2. For example, the increase at point 1 could result from a fluid bolus, sympathetic activity, or even a sudden fall in left ventricular afterload. Likewise, the drop in stroke volume at point 2 could result from hemorrhage, cardiac ischemia, or a sudden rise in afterload.

Figure 17.3b shows the same data, this time including heart rate, mean arterial pressure, and systemic vascular resistance. It becomes easier to determine the causes of the changes seen in stroke volume with this new data. At point 1, we now see that stroke volume rose along with arterial pressure, vascular resistance, and heart rate. This is consistent with sympathetic activity or a sympathomimetic, in this case a dose of ephedrine. At point 2, we now see that stroke volume and heart rate fell while vascular tone and arterial pressure rose dramatically. This is consistent with an alpha-agonist effect, in this case a dose of phenylephrine. Because of the interconnected nature of hemodynamics, it is only with the additional information provided from the other parameters that we can make inferences about observed changes in stroke volume.

There are a variety of control schemes which handle multiple-parameter input and output. A primary controlled variable could be chosen (e.g., cardiac output), with a single available intervention (perhaps fluid administration), with other monitored parameters used to inform decision-making about how to achieve control at any given time. Alternately, a true multi-input, multi-output (MIMO) controller could be designed to monitor multiple parameters simultaneously using multiple interventions (like fluid and pharmacologic agents).

Proportional-integral-derivative control (PID) is one of the most commonly used control schemes in control engineering. The three terms of the controller refer to the present, past, and future error between a target value for some measured parameter and the measured value from the system. PID controllers require tuning of the weights of the components to prevent oscillations in the system but once developed can provide very stable and robust control. One limitation of this control type for closed-loop hemodynamic

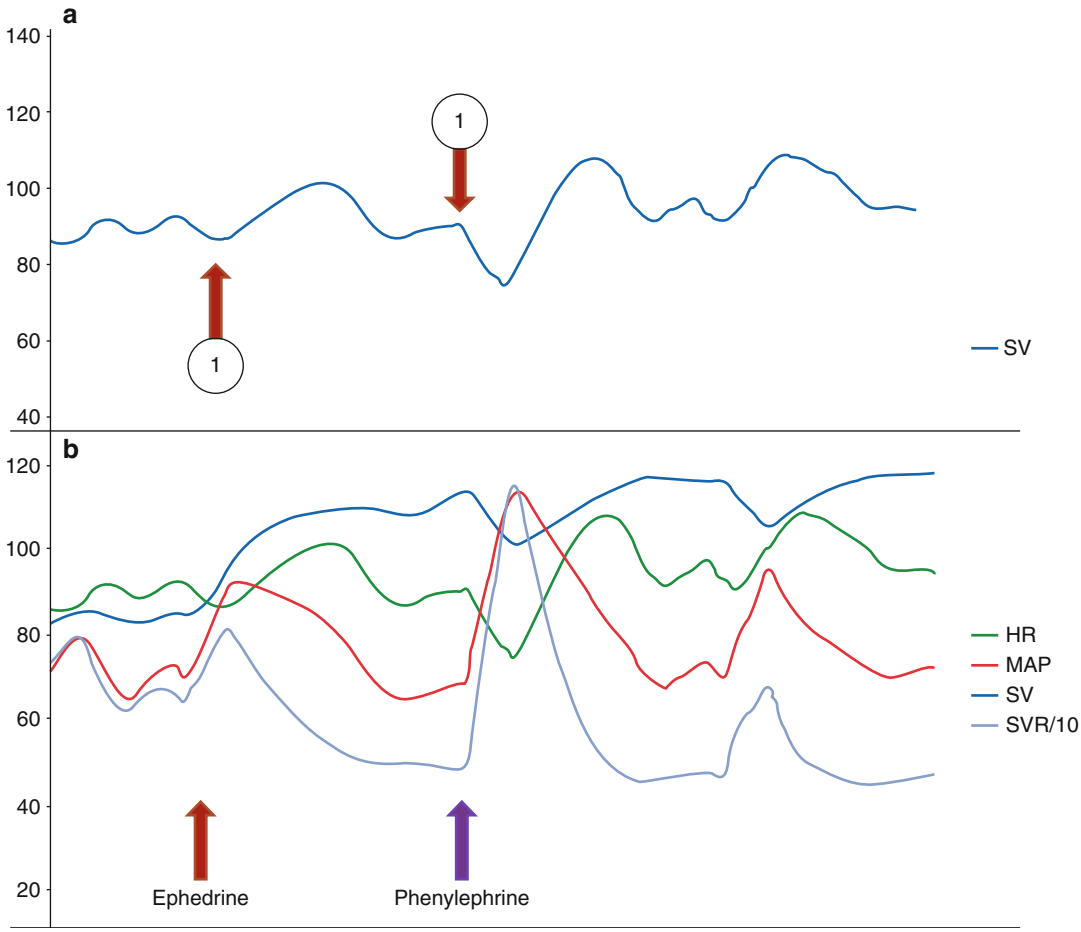

Fig. 17.3 Sample data from animal studies showing single versus multiparameter feedback. Hemodynamic data from unpublished animal hemorrhage studies. The *top graph* (**a**) shows only stroke volume (*SV*). The *bottom graph* (**b**) shows heart rate (*HR*), mean arterial pressure (*MAP*), and systemic vascular resistance (*SVR*) as well. It is much easier to determine what occurred at points *1* and *2* with the additional data in the second graph (see text for details)

applications is that PID control is best suited for single-parameter measurement. Additionally, for applications like fluid administration, the nonlinear and dynamic response of hemodynamics to volume expansion makes PID control less effective. It would be well suited, however, for control of a pharmacologic agent like phenylephrine to maintain a target blood pressure.

Model-based controllers use an underlying model of the system to be controlled to make predictions about the response to interventions, and these predictions are then used to guide control. Controllers like these are made more robust by incorporating correction factors for differences or error between the internal model and the actual system under control (referred to as "plant-model mismatch"). Model-based controllers, of course, require a reasonably predictive model of the system to be effective but are appropriate for MIMO applications if sufficient testing and fine tuning of the controller are done.

Artificial neural network-based controllers are very well suited to MIMO applications. These controllers are designed to mimic a small network of neurons, with inputs being "processed" through one or more layer of nodes before outputs are generated. Neural networks range from simple, single-layer, single-direction designs to

multilayer designs where later layers can feedback on earlier layers or even themselves. The chief challenge with this control type is the design of the network nodes and weights; this process is a specialty unto itself and requires extensive testing and system identification to tune the layers for appropriate outputs. If the controller design and testing can be accomplished, however, neural network control could be a very robust approach to hemodynamic management.

Finally, rule-based controllers are tailor-made rule sets, usually developed using expert guidance, that dictate what outputs to generate based on the inputs received to the controller. The complexity and capabilities of these controllers are limited only by the rule set, and thus they are more than capable of managing MIMO applications. Rule-based controllers, however, are particularly in need of extensive testing and validation because of the arbitrary nature of their design to assure stability and robustness of control.

Regulatory Considerations

There are no commercially available devices for management of fluid administration in clinical care at this time. All of the systems described or studied to date have been experimental. Figure 17.4 shows an experimental closed-loop fluid administration system in use during a clinical study. The subcomponents of the closed-loop system (sensor, controller, and intervention) in this case are encompassed in separate devices, as is often the case in prototype systems. It is unlikely that a setup like this would be approved for commercial use, however, given the risks involved with data transfer between the separate devices.

Regulatory requirements will in fact be one of the principle challenges faced by closed-loop devices in the years to come. In the case of fluid administration, one benefit is that the safety margin is quite large when compared to, for example, propofol delivery via closed loop. The flip side is that the clinical effect of propofol is relatively short-lived, whereas once IV fluid is administered, it is difficult to "remove" except via diuresis.

Specific guidelines have been issued in relation to closed-loop medical devices by the International Electrochemical Commission [23]. In addition to meeting these requirements, closed-loop devices will be expected to meet high safety standards before approval can be expected. Despite these challenges, however, the long-term gains in safety and standardization will benefit patients and providers alike.

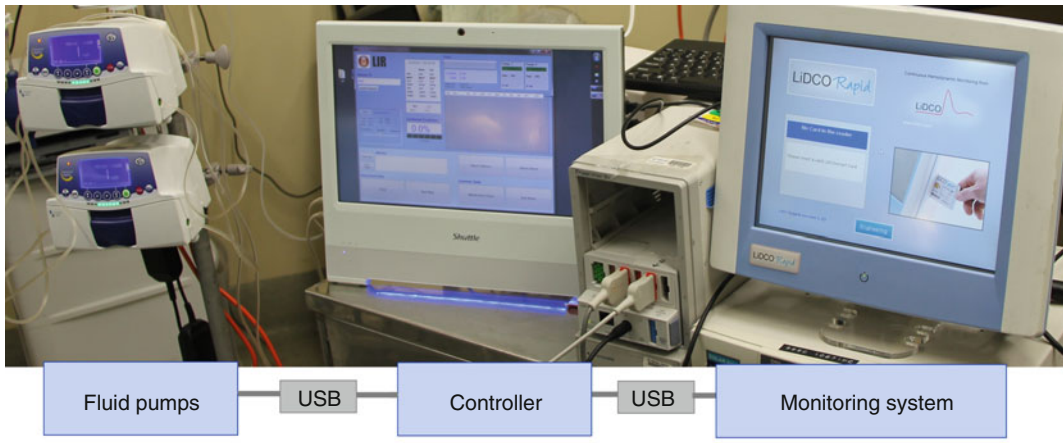

Fig. 17.4 Example experimental closed-loop fluid administration system. The system components are configured linearly from right to left in the figure above, and each component in this system is made by an individual manufacturer. Data are captured by the monitor, passed to the controller through a USB cable, analyzed, and an action determined and then passed through another USB connection to the fluid pumps, which are activated or disabled as appropriate

Control of Blood Pressure

In addition to fluid management and cardiac output optimization, there is a definite role for closed-loop control of inotropic and vasopressive agents in hemodynamic management. A comprehensive system would strive foremost for optimization of blood volume, using other interventions to temporize while blood volume is restored or to optimize blood pressure or oxygen delivery once volume is adequate.

A variety of studies over the years have performed closed-loop control of hemodynamics through the use of pharmacologic agents. Over 30 years ago closed-loop administration of nitroprusside for the management of hypertensive crises was discussed [24]. Other studies have since looked at nitroprusside [25–28], management of circulatory shock [29–32], vasopressor administration [33–35], and management of blood pressure during and after cardiac surgery [36, 37].

Conclusion

Closed-loop fluid management and hemodynamic optimization is not a new concept, but it is a concept whose time may have finally come. There is a great deal of work to be done in identifying appropriate combinations of parameters to monitor, learning how best to deliver fluid and pharmacologic interventions, and even in determining optimal control strategies for clinical care areas. Now that closed-loop control is a possibility in this arena, however, it is also an almost certain component of future clinical management.

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Suggested Reading

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Part III

Respiratory Monitoring

Introduction to Respiratory Monitoring

18

Boris Jung, Yannaël Coisel, and Samir Jaber

Mechanical Ventilation

Mechanical ventilation allows clinicians to provide both ventilation (removal of carbon dioxide) and oxygenation to provide tissues with enough oxygen to sustain normal function. It has a number of important hemodynamic effects on the body that are summarized in Fig. 18.1. It is not only a necessity for many invasive surgeries but also provides immediate lifesaving function to critically ill patients in the emergency department, intensive care unit, and other acute care environments. The proper application of mechanical ventilation is thus an incredible tool at our disposal but can quickly become a tragedy if applied incorrectly or poorly monitored. Large amounts of research have been directly towards identifying adverse outcomes after mechanical ventilation, in an effort to improve clinical care, and many of these studies primarily use monitoring information to identify relevant variables.

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Types of Respiratory Monitoring

Respiratory monitoring is needed at every step, from the point prior to intervention, during the placement of an airway via intubation, through the ventilation, and even post extubation. Both simple and complex monitors play a role in determining critical measurements:

- *Blood gas measurements*: standard arterial blood draw provides oxygen and carbon dioxide levels, as well as pH, bicarbonate, and hemoglobin levels.
- *Pulse oximetry*: noninvasive probe provides an estimate of percentage of hemoglobin occupied by oxygen (see Chap. 19, Oxygen Saturation Monitoring).
- *Capnometry*: chemical probe inside the ventilation tubing provides the amount of carbon dioxide exhaled (end-tidal carbon dioxide) (see Chap. 20, End Tidal CO_2 Monitoring).
- *Ventilator settings/monitors*: built into the ventilation unit are monitors that provide respiratory rate, tidal volume, pressure, temperature, humidity, and gas concentrations (see Chap. 22 and 23, Ventilators in the ICU and OR).

Stepwise Approach to Respiratory Monitoring

Our first step is to identify the status of the patient before we initiate an intervention. It is critical to identify starting hemoglobin levels, hemodynamic status, and thus perfusion of tissues, oxygenation

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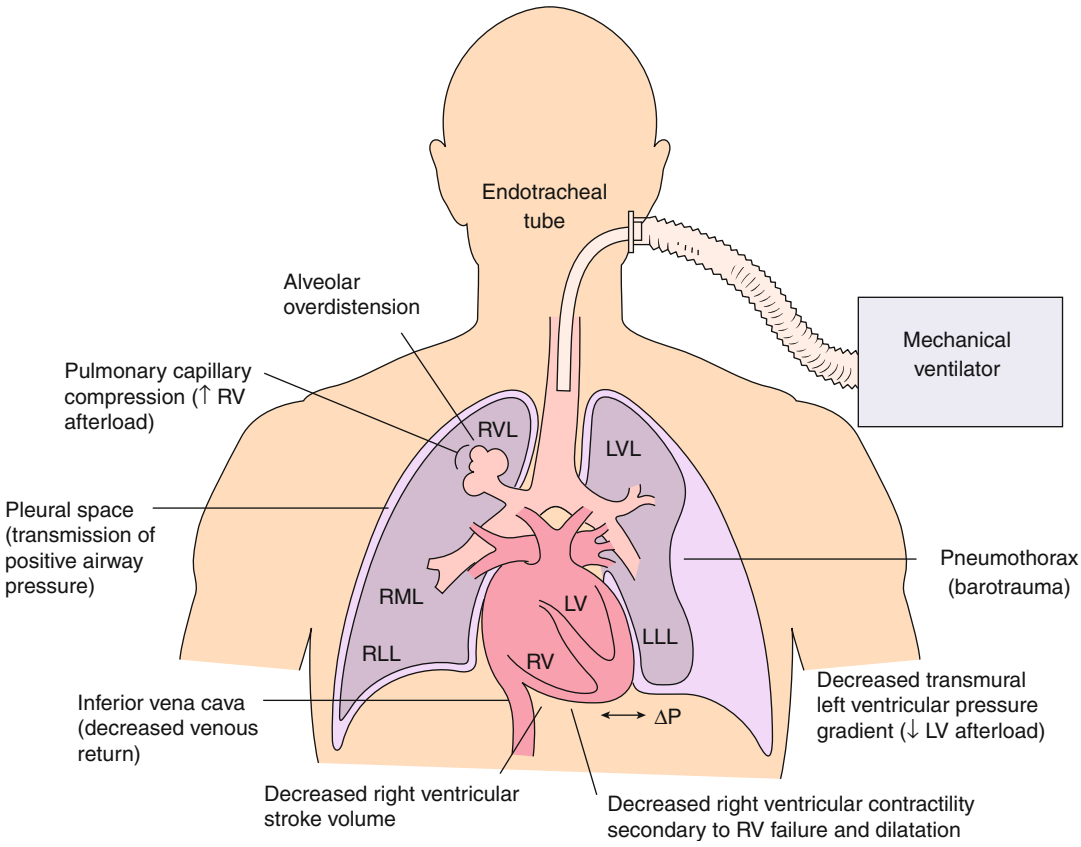

Fig. 18.1 Hemodynamic effects of mechanical ventilation. *ΔP* change in pressure, *LLL* left lower lobe, *LUL* left upper lobe, *LV* left ventricle, *RLL* right lower lobe, *RML* right middle lobe, *RUL* right upper lobe, *RV* right ventricle (Reproduced from Stoltzfus et al. [1]; kind permission from Springer Science + Business Media B.V.)

levels, and acid/base status. All of these factors will both provide a clear indication for and drive our evaluation of the effectiveness of mechanical ventilation. Our initial ventilator settings will be determined by these initial patient factors and our desired endpoint of ideal homeostasis.

Our next step is to establish a patent airway. As a patent airway is our fundamental starting point for initiating care, it must be secure and able to provide for adequate ventilation without excess resistance, leaks, or damage to surrounding tissues. Airway access in the critically ill can be challenging and is frequently associated with life-threatening complications [2, 3]. To ensure patient safety, capnometry monitoring is required to ensure that intubation is performed correctly and that the patient is able to expel adequate carbon dioxide. This quickly ensures that the clinician can quickly adjust or replace an airway before deoxygenation can take place and irreversible damage be done.

Once the airway is properly secured, the clinician can apply mechanical ventilation. The setting of which will be specific to the goals of treatment and properties of the patient themselves. These settings are further bounded by the risk of ventilation-induced lung injury. Monitoring becomes paramount to prevent the application of excessively high pressures or inadequate volumes. While mechanical ventilation is performed, routine blood gases should be evaluated along with trending information on oxygen saturation and end-tidal carbon dioxide. These period measurements and continuous monitoring will allow for adjustments in ventilator settings to ensure the patient progresses towards normal

homeostasis. Other basic mechanical respiratory parameters include plateau pressure (pressure applied to alveoli), total positive end expiratory pressure or PEEP (pressure maintained at the end of expiration to reduce alveolar collapse), respiratory system compliance (stiffness of lungs and chest wall), and airway resistance (mainly a function of radial size), and everyone who uses mechanical ventilation should learn their clinical significance well [4]. Several new monitors are emerging that may 1 day assist in monitoring active mechanical ventilation, such as electrical monitoring of diaphragm activity (see Chap. 21) and complex closed-loop ventilation systems (see Chap. 25). These newer monitoring techniques include advanced pulmonary mechanics (pressure and flow monitoring, pressure volume curves, transpulmonary and esophageal pressures); calculation of lung volumes using electrical bioimpedance tomography, CT, and ultrasound; functional residual capacity monitoring; and extravascular lung water [5]. It is the role of the physician and researchers to identify which monitors serve to improve care and which may be a poor utilization of resources. Appropriate utilization of mechanical ventilation, guided by clinical monitoring, can minimize the duration of ventilation and may reduce ventilator-induced diaphragmatic dysfunction [6, 7].

Extubation can also provide challenges to the clinician, and monitoring can play a role in identifying patients at risk of adverse events, as well as catch the rapid decompensation of respiratory function. While pulse oximetry and respiratory rate provide baseline monitoring for patient decompensation, we would ideally like to identify at-risk patients sooner to predict extubation failure. Monitoring tools exist for this procedure, from clinically obvious signs such as rapid shallow breathing (tidal volume and respiratory rate) to maximal inspiratory pressure and pressure generation rates which can assess the work of the respiratory muscles [8]. Post-extubation airway narrowing, resulting from trauma and irritation to the airway, may manifest as stridor but can be life-threatening; thus, cuff-leak test monitoring may help to predict its onset so that interventions can be made earlier [9].

Conclusion

To conclude, we would encourage all clinicians, including trainees and experienced practitioners, to practice with and understand the fundamental monitoring tools we have at our disposal in the clinical setting. The expert interpretation of core physiological factors will provide far more value than any advanced multifactorial data point.

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Photoplethysmography: Analysis of the Pulse Oximeter Waveform

19

Aymen A. Alian and Kirk H. Shelley

The photoplethysmographic (PPG) waveform was studied and used clinically long before the discovery of its utility in the calculation of arterial oxygen saturation [1, 2]. That discovery had such a profound impact on clinical monitoring that the other potential uses of the waveform quickly faded from the attention of clinicians. This chapter is a summary of those clinical observations with support from published studies. It is hoped that it will be an aid to developing a clinically useful understanding of this waveform.

Source of the Waveform

The pulse oximeter is based on photoelectric plethysmography that was first described in 1938 by Hertzman [3]. Beer's law of light is often used to describe the elements that contribute to the pulse oximeter waveform.

$$A_{\text{total}} = E_1 C_1 L_1 + E_2 C_2 L_2 + \& E_n C_n L_n$$

where A_{total} = absorption at a given wavelength, E_n = extinction coefficient (absorbency), C_n = concentration of the substance (e.g., hemoglobin), and L_n = path length of the light.

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Conceptually, it is useful to view the pulse oximeter waveform as measuring the change in blood volume (more specifically path length), during a cardiac cycle, in the tissue being studied (typically the fingertip or earlobe). The term "plethysmograph" is derived from the Greek root "plethysmos" meaning "to increase." There is a close correlation ($r = 0.9$) between the PPG and the more traditional strain gauge plethysmograph. The general consensus is that the waveform comes from the site of maximum pulsation within the arteriolar vessels where pulsatile energy is converted to smooth flow just before the level of the capillaries [4, 5]. On the other hand, others hypothesized that the source of the signal is from "open arteriovenous anastomoses in the cutaneous circulation" [6].

The PPG is a remarkably simple device consisting of a light source [most commonly a Light Emitting Diode (LED)] and light detector (photo diode). The detector can be placed either directly across from the light source for transmission plethysmography, with the light taking a more or less direct path through the tissue being studied (i.e., the fingertip or earlobe) or next to the light source to take advantage of the back-scattering of light to the surface (i.e., forehead) for reflective plethysmography. The plethysmographic waveform that is displayed on the commercial pulse oximeter is a highly processed and filtered signal. Typically it is inverted, autocentered, autogained, and subjected to bandpass filtering before being presented to the clinician. Of the two or more wavelengths measured by the pulse

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oximeter, traditionally only the infrared (IR) signal (approximately 940 nm) is presented. The information from this wavelength is displayed because it is more stable over time, especially when compared to the red signal (660 nm), which is more susceptible to changes in the oxygen saturation. There are two components of the waveforms: the pulsatile component or AC portion and the static component or DC (created mostly by the absorption of light by surrounding tissue); normally only the pulsatile component or AC portion is displayed. The DC is eliminated or heavily filtered by an autocentering routines used to ensure the waveform remains on the display screen. With changes in the degree of venous congestion, the waveform can be noted to drift partly off the screen and then return via the autocentering algorithm. All clinical pulse oximeters that display plethysmographic waveforms do so with an auto-gain function designed to maximize the size of the waveform displayed. Some manufacturers include an option to turn off this automatic resizing function. When attempting to use clinical monitoring devices as research devices, one must learn how to cope with these proprietary filters and algorithms.

Perfusion index (PI) which is also known as peripheral flow index (PFI) is a simple and accurate indication of changes in digital blood flow [7]. For the calculation of PI, the IR pulsatile signal (AC) is divided by the non-pulsatile IR pulse oximeter plethysmography signal (DC) and expressed as a percentage in the following equation. The IR signal is used because it is less affected by changes in arterial saturation than the Red signal.

$$\mathrm{PI} = \left[\left(\mathrm{AC}/\mathrm{DC}\right)\right] \times 100\,\%$$

It is hoped that equipment manufacturers will consider adding additional features that will allow their devices a broader range of use (Table 19.1).

The key to unlocking the potential of this waveform is unfettered access to the raw signal, combined with standardization of its presentation and methods of analysis [8]. At this time, no calibration procedure is known to standardize the PPG amplitude for comparing one patient's waveform to another therefore the signal is not given a unit designation.

Table 19.1 Desirable characteristics for a pulse oximeter used for waveform analysis

Waveform display:
Ability to change time scales
Switch between scroll and "erase bar" display modes
Wavelength selectable (IR versus red versus other)
Ability to turn off auto-gain function
Ability to turn off autocenter function
Ability to set the amplitude gain
Numeric display of amplitude and DC signal
Ability to use a wide range of probes (finger, ear, and reflective)
Digital and analog outputs of the pulse oximeter waveform to be captured by data collection equipment

Plethysmographic Waveform Analysis

PPG waveforms can be separated with the use of high-pass and low-pass filters into alternate current, pulsatile component (AC), and direct current (DC) components, respectively, as shown in Fig. 19.1. Recent research efforts have shown that the DC component is a measure of the venous blood movement driven by both cardiac activity (e.g., right atrial contraction) and ventilation. It does overlap with peripheral venous pressure waveforms recorded from peripheral intravenous catheter, and it has been shown that the saturation of the DC component is actually venous saturation [9, 10].

There are at least two methods of analysis used on photoplethysmographic (PPG) waveforms: namely, the time domain and frequency domain analysis. In the *time domain analysis*, the PPG waveforms will be to amplitude (peak), height, area, width and maximum slope (max slope), and minimum slope (min Slope), as demonstrated in (Fig. 19.2)

While with *frequency domain analysis*, the PPG waveforms can be described as a sum of sine and cosine functions. The PPG waveforms are analyzed using fast Fourier transformation (FFT)

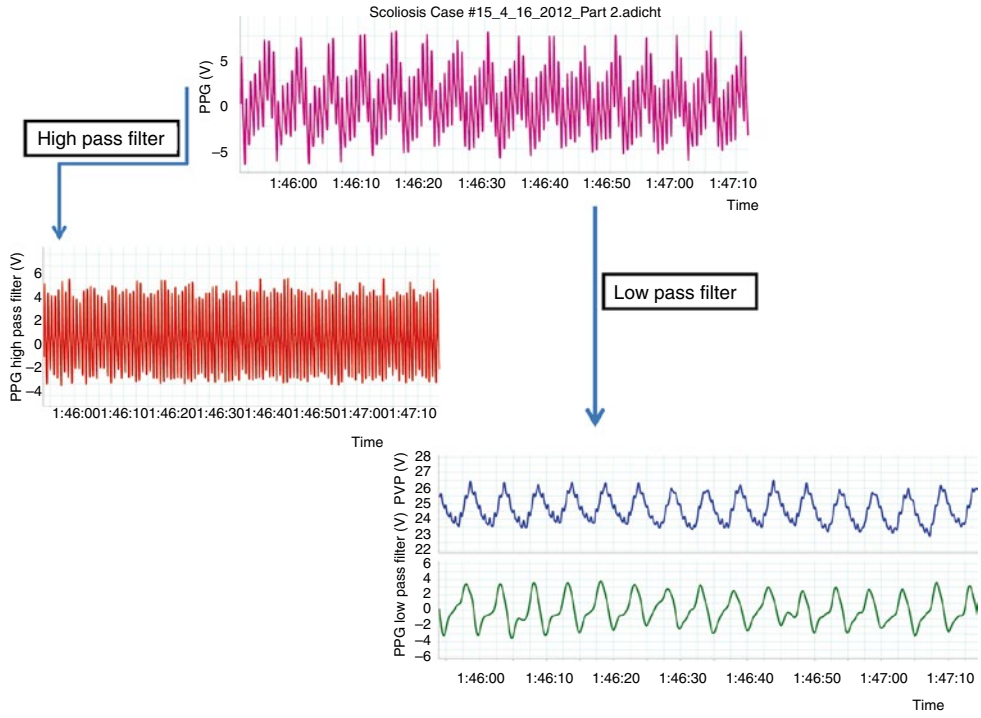

Fig. 19.1 Effect of high-pass (0.8) and low-pass filter (0.8) on the PPG waveforms. Note that the peripheral venous pressure waveforms are overlapping on the DC component of the PPG

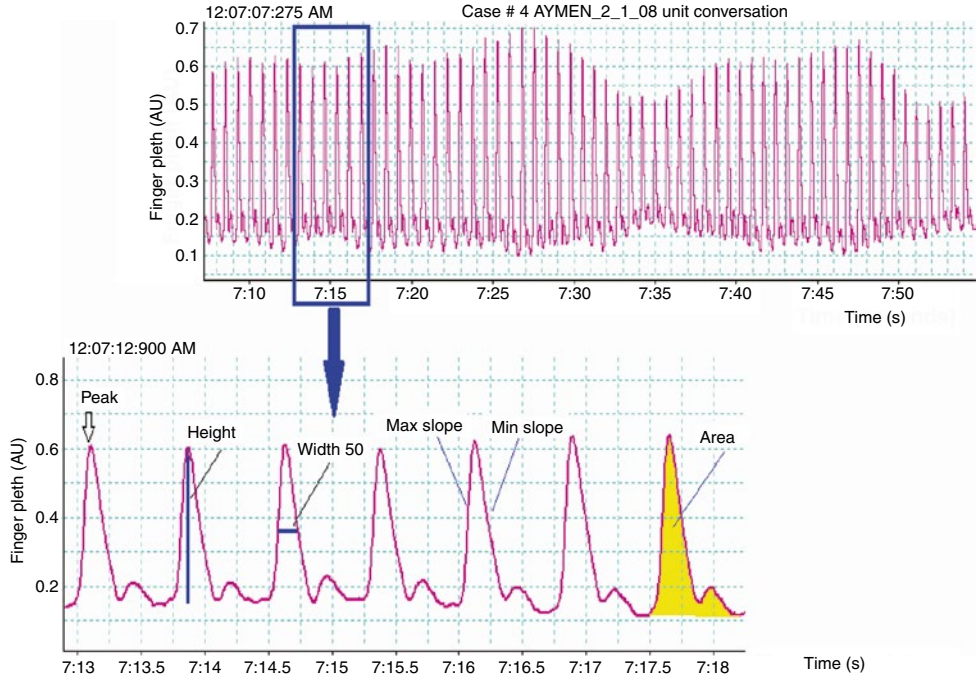

Fig. 19.2 Finger PPG waveform time domain analysis to PPG height, width 50, area, max, and min slops

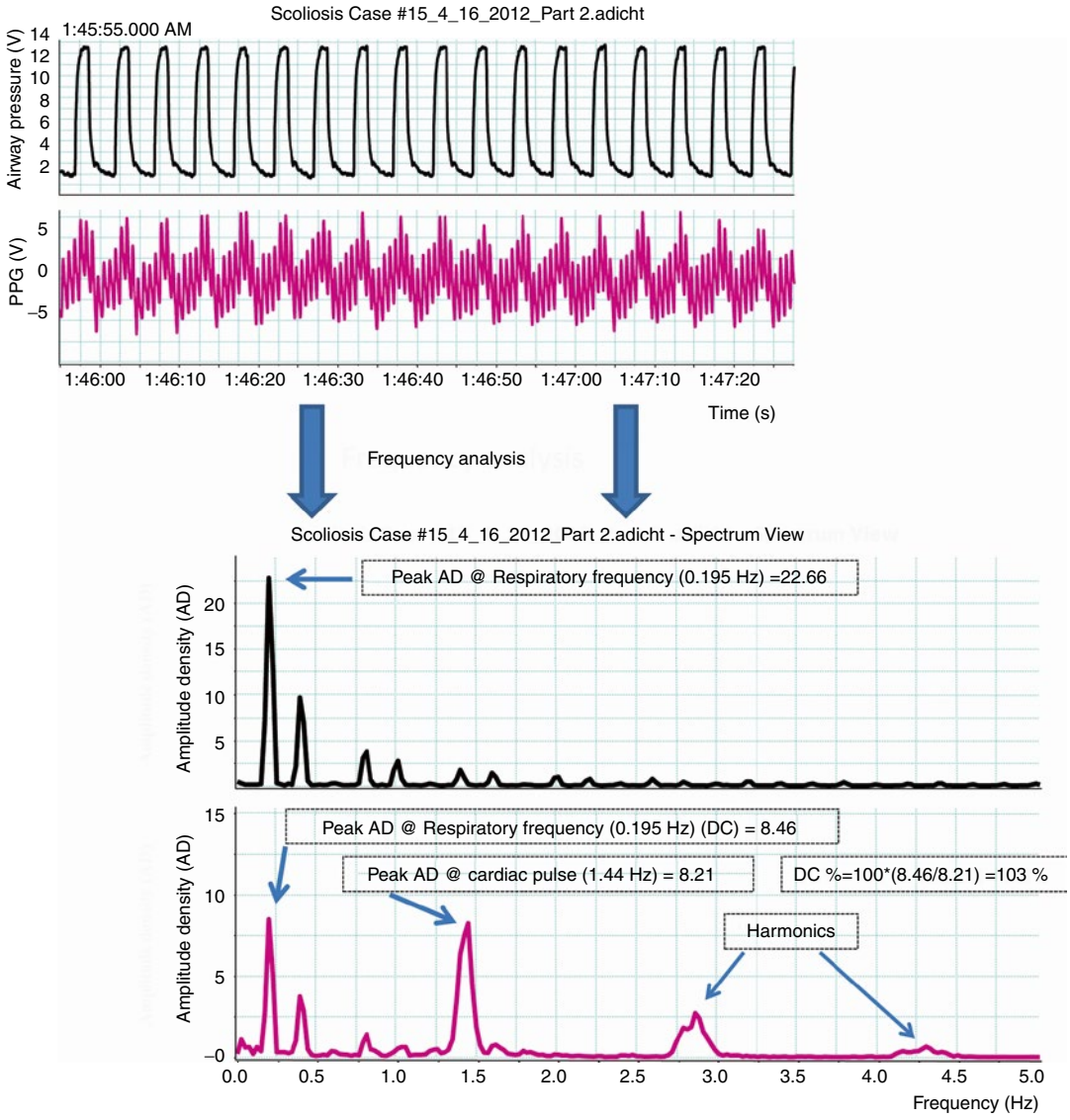

Fig. 19.3 Airway pressure and PPG waveform raw data collected at 100 Hz (*left side*), frequency analysis utilizing FFT window size of 4 K (hamming) with 93.75 % overlap, and amplitude density (*AD*) of airway pressure (respiratory) = 22.8 @0.195 Hz. The PPG DC (AD at the respiratory frequency) = 8.2 @ 0.195 Hz, while AD at the cardiac pulse = 10.0 @ 1.44 Hz. The DC% = 82 %

power spectrum, which allows independent analysis of the sine and cosine functions [11, 12].

Frequency domain analysis is dependent on window size, type, and percent of overlap. Longer time periods are required in order to accurately detect low frequency spectral information, as shown in Fig. 19.3.

Frequency domain analysis is less prone to artifact interference which is considered to be an advantage as regards waveform analysis. Analysis consists of measuring amplitude density of PPG direct current (DC) at the respiratory frequency and alternate current (AC, amplitude modulation) at the respiratory frequency.

Amplitude Analysis

There are multiple factors that can affect the plethysmographic waveform amplitude (Table 19.2).

When examining the PPG amplitude change over time, the region of the body being measured is important. In the finger, where the walls of the cutaneous vessels are richly innervated by α-adrenoceptors, the sensitivity to changes in the sympathetic system is greater than when compared to other areas of the body such as the earlobe [13]. Once a baseline measurement has been established, the pulse oximeter amplitude can be followed as a monitor of vascular sympathetic tone [14, 15]. An intriguing potential use of the plethysmograph may be as an indicator of MAC-BAR [16], the dose of anesthetic required to block adrenergic response in 50 % of individuals who have a surgical skin incision. The degree of sympathetic responsiveness a patient retains during an anesthetic might have important clinical implications (Fig. 19.4).

If the vascular compliance is low, for example, during episodes of increased sympathetic tone,

Table 19.2 Factors affecting pulse oximeter waveform amplitude

Increased amplitude due to vasodilatation
Pharmacological—nitroprusside
Physiologic—warming, sedation
Anesthetic—regional sympathetic blocks (spinal and epidural)
Decreased amplitude due to vasoconstriction
Pharmacological—phenylephrine, ephedrine
Physiologic—cold, surgical stress

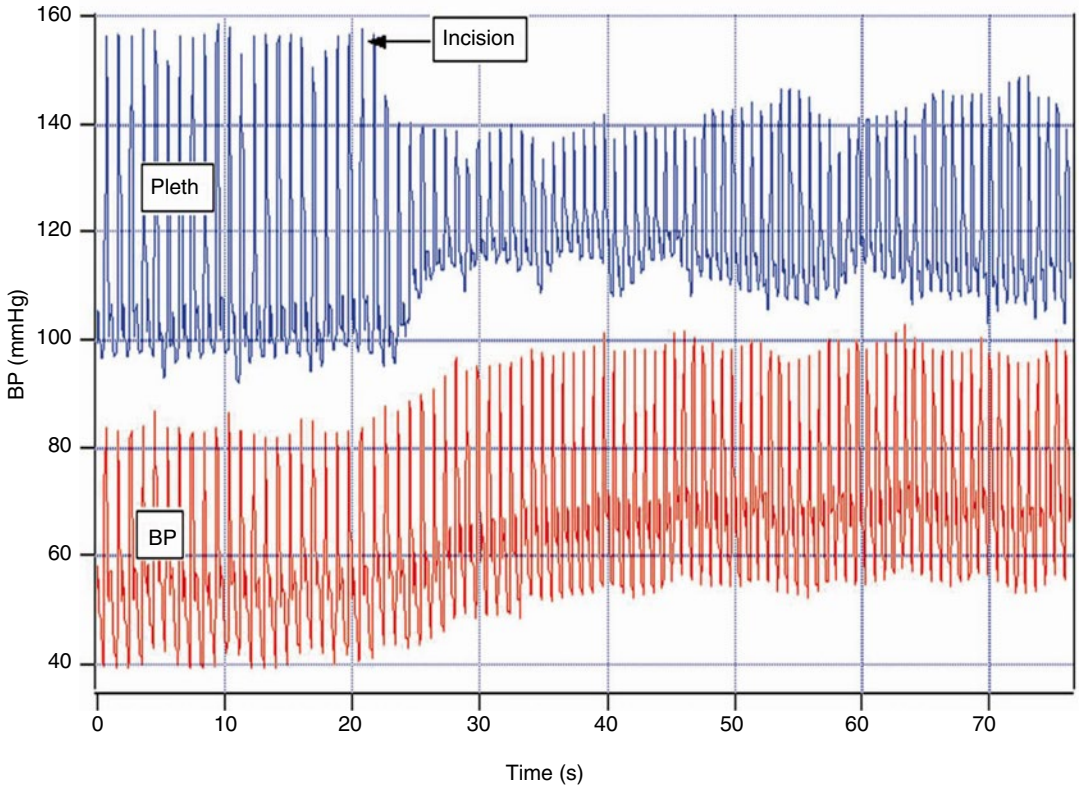

Fig. 19.4 Pulse oximeter waveform response to surgical stimulation. The pulse oximeter waveform is noteworthy for the sudden reduction in amplitude with skin incision. This is felt to be indicative of a sudden increase in sympathetic tone causing peripheral vasoconstriction. A concomitant increase in the arterial blood pressure (*BP*) supports this explanation

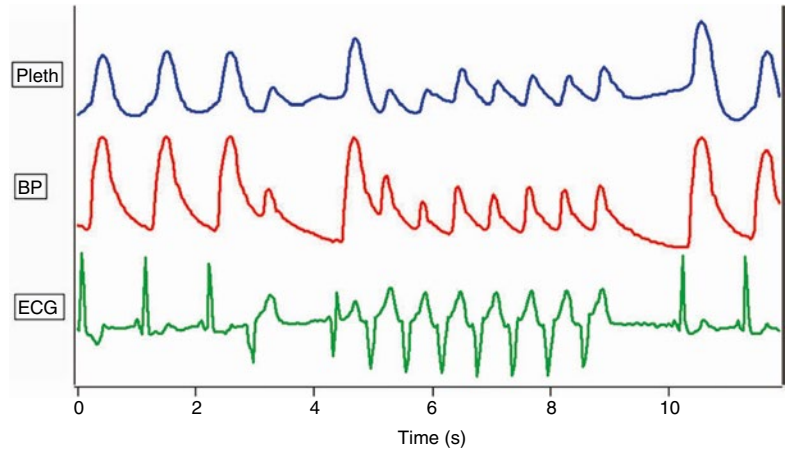

Fig. 19.5 The impact of ventricular tachycardia on the pulse oximeter waveform (*Pleth*), the arterial pressure waveform (*BP*), and the electrocardiogram (*ECG*). The sudden reduction in the amplitude of the pulse oximeter waveform, combined with the typical ECG pattern, should give an important warning regarding the presence of a dangerous situation

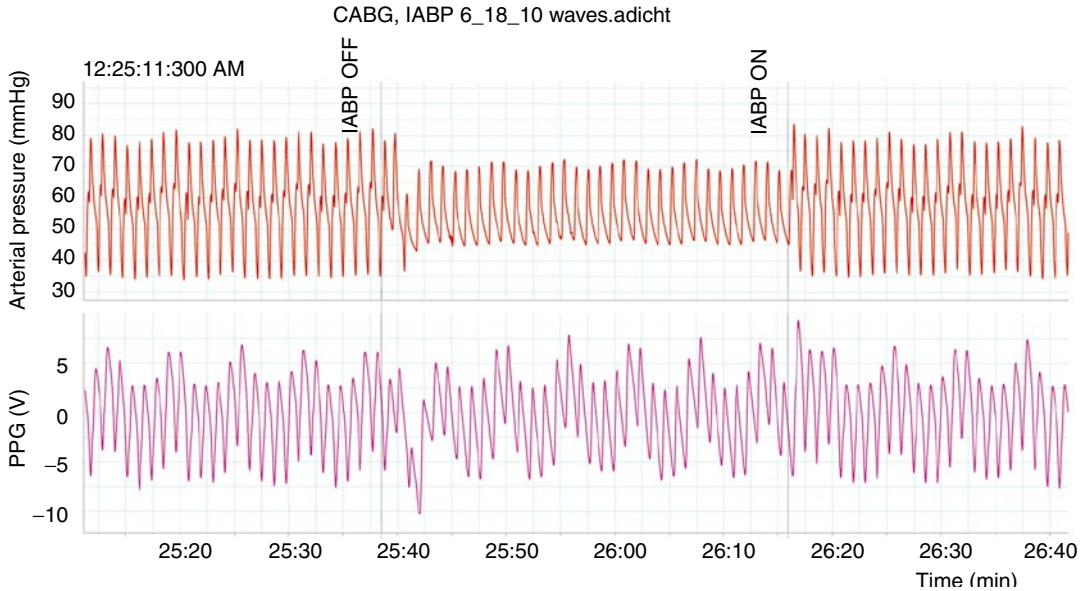

Fig. 19.6 The impact of intra-aortic balloon pump (*IABP*) on arterial pressure and PPG waveforms

the pulse oximeter waveform amplitude is also low, while with vasodilatation, the pulse oximeter waveform amplitude is increased. The plethysmographs were also used to monitor the effects of spinal, epidural, and regional blocks [17–20].

Rhythm Analysis

Pulse oximeter waveform can be a useful tool for detecting and diagnosing cardiac arrhythmias as shown in (Figs. 19.5 and 19.6).

To be used to maximum benefit, the pulse oximeter waveform is used in conjunction with the electrocardiogram. This can greatly help in correctly interpreting artifacts due to patient movement or electrical cautery [21]. A beat-to-beat change of the pulse oximeter amplitude is often the first clue that the patient has developed an irregular heart rhythm. Comparing the pulse oximeter waveform to the electrocardiogram is an excellent way to confirm these changes. As demonstrated in these figures, there exists a complex relationship between arterial blood pressure and the volumetric nature of the PPG [22]. Photoplethysmography variability (PPGV) has been shown to be highly correlated with the parameters of HRV; thus, PPGV could be used as an alternative measurement of HRV [23].

Dicrotic Notch Position

It has been speculated that the vertical position of the dicrotic notch, as detected with the pulse oximeter, can be used as an indicator of vasomotor tone. It appears that the dicrotic notch tends to descend toward the baseline during increasing vasodilation and climbs to the apex of the pulse waveform with vasoconstriction [24, 25].

Measurement of Regional Tissue Perfusion

A number of studies have been published using the pulse oximeter's plethysmographic capability to detect changes in tissue perfusion. Changes in the plethysmograph infrared light absorption have been shown to correlate well with local blood volume changes [26]. The advantage the pulse oximeter offers is the ability to do noninvasive, continuous monitoring of peripheral blood flow with readily available technology. Published studies using these techniques to determine tissue perfusion have been performed on small bowel [27], reimplanted fingers [28], and free flaps [12].

Hypovolemia and Respiratory Variability Analysis

The proper diagnosis of the degree of hypovolemia and fluid responsiveness in surgical patients is crucial for safe anesthesia management, although it is often challenging. Preload indices such as left ventricular end-diastolic volume, left ventricular filling pressure (PCWP), and right ventricular filling pressure (CVP) have been used extensively over the past decades to guide volume expansion, and even if measured correctly (at the end expiratory phase), ventricular preload parameters are a poor predictor of fluid responsiveness [29–31]. Variations in arterial pulse pressure (ΔPP) [32], vena cava diameter [33], stroke volume (SVV) [34], and aortic blood flow [35] have been shown to be more accurate predictors of fluid responsiveness. Recently variation in pulse oximeter waveform amplitude (ΔPOP) was shown to be strongly related to ΔPP and reported to be an accurate predictor of fluid responsiveness in both mechanically ventilated and spontaneously breathing patients [36–40]. With ventilation (spontaneous and positive pressure) there is fluctuation of both the baseline (DC) and pulsatile (AC) components of the plethysmographic waveform. The ability to detect the influence of the respiratory system on the cardiovascular system opens intriguing possibilities. The effect of positive-pressure ventilation on the arterial pressure waveform has been well described (Fig. 19.7). It is theorized that with each positive-pressure breath, venous return to the heart is impeded resulting in a temporary reduction in cardiac output. As a patient becomes volume-depleted, with a resulting decrease in venous pressure, positive-pressure ventilation has an exaggerated impact on the arterial blood pressure; a similar effect on the plethysmograph has been described. These cyclic changes that occur due to alteration in physiology have been described by various terminologies such as systolic pressure variability (SPV), pulse pressure variation (PPV), delta up/delta down, and respiratory waveform variation [32, 41–43]. An increase in SPV may be a significant clinical sign in a variety of critical conditions (Table 19.3) [44].

There are ongoing research efforts designed to find the best site and method of analysis for quantifying the effects of ventilation on the plethysmographic waveform [45, 46] (Fig. 19.8).

Masimo has developed a measurement Pleth Variability Index (PVI), which is a measure of the dynamic changes in perfusion index (PI) that occur during the respiratory cycle [44, 47]. The calculation is accomplished by measuring changes in PI over a time interval where one or more complete respiratory cycles have occurred. PVI, therefore, is displayed as a percentage. The lower the PVI, the less variability there is in the PI over a respiratory cycle, while a rising PVI may indicate developing hypovolemia.

$$\mathrm{PVI} = \left[\left(\mathrm{PI\,max} - \mathrm{PI\,min}\right) / \mathrm{PI\,max}\right] \times 100\,\%$$

Monitoring the respiratory variability (oscillation at the respiratory frequency) seen in the pulse oximeter waveform may be a useful method of detecting occult hemorrhage, with its resulting hypovolemia [40, 48]. As mentioned above, the cyclic changes in blood pressure and the plethysmographic waveform not only reflect changes in

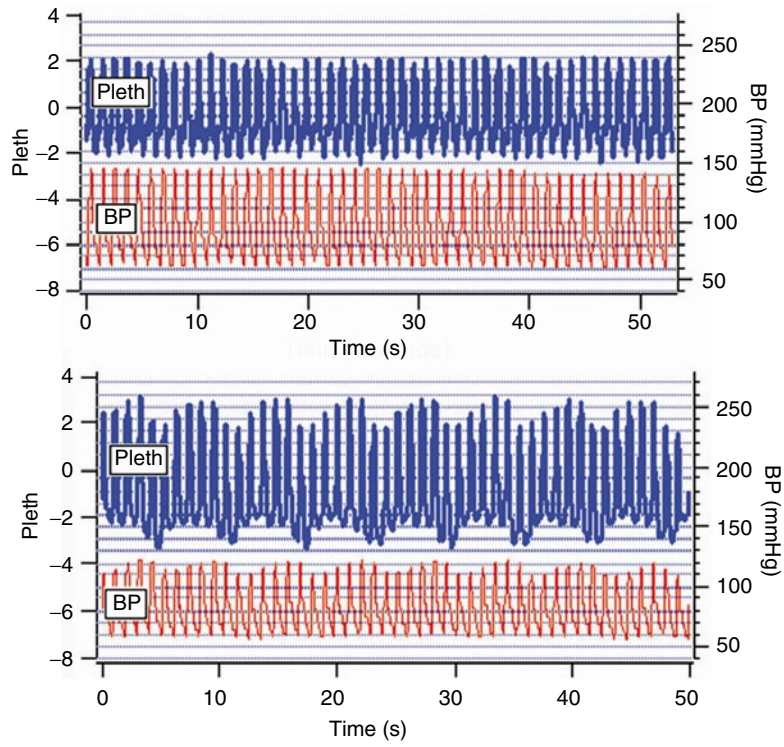

Fig. 19.7 The effect of blood loss on the pulse oximeter waveform (*Pleth*) and arterial pressure waveform (*BP*). The *upper diagram* shows the baseline waveforms of the patient under general anesthesia with positive-pressure ventilation. The *lower diagram* is after a 1,000 mL blood loss. The effect of positive-pressure ventilation is apparent in the lower diagram

Table 19.3 A variety of conditions are associated with increased systolic pressure variability

Cardiac causes	Noncardiac nonpulmonary causes	Pulmonary causes
Cardiogenic shock	Hypovolemia	Asthma
Cardiac tamponade	Septic shock	Tension pneumothorax
Pericardial effusion	Anaphylactic shock	
Constrictive pericarditis	Diaphragmatic hernia	
Restrictive cardiomyopathy	Superior vena cava obstruction	
Pulmonary embolism	Extreme obesity	
Acute myocardial infarction		

the intravascular volume status of patients but also can be caused by changes in intrathoracic pressure relative to the intravascular volume [49]. Asthma is one condition where intrathoracic pressures are greatly elevated when compared to normal, resulting in pronounced cyclic changes [50].

PPG and PVP Changes During Lower Body Negative Pressure (LBNP)

Combining information from pulse oximeter and peripheral venous pressure will give us more information about the volume status of the patient. Monitoring of the peripheral venous pressure (PVP) during lower body negative pressure (LBNP), where there is a sequestration of about 1.5–2 L of blood in the lower extremities (induced hypovolemia in spontaneously ventilated volunteers), showed reduction in the oscillation of PVP at the respiratory frequency. With restoration of the blood volume, there will be reduction in the pulse oximeter waveform oscillation, but there will be an increase in the PVP oscillation at the respiratory frequency [51]. While in asthma there will still be an increase in both plethysmographic and PVP oscillation at the respiratory frequency.

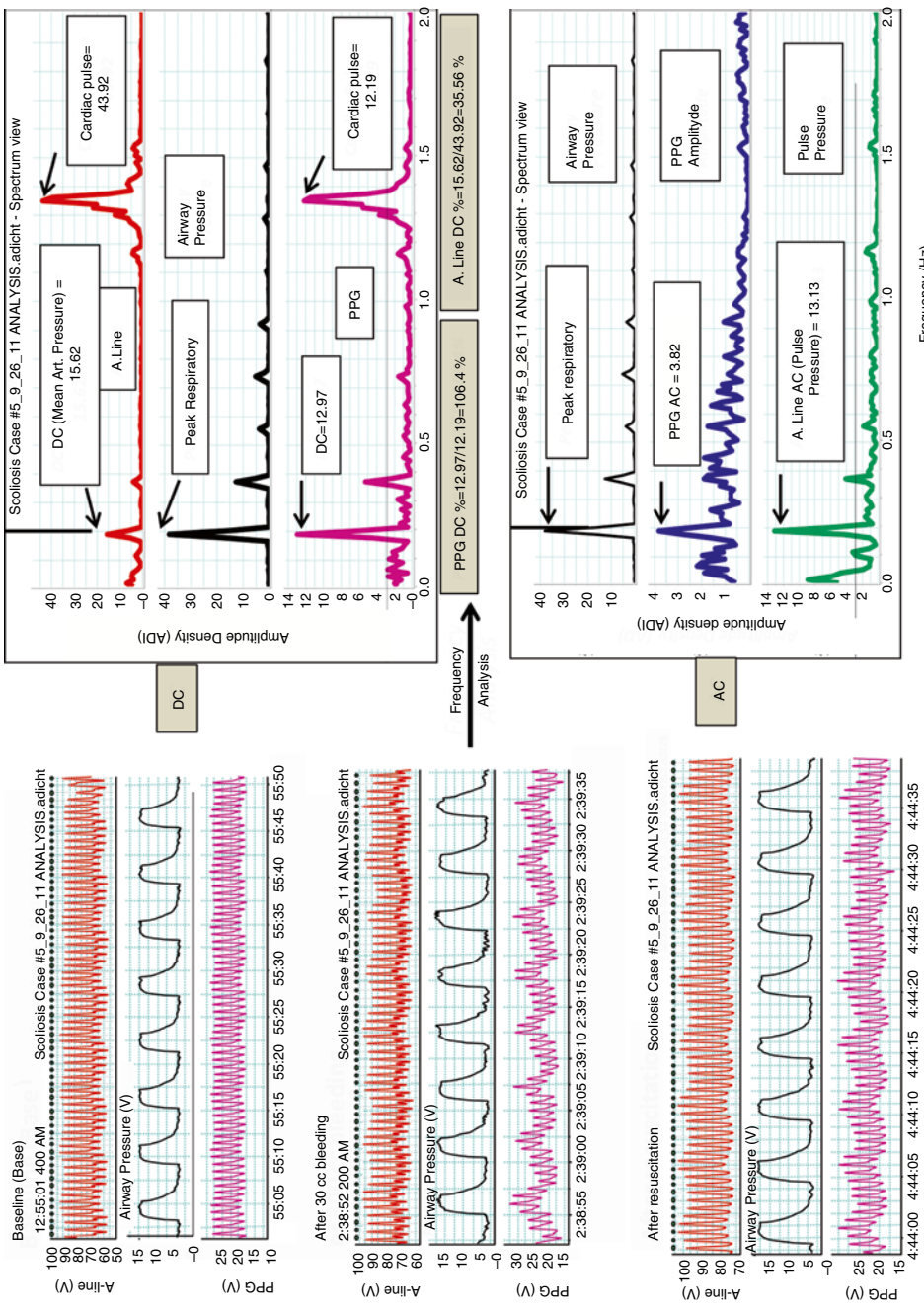

Fig. 19.8 *Left*: Raw data for three segments. *Right*: Frequency analysis of the arterial and PPG waveforms utilizing frequency analysis. The DC component is a measurement of baseline oscillation with ventilation, while the AC shows the effect of ventilation of the amplitude height of the waveforms

Autonomic Modulation

During lower body negative pressure (LBNP) protocol performed on spontaneously ventilated volunteers, there was an increase in the respiratory modulation of the ear PPG from baseline to the symptomatic phase as measured within the respiratory frequency band (0.19–0.3 Hz) (Fig. 19.9a). Within the ear PPG autonomic frequency (0.12–0.18 Hz), there was first an increase during the early

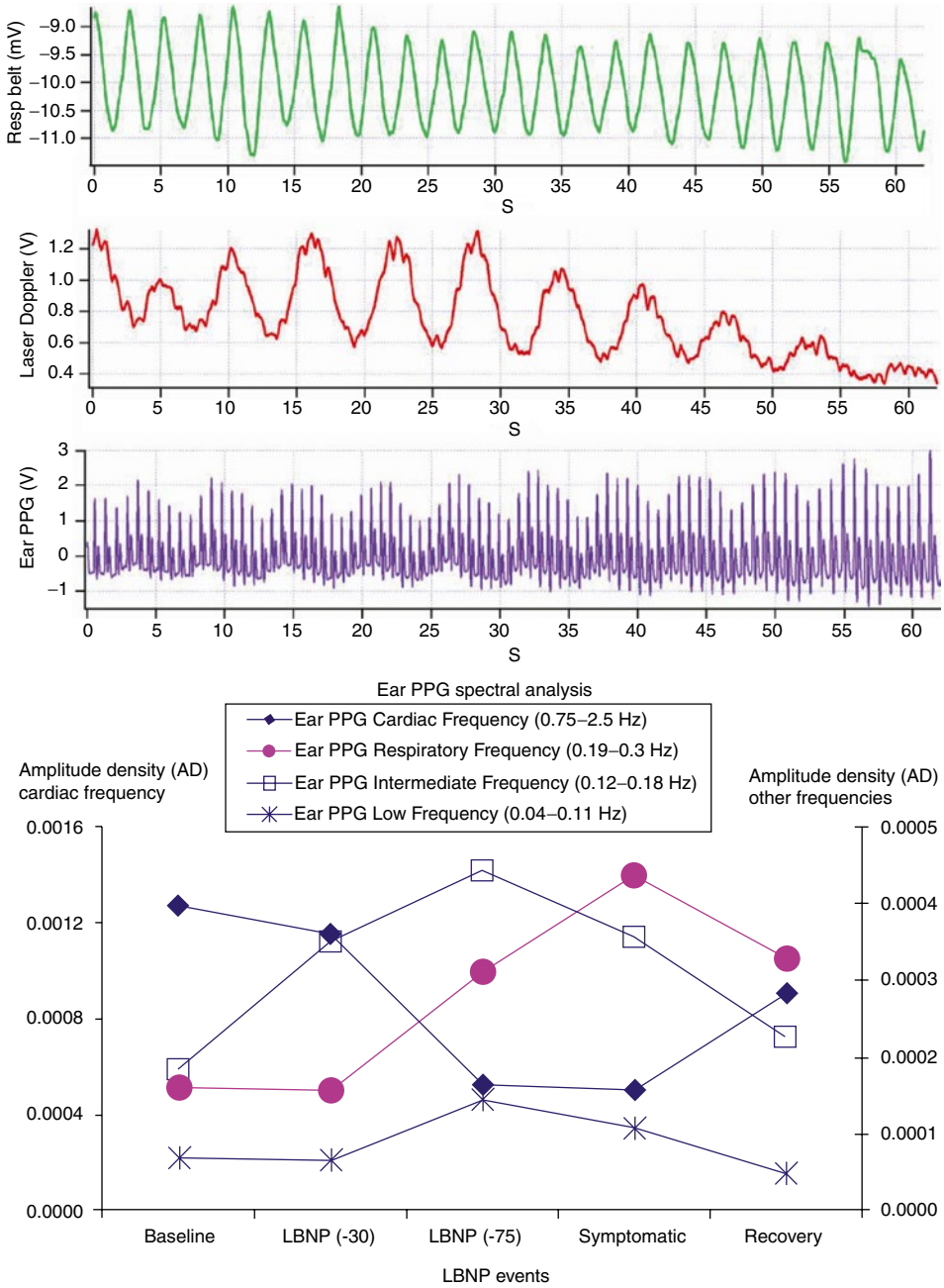

Fig. 19.9 Ear plethysmographic oscillation during lower body negative pressure (*LBNP*) protocol. *Top*: Waveforms of respiratory band, laser Doppler flowmetry, and ear plethysmography during the symptomatic phase of LBNP. Note that the frequencies of the ear PPG and laser Doppler flowmetry are similar, and both are different from the respiratory band frequency. *Bottom*: Ear oscillation at the respiratory frequency band (0.19–0.3 Hz) and autonomic frequency (0.12–0.18 Hz) during different phases of LBNP events

stages of LBNP, followed by a decrease (return to baseline) as the subjects became symptomatic; the same changes occurred with laser Doppler forehead flowmetry (Fig. 19.9b) [52]. This modulation appears to be due to the autonomic system, most likely parasympathetic in nature. The occurrence of autonomic modulation needs to be taken into account when studying signals that have their origins from central sites (e.g., ear and forehead).

Impact of Ventilation on the PPG Waveforms

Clinician should be aware of the impact of different modes of ventilation on the PPG waveforms as shown in Fig. 19.10 [53]. It is felt that baseline modulation is due to the movement of venous blood. While amplitude modulation is due to changes in stroke volume with each breath.

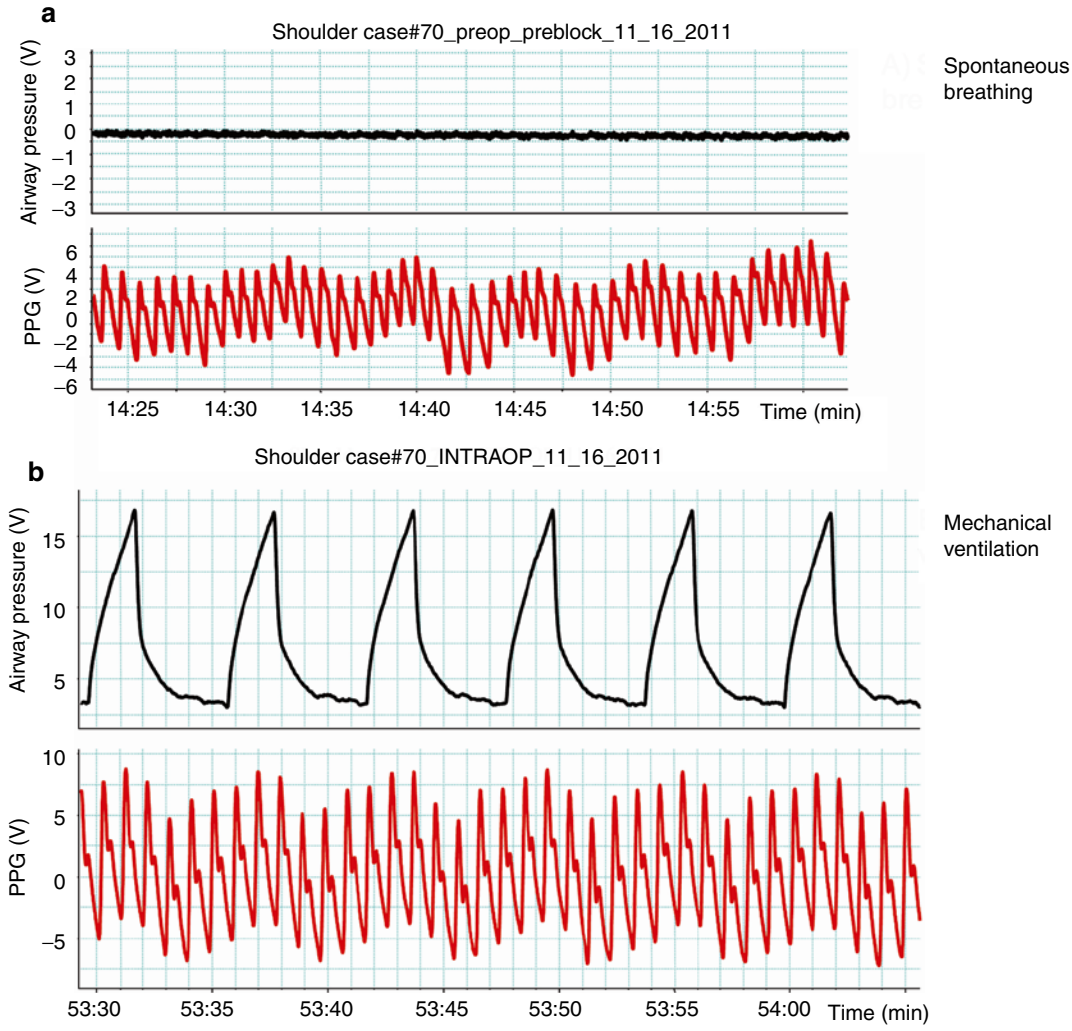

Fig. 19.10 The impact of different types of ventilation on PPG waveforms. (**a**) Spontaneous breathing. (**b**) The impact of volume-controlled mechanical ventilation on PPG waveforms. (**c**) Patient is blowing out through the incentive spirometry; patient is generating positive 20 cm H_2O. (**d**) Patient taking deep breath through incentive spirometry. Maximum negative airway pressure was around 30 cm H_2O; notice that PPG waveforms are an exaggeration of the normal spontaneous breathing. (**e**) Pressure-controlled ventilation (*PCV*). (**f**) An example of airway pressure release ventilation (*APRV*)

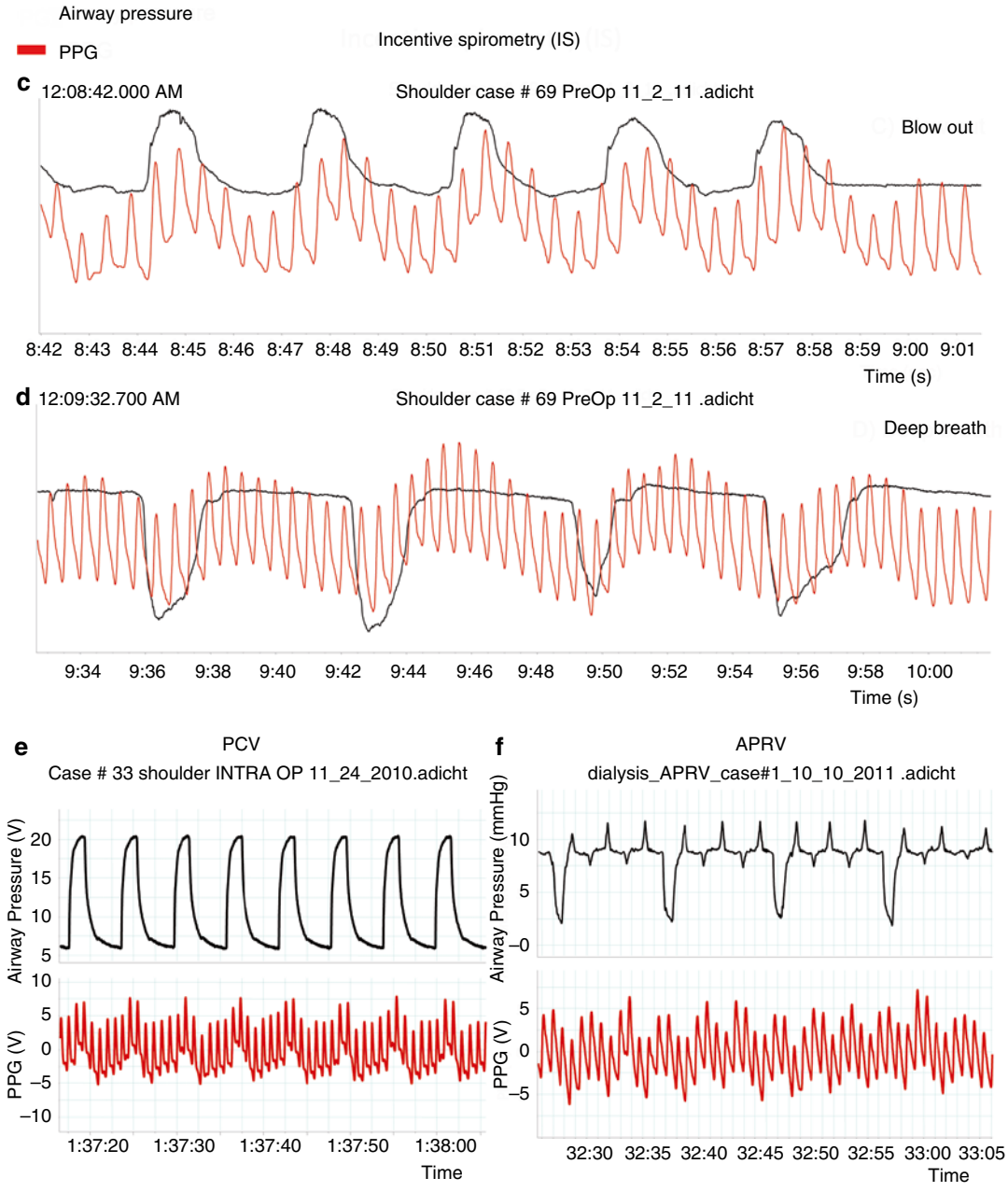

Fig. 19.10 (continued)

Conclusion

The key to the interpretation of the photoplethysmographic waveform is an understanding of the physiology behind regional blood volume variation. This variation is due to a complex interaction between the cardiac, respiratory, and autonomic systems. State-of-the-art digital signal processing methods are allowing for a detailed examination of the resulting waveform. The long-term goal should be the utilization of this examination to develop new techniques of patient monitoring.

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Time and Volumetric Capnography

20

Michael B. Jaffe

Brief History

Carbon dioxide was first measured in a quantitative fashion in the 1800s. One of the earliest known physical infrared measurements of expired carbon dioxide (referred to as *carbonic acid* at the time) was undertaken in John Tydall's laboratory [1] and presented in his famous Rede lecture, "On Radiation" [2]. Other physical and chemical methods were used to quantify carbon dioxide in the nineteenth and twentieth centuries, but it was not until infrared (IR) measurement technologies were developed in the 1940s and commercialized in the 1950s for clinical use by companies, such as Liston-Becker (later acquired by Beckman), did carbon dioxide analyzers gain wider use [3]. The publication of Smalhout's strip-chart recordings in An Atlas of Capnography[1] [4] and his tireless lecturing helped to popularize its use.

Volumetric capnography, which combines instantaneous carbon dioxide and flow (i.e., volume) measurements, allows a variety of physiologically useful parameters to be quantified. Even though the concept of dead space was elucidated in the late 1800s, the actual measurement of dead space from flow and carbon dioxide sensors evolved from breath samples collected over the course of expiration in the 1920s to data samples from IR sensors with computer-derived curve fits in the 1960s [5]. However, it was not until Fletcher presented – in his doctoral thesis (1980) and later in various publications – the concepts of dead space and CO_2 elimination in a unified framework as single-breath curves of CO_2 with an available commercial platform did volumetric capnography find clinical use [6].

Why Capnography?

Since 1986, when the American Society of Anesthesiologists (ASA) included requirements for monitoring of exhaled carbon dioxide, the usage and applications of capnography have grown. The use of capnography for increasing patient safety and for applications such as airway management and monitoring (e.g., hypoventilation, airway obstruction) has led to its inclusion in practice standards and guidelines of professional societies (e.g., anesthesiology, critical care, pediatrics, respiratory care, emergency medicine, gastroenterology, nursing), patient safety organizations (e.g., APSF), accreditation organizations (facilities), state medical societies (anesthesia), fire departments, and federal organizations in the United States and other parts of the world [7]. The original ASA guidelines and the need for monitoring exhaled respiratory gases have been credited for driving the development of the first carbon dioxide gas monitoring standard [8].

[1] From Godart's genericized trademark capnograph.

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Recent amendments to the ASA guidelines [9] have expanded the use of exhaled carbon dioxide to include moderate or deep sedation, and the American Heart Association's adult advanced cardiovascular life support (ACLS) [10] includes the new recommendations for "continuous quantitative waveform capnography … for confirmation and monitoring of endotracheal tube placement," as well as a discussion of the potential value of $P_{ET}CO_2$ as an indicator of the return of spontaneous circulation (ROSC) and as a tool to optimize CPR quality. The case for widespread use of continuous capnography for airway management during varying levels of anesthesia, nasogastric tube placement, assessment of the effectiveness of chest compression during CPR, and monitoring during patient transfer and postoperatively and during acute exacerbations of respiratory disease is effectively argued in a recent editorial [11]. The editorial further highlights unjustified expectations of the end-tidal value by noting that:

> The academic point of imperfect correlation between the $PaCO_2$ and the end-expiratory fractional concentration of carbon dioxide ($FECO_2$) in diseased lungs appears to have had a disproportionately inhibitory effect on the use of capnography in the critical care setting, whereas more important and fundamental patient safety issues have been seriously overlooked. [11]

With respect to volumetric capnography, it can be noted that "*an individual tracing of the time-based capnogram left a number of questions unanswered, which the single breath volume-based capnogram provides*" [12]. This includes physiologically and clinically valuable measures with diagnostic, screening, and therapeutic applications, such as dead space and their ratios and carbon dioxide elimination [12].

Terminology

The term "capnogram" usually refers to the time-based capnogram, which produces the trace of carbon dioxide in either partial pressure or gas fraction units over time. This distinguishes it from the volumetric capnogram, the trace of carbon dioxide (usually in gas fraction) over volume in which the inspiratory portion of the curve is usually not displayed. Each is described by three phases associated with the source of the expiratory gases: (1) gas from the dead space, (2) the transition between dead space and alveolar gas, and (3) gas from sequential emptying of the alveolar volumes (Fig. 20.1). Even though time and volumetric capnograms usually appear similar in shape, this can, at times, be misleading (Fig. 20.2).

From the time-based capnogram, estimates of respiratory rate, end-tidal CO_2, and inspiratory levels of CO_2 are commonly reported. Coupling capnography with flow (and volume) measurements provides the capability of estimating anatomic and physiologic dead space ratios, CO_2 elimination, pulmonary capillary blood flow, and a whole range of physiologic indices (Table 20.1) that allow insight into many cardiopulmonary disorders, including adult (acute) respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, and pulmonary embolism. Viewing the changes in carbon dioxide as a function of volume, rather than time, allows for easier interpretation of the reported values and changes in those values in a context consistent with known physiologic concepts.

The most well-known capnographic parameter, the end-tidal value, is actually one of the least understood. It is often expected to equate to the arterial value but, in fact, is dependent on how it is measured and the patient's physiology (diffusion, ventilation, cardiac output), with an end-tidal arterial gradient usually present. As the name suggests, end-tidal value refers to the carbon dioxide value at end-expiration. However, in practice, the intent is to provide a value as close to the alveolar value as possible, and other values, such as the highest value during expiration, may be reported.

Respiratory rate derived from the capnogram is generally determined as the time between successive expiratory and inspiratory transitions of each breath. On face value, the determination of

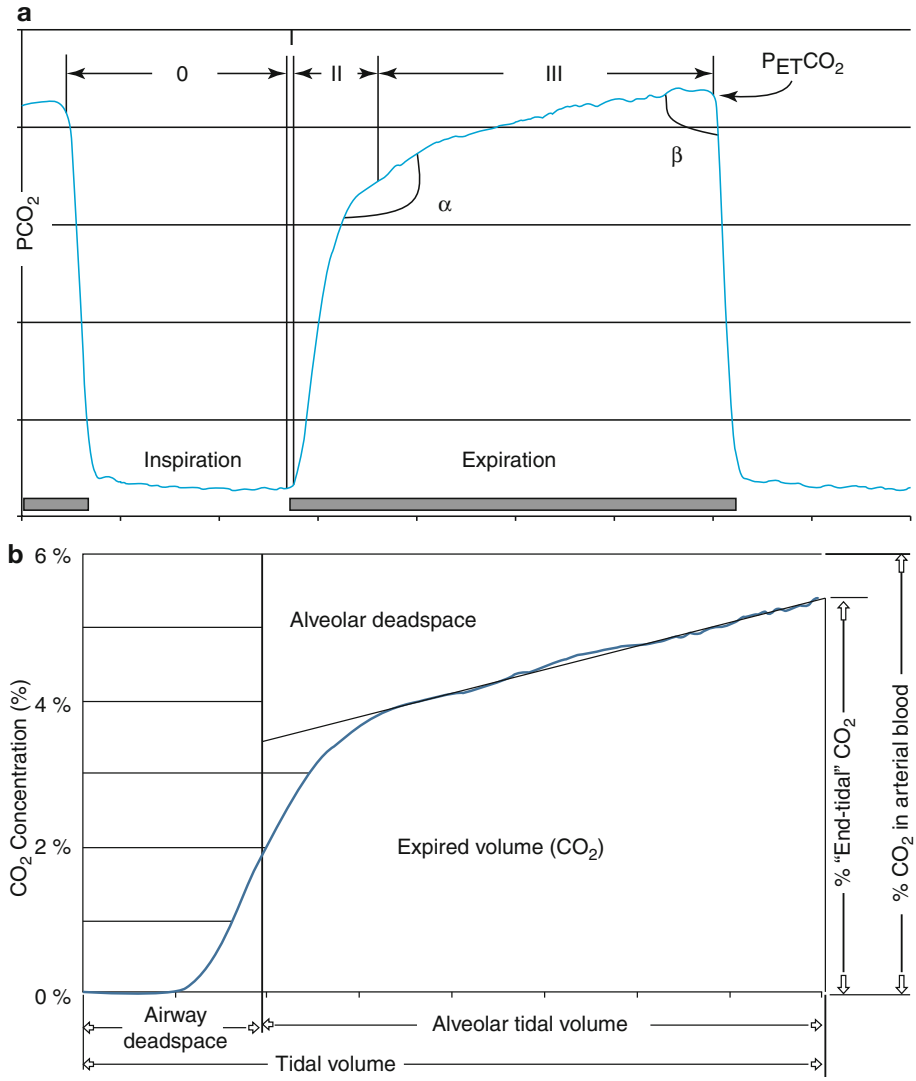

Fig. 20.1 (**a**) Time-based capnogram. Inspiratory segment (phase 0) and expiratory segment (divided into phases I, II, III) angle (α) = angle between phase II and phase III, angle (β) = angle between phase III and descending limb of phase 0 (inspiration) (Adapted from Bhavani-Shankar and Philips [13]). (**b**) Components of volumetric capnogram (CO_2/Volume Plot) (Adapted from Arnold et al. [14])

these transitions seems simple, but in practice, it can be quite complicated, and obtaining appropriate breath criteria is dependent on the clinical environment and application [15]. Note, however, that to help improve specificity and sensitivity, many manufacturers will apply additional "screening" using algorithms with names such as SARA [16] and RENE [17]

Technologies

A capnometer, by definition (per standard) [18], is either diverting (i.e., sidestream) or non-diverting (i.e., mainstream). A diverting capnometer transports a portion of the respired gases from the sampling site, through a sampling tube, to the sensor, whereas a non-diverting capnometer

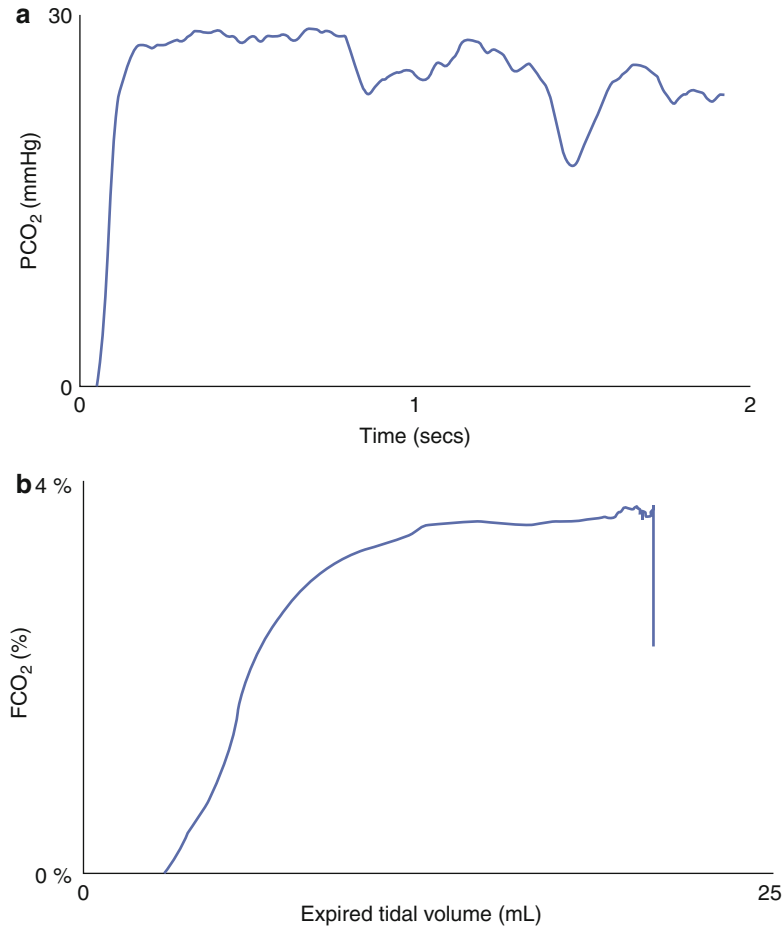

Fig. 20.2 (**a**) Time-based and (**b**) volumetric capnogram for a neonatal subject with a long expiratory pause. Note: CO_2 units for time capnogram are in mmHg, whereas units for the volumetric capnogram are often shown in % (Reproduced with permission from Philips Respironics, Wallingford, CT)

Table 20.1 Comparison of common measures available in volumetric and time-based capnography

	Volumetric capnography	Time-based capnography
End-tidal CO_2	Time-based average	Time-based average
Inspired CO_2	Various measures may be computed, including inspired CO_2 volume	Minimum value during inspiratory segment often calculated. Serves as rebreathing indicator
Breathing frequency	May be computed using flow waveform and/or capnogram	Inverse of time between the transition from expiratory to inspiratory segments of successive breaths
Inspiratory/expiratory time	Timing from start of inspiration and expiration determined from flow waveform	Approximate values may be calculated if dead space and rebreathing not significant
Mixed expired CO_2 ($PeCO_2$ or $FeCO_2$)	Volume-weighted average of CO_2	Not available
Expired tidal volume	Total volume expired by subject	Not available
CO_2 elimination (VCO_2)	Net volume of CO_2 measured at the mouth or airway and calculated as the difference between expired and inspired CO_2	Not available
Efficiency	Ratio of CO_2 volume contained in the breath and the volume of CO_2 that would have been eliminated by an ideal lung at the same effective volume and end-tidal fractional CO_2	Not available

Table 20.1 (continued)

	Volumetric capnography	Time-based capnography
Phases		
Phase I	CO_2-free gas from the airways	
Duration	Time from start of expiration to increase in PCO_2	Not available
Volume	Volume from start of expiration to increase in PCO_2	Not available
Phase II	Rapid S-shaped upswing on the tracing caused by the mixing of dead space gas with alveolar gas	
Duration	Time from end of phase I to intersection of predictive slopes of phase II and III	Approximate measure available
Volume	Volume during phase II	Not available
Slope	Curve fit of central portion of phase II volume	Curve fit of central portion of time-based phase II
Phase III	Alveolar plateau representing CO_2-rich gas from the alveoli	
Duration	Time from end of phase II to end of expiration	Approximate measure available
Volume	Volume during phase III	Not available
Slope	Curve fit of central portion of phase III volume	Curve fit of central portion of time-based phase III
Alpha angle	Angle between phase II and III	Angle between phase II and III (ranges between 100 and 110°)
Dead space(s)		
Airway ("anatomic")	Volume of the conducting airways at the "midpoint" of the transition from dead space to alveolar gas	Not available
Physiologic	Total dead space includes alveolar, airway, and apparatus dead spaces	Not available
Alveolar	Dead space that is not airway dead space volume and is calculated by subtracting the airway dead space volume from the "physiologic" dead space	Not available
Dead space ratios		
Airway	Functional anatomic dead space calculated via Fowler's method divided by expired tidal volume	Not available
Physiologic	Total dead space calculated graphically with Enghoff-modified Bohr equation or alternate methods	Not available
Alveolar	Alveolar volume divided by expired tidal volume	Not available

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does not transport gas away from the sampling site. In other words, one can view the difference between mainstream (non-diverting) capnography and sidestream (diverting) capnography as direct on-site instantaneous measurement of gas and remote measurement delayed typically by several seconds (Table 20.2).

Two of the most important specifications of a capnometer or respiratory gas monitor (RGM) are measurement accuracy and system response time. The required minimum measurement accuracy, defined as the "quality which characterizes the ability of an RGM to give indications approximating to the true value of the quantity measured" [18], is specified in the current standard as CO_2 ± volume fraction of 0.43 % plus 8 % of gas levels in volume fraction %. The standard defines total system response time as the time from the step function change in gas levels at the sampling site to the time a 90 % of a final gas reading is

achieved. This is often further subdivided into delay time and rise time. Delay time is sometimes called lag or transit time. Delay time only applies to sidestream systems and depends on sampling flow rate, the diameter and length of the sampling tube, and the sample viscosity. When comparing devices from different manufacturers, it is important that the reported delay and rise time include the sampling accessories (nasal cannula, airway sampling adapter, etc.).

Table 20.2 Comparison of mainstream and sidestream approaches

Feature	Mainstream	Sidestream
Airway connections		
Location of infrared analysis unit ("bench")	At the airway connector	In the monitor
Size of airway connector	Small	Small
Weight of airway connection	Medium (<2 oz)	Light
Location of airway connector	End of endotracheal tube	End of endotracheal tube (may replace "angle" connector
Use on extubated patients	Yes, with a facemask or mouthpiece; some monitors contain a pump to convert to sidestream mode	Yes, with nasal adapter or oxygen prongs
Connecting tube or cable	Thin, medium-weight flexible cable No sample tube	Small-bore sample tube
Required components to "sample" gas	Airway adapter and bench	Airway adapter, sample tube, filters, water trap, water-permeable tubing
Airway connector disposable or reusable	Bench reusable; airway adapters are reusable or disposable	Airway adapters are reusable or disposable
Durability of airway connector	Durable	Variable
Cost of replacing airway connector	Bench expensive to replace; AA inexpensive to moderately expensive	Very inexpensive on a per sensor basis – but on very wet patients may require frequent changes
Can be used in collaboration with simultaneous oxygen administration	Yes, with facemask. Possible dilution of sample with significant loss of seal. Mouthpiece or where available sidestream mode with nasal cannula	Yes, with nasal prong. Probable dilution of sample
Sample volume drawn	None	Less than 250 mL/min (may be compensated even in neonates or sampled gas can be returned to circuit)
Dead space added to airway connector	Small (<1 mL in neonates)	Minimal
Response and signal fidelity		
Delay between sampling and waveform display	None	Less than 3 s
Bench 10–90 % rise time	Typically <70 ms	Typically >200 ms
Waveform display	Crisp. No deformity of capnograms due to non-dispersion of gases	Smooth appearance because it is filtered by the sample line artifact and slower response time
Accuracy of waveform shape	Excellent. No effect due to variable pressure drop	Variable – depends upon factors including sample rate, mixing, sample cell design
Numeric display	Breath-to-breath or averaged end-tidal and breathing frequency	Breath-to-breath or averaged end-tidal and breathing frequency

Table 20.2 (continued)

Feature	Mainstream	Sidestream
Moisture and contamination		
Changes in water vapor pressure	Not affected	Affected due to condensation and drying of sample
Moisture handling	Bench at airway adapter contains a heater or other means to prevent condensation; water droplets may condense on window but usually clear rapidly	Water trap – modern water traps can be extremely efficient but tend to clog (some use Nafion tubing which equilibrates with ambient humidity)
Potential of cross-contamination between patients	None – disposable or reusable AA can be sterilized and then reused at no risk of contamination	Airway adapter and sample tubes can be disposed at low cost or sterilized and reused at no risk of contamination provided no purging or return of gas to patient breathing circuit
Gas scavenging ("pollution" risk?)	Not required	Gas outlet on monitor can be scavenged or permanently installed to return sampled gas to a connector at expiratory valve on circle system; carries no more risk than use of soda lime

Portions used with permission from Philips Respironics

With mainstream devices, the sensor, consisting of the sample cell and infrared bench, is placed at the airway.[2] This location results in a "crisp" capnogram that reflects, in real time, the partial pressure of carbon dioxide within the airway. On the other hand, sidestream devices aspirate a sample of gas from the breathing circuit through a six- to eight-feet long small-bore tube. This sample is then often passed through a water-handling accessory (e.g., water trap or Nafion tubing) and filters prior to being analyzed in a sample cell, which results in a delay time of about 3 s (with current systems and a sample flow rate of 50 mL/min) and a rise time of 200 ms or greater. It has been noted that this delay in total response time can be in some circumstances significant due to the need to provide the clinician the earliest warning possible [19].

[2] A number of technologies are known for measuring carbon dioxide in the breath including infrared absorption, colorimetric, photoacoustic, Raman scattering, and mass spectroscopy, but only infrared spectroscopy will be discussed.

The infrared bench for both mainstream and sidestream devices usually comprises an infrared source (either a broadband or narrowband source), filters at two wavelengths (one at which CO_2 is not absorbed and another usually about 4.25 μm at which CO_2 is strongly absorbed), and one or more infrared-sensitive detectors (thermal, microphonic, or photonic). With solid-state approaches, two detectors, each with a filter and appropriate optics, are used. With a filter wheel, filters placed on a wheel periodically interrupt (or chop) the beam of infrared radiation. The measured absorption of CO_2 can be altered by cross-interference and collision broadening due to the presence of gases such as nitrogen, nitrous oxide, and oxygen. Cross-interference, the overlapping of absorption bands of other gases, can occur from nitrous oxide due to the presence of strong absorption bands that slightly overlap both edges of the carbon dioxide band. The use of narrowband sources or narrowband filters in front of the detector can effectively eliminate the effect of cross-interference. On the

other hand, collision broadening tends to be less device specific and is a complex function of the total pressure and the presence of other gases. This effect is often compensated for by the system's software using nominal values. These and other technical aspects are reviewed in greater depth elsewhere [12].

While both mainstream and sidestream devices continue to improve in performance, the earlier criticisms of mainstream technology relating to weight and size have been largely overcome with the introduction of solid-state sources or miniature filter wheels, improved optics, and modern integrated circuits. Sidestream technology continues to improve; however, attention must continue to be given to water removal, differing conditions at the sampling site and sample cell (i.e., temperature and humidity), and the effect on waveform fidelity due to the mixing of the sample gas as it is drawn through the sampling system.

With the introduction of integrated microprocessor-based sensors, all of the calculations and algorithms are available within the sensor; thus, the measured capnogram and derived parameters, such as end-tidal CO_2 and respiratory rate, can be transmitted to the monitor, allowing for a simple flexible interface between the monitor and sensor and lower implementation complexity for the monitor. Table 20.3 summarizes the key characteristics of the more recently introduced integrated capnometers, including both mainstream and sidestream configurations. In these devices, filters integrated with the sampling tubing have supplanted water traps common in earlier systems.

The CO_2 and flow waveforms may each be measured in a sidestream and/or mainstream manner. However, to calculate anything other than carbon dioxide elimination, at least one of these waveforms needs to be in-line and proximal (mainstream). The various commercial offerings have included measurements using proximal flow with distal CO_2 (e.g., sidestream sampled or at the exhalation port), proximal CO_2 with distal flow, and proximal flow and CO_2. With each approach, potential error sources include the effects of compressibility and condensation, complexity of signal alignment, and ability to estimate accurate end-tidal and volumetric values. Of these approaches, only the use of proximal flow and gas measurements, as with an integrated CO_2/flow airway adapter (Fig. 20.3), can ensure that these sources of error are relatively minor. Software and breathing circuit additions have allowed volumetric capnography devices to extend their applicability to maneuver-based measurements, such as partial rebreathing cardiac output, lung recruitment, and functional residual capacity.

Clinical Applications

A complete review of the current and evolving applications of time and volumetric capnography will be left to textbooks on the subject [12] and the clinical literature. The organization and editing of the most complete text to date on the subject, *Capnography: Clinical Aspects* [12], required dealing with the question of how to best organize these applications. JS Gravenstein, lead editor on this text and pioneer in anesthesia safety, explained how he viewed CO_2 in a clear and wonderful context:

> CO_2 has four stories to tell: The first, starting from the outside, deals with the adequacy of breathing (and the occasional problem of rebreathing), that is with the transport of the gas from within the body to the outside. The next story has to do with transport of CO_2 in the body, bringing the gas to the lungs, which is dealing with the circulation and particularly with pulmonary blood flow. It includes the business of how CO_2 is transported in the blood. The third story has to do with the production of CO_2, which has to do with metabolism and temperature. The fourth story deals with the effects of CO_2 itself on the body where it not only drives the respiratory system but can produce mischief by changing the pH, blood flow to the brain, and affecting the lungs. [20]

Others [21] have since proposed similar classification schemes. Table 20.4 attempts to summarize and contrast, in single page, most of the applications from both a time and volumetric capnographic perspective that would be of interest to readers of this text. The AARC, in its latest clinical practice guidelines on time and volumetric capnography during mechanical ventilation (MV)

Table 20.3 Selected recently introduced commercially available integrated capnometers

Manufacturer	Oridion[a]	Philips Respironics		PHASEIN[b]		Nihon Kohden
						
Model	microMEDICO$_2$™	CAPNOSTAT® 5	LoFlo®	IRMA™	ISA™	CapONE™ (TG-950P)
Configuration(s) (sample flow rate)	Sidestream (50 mL/min)	Mainstream	Sidestream (50 mL/min)	Mainstream	Sidestream (50 mL/min)	Mainstream
Optical design	Solid state	Solid state	Solid state	Filter wheel	Filter wheel	Solid state
Distinguishing features of interest	Discrete emission line source, specialized accessories	Coaxial design, Capno2mask™	Removable sample cell	Micro-filter wheel	Micro-filter wheel Nomoline™	Miniature sensor head[c] and accessories for cannula and facemasks
Water handling	Blocking – hydrophobic filter with large surface area	N/A	Absorbing and blocking – hydrophilic fibrous element followed by a hydrophobic plug	N/A	"Active" water removal with a hydrophilic wick	N/A
External available/ interchangeable?	Yes Only sidestream	Yes CO_2nnect & Go™		Yes PLUG-IN and MEASURE…™		Yes N/A

The microMEDICO$_2$ image used with permission of Covidien plc. The CAPNOSTAT 5 and LoFlo images used with permission of Philips Respironics, LLC. The IRMA and ISA images used with permission from Masimo Corporation. The TG-950P image used with permission from Nihon Kohden Corporation. The listed trademarks are trademarks of the respective companies

[a]Acquired by Covidien

[b]Acquired by Masimo

[c]Separate cable-mounted module for additional electronics

Fig. 20.3 Combined pediatric CO_2/flow sensor, perspective view (Reproduced with permission from Philips Respironics, Wallingford, CT)

[22], includes most of the applications noted in Table 20.4 and is based on a literature review of about 250 papers that investigated capnography during MV.

Capnography is most well known for its use in airway management, particularly as a confirmation post-intubation and continued indication of the proper position of the endotracheal tube via the presence of a capnogram [12]. Similarly, the absence of a capnogram has been used to provide confirmation of nasogastric tube placement [23]. Capnography's value during cardiopulmonary resuscitation, recognized for decades [24] and mandated only recently by ACLS guidelines in 2010, was demonstrated recently in dramatic

Table 20.4 Applications of time-based and volumetric capnography contrasted

Clinical use		Time-based capnography	Status	Volumetric capnography	Status
Acute clinical situations					
Intubation	Avoiding esophageal intubation during ETT placement	Fast detection of exhaled CO_2 verifies placement. Can give false-positives	Accept	Presence of CO_2 and flow strongly indicative of tracheal intubation	Specul
	Avoiding tracheal intubation during NG tube placement	Fast detection of exhaled CO_2 to verify incorrect placement	Develop	Lack of CO_2 and flow strongly indicative of not being in the trachea	Specul
	Avoiding endobronchial intubation during ETT placement	Variable. Not sensitive. Significant changes in end-tidal levels may be observed	Develop	Combination of CO_2, flow, airway pressure, and derived measures can assist detection	Specul
Prognosis and adequacy of cardiopulmonary resuscitation		$P_{ET}CO_2$ can guide efforts and indicate patient's response; predictive of survival	Accept	In addition – provides a direct assessment of ventilation	Specul
Assessment of airway obstruction		Variable	Accept	Slope of phase III	Specul
Screening for suspect pulmonary embolism		Poor. Useful only in extreme cases	Develop	Alveolar dead space and fDlate combined with D-dimer	Develop
Routine monitoring					
Preoperative assessment of respiratory disease		Potential quick screening tool, as part of OSA screening	Develop	See airway obstruction – above	Specul
Mechanical ventilation	Detection of circuit leaks and/or rebreathing	Good but may miss some leaks, rebreathing assessment only qualitative	Accept	Allows for quantitative assessment of leaks and rebreathing	Develop
	Detection of disconnection	Monitoring of $P_{ET}CO_2$ and waveform in intubated patients helps identify tube displacement	Accept	Monitoring of capnographic and flow can alert clinician to even partial disconnects	Develop
	Weaning, outcome predictor	Limited use by itself	Develop	Allows for wide range of relevant measures used in protocols to be computed (i.e., VCO_2, RSBI)	Develop
	PEEP titration	Arterial end-tidal difference	Develop	VCO_2, slope of phase III	Develop

Table 20.4 (continued)

Clinical use	Time-based capnography	Status	Volumetric capnography	Status
$P_{ET}CO_2$ as a surrogate of $PACO_2$	Normal and constant ET-a gradients → improved $PACO_2$ est. and less blood gas samples	Develop	$P_{ET}CO_2$ predictive of $PACO_2$ if physiologic dead space not too large	Develop
Pulmonary capillary blood flow/ cardiac output estimation	$P_{ET}CO_2$ variable	Develop	VCO_2 surrogate with stable VE, partial rebreathing Fick method for PCBF	Develop
Monitoring during transport	Identifies tube displacement, verifies continuous ventilation, helps to optimize ventilation	Accept	Proximal CO_2, flow, and airway pressure (and derived variables) allow for continuous assessment of cardiorespiratory status	Specul
Intraoperative assessment	Good as frontline monitor *(see breathing circuit leaks and detection of disconnection)*	Accept	Proximal CO_2, flow, and airway pressure (and derived variables) allow for continuous assessment of cardiorespiratory status	Develop
Assessment/safety of sedation/ paralytic therapy	Improved patient safety	Accept	CO_2 with flow allows for better identification of hypoventilation	Specul

Adapted courtesy of Philips Respironics, Wallingford, CT
Key: *Accept* widely accepted as standard practice, *Develop* developing application, *Specul* speculative, *fDlate* late pulmonary dead space fraction

fashion with the survival and neurological recovery in a 54-year-old man following 96 min without a pulse [25]. Time capnography has only shown value with large pulmonary emboli [12], but volumetric capnographic measures, such as alveolar dead space and late dead space fraction (i.e., fDlate), often in combination with the D-dimer blood test, have shown potential as a screening tool [12, 26, 27]. The availability of volumetric capnography in critical care has been primarily driven by ventilation management activities (e.g., PEEP titration and weaning) and as an outcome predictor for extubation [28] and patients with ARDS [29]. These applications use breath-to-breath carbon dioxide elimination [30], dead space ratios, and other measures [31]. Carbon dioxide elimination and dead space ratios have been in use for decades, with the literature defining normal ranges. Only recently have efforts been undertaken to exploit some of the lesser known parameters [32].

The Future

The future of capnography, for both time and volumetric aspects, is bright. With the addition of requirements for monitoring carbon dioxide during procedural sedation and advanced life support, capnography is gaining greater adoption. Improved and more robust algorithms, for both respiratory rate and end-tidal measurements, that include environment-specific optimizations are being introduced by manufacturers. The development of indices (e.g., IPI index – Covidien, Boulder, CO) that use the information derived from the capnogram and other physiologic waveforms may allow easier interpretation and improve safety by providing an earlier indication of physiologic deterioration. An open-loop advisor (e.g., VentAssist, Philips Respironics, Wallingford, CT) and a closed-loop system (e.g., SmartCare, Dräger Medical, Lübeck, Germany) for the management of mechanically ventilated patients are now in clinical use and employ end-tidal CO_2 to determine if the delivered ventilator support is too low or too high. End-tidal carbon dioxide, in combination with other monitoring technologies, is being used in an investigational computer-assisted sedation system for the delivery of propofol (SEDASYS System, Ethicon Endo-Surgery). Even though it is not yet called out specifically in practice guidelines to date, the ASA Basic Monitoring standards, in addition to requiring the monitoring of carbon dioxide, strongly encourage monitoring

the other component of volumetric capnography, that is, exhaled volumes. The research into the automatic interpretation of time [33] and volumetric capnograms and estimation of unobservable measures (e.g., alveolar CO_2 partial pressure) using techniques such as fuzzy rule-based systems, neural networks, or Bayesian tracking has laid the foundation for future commercial implementations. Due to improvements and innovations in sensor technology and design, the hardware is following the usual technology trends of becoming smaller, faster, cheaper, and more integrated, thereby opening up applications that have previously been cost-prohibitive. Changes in equipment standards, availability of waveform databases [34], and improved test methods, including waveform simulators that can play back accurately prerecorded carbon dioxide waveforms, should allow for improved performance and provide the means to more effectively judge commercial systems [35]. With the growth of electronic health records and Anesthesia Information Management Systems, the recording of capnographic waveforms, already included in some systems, is anticipated to grow.

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Monitoring Diaphragmatic Function

21

Boris Jung, Yannaël Coisel, and Samir Jaber

Introduction

The process of ventilation is accomplished primarily via the diaphragm, and its failure becomes rapidly fatal if not compensated by mechanical ventilation. In the critically ill, critical-illness polyneuropathy and myopathy are the usual causes of diaphragmatic dysfunction that lead to ventilator dependency [1]. Several factors such as sepsis, multiorgan failure, hyperglycemia, medications (aminoglycosides, paralytics), metabolic disturbances (hypomagnesemia, hypophosphatemia, hypokalemia, hypocalcemia), and nutritional deficiencies can impair diaphragmatic dysfunction [1]. In the critically ill, patients mechanically ventilated for several days may also develop ventilator-induced diaphragmatic dysfunction, a condition that results in diaphragm inactivity, exaggerated proteolysis, impaired protein synthesis, autophagy, sarcomere disruptions, and impaired diaphragmatic dysfunction [2–4]. Pain, anesthetic agents, and thoracic, cardiac, and abdominal surgery have all been described to promote diaphragmatic dysfunction [5, 6]. Diaphragmatic dysfunction can lead to dyspnea, atelectasis, and respiratory failure.

The mechanical action of this respiratory muscle can be evaluated either directly or indirectly. For the most part, we measure the indirect features of this muscle by assessing the inspiratory flow rate and pressure. However, means exist to directly monitor the diagram by indirect visualization via either a CT scan or, more practically, an ultrasound. The electrical activity of the muscle itself can be monitored using electromyography. Table 21.1 presents a listing of relevant monitoring techniques available, with a discussion of their application in clinical medicine to follow.

Functional Respiratory Tests

- Measurement of the maximal inspiratory pressure (MIP) that a subject can generate at the mouth is a simple way to estimate inspiratory muscle strength. MIP is poorly reproducible and depends on the patient's participation, on the lung volume when the test is performed, and on the respiratory pattern [7].
- The decrease in airway pressure at 0.1 s (P0.1) after beginning of inspiratory effort against an occluded airway has frequently been used as an index of neuromuscular ventilator drive. Normal values range from 0.5 to 2 cm H_2O. Although a high value of P0.1 (>4 cm H_2O) always indicates enhanced respiratory center activity, a low value may signify not only

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Table 21.1 Tests currently available to evaluate the diaphragmatic function at the bedside

	Advantages	Disadvantages
Maximal inspiratory pressure (MIP)	Easy to perform	Needs the patient's participation Global respiratory muscle function test
Decrease in airway pressure at 0.1 s (P0.1)	Easy to perform	Not specific to the muscles function
Sniff test	Noninvasive	Needs the patient's participation Needs the patient to be spontaneously breathing and inspiring by the nostrils
Pressure–time product	Good surrogate of the respiratory muscles	Need a double balloon (esophagus and gastric)
Work of breathing	Good surrogate of the respiratory muscles	Need a double-balloon probe (esophagus and gastric)
Airway tracheal pressure after stimulation of the phrenic nerves	Easy to perform without a double-balloon probe	Need an expensive and dedicated device (magnetic stimulator)
Electromyography/NAVA	Specific surrogate of diaphragmatic function Might reduce patient-ventilator asynchronism	Needles might be dangerous in ventilated patients Need a dedicated tool (esophagus probe with electrodes)
Ultrasonography	Easy to perform, noninvasive	Interobserver reproducibility may be low depending on experience

reduced center output but also deterioration in the neural pathway [7]. P0.1 is available automatically on several modern ventilators.

- In spontaneously breathing patients, the sniff test which measures the pressure in the mouth, in the nasopharynx, or in one nostril after a sharp voluntary inspiratory maneuver has been reported to be a surrogate of the diaphragmatic dysfunction [7]. Maximal nostril pressure value greater than 100 cm H_2O has been reported to exclude diaphragm weakness [8]. Although sniff test needs only a pressure probe in the nostril and the participation of the patient, it is not currently used in routine practice. It can be used as a tool to evaluate our practice, though. It has been used to assess which analgesia is associated with a better outcome. In a pilot study, investigators reported that parietal analgesia delivered via a continuous preperitoneal wound infusion (ropivacaine) reduced postoperative diaphragmatic dysfunction induced by open colorectal surgery compared to intravenous morphine [9]. However, poorly motivated subjects, obstruction of the nose, or the presence of significant lung disease are limits of this technique.
- Several tests use an esophageal probe to measure esophageal pressure as an evaluation of pleural pressure. These tests are the pressure-time product which is calculated as the integration of the area under the esophageal pressure curve versus time and the work of breathing [7]. Work of breathing represents the integral of the product of volume and pressure. To measure the amount of work performed by the respiratory muscles, esophageal pressure is needed. Therefore, because an esophageal probe is needed, pressure-time product and work of breathing measurements are not routinely performed in clinical medicine and are used preferentially for research (Fig. 21.1).
- The gold standard of diaphragm contractile force measurement requires also a probe with a double balloon (esophageal and gastric). It allows the measurement of the transdiaphragmatic pressure, namely, the difference between the gastric and the esophageal pressure. Transdiaphragmatic pressure can however be approached by the measurement of the airway tracheal pressure [3, 11, 12]. Noninvasive stimulation of the phrenic nerves by a magnetic stimulator allows measure of the tracheal pressure, which is a surrogate of the transdiaphragmatic pressure. It can be used to follow the diaphragm force production over time during prolonged mechanical

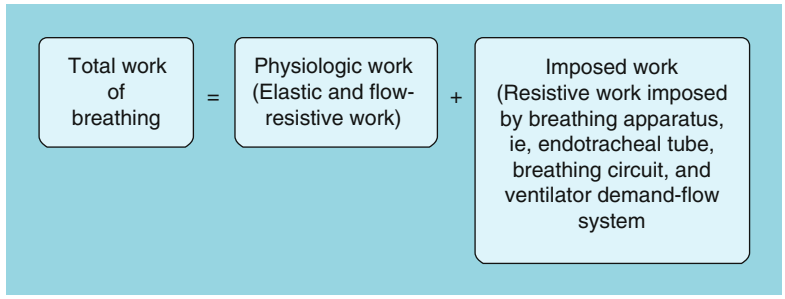

Fig. 21.1 Total work of breathing (Reproduced from Banner et al. [10]; kind permission from Springer Science + Business Media B.V)

ventilation [3] but does require dedicated expensive devices (magnetic stimulator).

Electromyography

Electromyography is the process by which we use physical probes to detect changes in electrical activity of a muscle. Even subtle changes can detect muscle activity, in the initiation not only of contracture but of the contractile force itself. Surface or needle diaphragmatic electromyography is difficult to obtain, invasive, and potentially dangerous (if needles are used) and may not be repeated during the hospital course of a patient. A promising tool might be the electrical activity evaluation of the diaphragm using an esophageal probe during NAVA® ventilation (MAQUET, Solna, Sweden) [13]. Electrical activity of the diaphragm may be interesting to monitor especially during the weaning period [14]. It may also help clinicians to optimize ventilator settings in aim to reduce patient-ventilator asynchrony.

Diaphragm Imaging

Routine assessment of the diaphragmatic dysfunction has been performed using ultrasonography and other modalities. Measuring the diaphragm displacement and velocity during inspiration in time movement or in two-dimension mode is possible. Several studies have reported that a diaphragm excursion lower than 25 mm was associated with a higher risk of prolonged mechanical ventilation after cardiac surgery [15]. A pilot study reported that prolonged mechanical ventilation is associated with a decrease in the diaphragm thickness [16]. Ultrasonography is noninvasive and allows the clinician to evaluate daily the diaphragm excursion and its thickness but may lack of interobserver reproducibility, as ultrasound is highly user dependent. Other techniques such as MRI to evaluate muscle metabolism or CT are promising techniques in research but still yet have to be evaluated.

Conclusion

Several promising approaches to evaluate diaphragmatic dysfunction are in development. Given that diaphragmatic dysfunction has important clinical consequences, monitoring of diaphragmatic motion and contractile force will likely be an increasingly valuable diagnostic tool. Ultimately, we expect that these monitors will help estimate a patient's respiratory function and identify patients at risk of developing acute postoperative respiratory distress. This will likely take the form of a combined ultrasound/electrical activity monitor that can monitor respiratory function in real time.

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The Anesthesia Machine as a Monitor

22

James H. Philip

Introduction

The anesthesia machine serves several purposes. As a therapeutic device, it delivers gases and vapors and provides for spontaneous and mechanical ventilation. In the future, drugs delivered by other modalities (e.g., intravenous) will be a component. As part of its function as a therapeutic device, it monitors its own function to ensure its performance is as adjusted by the anesthesia care provider, designed by the manufacturer, and approved by governing bodies. As a monitoring device, it monitors the physiological processes it controls or interacts with. By doing so it provides clinical information to the anesthesia care provider. How easily this information can be used in patient care depends on how well the information is displayed and/or transmitted to other displays used for monitoring. The close visual grouping of variables that are functionally related is very important to understanding the physiology of the clinical situation. Seeing graphic trends of the time course of changes plotted on axes with good magnitude and time scales is important. The more variables that can be displayed graphically on the same time axis, the easier it is to detect and treat changes.

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Internal Monitoring of the Anesthesia Machine

The gases the anesthesia machine delivers are oxygen for life support, nitrous oxide as an anesthetizing adjunct, and air as a diluent for the oxygen when a high inspired oxygen concentration is not desired. The vapors the anesthesia machine delivers provide part or all of the effects required for general anesthesia. These gases and vapors are usually delivered at a constant flow rate. This constant fresh gas flow of delivered gases and vapors passes to a breathing system.

The breathing system of most anesthesia machines incorporates a carbon dioxide absorber that keeps the inspired concentration of carbon dioxide zero no matter how low a fresh gas flow is delivered to the breathing system. The fresh gas flow can be lower than the patient's minute ventilation which is the flow of gases provided to the patient. In this way, the patient breathes part or all of the gases delivered from the anesthesia machine over and over again with carbon dioxide removed and gases and vapors added before each passage. If rebreathing is not performed, anesthetic gas and vapor use and waste are high. With rebreathing systems, use and waste are lower, but inspired concentration of gases must be continuously measured and displayed so the anesthesia care provider can adjust flows of gases and concentration of vapor to achieve the desired inspired concentrations. The instantaneous flow to the patient is always much higher than the fresh gas

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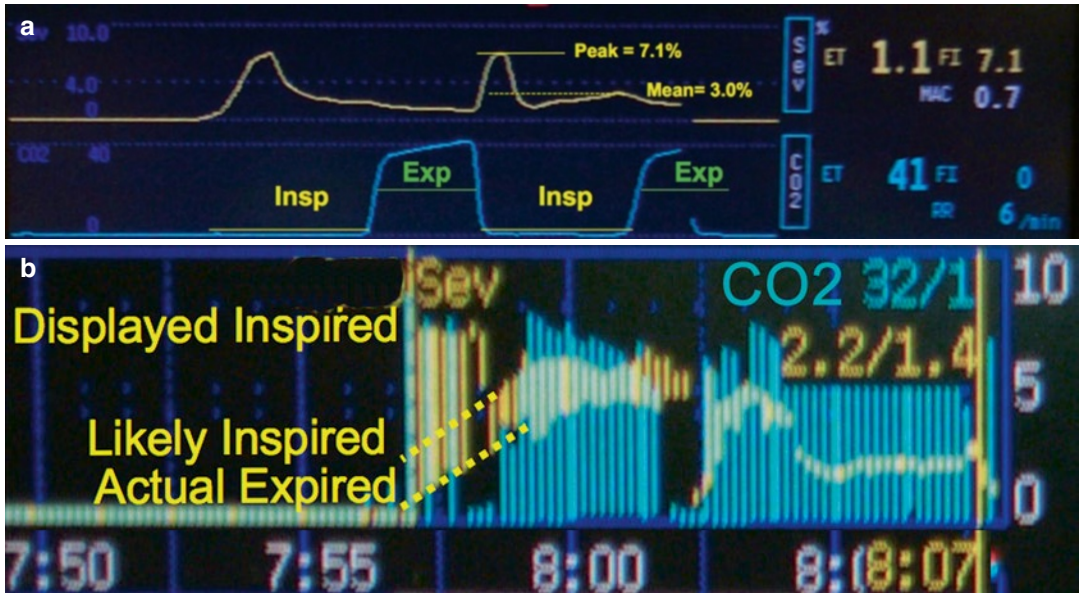

Fig. 22.1 Screens of AS-5 monitor connected to ADU anesthesia machine (both General Electric) show that peak and mean inspired agent concentration may differ greatly. (**a**) The synchronous waves of sevoflurane (*above*) and carbon dioxide (*below*). Two breaths are shown. For sevoflurane, inspired concentration rises rapidly to 7.1 % and then immediately falls to 3 %. Early versions of this monitor reported inspired equal to peak sevoflurane concentration (7.1 %). Despite this high reported concentration, anesthesia induction was not immediate. (**b**) The trend graph of inspired and end-tidal carbon dioxide (*blue*) and sevoflurane (*yellow*). The dotted lines show what likely would have been reported if mean inspired agent was computed in that display

flow. Under some situations, even when minute fresh gas flow exceeds minute patient ventilation, the inspired concentration of gas within each breath may be much less than planned and interfere with rapid control of anesthetic depth. On these occasions it is important that the anesthetic agent monitor computes mean inspired concentration [1]. Figure 22.1 shows an example of this problem. On most brands and models of anesthesia machine, if the inspired carbon dioxide level rises to above a threshold (e.g., pCO_2 >5 mmHg), the system alarms, notifying the care provider to replace the spent carbon dioxide canister.

When anesthesia is provided by purposefully and specifically controlling inspired concentration, the anesthesia care provider is relying on a preconceived notion of what inspired concentrations of gases and vapors are required. But, control of inspired concentration is a small part of the anesthesia care process. It is the anesthetic and oxygen levels in tissues that determine the physiological effect of drugs and oxygen. In tissues, it is the partial pressure or tension, not the concentration, that is responsible for physiological effects. At sea level (or 1 atmosphere =1 Atm) of pressure, partial pressure can be expressed as % of 1 Atm. After equilibration, tension of all gases and vapors is equal in end-expired gas, arterial blood, and tissues. Before equilibration, they differ. Gas Man shows this [2] (Fig. 22.2a, b).

The control of anesthetic depth with inhaled agents is produced by manipulating end-expired tension in such a way as to manipulate brain tension. The time constant of the delay from end-tidal to brain is approximately 3 min for inhaled anesthetics, intravenous anesthetics, and oxygen [2].

The anesthesia machine allows many ventilation modalities including spontaneous, supported, and controlled. In the process thereof, the anesthesia machine monitors the airway pressure and volume delivered in every breath (tidal volume). With rebreathing systems this is not simple because the fresh gas flow has the potential to

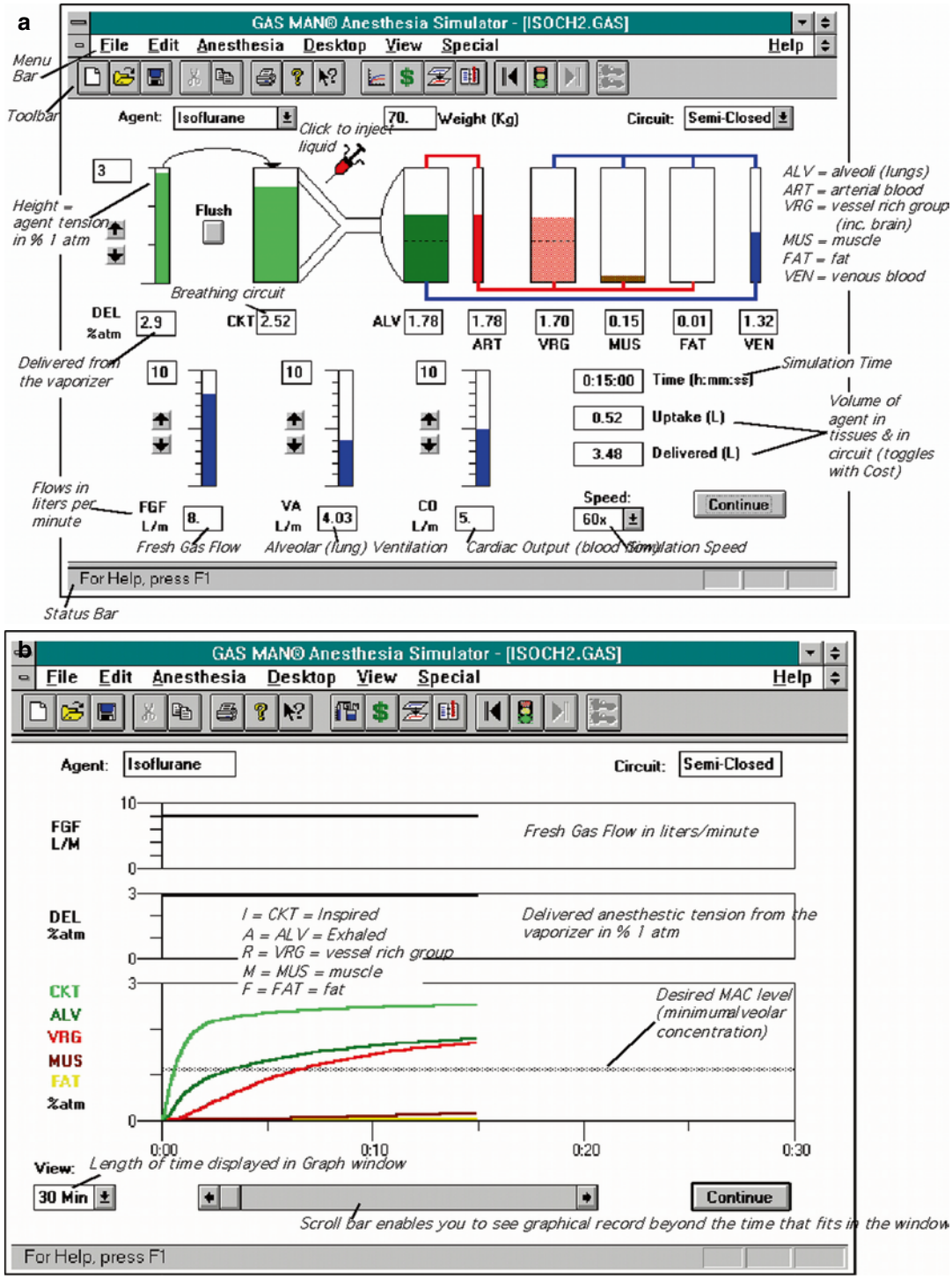

Fig. 22.2 The passage of gases and vapors from anesthesia machine to patient tissues depicted with Gas Man. (**a**) Top half shows the path of anesthesia partial pressure from left to right, from vaporizer to brain and spinal cord. (**b**) Bottom half shows the time course of partial pressure in all compartments

influence tidal volume. In older anesthesia machines (e.g., before the year 2000), ventilation and tidal volume were adjusted separately. Once they were combined during inspiration, the inspired tidal volume was equal to the sum of the set tidal volume plus the fresh gas that flowed during the inspiratory time. A fresh gas flow of 6 L/min with an I/E time ratio of 1:1 resulted in inspired minute volume (MV) increase of

$$\begin{aligned}\text{MV increase} &= (6\,\text{L/min}) * (1/2) \\ &= 3\,\text{L/min}.\end{aligned}$$

If respiratory rate was 10 breaths per minute, tidal volume (TV) increase of

$$\begin{aligned}\text{TV increase} &= (3\,\text{L/min}) / 10\,\text{breaths/min}) \\ &= 0.3\,\text{L/breath}.\end{aligned}$$

Because this increase was so great, the next generation of anesthesia machines was designed to offset this tidal volume increase in some manner. General Electric (GE) SmartVent uses feedback control of inspired tidal volume of a gas-driven bellows. Inspiratory flow is measured with a variable orifice flow meter, and bellows descent terminates when inspired tidal volume reaches set tidal volume. Expired tidal volume is monitored by a similar flow meter and if inspired and expired tidal volume differ by a significant amount the system alarms.

Most Draeger anesthesia machines (Primus, Apollo, Fabius, Tiro) use piston-driven inspiration, and the anesthesia machine controls inspired tidal volume by diverting fresh gas flow to the reservoir bag during inspiration and drawing the saved fresh gas from the reservoir when the piston refills during the early phase of expiration. This is the same reservoir bag used for manual ventilation. This is termed fresh gas decoupling. The anesthesia machine then measures exhaled flow and tidal volume using a hot-wire anemometer and alarms if it differs significantly from the set tidal volume.

Some modern anesthesia machines control gases and vapors automatically through feedback control of flows to achieve the desired agent and oxygen levels. GE Aisys ET Control controls end-tidal agent and end-tidal oxygen. Draeger Zeus controls ET agent and inspired oxygen. These machines are not approved for sale in all countries.

Physiological Monitoring Using the Anesthesia Machine

Because the anesthesia machine both delivers therapy and monitors physiological variables, it affords the opportunity to monitor many other things.

Some of these relationships are specifically disclosed by monitors, while some are left to the insight of the anesthesia care provider. Most have not yet been studied carefully.

The relationship between pressures measured as pause pressure (also known as plateau pressure) minus end-expiratory pressure and divided by tidal volume results in lung-plus-circuit stiffness. Stiffness or Elastance (E), is the inverse of compliance (*C*):

$$E = 1/C = \left(P_{\text{pause}} - P_{\text{EEP}}\right) / V_{\text{tidal}}.$$

The relationship between pressures measured as inspiratory peak minus inspiratory plateau and divided by inspiratory flow results in inspiratory resistance:

$$R_{\text{insp}} = \left(P_{\text{peak}} - P_{\text{plateau}}\right) / F_{\text{insp}}.$$

Resistance can rise for many reasons. Among them are kinked tracheal tube and bronchiolar constriction.

The difference or the ratio of inspiratory and end-tidal agent is reduced when cardiac output falls during shock [3]:

$$C_{\text{lagent}} - C_{\text{ETagent}} = K * V_{\text{A}} / \text{CO}.$$

Figure 22.3 is an example of this.

The ratio of end-tidal to inspiratory agent concentration several minutes after a step change in inspired anesthetic concentration is related to alveolar ventilation and inversely related to agent solubility times cardiac output [2]:

$$\left(C_{\text{ETagent}}\right) / \left(C_{\text{lagent}}\right) = V_{\text{A}} / \left(1 + \text{CO} * \lambda_{\text{B/G}}\right).$$

The instability of the relationship between inspiratory and end-tidal carbon dioxide shows changes in alveolar dead space or changes in carbon dioxide transport to lungs, usually the former. Alveolar dead space often arises from a fall

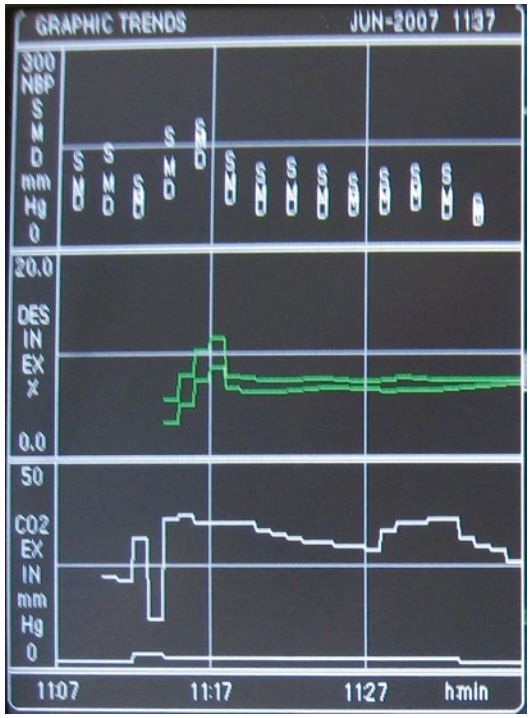

Fig. 22.3 Three sections showing a graphic trend of blood pressure, inspired and end-tidal desflurane, and inspired and end-tidal carbon dioxide. Note that when end-tidal carbon dioxide concentration falls, the inspired–expired desflurane concentration became smaller

in cardiac output and decreased perfusion to the upper regions of pulmonary capillary bed [3].

When oxygen saturation falls despite constant inspired oxygen concentration, then lung shunt has developed. Recruitment, PEEP, and other maneuvers may improve or correct this. Routinely administering high FiO_2 will mask detection of shunt using a pulse oximeter since saturation will continue to remain near 100 % [4].

The modulation of arterial pressure or finger plethysmograph amplitude by ventilation, especially with large tidal volume and low rate, suggests hypovolemia, which can be treated once it is detected and diagnosed. Here, the anesthesia machine provides the signal which drives the physiological change we monitor for.

In closed-circuit anesthesia administration, inspired and end-tidal oxygen concentrations and circuit volume are maintained constant by careful adjustment of oxygen flow into the breathing circuit. The patient's oxygen consumption is measured to be the oxygen delivered in the fresh gas flow. Monitoring oxygen consumption requires a closed circuit wherein gas sampled for analysis is returned to the breathing circuit and the oxygen flow control has a fine resolution, no greater than 10 mL/min.

Conclusion

The anesthesia machine is a therapeutic device that delivers gases, vapors, and ventilatory support and control. While providing this therapy, it monitors its own internal function and also the patient's response to that therapy. Observing the interaction can provide clinical insight.

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Ventilator Settings in Acute Care Environments

23

Yannaël Coisel, Boris Jung, and Samir Jaber

Introduction

Ventilators are commonly used in acute care environments including the emergency department, intensive care unit (ICU), and operating room (OR). The field of mechanical ventilation remains large, with many recent technological advances. All ventilators regulate mechanical ventilation by either one of the following two methods:

- Volume control, such as continuous mandatory ventilation (CMV), assist-control ventilation (A/C), and synchronized intermittent mandatory ventilation (SIMV)
- Pressure control, such as pressure control ventilation (PCV) or pressure support ventilation (PSV) (Fig. 23.1)

When a *volumetric mode* is chosen, the clinician sets a tidal volume and should monitor the resulting pressures. When a *pressure mode* is chosen, the clinician sets inspiratory airway pressure (only one airway pressure in this mode) and should monitor the resulting tidal volume (depending on the respiratory system compliance and resistance). Monitoring airway pressure and flow can inform about the mode chosen (Fig. 23.2, for volumetric mode, and Fig. 23.3, for barometric mode).

Lung-Protective Ventilation Strategies

In choosing ventilator settings, one should aim to (1) ensure appropriate gas exchange and (2) utilize a "lung-protective strategy," which has been developed from large studies conducted on patients with acute respiratory distress syndrome (ARDS) [1, 2]. This strategy aims to avoid the complications associated with mechanical ventilation in healthy and non-healthy lungs such as barotrauma (induced by high alveolar pressure [3]), volutrauma (induced by high tidal volume [4]), atelectrauma (induced by repeated opening and closing of alveoli [5]), and biotrauma (mediator-related lung damage initiated by mechanical ventilation [6]). The physician should also try to avoid "ventilator-induced diaphragmatic dysfunction," a complication linked to prolonged mechanical ventilation that increases oxidative stress, atrophy, and injury of the diaphragmatic muscle fibers [7, 8].

An Approach to Setting the Ventilator

The clinician should first choose the ventilation mode (volumetric or pressure) and the modality (controlled ventilation, assisted ventilation, or

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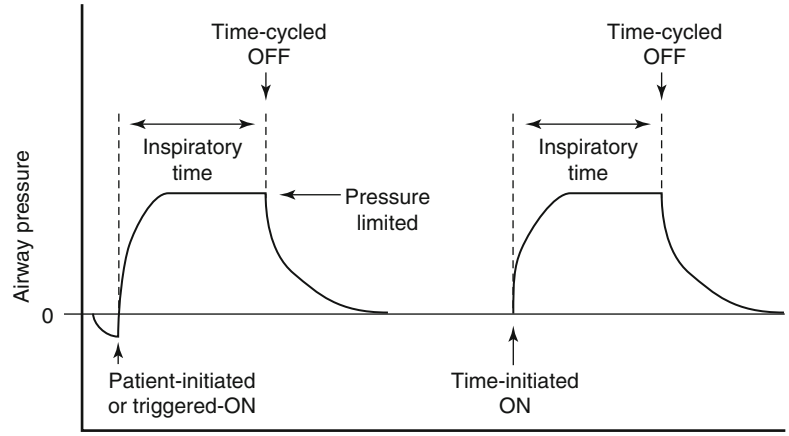

Fig. 23.1 Pressure-controlled ventilation. Pressure-controlled ventilation (PCV) may be applied with a normal or an inverse inspiratory-to-expiratory time ratio (I/E). PCV may be either patient-initiated (triggered) or time-initiated ON or pressure-limited, time-cycled OFF mechanical ventilation. I/E time ratios with PCV are variable; e.g., I/E may be set at 1:2 or 1:3 or inverted at 2:1. Under the latter condition, the mode is correctly referred to as pressure-controlled inverse ratio ventilation (PC-IRV). PCV is used in the management of infants with hyaline membrane disease and adults with acute and chronic respiratory failure. Tidal volume is the product of the preset pressure limit and compliance of the respiratory system (V_T = pressure limit × compliance respiratory system, e.g., 500 mL = 25 cmH_2O × 20 mL/cmH_2O) (Reproduced from Banner et al. [16]; kind permission from Springer Science + Business Media B.V.)

spontaneous ventilation). Then the clinician should adjust the respiratory parameters (which will differ depending on the ventilation mode and modality chosen). Initial settings might include:

- *Tidal volume in volumetric mode*: low tidal volume, i.e., between 6 and 8 mL/kg of ideal body weight, according to ARDS network formula [1] or estimated by this formula: ideal body weight (Kg) = height (cm) − 100 for male or height (cm) − 110 for female.
- *Inspiratory pressure in pressure mode*: inspiratory pressure should be set to obtain low or limited tidal volume as previously mentioned.
- *Respiratory frequency*: for controlled and assisted ventilatory mode. Respiratory frequency should be adapted for an end-tidal CO_2 ($ETCO_2$) between 35 and 40 mmHg in most of cases. When needed, targeted $ETCO_2$ may be elevated as high as 50–60 mmHg (permissive hypercapnia in severe ARDS, e.g., [9, 10]).
- *Positive end-expiratory pressure* (*PEEP*): ideally, PEEP should be set at least at 5 cmH_2O to avoid atelectasis. PEEP should also be adapted to patient's comorbidities: higher in the case of obese patients (up to 10 cmH_2O) and ARDS patients or lower in case of hemodynamic failure. However, plateau pressure should be not exceeded 30 cmH_2O.
- *Inspiratory-to-expiratory ratio* (*I/E*): usually set at 1:2, I/E can be adapted to when the patient has respiratory comorbidities where a longer expiratory time is desired (asthma, bronchospasm, or COPD). In these cases, I/E might be set between 1:3 and 1:5. For some ventilators, I/E is indirectly set by the inspiratory time (Ti).
- *Inspiratory flow*: is constant in volumetric mode and should be around 60 L/min (or 1 L/s) [11]. For some ventilators, inspiratory flow is only adjusted by setting I/E. In pressure mode, ventilators deliver maximal flow at the opening of the inspiratory valve and then decrease (decreasing flow, see Fig. 23.3), so that inspiratory flow is not available.
- *Inspiratory pause*: in volumetric mode, inspiratory pause is the time between closing inspiratory valve and opening expiratory valve (see Fig. 23.2). During this time without airway flow, pressure monitored by the ventilator (called "plateau pressure") corre-

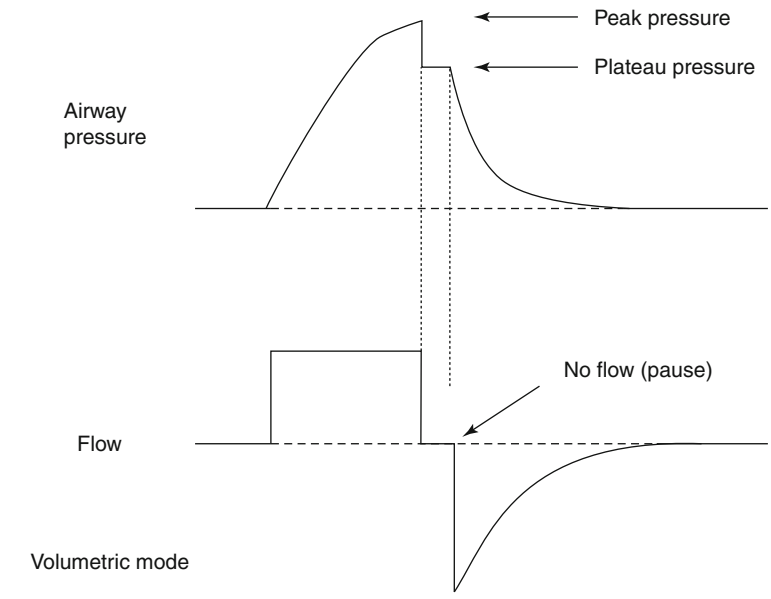

Fig. 23.2 Airway pressure and flow in volumetric mode. Note that the flow inspiratory pause induces a stability in the airway pressure called "plateau pressure"

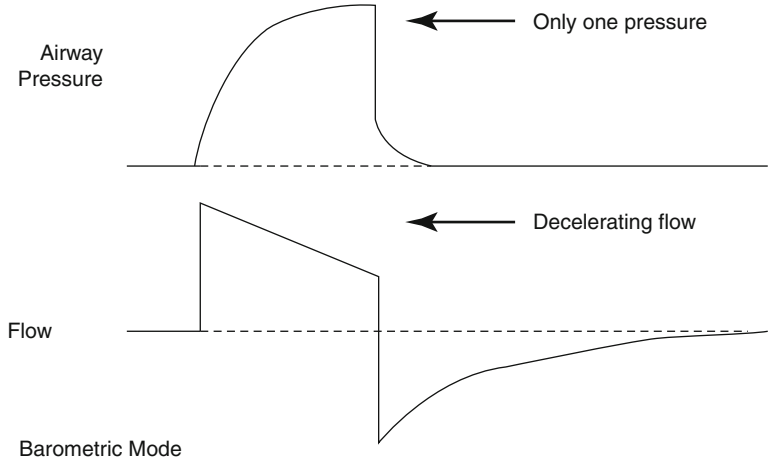

Fig. 23.3 Airway pressure and flow in barometric mode. Note that there is only one airway pressure and the decelerating flow

sponds to alveolar pressure and can inform the clinician about thoraco-pulmonary compliance. Inspiratory pause can also increase CO_2 diffusion in ARDS with lung-protective strategy [12]. Inspiratory pause should be set as short as possible while still measuring this value (around 0.1–0.3 s for most ventilators).

- *Inspiratory trigger*: when flow or pressure is above this threshold, the ventilator begins the inspiratory cycle. This trigger is only available in assisted or spontaneous modes (not in controlled modes). It should be set at the lowest possible value that does not induce auto-triggering.
- *Inspired oxygen fraction* (FiO_2): between 21 and 100 %, according to the patient's respiratory needs.
- *Sigh*: on some ventilators, it is possible to add a regular sigh in order to improve alveolar recruitment recruiting the lung of patients. This strategy is still controversial [13, 14], and a clinical-based recruitment of the lungs when needed seems better than a systematic sigh [15].

When setting a ventilator, clinician should also set ventilator alarms in correct ranges, such as low or high VT, low or high minute ventilation, high airway pressure, and low or high

$ETCO_2$. This will enable to clinical team to recognize changes in the patients respiratory status, ventilator malfunction, and a series of other critical events more quickly.

Conclusion

The clinician should choose ventilator settings that are customized to the patient's needs, ideally taking into consideration lung-protective ventilation techniques. This will enable the prevention of barotrauma, volutrauma, atelectrauma, and biotrauma. The first step in setting a ventilator is to choose the ventilation mode (typically volume or pressure) and the modality (controlled, assisted, or spontaneous). Finally, alarm setting should be adjusted depending on the clinical scenario.

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Monitoring Respiratory Rate

24

Michael Ramsay

Introduction

Alveolar ventilation is essential to maintain human life. It provides oxygen (O_2) to meet the energy requirements of the body and removes carbon dioxide (CO_2) produced in this process, maintaining the acid-base state of the internal milieu. Respiratory rate and tidal volume, which maintain alveolar ventilation, are controlled by central and peripheral chemoreceptors that respond to the partial pressures of oxygen and carbon dioxide (PaO_2, $PaCO_2$) and pH. The central control is the respiratory center that is located on the ventral surface of the medulla. It is very responsive to small changes in pH in the cerebrospinal fluid. Carbon dioxide (CO_2) rapidly crosses the blood-brain barrier and alters the pH of the cerebrospinal fluid. The respiratory center also responds to metabolic causes of change in pH. The peripheral chemoreceptors that are found in the aorta and in the carotid bodies respond to changes in PaO_2 and pH by increasing or decreasing minute ventilation. $PaCO_2$ again alters the pH, causing the respiratory center to be stimulated. The body maintains a normal environment by increasing respiratory rate and tidal volume in response to hypoxia, hypercarbia, and acidosis.

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Value of Respiratory Rate Monitoring

The recording of five vital signs – pulse rate, blood pressure, respiratory rate, temperature, and more recently a pain score – is regularly expected to be found in the medical record. However, respiratory rate is often either not recorded or noted as being between 12 and 16 breaths/min based on only a brief observation and, hence, is rarely accurate [1]. Respiratory rate is an important indicator of serious illness and a predictor of outcome [2, 3]. Respiratory rate alone is a physiological early warning score for poor outcome; a rate greater than 25 breaths/min is a predictor of potential death in 21 % of hospitalized patients, and a rate greater than 35 breaths/min for 35 % mortality [4]. Goldhill also noted that a respiratory rate less than 6 breaths/min was associated with a greater than 35 % mortality. In another study, patients with a respiratory rate less than 6 breaths/min had a 14.4-fold increase in risk of death, and if this was the last recorded rate prior to discharge from the hospital of an otherwise healthy patient, it was associated with a 13.7-fold increase in risk of death after release from hospital [5]. Many other studies have demonstrated the importance of monitoring respiratory rate and the predictive value of this integer with other vital signs as an early warning score for an adverse outcome [6–9].

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Postoperative Opioid-Induced Respiratory Depression

The central respiratory pacemaker within the medulla will respond to changes in acid-base balance to maintain a normal pH. However, the use of respiratory-depressive medications such as opioids depresses the response of the respiratory pacemaker, and this can lead to respiratory failure and death [10]. The respiratory-depressive effects are mediated mainly through the mu-opioid receptor (MOR). The pharmacokinetics and pharmacodynamics of an opioid should be understood before administering the drug. After intravenous injection into the bloodstream, the drug diffuses across various tissues and a plasma concentration is established. From the plasma the opioid crosses the blood-brain barrier to reach the effect compartment, which is the brain. The speed of this transfer depends on the properties of the drug, whether they are lipophilic (fast transfer) or hydrophilic (slow transfer). The drug then interacts at the opioid receptor site with a constant for association and dissociation that again varies for each opioid. In the case of fentanyl, this association is 5–15 min and dissociation <0.1 min. This is an example of a fast "on and off" opioid [11]. In the case of morphine, the transfer to the effect site may take 1–2 h for the full effect, and then the active metabolite morphine-6-glucuronide will further prolong the action of the drug. While opioid use is generally safe for most patients, opioid analgesics may be associated with adverse effects [12]. The most serious side effect is respiratory depression, which is generally preceded by sedation [13]. This has resulted in The Joint Commission publishing a Sentinel Event Alert [14]. This Alert Bulletin recommended screening patients who may be at increased risk for respiratory depression, but it did not go as far as recommending genetic testing as has been put forward by some experts [15]. The Joint Commission also advised taking extra precautions when discharging home patients who have received opioids, as the time taken to reach maximum levels in the "effect site" must be considered.

The Federal Drug Administration has just placed a "black box" warning on the use of codeine for children postoperatively. This was based on reports that children had died following the administration of codeine as an analgesic following tonsillectomy [16, 17]. Codeine is a prodrug; the analgesic properties are dependent on its conversion to morphine that relies on the CYP2D6 pathway. Polymorphisms in this gene cause either poor or extended metabolism (EM) or ultrarapid (UM) metabolism. This results in varying amounts of morphine produced from a standard codeine dose (Fig. 24.1). These children

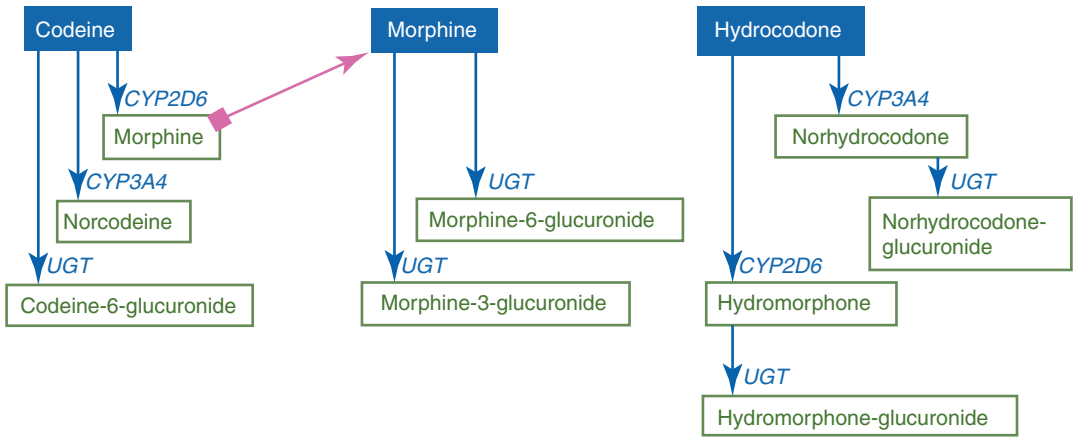


Fig. 24.1 Metabolic pathways of codeine, morphine, and hydrocodone. *UGT* uridinediphosphate-glucuronosyltransferase (Reprinted from Niesters et al. [17], by permission of Oxford University Press)

that died had evidence of being ultrarapid metabolizers of codeine, which is an inherited ability that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body. Each child had received doses of codeine that were within the typical dose range. The knowledge of genetic differences amongst individuals in metabolizing drugs is a step towards personalized pain management programs that will become popular as genomic screening becomes more affordable. The pharmacogenomics of pain medicines will determine which analgesics will be effective and which will not. It will also identify those opioid analgesics that may have profound adverse affects. These factors all emphasize the importance of monitoring ventilation, and one component of this is respiratory rate. Respiration is vital to human life.

Respiratory rate monitoring is one of the five vital signs and is the most frequently neglected [18]. One reason for this is that for the spontaneously breathing patient, there has not been a reliable automatic technology for recording respiratory rate. The Joint Commission suggested a series of actions that hospitals could take to reduce adverse events associated with the use of opioids. These included the continuous monitoring of quality and adequacy of respiration. The Anesthesia Patient Safety Foundation held a conference to address "Essential Monitoring Strategies to Detect Clinically Significant Drug-Induced Respiratory depression in the Postoperative Period" [19]. A conclusion from the conference was that continual electronic monitoring should be utilized for patients receiving postoperative opioids. Included in the technologies assessed was the monitoring of respiratory rate. Respiratory insufficiency can be very difficult to assess visually and may develop rapidly or slowly into a life-threatening respiratory failure and potentially serious harm to the patient. Therefore, patients at risk for respiratory depression should be monitored with technology to assess ventilation together with respiratory rate. Despite respiratory rate being one of the key vital signs, it is frequently not monitored and has become labeled as "The Neglected Vital Sign" [18].

Measuring Respiratory Rate

An adult human has a respiratory rate of approximately 12–15 breaths/min at rest and has a minute volume of approximately 6–8 L of air. As the fifth vital sign, respiratory rate is assessed by manual observation on many patients routinely, but intermittently, and on postsurgical patients more frequently, especially when postoperative opioids are being administered. The ideal human assessment of ventilation should include an assessment not only of respiratory rate but also of respiratory pattern, depth, and quality. Acute respiratory failure is a risk for those patients administered with opioids postsurgery. The mortality associated with this event is unacceptably high and could be avoided by the continuous monitoring of ventilation and oxygenation. The continuous monitoring of respiratory rate could predict a patient at risk and could therefore be lifesaving [20].

Human Observation of Respiratory Rate

The human observation of respiratory rate is extremely time-consuming, even to monitor for intermittent periods, yet alone continuously. The importance of accurately measuring respiratory rate is not well known by nurses or physicians in many hospitals [18]. The pulse oximeter is frequently used as a surrogate for counting respiratory rate, and yet its function is poorly understood by many practitioners [21]. The results of human observation and monitoring of respiratory rate cannot be audited on review, and the accuracy may be poor, as it is very difficult to determine actual air movement if only counting the movement of the abdomen and chest wall. There could be little or no tidal volume and this may not be observed unless a stethoscope is used to auscultate the breath sounds while counting them, to confirm adequate tidal volume [22] (Fig. 24.2).

The stethoscope invented by Rene Laennec in the 1840s in France has been a very useful clinical tool but is gradually being abandoned by the increasing use of the pulse oximeter, with poor

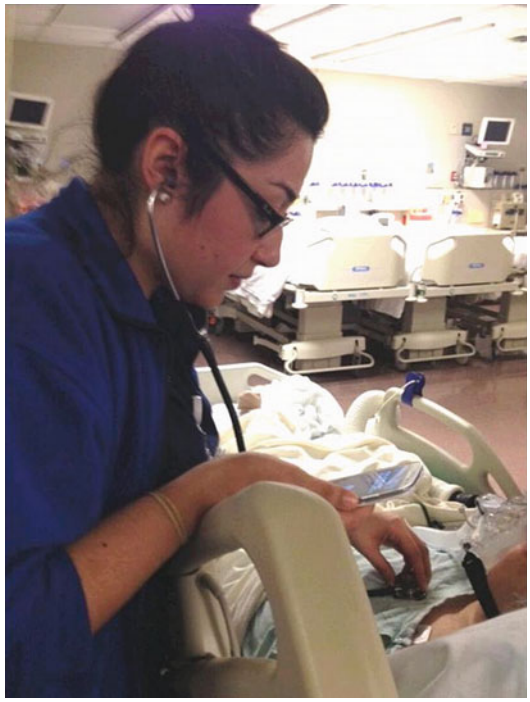


Fig. 24.2 Manually counting the quality and rate of respiration using a stethoscope

understanding that it only measures oxygenation and not directly the quality and quantity of airflow and the rate of respiration.

The Automatic Monitoring of Respiratory Rate in the Non-intubated Patient

Transthoracic Impedance Plethysmography

The chest wall expands with each inspiration, causing variations in the air volume in the lungs and altering the thoracic impedance. This change in impedance has been used as a continuous monitor of respiratory rate [23]. This technology historically has had limited deployment because of a significant error rate in detecting obstructed breathing, particularly in patients with obstructive sleep apnea. The continued chest wall movement has presented a signal that is recorded as respiratory rate despite the obstructed glottis and minimal air movement [24]. Many of these technologies require calibration with a spirometer to accurately measure tidal volume [22]. Movement of the patient may also artifact with this technology [25]. Newer advances in impedance technology have now produced monitors of continuous minute volume and tidal volume with approximately 90 % accuracy and respiratory rate with approximately 98 % accuracy. This technology can also detect obstructed apneic episodes in human volunteers. Across all subjects the measurements had a coefficient correlation of 0.91–0.99 [26].

Airflow Sensors

Sensors can detect airflow as expired air is warmer and more humid and contains carbon dioxide compared to ambient air. The flow of air in the airway also causes sounds that can be measured electronically as well as manually with a stethoscope. Many airflow sensing technologies such as capnography require a sensor to be placed very close to the airway to sample the expired gas. This may not be tolerated well by some patients.

Temperature

Measuring changes in temperature between inhaled and expired gas can be used to monitor respiratory rate but requires a sensor be placed close to the airway [27]. Newer technology using real-time infrared thermography has now been developed to provide a noncontact technology that may be used for both adults and neonates [28, 29] (Fig. 24.3). In the neonate respiration was successfully monitored based on a 0.3–0.5 °C temperature difference between the inspiration and expiration phases [29].

Humidity

Respiratory rate may be monitored and calculated by quantifying the humidity of exhaled air

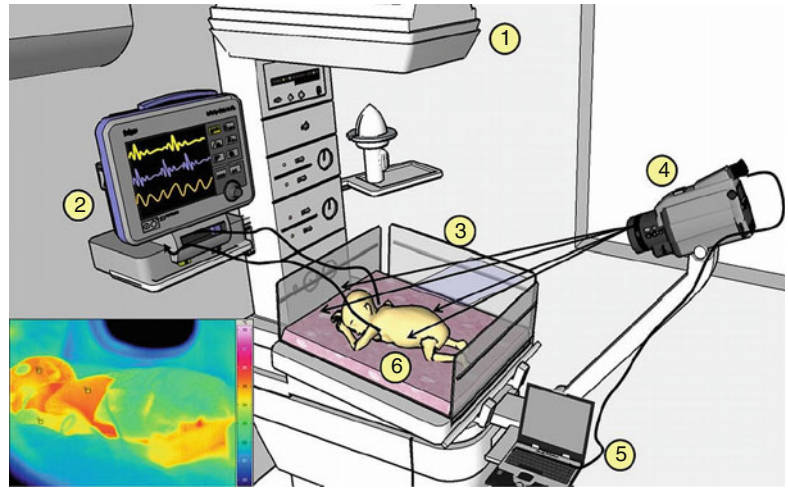


Fig. 24.3 Infrared thermography clinical imaging setup. (*1*) Radiant warmer bed; (*2*) bedside monitor; (*3*) camera field of view; (*4*) infrared thermal camera; (*5*) analysis workstation; and (*6*) infant (Reprinted from Abbas et al. [29]. Copyright ©2011 Abbas et al.; licensee BioMed Central Ltd. Open Access)

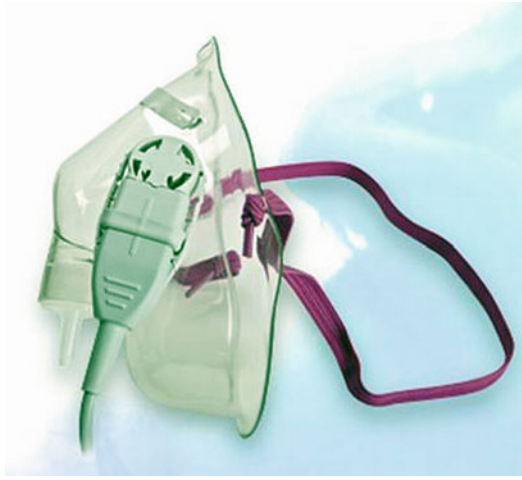


Fig. 24.4 The respiR8 attached to an oxygen mask (www.masimo.com) (Photo courtesy of Masimo)

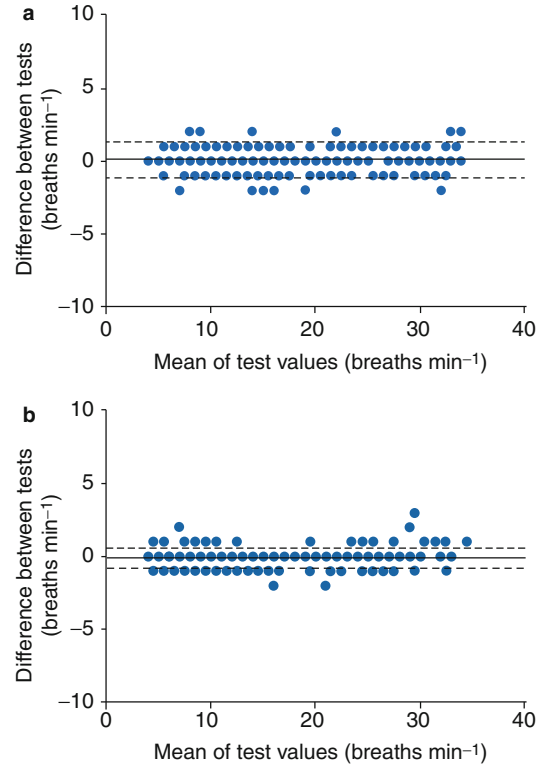


Fig. 24.5 Respiratory rate measured in volunteers: a Bland-Altman analysis of respiR8 with (**a**) manual counting and (**b**) capnometry (Reprinted from Niesters et al. [30], by permission of Oxford University Press)

[30]. A commercially available respiratory rate counter, respiR8 (Anaxsys Technology Ltd., Surrey, UK), has been demonstrated in human volunteers and postoperative patients to accurately measure respiratory rate when compared to capnography. A humidity sensor is placed on a facemask and measures the water vapor of the exhaled air (Fig. 24.4). The humidity signal is used to calculate respiratory rate on a breath-by-breath basis using a 3-breath averaging algorithm (Fig. 24.5).

A miniature optical humidity sensor has been developed based on an agarose-infiltrated photonic crystal fiber interferometer [31]. This sensor is very compact and has a high resolution and a fast response time.

Exhaled Carbon Dioxide Monitoring

Continuous end-tidal carbon dioxide ($ETCO_2$) concentration monitoring is used routinely during the administration of anesthesia and sedation by anesthesiologists to monitor ventilation. Infrared technology is most commonly used to measure the partial pressure of carbon dioxide ($PACO_2$) and to produce a waveform. Respiratory rate is calculated from the start of inspiration to the start of expiration. There are two commonly used sensor types, mainstream and sidestream. In the mainstream technique, the carbon dioxide is measured across the airway, and in sidestream capnography, the expired gas is aspirated via a sampling tube and directed to an infrared sensor in the accompanying monitor. This latter technique results in a few seconds delay in the display of the values. The accuracy of mainstream over sidestream capnography has been shown to be better [32]. A time-based capnogram is most commonly displayed on the monitor together with a numerical presentation of the respiratory rate (Fig. 24.6).

A significant amount of clinical information may be obtained from the shape and value of the capnogram. Adequate perfusion generated during cardiopulmonary resuscitation may be assessed by the presence of a good capnogram. An elevated $ETCO_2$ value may be indicative of a hypoventilation or a hypermetabolic state. A decreased $ETCO_2$ reading may indicate hyperventilation, hypothermia, or a significant decrease in perfusion of the lungs such as with a pulmonary embolus or in cardiogenic shock. The accuracy of respiratory rate monitoring by capnometry in extubated patients has been demonstrated to be more accurate than thoracic impedance pneumography measured using ECG electrodes [33].

Acoustic Methods

Lung sounds auscultated by a stethoscope are used by nurses to manually count respiratory rate intermittently. The lung sounds do provide additional information regarding the health of the patient. Wheezes, rhonchi, and crackles may all be detected and used to assist in a systemic assessment of disease. In order to monitor respiratory rate continuously, sound sensors have been developed that can extract the airflow signal and transduce it to a respiratory signal. The peak of the respiratory signal may be detected electronically by a sensor placed on the throat close to the trachea and used to calculate respiratory rate [34] (Fig. 24.7).

Another experimental approach is to record respiratory flow rate and tracheal sounds using a pneumotachograph and a microphone [35]

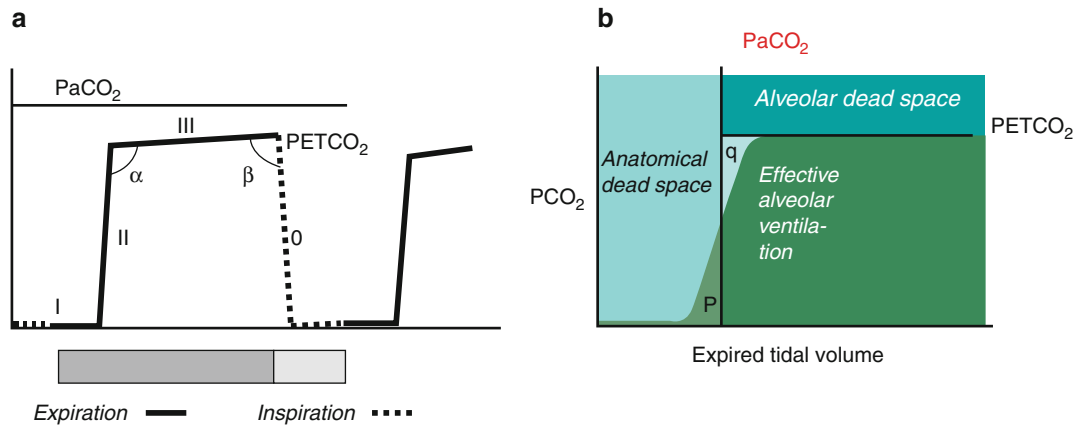


Fig. 24.6 Time capnogram demonstrating three phases of expiration, I, II, III, and inspiration phase O. The end-tidal CO_2 is lower than arterial $PACO_2$ because of the alveolar dead space (Reprinted with permission from Kodali [40])

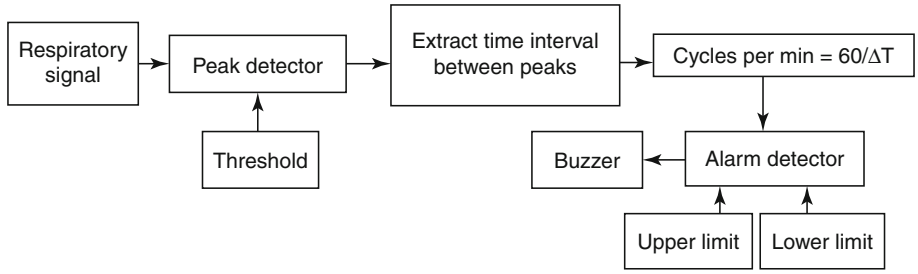


Fig. 24.7 Respiratory rate measurement (Reprinted in Sahgal [34]. Copyright © 2011 Sahgal, publisher and licensee Dove Medical Press Ltd. Open Access)

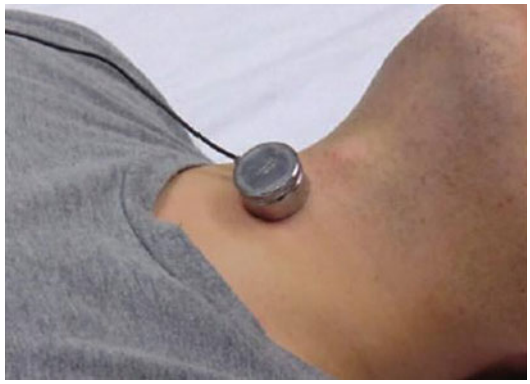


Fig. 24.8 Microphone attached to neck anterior to trachea (Reprinted with permission from Yu et al. [35])

(Fig. 24.8). In a sedated human volunteer study, this technique of monitoring respiratory rate detected obstructive and central apnea with 95 % sensitivity and 92 % specificity [35].

A commercially available acoustic monitoring technology (Rad-87, version 7804, Masimo Corporation, Irvine, CA) has been developed using an adhesive bioacoustic sensor (RAS-125, rev C) applied to the subject's neck, lateral to the cricoid cartilage (Fig. 24.9). This sensor has an integrated acoustic transducer that collates respiratory vibrations to detect inspiratory and expiratory flow (Fig. 24.10). This acoustic signal is converted into a continuous display of respiratory rate (Fig. 24.11). The advantage of this sensor over the microphone and other devices, which are placed in front of the airway, is that the device is well tolerated, as it is similar to having an adhesive bandage applied to the neck.

Fig. 24.9 Bioacoustic sensor applied to neck (www.masimo.com) (Photo courtesy of Masimo)

In two studies the bioacoustic sensor technology compared well with capnography for precision and accuracy [36, 37]. The bioacoustic sensor, similar to the microphone, was very sensitive to detecting apnea episodes [37] (Fig. 24.12).

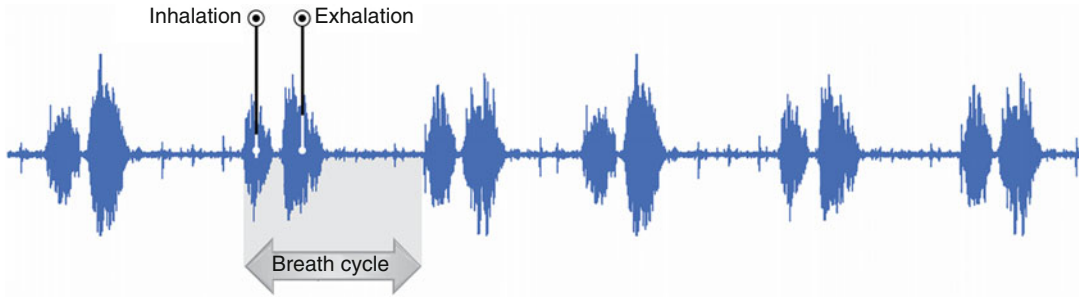
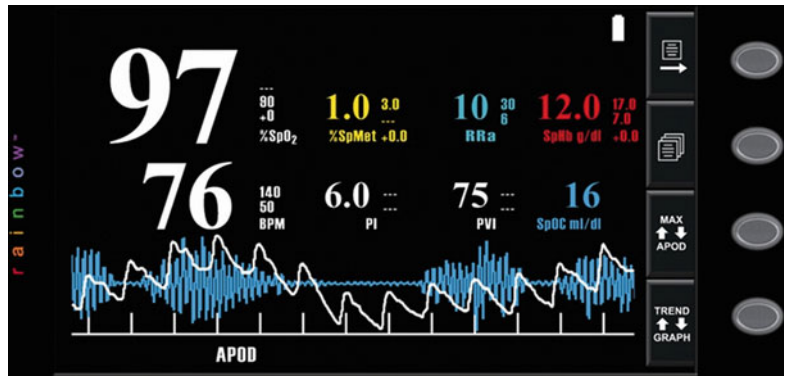


Fig. 24.10 Display of respiratory wave form signals from a bioacoustic sensor (www.masimo.com) (Photo courtesy of Masimo)

Fig. 24.11 Respiratory rate and waveform integrated into a vital signs monitor screen (www.masimo.com) (Photo courtesy of Masimo)



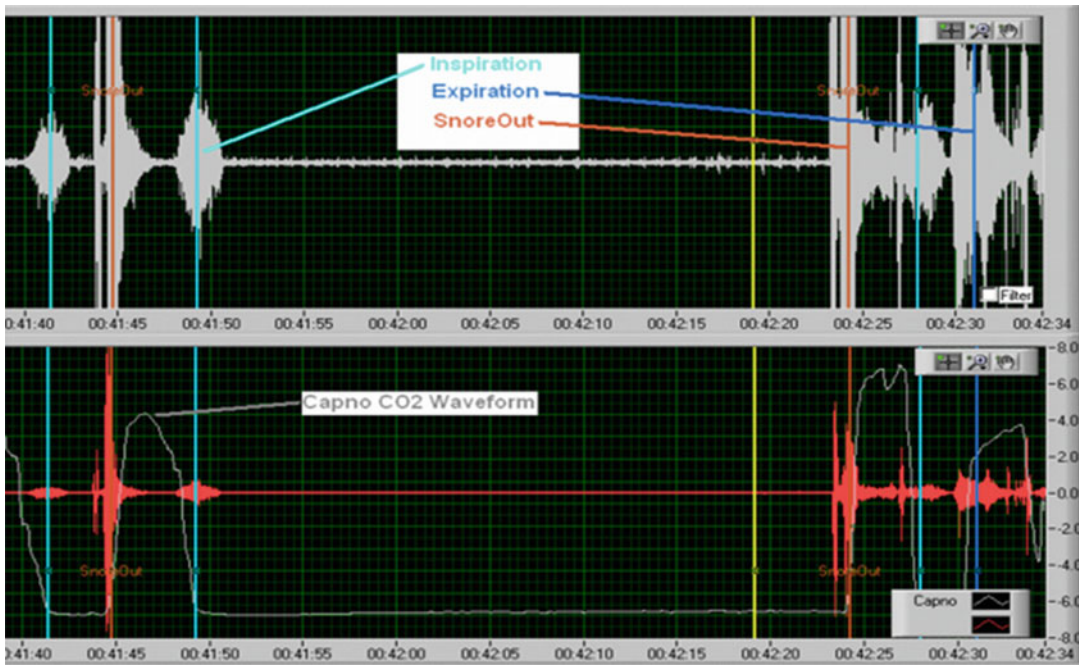


Fig. 24.12 Screen shot of patient file as displayed by Tag Editor program showing acoustic monitoring waveform (*upper trace*, *1*) and capnometry (*lower trace*, *2*), demonstrating snoring and apnea

Conclusion

Breathing moves air in and out of the lungs, providing an adequate oxygen supply to meet energy needs and removing CO_2 to maintain a stable acid-base environment. Respiratory rate is a very important vital sign, and yet it is rarely reliably monitored. The observation and manual documentation by the bedside nurse has been demonstrated to have poor validity [18, 38, 39]. Noninvasive technologies are available to automatically and continuously monitor respiratory rate. Many of these technologies may also give further information regarding the well-being of the patient. Adverse events related to unintended and unnoticed respiratory depression following the administration of postoperative opioids could be markedly reduced by the increased use of respiratory rate monitors.

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Closed-Loop Mechanical Ventilation

25

Marc Wysocki

Introduction

While mechanical ventilation is an important part of the modern-day acute care medicine, it is also a sophisticated technique with a very narrow therapeutic range. It is highly efficient and able to keep alive the most severe patients, but with considerable side effects and unwanted complications if not properly and timely used [1, 2].

Considerable knowledge has been acquired in optimizing the benefit/risk ratio of mechanical ventilation, but research constantly reports slow process or failure to implement protocols that can make it safer [3, 4] with a still significant number of patients receiving ventilation with dangerous settings, such as high tidal volume and airway pressure [5, 6].

Human and organizational factors are at least partially responsible for such situation [7] but also the vast variability of patient types and conditions that change over time. These factors make institution of one protocol/rule/guideline impossible to fit all situations.

Computerized protocols, closed-loop systems, and decision support are all techniques that may help make mechanical ventilation safer, and more efficient, than conventional ventilation techniques. This chapter will provide a brief overview of the technical and engineering considerations for closed-loop controlled ventilation, as well as tangible evidence supporting their use.

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Definitions

A protocol is a document that aims to guide clinical decisions regarding diagnosis, management, and treatment in specific medical situations. Most protocols are based on the medical knowledge acquired from physiological studies, expertise, or peer-reviewed evidence and can be generated by individuals or by consensus obtained from a group of physicians or experts. Protocols are often not precise enough to generate a decision at the bedside in a specific situation and still generate significant inter-clinician variability.

An explicit protocol aims to give enough details to generate patient-specific therapy instructions that can be carried out by different clinicians with virtually no inter-clinician variability [8]. Importantly, individualization of patient therapy can be preserved by explicit protocols when it is driven by individual patient data. Considering the number of the clinical situations and inputs from a given patient, explicit protocols rapidly become so complex that computers are required to integrate the large amount of information and provide specific answer to the user.

An explicit computerized protocol (ECP) is an explicit protocol supported by computer science to apply the instruction for a given patient at a given time. ECP might be in a laptop or

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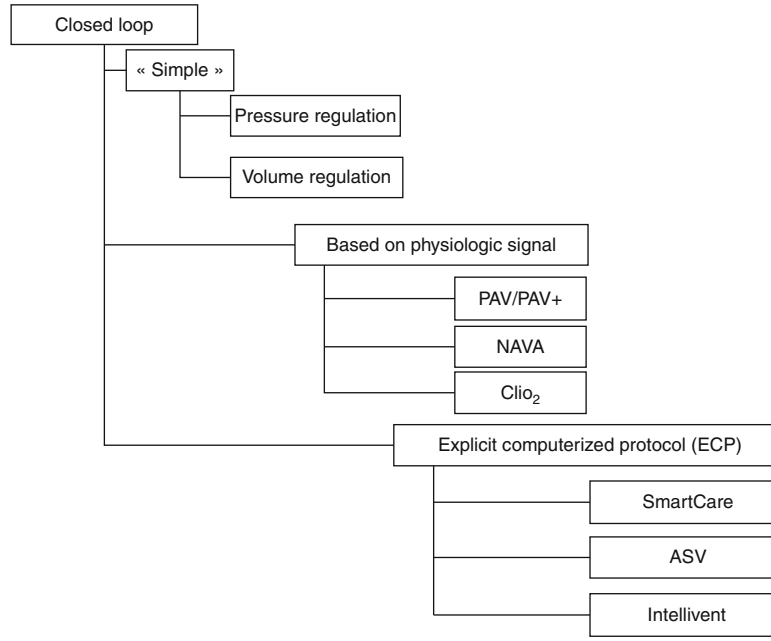

Fig. 25.1 Different levels of closed-loop mechanical ventilation. See text for further explanation

integrated into the ventilator or monitoring device. In ECPs the medical knowledge is usually implemented through "*if* … *then*" rules. For example, *if* the SpO_2 is below 88 %, *then* increase FiO_2 by 10 %. The rules can be more complex and based on physiological concept like the Otis least work of breathing concept in the Adaptive Support Ventilation (ASV) mode [9].

A rule can be in open or closed "mode." The rule is an open mode if it displays a therapeutic or diagnosis recommendation, but the caregivers is still in a position to make the final decision with regard to applying (or not) the recommendation. Such systems are also called *clinical decision support systems* as they are *supporting* but not making the decision [10]. In closed mode, the system not only makes recommendations, but it also takes action in order to implement them (e.g., by automatically adjusting ventilator settings). Such systems are usually called closed-loop mechanical ventilation.

The chapter will mainly focus on closed-loop explicit computerized protocol (closed-loop ECP) (i.e., sophisticated systems where complex protocols are computerized, implemented in mechanical ventilators, taking decision, and setting the ventilator continuously according to the patient's condition within predefined safety limits). Closed-loop ECPs are the most advanced form of automation, but closed-loop systems already exist in almost all ventilators available at a simple level (Fig. 25.1). This chapter will not discuss relatively simple closed-loop systems based on physiological inputs such as proportional assist ventilation (PAV) or the neurally adjusted ventilatory assistance (NAVA). The reader will find large overviews on such modes elsewhere [11, 12].

The Need for Closed-Loop Explicit Computerized Protocols for Mechanical Ventilation

A human's brain has limited capacity in integrating data and information in order to take decisions [13]. This capacity is even worse at night, under stress, or during times of extreme pressure. This is sharply in contrast with the "real ICU clinical life" where hundreds of variables need to be integrated by caregivers and decisions made 24 h a day. This is particularly true when it comes to the case of mechanical ventilation. The gap between the human capacity and the

vast amount of data and information that need to be integrated contributes to variation in clinical practice and explains some degree of medical errors and mistakes. In the aviation industry, a less complex environment, closed-loop computerized protocols have been developed and implemented to improve safety. This has resulted in a benchmarking model of safety management [14]. Additionally, patients are becoming more and more complex, and experts are not always available at the bedside to continuously adjust ventilation according to the specific patient's changing condition. Given that the human lung can be damaged with just one poorly delivered mechanical breath, it seems crucial to continuously adjust the ventilator settings on a breath-by-breath basis, in order to ensure that mechanical ventilation is as safe as possible. Interestingly in a recent investigation, where breath-by-breath information was acquired over a period of 4 h of conventional ventilation (i.e., set by the caregivers according to written protocols), patients were ventilated with optimal ventilation only 12 % of the time [15].

Development of Closed-Loop Explicit Computerized Protocols

Design and implementation of a closed-loop ECP requires a multidisciplinary approach: the team should include clinical expert(s) to generate the "knowledge" and to check the clinical relevance of the rules, computer scientists and biomedical engineers to implement and to test the rules into a medical devices, and industrial partners to set up proper documentation and to finalize a product that can pass all the regulatory requirements and testing needed to receive a CE marking and an FDA approval.

As "the devil is in the details," a very pragmatic and poorly scientific but heuristic approach is needed to generate closed-loop ECPs. A more-than-one consensus is often missing today with respect to several aspects of mechanical ventilation (for instance, what is the optimal level of PEEP, how often should one set PEEP, do we need a recruitment maneuver, what sort of maneuver, how often), and numerous "grey zones" exist. A conservative position would be "no scientific certitude = do nothing." A progressive position would be "no scientific evidence = try something." Closed-loop ECPs should be able to manage such "grey zones" by having an easy switch in manual mode and clearly acknowledging its limitations in addressing all clinical situations and patient types.

From the engineering side, there are also several approaches, none of which have been scientifically proven to be the most appropriate. Most of existing closed-loop ECPs can be describe with a classical model (Fig. 25.2) even if they do not exactly follow classical control theory [8]. Inputs are crucial to trigger the controller and make adjustments and should be "treated" by smoothening, averaging, rejection of artifacts,

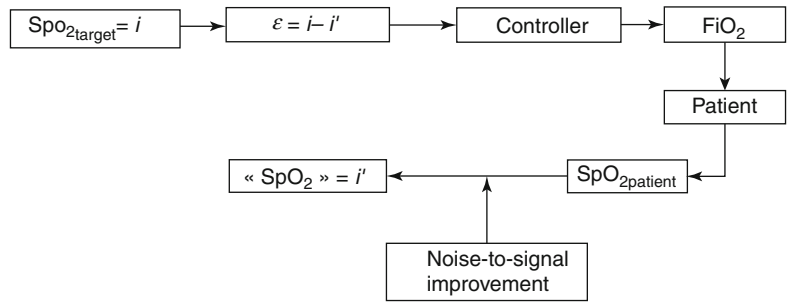

Fig. 25.2 The classical model of closed-loop controlled applied to FiO_2 automatic regulation based on SpO_2 information. The patient's SpO_2 is analyzed and treated in a way to improve the noise-to-signal ratio and "SpO_2" information is compared to a set point value (or range of values). If "SpO_2" is below the set point or the range of values, then the FiO_2 is increased, and vice versa

etc., in order to improve the signal-to-noise ratio. For example, engineers had to be very creative to make an SpO_2 signal reliable enough before one could use an SpO_2 signal in a continuous adjustment loop to vary the FiO_2 delivered. Not only one but sometimes several inputs need to be integrated at the same time before a rule can be generated, as it is the case for the SmartCare system [12]. A combination of theories can be used to cover a maximum of clinical scenarios, as it is with INTELLiVENT [16, 17]. Rules are usually "*if … then*" rules but some ECPs have been developed using fuzzy logic [18] (i.e., integrating patient information in a fuzzy way as to mimic human brain) [19, 20]. Despite the use of fuzzy logic in aircraft autopilot and in various other applications [20], to our best knowledge, fuzzy logic has not been used to date in commercialized medical ECPs.

Closed-Loop ECPS on the Market and Clinical Evidence

Saxton and Myers in 1957 reported the first ECP to adjust the end-tidal PCO_2 ($EtCO_2$) by regulating the negative pressure of an iron lung ventilator in poliomyelitis patients [21]. At the time, pediatricians were rapidly concerned about tightly adjusting the FiO_2 in order to avoid hypo-/hyperoxemia and its related side effects [22, 23]. Dugdale in 1998 [24] and more recently Urschitz [25] reported preliminary studies comparing automatic versus manual FiO_2 adjustment, demonstrating much more optimal oxygenation using automatic adjustment. Claure and Bancalari also conducted a research program aimed to develop closed-loop FiO_2 adjustment system using SpO_2 information [26, 27] and recently finalized a multicenter randomized clinical trial that included mechanically ventilated preterm infants. The patients were ventilated during two consecutive 24-h periods, one with FiO_2 adjusted by caregivers and the other by an automated system, in random sequence. Automated FiO_2 adjustment kept the SpO_2 within the intended ranges more often and reduced the total time exposure to high FiO_2 [28]. This closed-loop ECP is now commercialized (not FDA approved) as $CLiO_2$ (CareFusion, Yorba Linda, USA) and implemented in a respirator.

Keeping the patient on the ventilator more than required is probably the most dangerous situation for a given patient. Numerous studies have reported that daily adjustments of the ventilator and warning the physician in charge may help reduce the time spent by the patient ventilated [29]. To this end, several closed-loop ECPs have been designed to expedite the weaning from ventilatory support as fast as possible. The SmartCare (Draeger Medical, Lübeck, Germany) is one of them. The system automatically reduces the level of ventilatory support as soon as the patient's respiratory rate, tidal volume, and $EtCO_2$ are within acceptable ranges. Once the patient is weaned to a certain level of pressure for a given amount of time, the system starts an equivalent of T-tube trial and generates a message informing the caregivers that the patient might be ready for a separation from the ventilator. After a preliminary study in a small number of pediatric patients showing that SmartCare kept the patients in the "respiratory comfort zone" 91 % of the time [4], a randomized clinical trial found that in similar patients the weaning duration was significantly reduced with SmartCare as compared to usual care [30]. Similarly, in adult patients, such a system was able to shorten the time spent by the patient on the ventilator [31] or to give similar results as compared to a well-staffed weaning-oriented team of physicians and nurses [32].

Adaptive Support Ventilation (ASV) was first reported in 1994 by Laubscher and coworkers [9] and was designed to accommodate passively ventilated patients but also patients who are actively breathing. ASV is a pressure-targeted form of closed-loop ECP, which optimizes the relationship between tidal volume and respiratory frequency based on lung mechanics. As respiratory mechanics change, ASV automatically determines the tidal volume and respiratory rate that best maintains the peak pressure below the target level [33]. ASV recognizes spontaneous respiratory activity and automatically switches the patient between mandatory

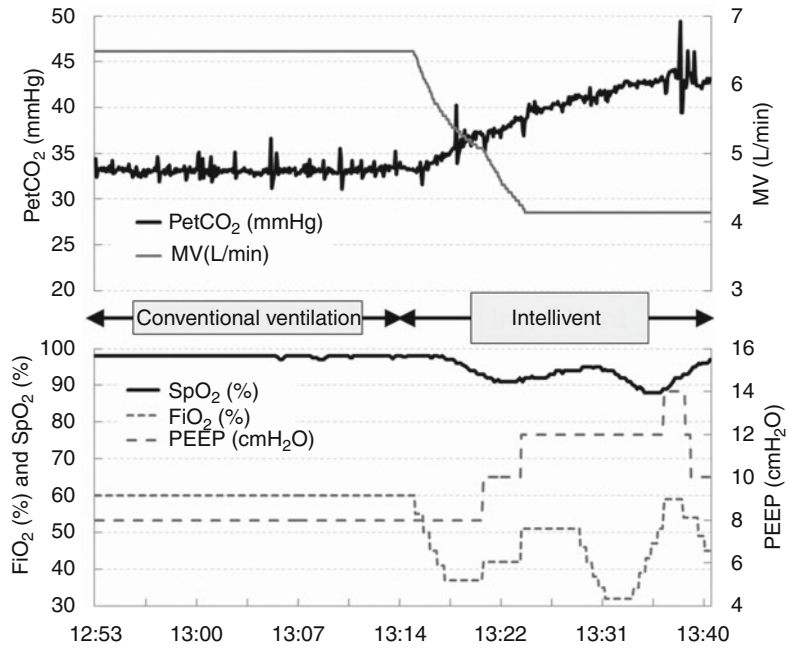

Fig. 25.3 Typical trends in a patient ventilated first in conventional ventilation (Adaptive Support Ventilation in this case) and INTELLiVENT. With conventional ventilation, the ET_{PCO2} was low. As soon as the patient was on INTELLiVENT, minute ventilation is automatically reduced to have a more physiological ET_{PCO2}. As a possible consequence, the SpO_2 decreased and the system reacted by adjusting the FiO_2 and ultimately the PEEP at higher level (With kind permission from Springer Science + Business Media: Arnal et al. [16])

pressure-controlled breaths and spontaneous pressure-supported breaths and further automatically decreases the level of support as soon as the patient's tidal volume is above the target. Several randomized controlled trials, mainly [34–36] but not only [37], in post-cardiac surgery patients found a shortened time on the ventilator with ASV, as compared to conventional ventilation and weaning modes.

Very recently, a closed-loop ECP including automatic control of minute volume (using ASV in the background), PEEP, and FiO_2 has been introduced on the market (not FDA approved). Such system (INTELLiVENT, Hamilton Medical AG, Bonaduz, Switzerland) continuously monitors the usual mechanical ventilation parameters plus $EtCO_2$ and SpO_2. The system automatically adjusts the minute ventilation to keep $EtCO_2$ and/or the patient's respiratory rate within acceptable values, as well as FiO_2 and PEEP to keep the SpO_2 within acceptable values. The system is fully bounded by safety rules and limitations which make it safe and reliable. In a preliminary study, INTELLiVENT was trialled for several hours in 15 stable children weighing more than 6 kg during the weaning phase of their care and was reported to be both safe and able to keep the patients in "zones of respiratory comfort" comparably to PSV or ASV [38].

In adult patients, INTELLiVENT has been investigated in post-cardiac surgery [15] patients and also mixed ICU patients [16]. The image in Fig. 25.3 represents a typical patient ventilated first in ASV and then with INTELLiVENT. Very obviously, INTELLiVENT adjusts the ventilator more often to maintain physiological values within the predefined ranges. In 60 post-cardiac surgery patients, a randomized controlled study found that during 4 h of ventilation, the average number of manipulations on the ventilator was significantly reduced from 148 in the control group (adjustments made according to written protocol) to 5 with interventions with INTELLiVENT while at the same time keeping patients in the intervention group with an optimal ventilation and low tidal volume (Fig. 25.4) [15].

Interestingly, in the most severe patients, the study from Arnal et al. [16] found that INTELLiVENT was able to keep similar PaO_2/FiO_2 ratio and lower dead space with lower tidal volume and airway pressure, altogether suggesting a more efficient ventilation when using INTELLiVENT.

Finally, a very recent investigation comparing pressure support ventilation and INTELLiVENT

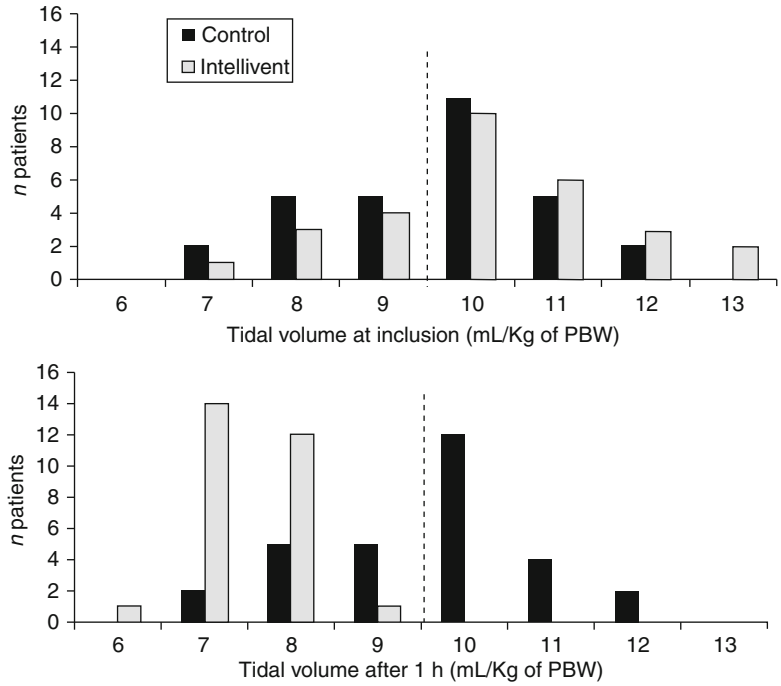

Fig. 25.4 Tidal volume distribution between controlled ventilation with written protocols ($n=30$ patients) and INTELLiVENT ($n=30$ patients) at the admission and after 1 h of ventilation in post-cardiac surgery patients. The mean tidal volume was significantly reduced with INTELLiVENT after 1 h of ventilation. The difference remains during the ventilation course (With kind permission from Springer Science + Business Media: Lellouche et al. [15])

in a group of actively breathing patients found that the oxygenation estimated from the PaO_2/FiO_2 ratio was better, in parallel with more variable ventilation during INTELLiVENT [39].

Additional Considerations for Closed-Loop ECPs

The Graphic User Interface

Mechanical ventilation and related monitoring information are becoming more and more complex, generating an overwhelming amount of data, output, and curves, which are often not understandable by nonexperts and most of the time simply not read or evaluated at the bedside. Closed-loop ECPs have an additional issue called the "black-box effect"; if the end user is not able to visualize and understand in a quick and simple way what is happening inside the ventilator, he/she will likely reject the device. Considerable work therefore must be done to make the graphic user interface for closed-loop ECPs more intuitive and easier to understand [40]. Some improvements have been made recently to make a ventilator's graphic user interface compatible with complex closed-loop ECPs [41].

Alarms and Closed-Loop ECPs

Mechanical ventilation generates a considerable number of alarms, most of which are ineffective and subsequently ignored [42]. More sophistication (closed-loop ECPs) may generate more alarms and ultimately annoy clinicians and cause poor decision making. Therefore, the alarm strategy should be wisely designed for sophisticated closed-loop ECPs. In addition, the monitoring variables and alarms should be designed from a different perspective: for instance, with INTELLiVENT, as the system is designed, it will keep $EtCO_2$ within predefined values, and therefore, alarming on $EtCO_2$ is of limited value. Instead, the alarm needs to be on minute ventilation, allowing the user to be informed when minute ventilation increases over a certain value. This is also true for the SpO_2-FiO_2 closed loop as most clinicians want to be informed when the FiO_2 increases, even if SpO_2 is kept within a safe range.

Training

More sophistication and complex automation in the ventilator does not mean that caregivers should give up trying to understand what is happening inside the "box." A very common criticism regarding closed-loop ECPs is related to the risk of losing basic and important knowledge. Such a fear is logical, and also very common, when innovation arises. At the same time algorithms in closed-loop ECPs are so complex that traditional teaching is insufficient. Innovative trainings must be implemented such as in-the-ventilator simulators and/or sophisticated virtual patients which mimic cardiorespiratory interactions. Virtual patient may also help with designing, testing, and debugging the algorithms and making the product safer before being brought into the marketplace.

Safety

In our intention to improve patient safety by reducing human factor-related safety problems, we should be aware that technology-related errors and mistakes might be more frequent. This has not been yet investigated with mechanical ventilation closed-loop ECPs, but there is already some evidence that poorly developed, implemented, customized, or operated computerized systems may cause or facilitate these new types of errors [43].

Ethical Considerations and Legal Issues

Finally, closed-loop ECPs have some specific ethical and legal considerations. Today the physician is liable for the way he/she sets the ventilator, and if the settings are "atypical" (e.g., a tidal volume twice our accepted standards), he/she will have to justify his/her choice. With closed-loop ECPs, the liability is transferred to the device and more precisely to the manufacturer which does not have the competence for overtaking a medical decision. An extensive dialogue between jurists, ethicists, physicians, and manufactures will need to occur in order to prevent future conflicts and more importantly make the healthcare system more confident in using closed-loop ECPs.

Conclusion

Considering the growing number of patients requiring mechanical ventilation on one hand and the lack of resources and expertise on the other, closed-loop ECPs will have an increased role in the future, and several manufacturers have already brought to market a number of sophisticated systems such as SmartCare and INTELLiVENT. Preliminary clinical studies have already shown promising results with patients spending more time in a zone of safe ventilation and also being weaned earlier from the ventilator. Additional studies are needed, particularly to assess global outcomes and cost-utility for the health care system. Finally, as closed-loop ECPs will be used more widely, additional refinement and adjustments to graphic user interfaces, alarms, and training must be undertaken.

Conflict of Interest Dr. M. Wysocki was head of medical research for Hamilton Medical AG (the manufacturer of INTELLiVENT) until 2011, and he is co-sharing several patents related to INTELLiVENT. At the time he wrote this chapter, he had no conflict of interest. Starting July 2012, he is medical director for GE Life Care Solution, Europe.

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Part IV

Neuromonitoring

Introduction to Neuromonitoring

26

Tod Sloan and Antoun Koht

Monitoring of the central nervous system is being utilized with increasing frequency during anesthesia and surgical management in patients undergoing procedures on the central nervous system (CNS). In such cases, IOM facilitates improved procedure and anesthesia decision making and patient care. These techniques allow monitoring at the neuronal level to provide insight that is not apparent by simply monitoring the blood pressure and other general measurements of physiology. As such, they have become commonplace in orthopedics, neurosurgery, otologic surgery, vascular surgery, and other procedures where the nervous system is at risk for injury.

Neuromonitoring is frequently used to monitor the brain during procedures that may be associated with structural or vascular compromise such as procedures on the aortic arch, carotid endarterectomy (CEA), coronary bypass procedures, or surgery involving the intracranial vasculature (e.g., aneurysm clipping). In these cases, monitoring is used to detect unexpected ischemia or neural compromise.

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Several methods have been used to assess cerebral blood flow. Transcranial Doppler (TCD) measures cerebral arterial flow velocity which reflects blood flow and arterial diameter. Changes in blood velocity may be used to monitor changes in blood flow or identify the presence of vascular spasm. Alternatively, monitoring the balance of oxygen delivery and consumption can be done by using transcutaneous cerebral oximetry utilizing near-infrared spectroscopy (NIRS) or mixed venous oxygenation. NIRS assesses primarily the cerebral venous oxygenation saturation of the frontal lobe region. Jugular venous oxygen saturation (SvjO2) also measures the balance of oxygen supply and metabolism of the brain by measuring the mixed venous effluent from the majority of the brain in the right jugular vein.

Changes in these monitors have correlated with neural morbidity and improved outcome. Reductions in TCD velocity have been shown to correlate with markers of brain injury and may detect emboli associated with cerebral morbidity [1]. In both adult and pediatric cardiac surgeries, monitoring is associated with improved outcome including reduced morbidity, mortality, postoperative cognitive decline, shorter hospital stays, and lower costs [2–6]. Some authors consider electroencephalography (EEG) and NIRS a standard of care in perioperative cardiac procedures [7]. Other studies in geriatric patients undergoing general surgery showed monitoring resulted in quicker recovery and better scores on cognitive examinations at 7 days postoperatively [8].

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During specific procedures, neurophysiological monitors provide unique management tools. For example, during profound hypothermia and circulatory arrest, NIRS is the only monitor suitable to assess if residual metabolism has exhausted the available energy reserves. Similarly, TCD is the only continuous direct measurement of cerebral hyperperfusion seen after CEA which is associated with longer and more costly hospital stays [9, 10]. A recent CEA meta-analysis showed a 38 % reduction in the incidence of brain infarcts when monitoring was used to direct selective shunting [11]. In head injury, SvjO2 has been shown to correlate with outcome and has been used to optimize the management of cerebral perfusion pressure and guide the use of hyperventilation [12, 13].

Monitoring has become an important tool to guide techniques that protect the brain prior to an expected ischemic event (e.g., ensure adequate hypothermia) or maneuvers used to improve blood flow during compromised flow (e.g., during temporary clipping of intracranial aneurysms, selective antegrade or retrograde cerebral perfusion during cardiopulmonary bypass) [14, 15]. As the number of procedures increases in our aging population, the reduction of stroke and postoperative cognitive decline associated with IOM will lower the cost of health care and the quality of life.

An alternate approach to assessing the status of the CNS tissue is to examine the altered or absent electrical activity resulting from compromised oxygenation. EEG and sensory and motor evoked potentials are used to monitor the viability of the select neural tissue involved in stimulation, conduction, and generation of the monitored responses. These are particularly useful with surgery on the intracranial vasculature such as aneurysm clipping.

Intracranial pressure monitoring (ICP) is important monitor to assess brain perfusion since the net supply of blood (cerebral perfusion pressure, CPP) is determined by subtracting the ICP from the mean extracranial blood pressure. The Brain Trauma Foundation (BTRF) guidelines recommend measurements of ICP in severe head trauma to guide the management of therapies to lower ICP, optimize CPP, and improve outcome [16].

Neurophysiological monitoring of the spinal cord has become commonplace in surgery to correct spinal column abnormalities, intramedullary spinal cord tumors, and procedures that place the spinal cord circulation at risk. One of the earliest methods of monitoring was the Stagnara wake-up test which involved awakening the patient during Harrington rod distraction for the correction of scoliosis [17]. In the United States, Clyde Nash, MD, an orthopedic surgeon; Richard Brown, PhD, an engineer; and Betty Grundy, MD, an anesthesiologist, used somatosensory evoked potentials (SSEP) to advance the monitoring to a more continuous technique. This work was simultaneously developed in Japan (Tetsuya Tamaki, MD, and K. Shimoji, MD) and has allowed surgeons to monitor procedures with multiple potential risk factors (e.g., sublaminar wires, hooks) [18]. This was rapidly adopted and its efficacy confirmed by the Scoliosis Research Society (SRS) who found that the incidence of paralysis was markedly reduced and the overall cost of patient care decreased when SSEP monitoring was performed [19–21]. Unfortunately, since the SSEP monitors only the posterior column pathways of proprioception and vibration, served by the posterior spinal arteries, an occasional motor pathway injury occurred undetected (approximately 1 in 787 patients in the SRS study). As such, the wake-up test remained an occasional method to confirm motor pathway integrity.

As the complexity of instrumentation has increased, monitoring techniques have evolved and extended to other surgeries. Electromyography (EMG) has been used to monitor mechanical nerve root irritation or thermal injuries and to assess reflex pathways in the cauda equina [22, 23]. More recently, the introduction of transcranial motor evoked potentials (MEP) has allowed monitoring of the anteriorly located corticospinal tract and the spinal grey matter. This has largely replaced the wake-up test.

Because the MEP monitors the spinal tissue supplied by the anterior spinal artery, it has been used to monitor the spinal perfusion during

surgery on the thoracic aorta [24]. In addition to the compound muscle action potential measured by the MEP, the response can also be measured in the epidural space as a D wave. The amplitude of the D wave is thought to be an index of the number of fibers activated in the corticospinal track. As such, monitoring of the D wave during intramedullary spinal tumor surgery has allowed quantitative endpoints for these resections [25].

The importance of spinal monitoring has been reaffirmed in a recent evidence-based analysis by the American Academy of Neurology [26]. The report concluded that monitoring is established as an effective method to predict an increased risk of adverse outcomes of paraparesis, paraplegia, and quadriplegia in spinal surgery. Since monitoring changes can warn of impending injury, this allows anesthesiologists and surgeons to intervene and reduce the incidence of injury as observed in the SRS study and numerous articles in the literature. Thus, monitoring has allowed more aggressive spinal procedures and is considered by some a current standard of care in complicated spine surgeries [27].

Monitoring of the CNS also has potential applications for the anesthesiologist since this is the major target organ of anesthetic medications. Of the four major general anesthetic goals, unconsciousness, amnesia, immobility, and blocking of noxious sensory stimuli (analgesia in the awake patient), the frontal EEG has been used in an attempt to quantify the drug effects related to the first two [28]. At present, the frontal EEG and EMG have shown a correlation with the degree of sedation with many sedative agents. A complete measurement of all anesthetic effects is because other regions of the CNS are involved in immobility (e.g., reflex pathways in the spinal cord), amnesia (e.g., amygdala, hippocampus), and blocking of noxious stimuli (e.g., dorsal horn of spinal cord, periaqueductal grey). Clearly the success in identifying indices of these CNS functions will be welcomed in the management of anesthesia and allow techniques to provide computerized feedback to assist in the control of all anesthetic goals.

In conclusion, monitoring of the brain allows a portal to assess and improve anesthesia and procedural decision making that may reduce the incidence of iatrogenic periprocedural neural injury. As the complexity of procedures has advanced and the comorbidities and age of our patients have risen, monitoring is a welcome and needed addition to our management armamentarium.

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Transcranial Doppler

27

Roy C. Neeley

Cerebral Physiology

In healthy individuals, the brain typically receives approximately 15–20 % of the cardiac output (Fig. 27.1) [1]. The brain has relatively no energy reserve and is highly dependent on aerobic metabolism, thus requiring an uninterrupted blood supply. Less than 30 mL/100 g/min can lead to neurologic symptoms [2, 3]. Significantly less than 15 mL/100 g/min can lead to electric failure and, if prolonged, can lead to irreversible neurologic damage.

Cerebral blood flow (CBF) is dependent on a combination of blood viscosity, cerebral perfusion pressure, and vessel radius. This is expressed in the Hagen-Poiseuille formula: $Q = (P \times \mathrm{pi} \times r^4)/8 \times (n \times L)$, where P is the cerebral perfusion pressure, r is the radius of the vessel, n is the viscosity of the blood, and L is the vessel length. Based on this equation, the adequate delivery of oxygenated blood to the brain can be affected dramatically by the vessel radius. The changes in vessel radius seen in SAH patients can be especially harmful, such that unrecognized and untreated vasospasm can lead to delayed cerebral ischemia (DCI) and stroke. The relationship between cerebral blood flow, cerebral blood volume, and intracranial pressure is shown in Fig. 27.2. In recognizing the impact vasospasm has on patient outcomes, TCD has emerged as a valuable tool in assessing for vasospasm in the SAH population [4–8].

Though the intracerebral vessels are not directly visualized with TCD, the vessel diameter is assessed indirectly using the Doppler effect and calculating the Doppler shift, which is the difference between the frequencies of the transmitted and received ultrasonic waves. The Doppler shift is proportional to the velocity of the blood [9]:

$$f = 2 \times f_o \times V / C$$
$$V = f \times C / 2 \times f_o$$

where f_o is the transmitted ultrasound frequency (1–2 MHz), C is the velocity of sound in blood, and V is the velocity of blood flow. By assessing for changes in the blood flow velocity (BFV), one can infer a change in vessel diameter is also occurring. Higher velocities frequently are associated with pathologic conditions, such as vasospasm or stenosis. Common transcranial Doppler findings are shown in Fig. 27.3.

TCD Velocities and Indices

When performing TCDs, one records the peak systolic flow velocity (V_s) and the end-diastolic flow velocity (V_d). Using these values, the mean flow velocity (MFV) is calculated ($\mathrm{MFV} = (V_s - V_d/3) + V_d$) [10]. The normal TCD values for

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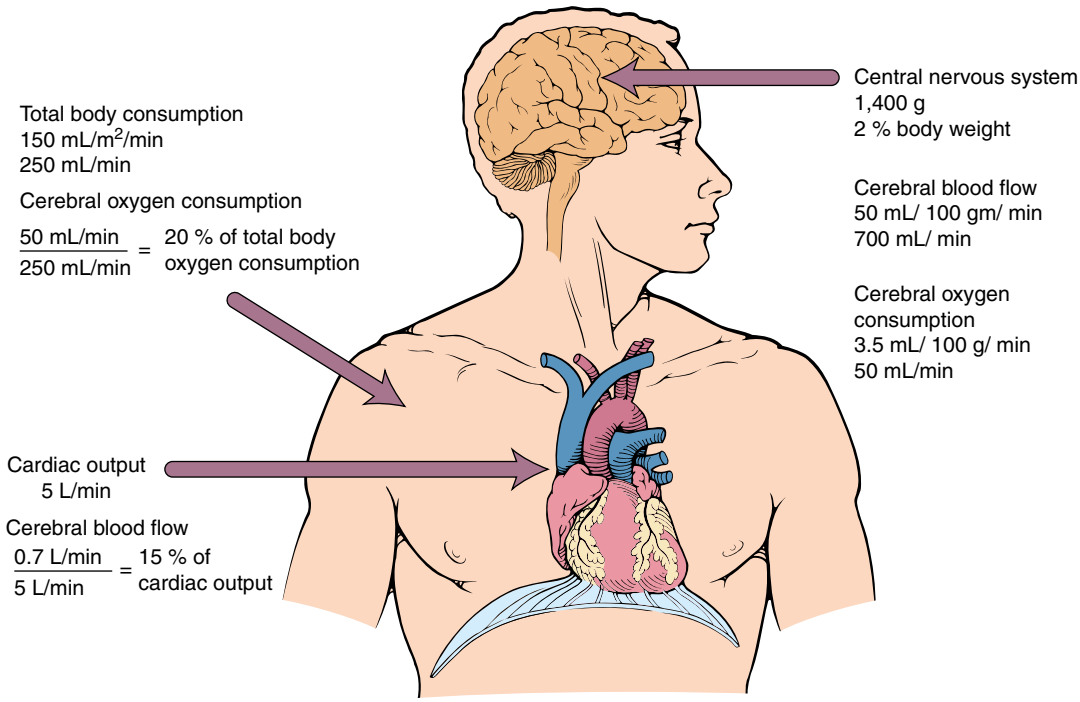

Fig. 27.1 Cerebral blood flow. In awake humans under normal conditions, cerebral blood flow averages 50 mL/100 g of brain tissue/min. The central nervous system represents about 2 % of body weight, but because of its high metabolic state, it receives 15 % of cardiac output and uses 20 % of total body oxygen consumption. To utilize 20 % of total body oxygen consumption from 15 % of the cardiac output, the brain extracts oxygen to lower venous hemoglobin saturation. Cerebral venous oxygen saturation is approximately 65 %, whereas normal mixed venous oxygen saturation is approximately 75 % (Reproduced from Brian et al. [22]; kind permission from Springer Science + Business Media B.V)

MFV for males and females can be seen in Tables 27.1 and 27.2, respectively.

Frequently, measured velocities can be elevated for various reasons. The Lindegaard index (LI) was developed as a way to correct for systemic increases in hyperdynamism [12]. It is not uncommon for patients with a SAH to be receiving inotropes or triple H therapy (hypertension, hypervolemia, and hemodilution) to improve delivery of blood to the brain. This can translate to increases in the flow velocities within all cerebral vessels due to an augmented cardiac output. To calculate the LI, the MFV of the middle cerebral artery (MCA) is compared to the MFV of the proximal portion of the ipsilateral internal carotid artery (ICA). This helps differentiate global hyperemia and hyperdynamism from vasospasm, $LI = MFV_{mca}/MFV_{ica}$. LIs greater than 6 indicate severe vasospasm, 3–6 reflective of mild to moderate vasospasm, and less than 3, hyperemia [13].

In regard to the MCA, velocities between 120 and 200 cm/s reflect a reduction of lumen diameter between 25 and 50 %. Velocities greater than 200 cm/s are generally associated with severe vasospasm and a diameter reduction of greater than 50 % [14]. Identifying vasospasm in the posterior cerebral artery (PCA) and anterior cerebral artery (ACA) can pose more of a challenge because of difficulty in obtaining adequate windows and also due the directional changes of the vessel [15]. Lower velocities are associated with lower sensitivity and specificity, even in technically adequate

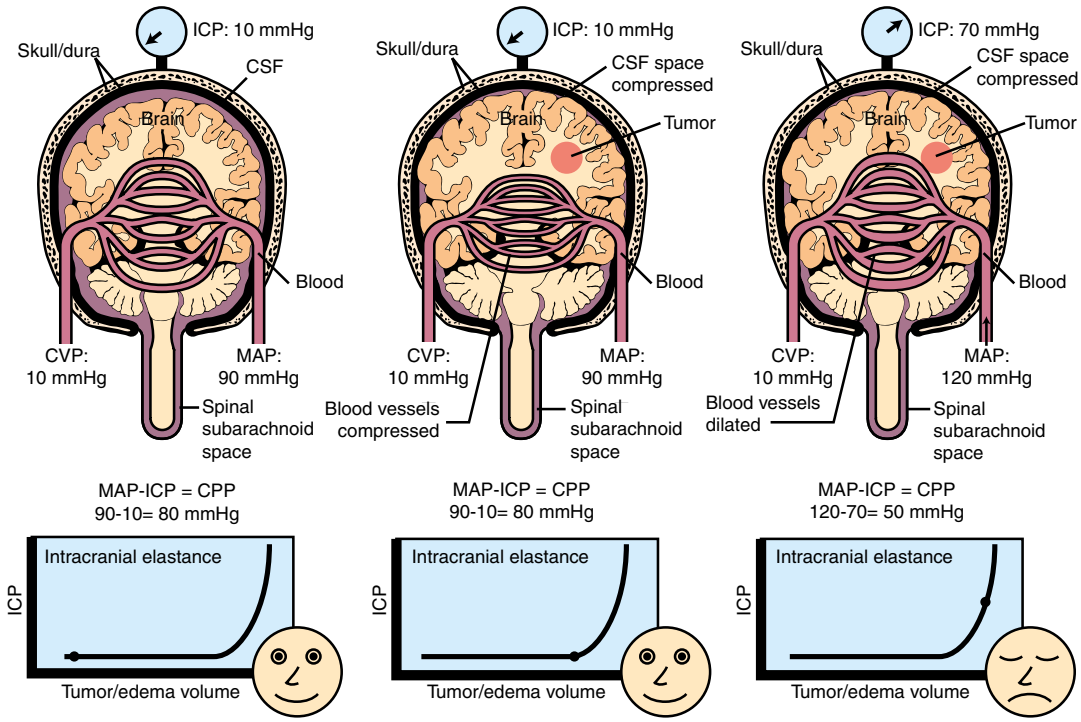

Fig. 27.2 Cerebral blood flow, cerebral blood volume, autoregulation, and intracranial pressure (*ICP*). In patients with defective autoregulation and reduced intracranial compliance, increased blood pressure can lead to increased ICP. When cerebral blood vessels lack autoregulation, increased blood pressure increases blood flow and volume in these vessels. *CPP* cerebral perfusion pressure, *CSF* cerebrospinal fluid, *CVP* central venous pressure, *MAP* mean arterial pressure (Reproduced from Brian et al. [22]; kind permission from Springer Science + Business Media B.V)

studies. Conversely, higher measured velocities more consistently identified patients in vasospasm [15]. Instead of relying completely on the exact velocity, it may be more beneficial to follow the serial trend in the velocities, where increases in MFV of greater than 50 %, or greater than 50 cm/s, compared to the previous study will identify patients at risk for vasospasm and DCI.

Performing Transcranial Doppler

Considering that ultrasonic waves do not easily pass through bone, one of the challenges with TCD is finding the optimal location to place the probe. Early studies by Aaslid et al. determined that a frequency of 2 MHz penetrates the skull better than higher frequencies [16]. In performing TCDs, there are specific parts of the skull, or windows, where the bone is the thinnest and offers the best visualization of the cerebral vasculature. Commonly used windows are the transtemporal (Fig. 27.4), transorbital (or transoptic), and suboccipital (or foramen magnum), followed by a view of the extracranial internal carotid artery, via the neck, which is used for calculating the Lindegaard index. The operator will commonly have to adjust the angle of the probe in order to acquire an image with the optimal blood flow velocities.

With the transtemporal view, above the zygomatic arch, one can visualize the middle MCA (Fig. 27.5), ACA, and PCA. The suboccipital view is used to insonate the basilar and vertebral arteries. With the transorbital view, one can find segments of the ICA and the ophthalmic artery. The MCA can be seen at a depth of 25–50 mm and all other vessels approximately at a depth of 50–70 mm [17].

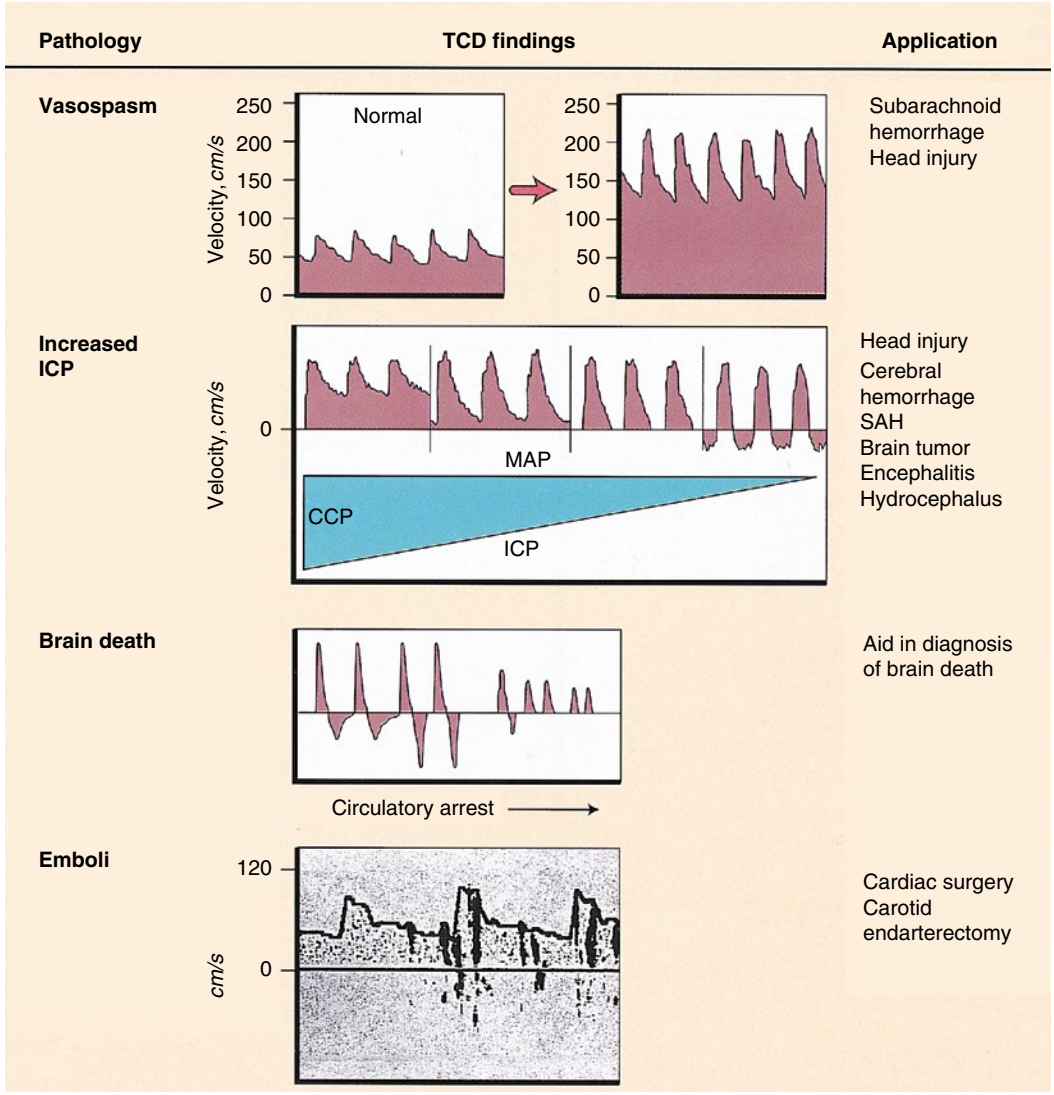

Fig. 27.3 Transcranial Doppler monitoring findings. In vasospasm, blood flow velocity increases, by the Bernoulli effect, when arterial diameter is reduced. Middle cerebral artery (MCA) velocity greater than 120 cm/s and velocity in the MCA three times or greater than that of the velocity in the internal carotid artery (ICA) are indicative of vasospasm. MCA velocity greater than six times ICA velocity indicates severe vasospasm. TCD findings in vasospasm are useful in the diagnosis of subarachnoid hemorrhage and head injury (Reproduced from Schell et al. [23]; kind permission from Springer Science + Business Media B.V)

When surveilling for vasospasm, TCDs can be performed either on a daily basis or every other day. It typically will depend on the discretion of the provider and the availability at the institution. TCD provides a snapshot of one moment in time, and there exists a chance that periods of vasospasm could be missed between TCD studies. Even if a patient is not in vasospasm, based on the MFV values, by repeating TCD serially, one can follow the trend, identify patients at higher risk of evolving vasospasm, and correlate this information with any changes in the patient's neurologic exam. Conversely, there are instances when vasospasm is identified on TCD, and there is no clinical manifestation.

Table 27.1 Normal reference TCD values for males

Insonated vessel	MFV[a]		
	Age 20–39	Age 40–59	Age >60
ACA	54–62	51–61	45–55
MCA	66–74	62–69	55–62
PCA (P1)	48–53	41–48	40–45
PCA (P2)	43–49	40–45	39–45
Vertebral	37–43	29–36	30–35
Basilar	39–49	27–39	30–37

Data from Martin et al. [11]
Abbreviations: *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *MFV* mean flow velocity
[a]Range in cm/s

Table 27.2 Normal reference TCD values for females

Insonated vessel	MFV[a]		
	Age 20–39	Age 40–59	Age >60
ACA	57–64	62–71	44–58
MCA	73–80	73–83	53–62
PCA (P1)	52–57	50–56	37–47
PCA (P2)	45–51	50–57	37–47
Vertebral	45–51	44–50	31–37
Basilar	51–58	47–56	29–47

Data from Martin et al. [11]
Abbreviations: *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *MFV* mean flow velocity
[a]Range in cm/s

Regardless, TCD offers many benefits. It is inexpensive and noninvasive. Additionally, due to its portability, TCD can be performed at the bedside, quickly, thus avoiding the risks associated with transporting a critically ill patient outside of the ICU. Unlike the angiographic modalities, there is no risk of contrast exposure with TCD.

Disadvantages of TCD

Despite its advantages, there are still many factors that can affect visualization of the cerebral vasculature and MVF measurements. Getting accurate imaging is frequently related to the level of experience of the person performing the TCD. For this reason, it is best to have one skilled person that performs the TCD to maintain accuracy and avoid interobserver error as studies are serially performed. In some patient populations, it will be difficult to get adequate acoustic windows due ossification of the skull, specifically the elderly. Furthermore, variation in the probe angle in respect to the direction of the blood vessel can negatively impact the measured MFV, giving falsely low velocities.

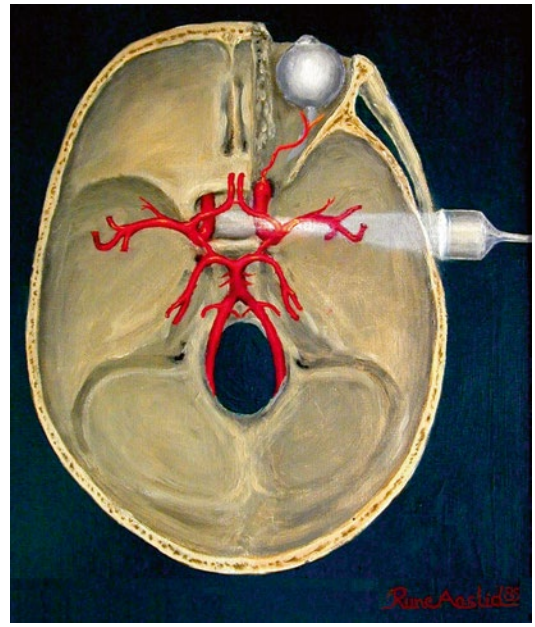

Fig. 27.4 Transtemporal view

Other Uses and Future Directions

The role of TCD has been primarily limited to assessing for vasospasm in the SAH population. However, studies looking into new roles for TCD are emerging. TCD is being used to guide transfusion therapy in sickle cell patients and possibly lower their incidence of stroke [18, 19].

TCD can also be used to assess a patient's stroke risk, either by gauging the degree of cerebrovascular stenosis, as determined by the MVF, or by detecting microembolic signals (MES) as they pass through the cerebral vasculature. MES have been detected in various settings: carotid artery stenosis, atrial fibrillation, myocardial infarction, prosthetic heart valves, and patent foramen ovale [20].

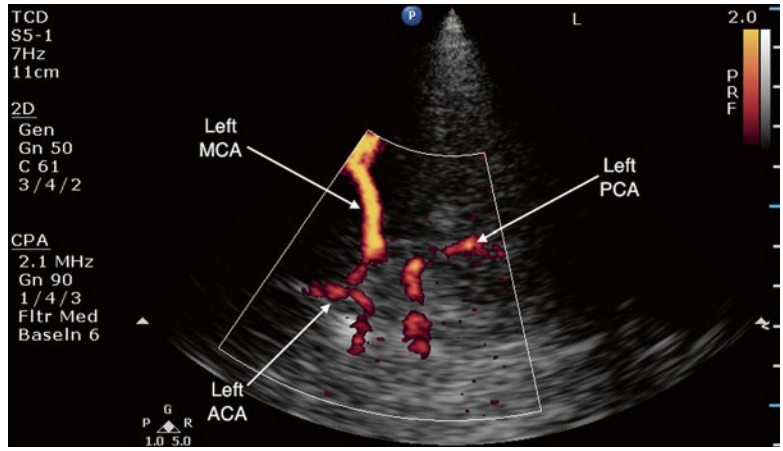

Fig. 27.5 TCD image. Left transtemporal view. *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery

Rosengarten et al. look to combine functional TCD with EEG and investigate the relationship between electric neuronal and vascular responses [21].

Conclusion

Because of its reliability and ease of use, the TCD has become a mainstay in the care and management of SAH patients. As with any study, the findings should be correlated with the patient's overall course and clinical picture. Trends in the MVFs should be followed closely to anticipate which patients will be at risk for vasospasm and will benefit from intervention.

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Brain Oxygenation

28

Davinder Ramsingh

Introduction

Cerebral oximetry (ScO_2) has been studied for more than 30 years and has been commercially available to clinicians for more than two decades [1]. Despite this, only recently has this technology begun to be used more widespread clinically. The brain receives approximately 15–20 % of the cardiac output and consumes approximately 20 % of the total body O_2. Interruption of this oxygen delivery for as little as 10 s can result in unconsciousness [2]. In 3–8 min, one can have ATP depletion that can result in irreversible damage [3]. This explains why neurological complications following periods of hypoxemia are a cause of significant morbidity and mortality. Neurological complications are also the single largest percentage of intraoperative malpractice claims [4]. Given this high level of risk, cerebral oximetry has gained increasing popularity in a variety of acute care settings as a monitor capable of detecting cerebral ischemia.

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Transcutaneous Measurement of Oxygen Saturation

Cerebral oximetry estimates the oxygenation of regional tissue by transcutaneous measurement of the frontal cerebral cortex, which is an area of the brain that is particularly susceptible to hypoxia [5]. This is accomplished with adhesive pads applied over the frontal lobes that consist of two photodetectors with each light source that both emit and capture reflected near-infrared light to different depths passing through the cranial bone to and from the underlying cerebral tissue (Fig. 28.1). Unlike conventional pulse oximetry, NIR spectroscopy tissue oximetry does not rely on a pulsating flow and measures a weighted average of arterial (25 %), capillary, and venous blood oxygenation (70–75 %) [6]. Based on this distribution, normal cerebral oximetry saturations have been reported to be in the range of 60–80 %; however, this value is highly variable. This is why the majority of the clinical use of this technology has been reported as monitoring trends in the change from baseline cerebral oximetry values determined on room air when the patient is awake.

Cerebral Oximetry Components

Cerebral oximeters have three main components: a light source, a light detector, and a computer. The light source produces NIR light of

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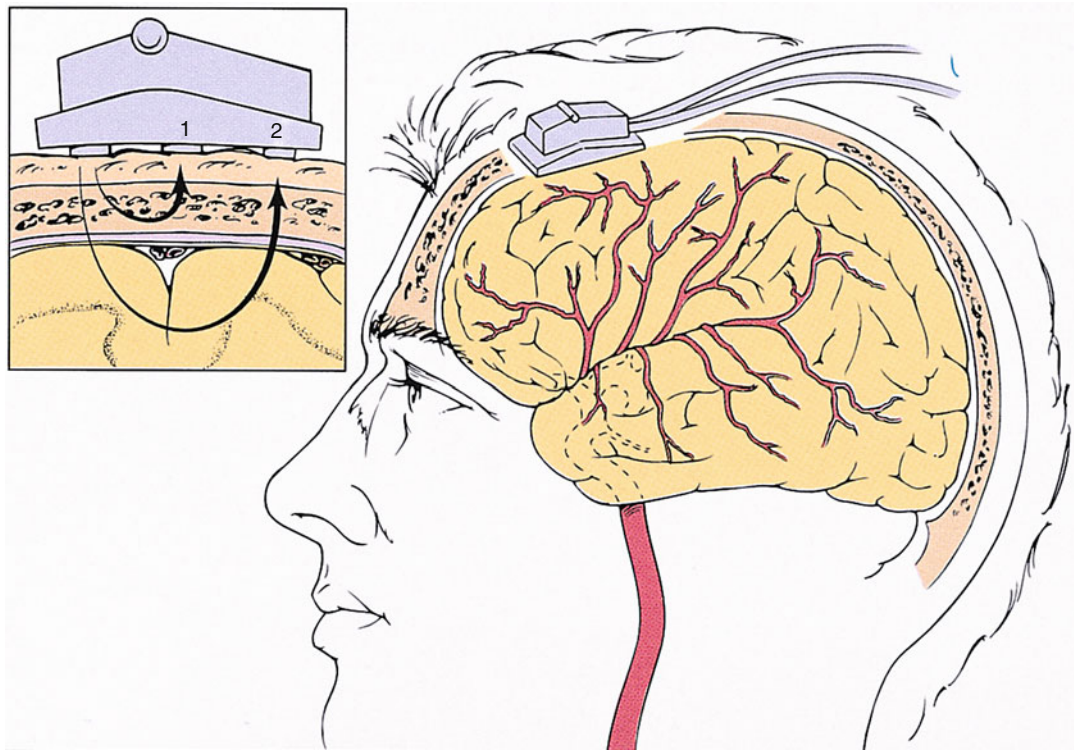

Fig. 28.1 Cerebral oximetry. Transcranial cerebral oximetry measures regional cerebral oxygen saturation (rSO_2) of hemoglobin by reflectance spectroscopy using light in the near-infrared range. Infrared light propagates through the scalp, skull, and cerebral parenchyma and returns to receiver fibers. The first detector (*#1*) receives light reflected from superficial tissue, thus ensuring that extracerebral blood oxygen saturation is subtracted from the deeper sampling of brain tissue with the second detector (*#2*). The rSO_2 measurement is a combination of venous, arterial, and capillary blood oxygen saturation, although the majority (approximately 70 %) is venous (Reproduced from Schell et al. [17]; kind permission from Springer Science + Business Media B.V)

known wavelengths and intensity which passes through cerebral tissue. Cerebral oximetry uses two photodetectors with each light source. By using two sensors, it allows selective sampling of tissue beyond a specified depth beneath the skin. Finally, a computer uses an algorithm to convert the intensity of light exiting the cerebral tissue into the amount of O_2Hgb and Hgb (oxygen saturation). In addition, near-field photodetection then can be subtracted from far-field detection to provide selective measurements of cerebral cortex tissue oxygenation. The approximate depth of penetration for the tissue sampled is 1.5 cm (which is one-third of the distance between the light emitter and detector).

Commercial Cerebral Oximetry Devices

Currently, there are four commercially available FDA-approved cerebral oximeters: (1) CerOx (Ornim), (2) Equanox (Nonin), (3) Fore-Sight (CASMED), and (4) INVOS (Covidien). The CerOx uses three laser diodes (LD) instead of light-emitting diodes (LED) and is the only device that also provides a simultaneous, yet independent, measure of HbO_2 saturation and blood flow measured by a small ultrasound transducer. This technology referred to as *UTLight* technology is unique among all other commercially available NIRS products. The Equanox system uses LED light at three wavelengths. It is referred to as a cerebral

oxygen trend monitor and is nonquantitative. The Fore-Sight system uses laser light at four wavelengths and is reported to quantitatively measure actual absolute cerebral oxygenation. Finally, the product by Covidien uses LED light at two wavelengths and is considered a nonquantitative cerebral oxygen trend monitor. The vast majority of research in this area has been with this device. Unfortunately, the optical probes and the algorithms of commercial cerebral oximeters are different and no standardization is available currently.

Despite the differences in their underlying technology, all four devices provide several of the same advantages: the most important being that they provide real-time oxygenation status of the region of brain being monitored. Furthermore, by measuring predominately venous versus arterial saturation, these monitors provide information about oxygen demand and supply balance. Additional advantages of these devices include that they are (1) noninvasive and require no specialized training, (2) can be used at the bedside, and (3) do not require radioactive tracers. Similarly, these devices share several limitations. This includes the fact that the monitor is not a measure of global oxygenation and, secondary to the limited depth of penetration, a large area of the brain is not monitored. In addition, these devices only represent intravascular oxygenation, and this may not be a true reflection of intracellular oxygen availability. Finally, electrocautery can cause also interference [4].

Interpretation of a Cerebral Oxygen Monitor

Specific, normal cerebral oxygen saturation (ScO_2) values are available for each manufacturer's device. Generally, however, all the monitors recommend a baseline measurement on room air and suggest that greater than 20 % trend reduction from baseline values is clinically relevant. However, values must be interpreted in the context of available clinical information because many factors alter measurements. These factors include cardiac output, blood pressure, hypo-/hypercapnia, arterial pH, inspired oxygen concentration, temperature, local blood flow, hemoglobin concentration, hemorrhage, embolism, preexisting disease (particularly cerebral infarction), and change of position. This highlights the challenge of cerebral oximetry, in that alterations in ScO_2, although highly sensitive, are relatively nonspecific. Previous studies have demonstrated that various factors, such as hemoglobin concentrations, extracranial blood flow, and changes in cerebral arterial-to-venous blood volume ratio, had an effect on near-infrared spectroscopy measurements [7–9]. It is for the clinician therefore to determine whether a decrease in ScO_2 reflects a derangement of systemic perfusion, regional cerebral hypoperfusion, relative hypoxemia, increased cerebral metabolic rate, or some other such combination of factors.

Despite this, preliminary clinical studies in humans suggest that cerebral oximetry may be a useful monitor in acute care settings. In on-pump cardiac surgery, Heringlake et al. present compelling evidence, from 1,178 patients, that baseline cerebral oxygen saturation (ScO_2) is an independent risk factor for 30-day and 1-year mortality [10]. It has also been shown that actively limiting intraoperative decreases in ScO_2 in cardiac surgical patients resulted in a significant reduction in overall systemic morbidity and mortality [11]. In a retrospective study of 2,279 patients, Goldman and colleagues demonstrated a decrease in the stroke rate in cardiac surgical patients after implementation of cerebral oximetry in their practice [5]. The role of cerebral oximetry as an index for systemic oxygen balance is further supported by several studies that show changes in cerebral oxygen saturation correlated with changes in pulmonary artery oxygen saturation [9, 10]. Casati and associates demonstrated, in a randomized prospective study, an association between reductions in cerebral oximetry and postoperative neurocognitive dysfunction in elderly patients undergoing major abdominal surgery [12]. In this study, they suggested a protocol (highlighted below) that was used in the treatment group to maintain ScO_2 values to within 75 % of baseline values [12] (Table 28.1).

Table 28.1 Cerebral desaturation treatment algorithm reported by Casati et al.

1. Ensure inspired oxygen is increased to 100 %
2. Verify that head and central venous catheter position is optimized for adequate venous drainage
3. Verify $PaCO_2$ is >40 mmHg
4. Increase mean arterial pressure to >60 mmHg
5. If hematocrit is <20 %, consider transfusion
6. If the above interventions do not improve cerebral saturation, decrease cerebral oxygen consumption by increasing anesthesia depth

Adapted from Casati et al. [12]

Beyond providing continuous insight into regional oxygenation of the brain, cerebral oximetry may provide additional utility for patient care. For instance, it may allow clinicians to use the brain as an index organ that represents the adequacy of tissue perfusion and oxygenation of other vital organs. Also, there is increasing interest in the utilization of cerebral oximetry sensors to monitor adequacy of tissue perfusion when placed on somatic sites in both adult and pediatric patients [13–15]. This concept of using these oximetry devices to detect inadequacies of tissue oxygenation via somatic monitoring was supported in a study performed by Smith et al. in which it was shown that a minimum somatic saturation <70 % correlated with the need for blood transfusion with a sensitivity of 88 % and a specificity of 78 % in trauma patients thought to be at high risk for hemorrhagic shock [16]. Interestingly, this study also showed that the need for blood transfusion within 24 h of arrival was not predicted by hypotension, tachycardia, arterial lactate, base deficit, or hemoglobin, which suggests that somatic tissue oxygenation may represent an important screening tool for states of poor oxygen delivery.

Conclusion

In acute care environments, the development of a neurological monitor capable of detecting ischemic events can provide useful information for patients where a neurological exam is not possible. Emerging evidence suggests that cerebral oximetry may be capable of detecting ischemic events, aid in guiding therapeutic interventions, and possibly reduce the incidence of neurological and systemic insults. Currently, however, most of the research has been with the INVOS product, and data from other products as well as more definitive studies still need to be performed. Despite this, this new modality of tissue oximetry may prove to be a vital monitor for the detection of stressed states.

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Intracranial Pressure and SvjO2

29

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Intracranial Pressure Monitoring

The cranial vault is a non-distensible compartment following the closure of the cranial sutures during the first year of life. The pressure within this enclosed compartment is the sum of the pressure produced by the contained components: blood, brain, meninges, and the cerebrospinal fluid (CSF). Glial cells account for nearly 90 % of the brain matter by mass. The average human brain weighs 1,500 g and 77 % of that is water. Water homeostasis is controlled by an intricate system of water and ion channels between the neurons and glial cells [1] and can be manipulated to affect intracranial pressure (ICP) [2]. CSF comprises 150 mL or 10 % of the total brain volume. Changes in its reabsorption, production, and relocation to the spinal canal can also compensate for increases in pressure. Similarly, changes in sympathetic tone of the cerebral blood vessels will affect blood volume (110 mL or 7 %) and provide another method of pressure compensation [3, 4]. Monitoring intracranial pressure provides insights into cerebral pathophysiology and the response to treatment interventions directed chiefly at water content and cerebral blood volume.

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Noninvasive Methods of Monitoring Intracranial Pressure

ICP can be monitored directly or indirectly. Indirect measures rely on surrogate markers of pressure and are therefore inherently less accurate than direct pressure sensors. Transcranial Doppler (TCD) measures velocity of blood flow through vessels, based on the change in frequency of ultrasound on reflection by red blood cells. It is most accurate when the angle of insonation is 0° from the probe. The inherent tortuosity and depth of the vessel, the thickness of the cranium, and the fact that it is a blind technique present limitations to the wide use of TCD [5, 6].

Simultaneous analysis of mean arterial blood pressure (MAP) and TCD cerebral blood flow velocities (and thereby the pressure required to develop those velocities) allows derivation of ICP from the formula: cerebral perfusion pressure (CPP) = MAP − ICP. The estimated cerebral perfusion pressure (eCPP) is determined by dividing the mean flow velocity in the middle cerebral artery (MCA) by the difference between the mean and the diastolic flow velocity, then multiplied by the difference between the mean and diastolic systemic blood pressure [7]:

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$$\frac{[FV_{mean}]}{[FV_{mean} - FV_{diastolic}]} \times (BP_{mean} - BP_{diastolic}) = eCPP$$

Accuracies of 80–85 % in measuring ICP have been reported, but the technical limitations of ultrasound, as well as the mathematical imprecision consequent upon application to a dynamic organic system, introduce inconsistency into this technique [8, 9]. The advantages of noninvasive ICP monitoring include decrease in the risk of infection and the inherent risk of placement and maintenance of a probe. The most important disadvantages are the cumbersome nature of the recording devices, an inability to keep them fixed in place and the degree of training that is involved in obtaining and interpreting the results. Other sophisticated systems of measuring intracranial pressure are available, mostly for research purposes. A list of noninvasive methods appears in Table 29.1.

Invasive Methods of Intracranial Pressure Monitoring

Direct access to intracranial pressure measurement can be via placement of a probe in the parenchyma or the epidural, subdural, or subarachnoid space(s) (Fig. 29.1). The latter includes lumbar puncture catheterization where continuity between intracranial and lumbar CSF spaces allows for measurement of ICP. The intraventricular catheter is the gold standard.

The External Intraventricular Catheter (EVD)

The external intraventricular catheter is a percutaneous drain that is commonly placed by anatomical landmarks (although radiologically guided imaging can be employed) and is connected to a fluid-filled system with external pressure transducer. The EVD provides accurate ICP monitoring over a large range of pressures and by titrated drainage also serves as a treatment tool. Additionally, it may be used to remove blood products after hemorrhage, as well as permit intrathecal drug administration. It is relatively easy to set up and maintain, with simple calibration of the external transducer, and this simplicity renders the system reasonably robust and reliable [10]. The technique is not without risk; routine CT scan after placement demonstrated a 10 % risk of hemorrhage compared to a 1.5 % risk with no such routine scan. However, only 0.6 % of the hemorrhages were

Table 29.1 Comparison of noninvasive intracranial monitors

Method	Technology	Availability	Bedside utility	Ease of use	Continuous
Transcranial Doppler	Direct measurement of MCA velocities	Widely used	Yes	Requires training	No
A-line and TCD waveform analysis	Requires a software analysis of the two wave forms and MCA velocities	Not widely available	Yes	Requires maintenance of TCD probe, arterial line, and computer	Yes
Ophthalmodynamometry	Direct pressure to globe with ultrasound measurement of ophthalmic artery pressure	Not widely available	No	Requires advanced training	No
Time-to-flight	Ultrasound measurement of the speed of trajectory across the head	Not widely available	Yes	Accuracy is highly dependent on device placement	No
Ophthalmic vein pressure	Pressure in the ophthalmic vein reflects ICP	Not widely available	No	Requires advanced training	No
Magnetic resonance imaging elastance measurement	Measures changes in compressibility of structures	Yes	No	Requires neuroradiologist	No

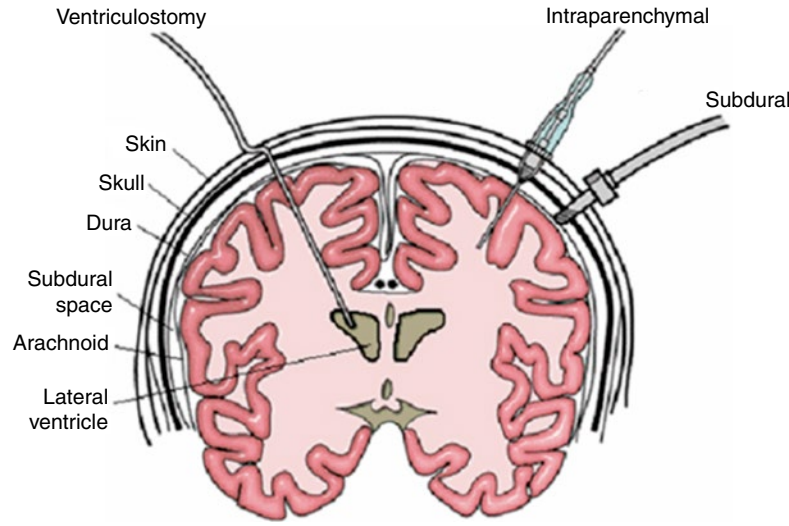

Fig. 29.1 Positioning of invasive intracerebral pressure measuring devices (Reprinted with permission from Sociedade Brasileira de Pediatria. Katia et al. [43])

clinically significant [11]. The fluid connections create the risk of infection, which is the most frequently cited complication. Reported rates depend on definitions of active infection versus colonization. Review articles quote rates from 2 to 7 % [12], but a more recent study found the rate to be 2.98 % in non-antibiotic-impregnated catheter and 2.5 % in impregnated catheters [19]. Infection control techniques and careful management of sampling ports are key in rate reduction [13]. Misplacement of the catheter was associated with increased infection risk due to damage to adjacent structures and the requirement for another catheter insertion [14, 15]. Prophylactic antibiotics for EVD are commonplace, but this practice is being questioned with studies suggesting no difference in outcome. One study showed an incidence rate of 3.8 % for a group receiving scheduled antibiotics versus 4 % for those receiving preoperative prophylaxis only. Estimated savings were $80,000/year [16]. Current practice is to leave the catheter in place and only exchange based on clinical evidence of malposition or infection [17]. Most EVD malfunctions are due to impaction of blood, debris, or brain matter into the proximal port of the system. Other system malfunction is infrequent, after successful placement [18, 19]. There are real risks of excessive drainage associated with movement and change in position, especially in the cognitively impaired patient.

Subarachnoid Bolt (SAB)

This device is a hollow screw placed via a burr hole, which in leading to the subdural space transmits intracranial pressure to a strain gauge transducer, which in turn translates it to electrical signals [20]. A comparison of the subarachnoid bolt, a subarachnoid catheter (SAC), and the EVD showed a good correlation between the SAC and EVD. However, the variance of the SAB waveform was 38.5 times higher than variance with SAC [21]. There are case reports of normal ICP readings and waveform via the SAB, in circumstances of actual increased ICP, leading to major morbidity and one death [22]. The variable accuracy and the availability of other devices has significantly limited use of the SAB.

Intraparenchymal Pressure Monitors

Intraparenchymal pressure monitors are implanted strain gauges or fiberoptic transduction systems, providing ICP measurement with no fluid connection to the periphery. They are often placed ipsilateral to the brain mass or area of edema to get a better estimation of pressure in the area of interest. The compartmentalization of brain tissue by falx and tentorium lends weight to this approach. The size of the probe minimizes hemorrhage but traumatic placement and parenchymal

damage are possible [23, 24]. The rate of infection is extremely low but calibration can only be performed before the sensor is placed [25]. Advantages include the relative ease of placement and accuracy as compared with the EVD. In a study of 128 patients, the ICP measured by EVD was 18.3±0.3 and the microsensor was 19.0±0.2 [26]. Cited disadvantages include the degree of drift in accuracy over time, the inability to recalibrate, and the inability to drain CSF for treatment purposes. The Camino intraparenchymal sensor (Integra Lifesciences Corporation, Plainsboro, NJ, USA) uses a fiberoptic sensor to detect pressure. In a study of 163 severely head-injured patients, it malfunctioned 9.8 % of the time requiring an exchange. There was no significant infection risk and a low rate of drift [26]. Pressure monitoring can now be combined with a brain oxygen tension-measuring component in a single device.

The differences between the Pressio (Sophysa USA Inc. Crown Point, IN, USA) and the Codman (Codman & Shurtleff, Inc. Raynham, MA, USA) strain transducer devices appear to be insignificant and not clinically relevant; in a head-to-head study with the EVD, the authors found a difference of ±7 mmHg [27]. The Neurovent-P (Raumedic AG, Munchberg, Germany) is a recent addition to this category. It is worth noting that in most studies, intraparenchymal devices overestimate the ICP even if this difference is not clinically significant [26–29].

The Spiegelberg pressure sensor (Spiegelberg GmbH & Co., Hamburg, Germany) uses a pneumatic balloon catheter to sense pressure and can self-recalibrate after placement [28]. When compared to the EVD, the sensor had a low complication rate, while there was an absolute difference in measurement of ±3 mmHg in 99.6 % and less than 2 mmHg in 91.3 %. The authors describe "significant trend towards 10 % lower" readings when the ICP was greater than 25 mmHg [29]. In laboratory testing the transducer underrated the true ICP by less than 1 mmHg when the pressure was less than 40 mmHg. The major cited advantage of the Spiegelberg sensor is the ability to measure intracranial compliance by varying its balloon volume (Fig. 29.2) [30].

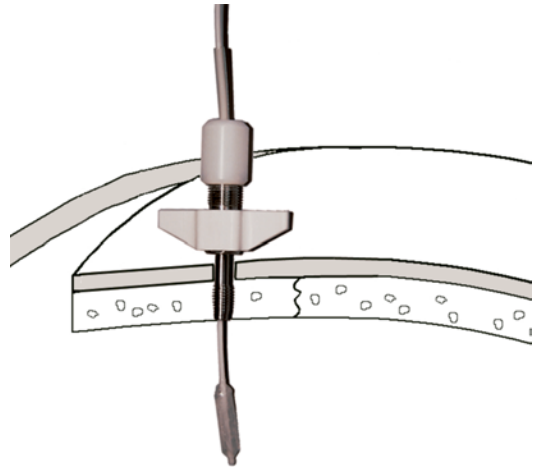

Fig. 29.2 Spiegelberg catheter with inflatable balloon (Reprinted with permission of Spiegelberg Medizintechnik GmbH Hamburg)

Jugular Bulb Saturation Monitoring ($SjvO_2$)

Jugular bulb saturation is measured by retrograde placement of a jugular catheter to sample cerebral venous outflow. If placed or drawn too rapidly (in excess of 2 mL/min), there is a risk of extracranial contamination from the facial vein [31]. A spectrophotometric catheter can be used to provide continuous saturation measurement. Cerebral extraction and utilization of oxygen can be measured by the Fick principle, utilizing the following equation:

$$\begin{aligned}&\text{Cerebral metabolic rate for oxygen}\left(\text{CMRO}_2\right)\\&=\text{Cerebral blood flow}\left(\text{CBF}\right)\\&\times\left(\begin{array}{l}\text{Arterial oxygen content}\\-\text{Venous oxygen content}\end{array}\right).\end{aligned}$$

With a stable hematocrit, the $SjvO_2$ is directly related to the balance between supply and demand. The normal range found in healthy volunteers is 55–71 % [32].

Jugular oxygen saturation can be increased by a reduction in oxygen consumption, e.g., hypothermia, deep anesthesia, or major ischemic stroke. Decreased saturation can arise secondary to increased $CMRO_2$ during fever or seizure episodes [33]. During surgery,

Table 29.2 Invasive intracranial monitoring

Method	Technology	MRI compatible	Bedside	Ease of use	Continuous	Treatment
Extraventricular drain	Direct measurement of pressure via transducer	Yes	Yes	Very easy	Yes	Yes
Subdural evacuating system (SEPS)	Purely an evacuating system	No	Yes	Yes	No	Yes
Subarachnoid bolt	Metal device	No				
Intraparenchymal monitors	Multiple	Neurovent-P©, Spiegelberg©, and Codman© – yes Camino© and Pressio© – no	Yes	Yes	Yes	No

hyperventilation-induced hypocapnia, or systemic hypotension, may decrease saturations, alerting to decreased CBF and possible ischemia.

SjvO2 monitoring has been used during coronary artery bypass grafting (CABG) to evaluate the adequacy of brain perfusion, and significant changes have occurred with rewarming after hypothermia and postoperatively [34]. However, there is no meaningful correlation with long-term cognitive deficiency [35]. Jugular bulb saturations are not widely used for CABG due to the lack of evidence that they provide useful a clinically relevant information during surgery.

$SjvO_2$ is used in some centers during neurovascular procedures to determine extraction ratios and follow cerebral metabolism. In a comparison of sevoflurane and propofol anesthesia for craniotomy, the propofol group was found to have lower saturation scores under deliberate mild hypothermia conditions. The authors warn that careful management of hyperventilation has to be exercised to prevent possible hypoxic complications [36].

Connection of a pressure transducer permits comparison of jugular bulb pressure and central venous pressure at the time of surgical positioning for intracranial surgery. If the difference exceeds 5 mmHg (allowing for moderate reverse Trendelenburg positioning), then there may be excessive rotation of the neck with subsequent effect on venous drainage. The authors use this maneuver to limit venous distension peroperatively.

In the intensive care unit, $SjvO_2$ may be used as another cerebral monitor after surgery and trauma. Cruz used it to guide treatment of cerebral hypoperfusion or hypoxia with hyperventilation, osmotherapy, or pressors [37, 38]. In a study of 75 patients with traumatic brain injury (TBI), they found that patients that spent more time with a $SjvO_2$ below 45 % had worse outcomes at 12 months [39]. Increased saturations, perhaps denoting abnormally low metabolic demand, have also been associated with worse outcomes [40]. The development of direct measurement of brain tissue oxygen content has replaced the jugular bulb catheter in many centers. However, at least one study demonstrated that jugular oximetry is more sensitive to desaturations from hyperventilation, making it useful when instituting hyperventilation for increased ICP in TBI patients with impaired autoregulation [41]. Measuring arteriovenous difference in lactate as well as oxygenation provides a stoichiometric assessment of aerobic versus anaerobic metabolism that may offer insight into cerebral pathophysiology. However, difficulties in accurate placement and maintaining the catheter as well as the need of experience in interpretation of findings have led to a decreased frequency in use within critical care units [42].

A list of invasive monitoring methods appears in Table 29.2.

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Monitoring the EEG for Assessing Depth of Anesthesia

30

Guy A. Dumont

Introduction

Electrophysiology finds its roots in the discovery in 1791 of bioelectricity by Luigi Galvani, who demonstrated that nerve cells pass signals to muscles via electricity. Then, in the 1870s, Waller performed the first electrocardiographic signal measurements [1]. The first measurements of cerebral electrical activity are those published in 1875 by Caton who studied exposed rabbit and monkey brains [2]. Modern electroencephalography started with the work of Berger, who in 1924 performed the first electroencephalographic recordings in humans and would in 1929 publish his seminal paper [3]. After decades of improvements and technological developments, the electroencephalogram (EEG) has become a standard tool to study the brain in both research and clinical settings. For a very long time, general anesthesia has been known to induce changes to the EEG [4, 5]. This has led to the development of many potential techniques to monitor the effect of anesthetics, particularly of hypnotic drugs. Those efforts have in particular led to the commercialization and clinical use of a number of EEG-based systems for the monitoring of anesthesia and sedation, even opening the way toward closed-loop control of anesthesia.

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Overview of the EEG

The electroencephalogram is a reflection of simultaneous synaptic activity of pyramidal cells within the superficial cortex, each scalp electrode detecting the activity of the dendritic tree of up to half a million pyramidal neurons. Although it has a high temporal resolution (<1 ms), the EEG has poor spatial resolution (~1 cm) compared to, say, fMRI. As the activity of the pyramidal cells synchronizes, the EEG will increase in amplitude and decrease in frequency. Berger highlighted and defined two frequency bands: the alpha-band (8–12 Hz), dominant in a relaxed awake subject with eyes closed, and the beta-band (12 to 25–30 Hz), dominant in a normal conscious awake subject engaged in a cognitive task. Rather arbitrarily, other frequency bands have since been defined: the delta-band (0.05–4 Hz) appears in slow-wave sleep, and the theta-band (4–7 Hz) is seen in some sleep stages as well as in meditation, while the gamma-band (30–80 Hz) is associated with consciousness, multisensory perception, and thalamocortical connectivity [6] (Fig. 30.1).

A major use of EEG is in polysomnographic studies of sleep, during which a number of physiological parameters are recorded for a sleeping subject. EEG is used extensively to determine the various sleep stages (Fig. 30.2), as EEG features allow the classification of sleep in four different levels or stages (Table 30.1). Recent work has discussed the relevance of sleep and sleep EEG for anesthesia [7].

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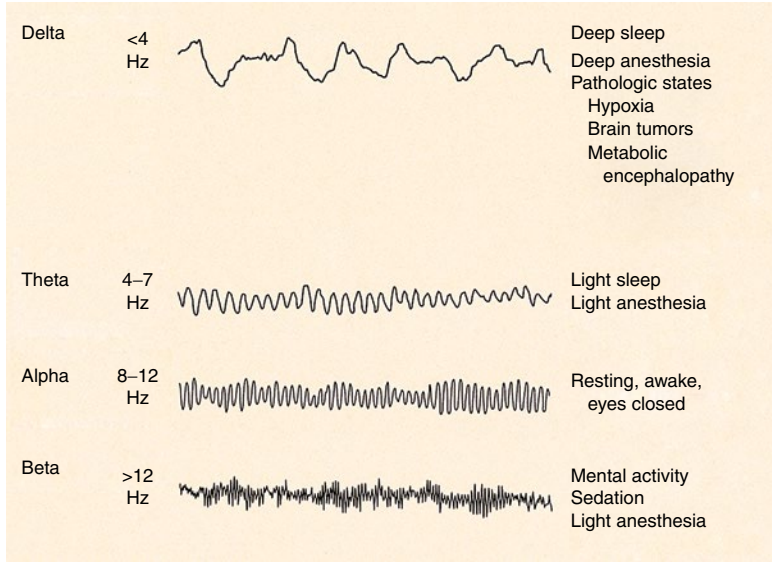

Fig. 30.1 Basic electroencephalogram (EEG) frequencies. The EEG uses surface electrodes to record electrical activity in the brain generated by pyramidal cells in the cerebral cortex. The traditional EEG is a plot of voltage against time. Frequency is measured in hertz (Hz) and amplitude in microvolts (μV). The frequency bands are divided into delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (>12 Hz) rhythms. Delta rhythm is seen in deep sleep, deep anesthesia, and hypoxia; theta rhythm in sleep and anesthesia; alpha rhythm in the resting awake adult with eyes closed and predominantly in occipital leads; and beta rhythm with mental activity and light anesthesia. Induction of anesthesia usually produces a decrease in alpha and increase in beta activity. With increasing depth of anesthesia, the EEG frequency decreases until delta and theta rhythms predominate progressing to a burst suppression pattern and finally to isoelectricity (e.g., isoflurane, thiopental) (Reproduced from Schell et al. [18]; kind permission from Springer Science + Business Media B.V)

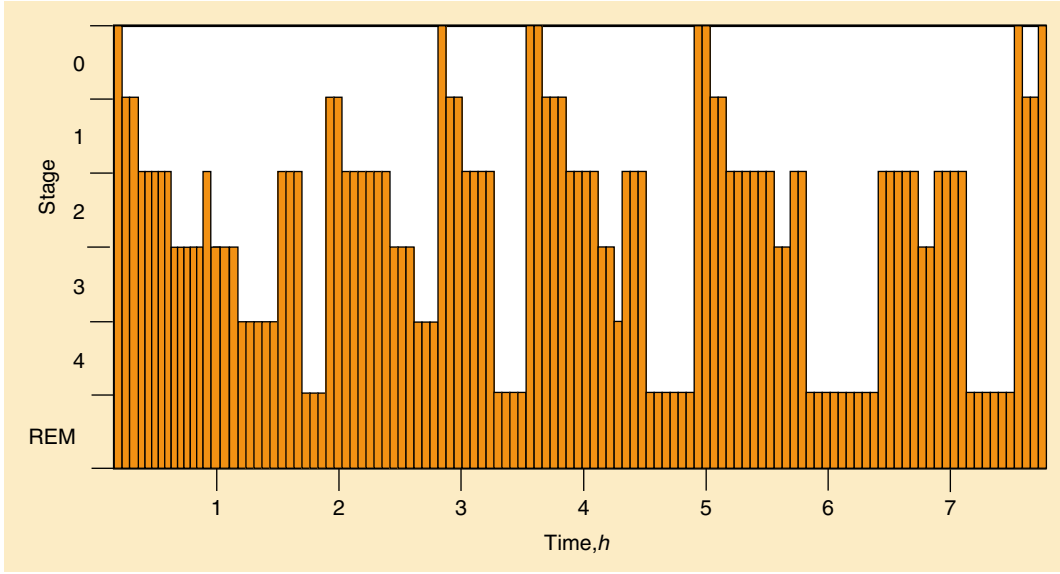

Fig. 30.2 Normal sleep histogram. This figure represents normal sleep staging. Time across the night is represented on the *x*-axis in hours. Stage 0 represents wakefulness. Humans cycle through stages 1–4 and REM in a characteristic pattern, with stages 3 and 4 (slow-wave sleep) predominating the first third of the night. REM sleep occurs after 70–100 min (average 90 min) and then cycles every 90 min thereafter, with each progressive REM period lengthening during the night (Reproduced from Patel et al. [19]; kind permission from Springer Science + Business Media B.V)

Table 30.1 Sleep stages and EEG features

Sleep stage	EEG features
N1 (somnolence, drowsiness)	Transition from alpha to theta activity
N2 (predominant sleep stage)	Spindles (11–16 Hz), theta-band activity
N3 (slow-wave sleep)	Large amplitude delta-band activity
REM (paradoxical sleep)	Sawtooth (theta) and beta-band activity

Table 30.2 Anesthesia stages and EEG features

Anesthesia stage	EEG features
Induction	Transition from alpha to theta activity, paradoxical increase in beta activity
Maintenance (light)	Reduced beta activity, increased alpha and delta activity
Maintenance (general)	Large amplitude delta activity
Maintenance (deep)	Flat periods with bursts of alpha and beta activity (burst suppression)
Emergence	Transition back to alpha and beta activity

Effects of Anesthetics on the EEG

Although some EEG effects are specific to particular anesthetic agents, most anesthetics have similar effects on EEG features. Table 30.2 describes in broad terms the features associated with each phase of anesthesia, namely, induction, light anesthesia, general anesthesia, deep anesthesia, and emergence. Those effects are produced by GABAergic anesthetics, either intravenous ones such as propofol or inhaled ones such as isoflurane or sevoflurane.

From this table, one can see that the EEG during general anesthesia has strong similarities with that of slow-wave sleep. Some drugs, however, have very different effects on the EEG, including ketamine, which produces dissociative anesthesia by acting through the excitatory NMDA receptors, provoking a significant increase in beta activity.

Gamma oscillations (>30 Hz) are thought to play an important role in cortical integration and perception and in thalamo-corticothalamic connections. Views that anesthetics lead to cortical disintegration and interrupt the thalamo-corticothalamic loop seem to be supported by recent evidence that gamma-band activity is greatly affected by anesthetic agents [8].

Quantitative EEG Analysis

Looking in real time at a number of raw EEG channels to assess the depth of anesthesia of a patient is an impossible task. This has led to the development of a number of techniques to extract the features relevant to depth of anesthesia. Because as sleep, anesthetics affect the frequency content of the EEG, it is natural to derive frequency-based indices for monitoring anesthesia. This is readily achieved by using a fast-Fourier transform (FFT) on the raw signal to decompose it into its frequency components. Some simple methods based on this approach have been proposed in the past. The power spectrum P_{ff} (expressed in $\mu V^2/Hz$) for consecutive epochs can be displayed as a three-dimensional surface (compressed spectral array, or CSA) or a color-coded image (density spectral array, or DSA) for visual inspection. Alternatively, the respective energy in the various frequency bands defined above can be displayed and plotted. Parameters such as the EEG median frequency, spectral edge frequency (*SEF*) (at 80, 90, or 95 % quintile), or various power band ratios (theta/delta, alpha/delta, or beta/delta) have also been proposed. However, none of those parameters proved adequate as a depth-of-anesthesia index. Another important time-domain parameter is the burst suppression ratio (*BSR*), calculated as the percentage of isoelectric silence occurring over an epoch. A high BSR value indicates a severe depression of cortical activity and is indicative of too deep an anesthetic state, which should be of concern, particularly in the fragile patient. A burst-compensated SEF has been proposed for isoflurane and desflurane anesthesia [9]:

$$\mathrm{BcSEF} = \mathrm{SEF} \times \left(1 - \frac{\mathrm{BSR}}{100}\right)$$

Despite those proposed measures and indices, it is only with the advent of commercial depth-of-anesthesia monitors such as the BIS monitor that the use of depth of anesthesia as a novel monitored parameter has become of clinical relevance.

Intraoperative Monitors

The BIS Monitor

The bispectral index (BIS, Covidien, Boulder, CO, USA) introduced in the 1990s consists of an empirically developed combination of a number of EEG-derived measures, the EEG being acquired from frontotemporal electrodes. Although the actual algorithm is proprietary, the basic principles have been described in the literature [10]. At the heart of the BIS calculation lies bispectral analysis, which preserves the phase correlation between the various EEG frequency components, thus capturing synchronization between frequencies. Based on a prospectively collected set of data (1,500 subjects, 5,000 h), the BIS consists of an empirical combination of a number of EEG measures, including BSR, the BetaRatio, and the SynchFastSlow indices, defined respectively as

$$\text{BetaRatio} = \log\left[\frac{P_{30-47\ \text{Hz}}}{P_{11-20\ \text{Hz}}}\right]$$

$$\text{SynchFastSlow} = \log\left[\frac{B_{0.5-47\ \text{Hz}}}{B_{40-47\ \text{Hz}}}\right]$$

where P_{x-y} *and* B_{x-y} are, respectively, the spectral power and the bispectral power from x to y Hz. The combination of empirical parameters was iteratively tuned to discriminate between anesthetic states. The result is a dimensionless number between 0 and 100, 100 corresponding to a fully conscious patient, 0 to an isoelectric (i.e., flat) EEG, the range (40–60) to general anesthesia (i.e., low probability of explicit recall and unresponsive to verbal stimulus) and values below 40 to a deep hypnotic state (with likely presence of burst suppression). Since the original work, there have been a number of BIS algorithm updates based on an increasing database, as well as a recently released bilateral version for simultaneous monitoring of the two brain hemispheres. To date, the BIS monitor remains the most validated and used brain monitor of anesthesia.

The GE Datex-Ohmeda Entropy Module

Entropy measures the irregularity in a signal, decreasing as the signal becomes more regular and predictable. Because the EEG becomes more regular and periodic with depth of anesthesia, one can expect entropy to decrease as anesthesia becomes more profound. This is the basic principle behind the GE Entropy Module, first introduced in 2003 by Datex-Ohmeda. The normalized spectral entropy for a signal for N frequencies in the frequency range $[f_1, f_2]$ is defined as [11]

$$S_N[f_1, f_2] = \left(\sum_{f_i=f_1}^{f_2} P_n(f_i)\log\left(\frac{1}{P_n(f_i)}\right)\right) \Big/ \log(N)$$

The Entropy Module computes two entropies, the State Entropy (SE) over the range from 0.8 to 32 Hz and the Response Entropy (RE) over the range 0.8–47 Hz. SE is mostly EEG, while RE may contain some EMG and thus may rise suddenly in case of nociceptive arousal. When no EMG is present, then SE and RE are equal, and the difference may be used as a nociceptive index. Both are presented as a dimensionless index from 91 to 0 for SE and from 100 to 0 for RE, after scaling through a spline function. The monitor also includes a BSR calculation algorithm.

The Narcotrend Monitor

The Narcotrend monitor finds its origins in sleep stage classification. It generates a dimensionless index from 100 to 0 corresponding to six stages and 15 substages from awake (A) to isoelectric (F) via general anesthesia (D). The Narcotrend combines a number of time domain, including parameters from autoregressive modeling of the EEG, and unspecified frequency domain

measures from a single-channel EEG on the patient's forehead. The Narcotrend classifier was developed using a database of examples for each substage, selecting the parameters that maximized the discriminating power between stages [12].

The NeuroSENSE Monitor

The NeuroSENSE monitor (NeuroWave Systems Inc., Cleveland Heights, OH, USA) was developed specifically for use in closed-loop control of anesthesia, and consequently particular attention was paid to its dynamic behavior. Like the Entropy monitor, it computes a property of the EEG that changes with the level of anesthesia, but it is not based on a classifier of anesthetic states. It is thus termed a cortical activity monitor. The NeuroSENSE relies on wavelet decomposition of the EEG with particular emphasis on the gamma-band frequencies, and its algorithm has been fully disclosed in the open literature [13]. It relies on the fact that the shape of the probability density function of the wavelet coefficients in the gamma-band evolves from a wide and flat distribution for an awake patient to a narrow and sharp spikelike distribution for a deeply anesthetized patient, with a consistent monotonic evolution between those two extremes. A dimensionless metric, the WAV_{CNS}, is then derived by computing the distance between the distribution for the current 1s epoch and those two extremes. It results in an index with a scale from 100 (awake) to 0 (isoelectric) and the range from 40 to 60 corresponding to general anesthesia. When it is nonzero, the BSR biases the index in a linear fashion toward zero. The NeuroSENSE was designed as a bilateral index from the onset.

The SEDLine Monitor

The SEDLine monitor (Masimo, Irvine, CA, USA) is based on the patient state index (PSI) originally developed at the Brain Research Laboratories of the NYU School of Medicine and first marketed as the Patient State Analyzer by Physiometrix [14]. Three extensive EEG databases were used for the tuning and calibration of the PSI. While the PSI is based on similar principles as the BIS monitor (i.e., composite index tuned from EEG databases and clinical cases), it does not use bispectral parameters. Instead, the PSI focuses on the power shift in specific frequency components between EEG electrodes. The PSI is derived from four EEG channels, from which a number of features such as mean frequency, absolute delta power, power gradient between frontopolar and vertex regions in the gamma-band, and power changes between frontal and parietal region in the alpha-band were derived. Using those features, a multivariate discriminant analysis was then performed to infer the hypnotic state in the PSI, a dimensionless number from 0 (isoelectric EEG) to 100 (awake patient), with the range from 25 to 50 corresponding to general anesthesia.

Summary of EEG Monitors

The monitors described fall into two broad categories – those that attempt to predict the anesthetic state of the patient and have been derived from a database of EEG records corresponding to those different anesthetic states and those that simply compute a characteristic of the EEG that is affected by anesthetic drugs. In the first category, we find the BIS, the Narcotrend, and the SEDLine monitors, while the GE Entropy Module and the NeuroSENSE monitors clearly belong to the second category, as they do not attempt to infer the anesthetic state.

All monitors also calculate the burst suppression ratio but do not necessarily factor for it in the calculation of the displayed index. Also, all monitors are somewhat affected by facial EMG because it is difficult to separate from high-frequency EEG activity. The response times of the monitors vary widely and, for some monitors, vary according to the anesthetic state and direction of change. The monitors using an inference-based methodology exhibit long and variable delays.

A study of the dynamic behavior of the BIS, Entropy, and NeuroSENSE monitors concludes that only the latter has predictable, linear,

time-invariant dynamics, a must for use in closed-loop control of anesthesia [15]. Although developed to monitor the depth of hypnosis, those monitors are to various degrees affected by analgesic drugs and nociceptive stimuli. Essentially, the variability of most indices decreases with increasing doses of analgesics, while they tend to suddenly increase in case of a somatic response strong enough to provoke cortical arousal [16]. This fact has, for instance, been exploited to develop the composite variability index (CVI) for monitoring nociception [17]. In addition, for the Entropy monitor, the difference between RE and SE has been proposed as a nociception index on the ground that it may contain significant EMG activity, a sign of nociceptive reaction.

Conclusion

Because anesthetics induce a reversible state of unconsciousness and amnesia, monitoring their effect on the brain via scalp electroencephalography makes sense. As a result, a number of EEG-based monitors have been developed, in the hope of capturing the hypnotic state of the anesthetized patient. All those monitors attempt to capture this state in a single number. Obviously the effects of those drugs on the patient are far too complex to be summarized by a single number between 0 and 100. Consequently, those indices should be interpreted by the clinician in the context of other physiological signs, rather than be treated in isolation. In the end, it is important for the clinicians using this technology to remember that "they are treating a patient, not a number."

Conflict of Interest Statement GA Dumont is coinventor of the NeuroSENSE monitor (NeuroWave Systems Inc., Cleveland, OH). He has consulted for NeuroWave Systems Inc and GE Healthcare.

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Monitoring Analgesia

31

Anjali Dogra and Hadi S. Moten

Introduction

Pain is a frequently experienced problem affecting many aspects of the health-care system and presenting in a variety of settings. From chronic pain to pain in ICU patients to acute postoperative pain, the experience of pain has been shown to increase morbidity and mortality in addition to decreasing patient comfort and quality of life. Appropriate assessment and treatment of pain have been shown to have long-lasting implications on development, particularly, when pain occurs at a young age [1]. With the potential for pain to cause physiologic changes in ventilation, perfusion, cardiovascular abnormalities, increased metabolic demand, tissue catabolism, impaired immune function, delayed wound healing, and abnormal behavior, it is clear that it is therefore important not only to obtain an initial accurate assessment of pain but to then monitor the effects of analgesia offered to ensure adequate pain control [2].

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The International Association for the Study of Pain asserts self-reporting by the patient to be the gold standard for pain reporting. However, there are unfortunately many circumstances where self-reporting is either unreliable or impossible, and these case-substituted methods are needed. For example, the behavioral pain scale (BPS) was developed for measuring the severity of pain or effectiveness of analgesia in sedated, mechanically ventilated, and unresponsive patients, whereas the numerical rating scale (NRS) and visual analog scale (VAS) have been validated specifically for acute pain [3].

Research in the monitoring of analgesia is an ongoing process. With rodents having been shown to experience pain at similar levels to other mammals including humans, these models have been and continue to be used to shed light on improved methods to assess and monitor pain and analgesia in humans [2]. Current assessment and monitoring focus on communicative self-assessment and noncommunicative assessment tools, which incorporate observed behavior and physiologic measurements [4].

Self-Assessment Scales

Self-assessment scales are the mainstay of analgesia monitoring in patients that have insight into their condition, can reflect on their level of discomfort, and subsequently communicate this to their health-care providers.

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The visual analog scale (VAS), as shown in Fig. 31.1, is a 100-mm ruler with "no pain" written on the left, "worst possible pain" on the right, and a movable cursor which the patient can use to indicate their pain rating. The maximal acceptable pain score using the VAS is 30 mm [5]. The numerical rating scale (NRS) (Fig. 31.2) is based on a scale from 0 to 10 where 0 is no pain and 10 the worst possible pain and has a maximal acceptable pain score of 3 [3]. A strong positive correlation has been demonstrated between the NRS and VAS patient reporting for responsive patients though the correlation is slightly lower in cardiothoracic than non-cardiothoracic patients, and of note, when compared to the NRS, the VAS is not an adequate tool when monitoring patients with decreased consciousness [3].

Observed Assessment Pain Scales

While self-assessment is considered the superior pain and analgesia assessment method, this is not feasible for patient populations with ailments that preclude proper self-reflection or the ability to communicate. This includes patients who are cognitively impaired as well as those that are sedated, are mechanically ventilated, or have language difficulties. Practitioners are often left to develop their own system of assessment for these patients, often combining observed behavior and physiologic measurements, as a single assessment tool for noncommunicative patients has yet to be identified [6].

Intraoperative and ICU analgesic monitoring can pose a particular challenge since patients that are intubated and/or sedated are unable to complain and may have their physiology pharmacologically controlled. While several assessment tools have been developed in an attempt to monitor analgesia in noncommunicative patients, none has emerged as the single best practice. In the absence of such a tool, these assessments tend to be provider dependent. The need for improvement in this area is clear, as current studies have demonstrated that nurses underestimate their patients' pain approximately 35–55 % of the time and that 64 % of patients did not receive medication before or during painful procedures [7, 8].

Protocols aimed at improving evaluation of analgesia in ICU patients such as the Awakening and Breathing Controlled trial have led to significant benefits such as an overall decrease in benzodiazepines and opioids delivered and an associated decreased total duration of mechanical ventilation [9]. In addition to being considered improper patient care, inadequate analgesia can have physiologic and pathologic ramifications, particularly in patients with coronary artery disease or respiratory difficulties [10]. It has also been associated with increased likelihood of developing delirium, and delirium in mechanically ventilated patients has been associated with a threefold increase in death 6 months post-discharge [11].

A direct correlation between the ability to assess pain and the ability to adequately treat pain has been clearly demonstrated, and to this end, a number of observed assessment tools have been developed in an effort to improve analgesia

Fig. 31.1 Visual analog scale

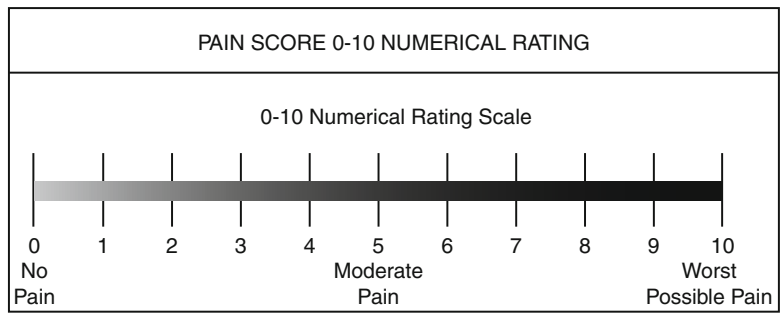

Fig. 31.2 Numerical rating scale

in perioperative and ICU patients who are non-communicative [12].

The FLACC scale, originally designed to standardize pain treatment in the pediatric population, utilizes behavioral indicators and body movements for assessment and has been validated in assessment of pain in children who are cognitively impaired and those in postoperative pain. However, this scale is limited by the inclusion of criteria such as crying and consolability and is also thusly not applicable to adult and mechanically ventilated patient populations [13]. The adult nonverbal pain scale is a modified FLACC scale that, while not compared to other adult pain scales, has been shown similar utility compared to the FLACC score in pediatric patients [14]. The COMFORT scale, originally designed for pediatric ICU, utilizes behavioral and physiologic factors in an eight-item assessment where each item is scored from 1 to 5 [15].

The behavior pain scale (BPS), as shown in Table 31.1, is used after an observation of the patient for 1 min and has been validated in critically ill, sedated, and mechanically ventilated patients. It is exclusively used for sedated and mechanically ventilated patients and is based on the sum of three subscales which include facial expression, upper limb movements, and compliance with mechanical ventilation [3]. Each subscale is scored from 1 (no response) to 4 (full response). Therefore, BPS scores range from 3 (no pain) to 12 (maximal pain) with a maximal acceptable pain score of 5 [16]. BPS correlates well with the NRS and is reliable for measuring the severity of pain in sedated and mechanically ventilated patients and is excellent at differentiating between painful and non-painful procedures. The use of the BPS in the ICU has been shown to decrease the number of severe pain episodes as well as the total duration of intubation [17]. However, this scale is limited in that it is affected by the patients' level of sedation.

Table 31.1 Behavioral pain scale

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Grimacing	3
		4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

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Pediatric Analgesia

Because of the challenges of communication, the pediatric population poses similar difficulties to that of the ICU patient. The Newborn Drug Development Initiative and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) have recommended multidimensional outcome domains and measures for assessment and monitoring of pediatric acute and chronic pain [18].

Extremely low-weight infants demonstrate particularly inconsistent pain responses over time because responses are dampened and modified by contextual factors such as severity of illness, painful stimuli, proximity to feeding, maternal contact, and the use of anesthesia. Of note, peripheral and spinal nociceptive pathways are substantially developed by 25 weeks postconception. Untreated pain in premature infants may evoke hyperalgesia, stress responses, and short- and long-term sequelae [19]. Ongoing research for assessment and ongoing monitoring of pain and analgesia in the pediatric population include cerebral near-infrared spectroscopy, other neuroimaging techniques, and biomarkers such as heart rate and cortisol production, though these have not yet demonstrated reliability of validity.

Additional Assessment Methods

Pain modifies the surgical stress response and subsequent physiology that is associated with sympathetic discharge. This increase in sympathetic tone leads to an increase in the activity of

sympathetic postganglionic cholinergic neurons leading to a change in sweat glands and a resultant change in the extent of skin conductance. The number of fluctuations in mean skin conductance per second correlates with intraoperative noxious stimuli as well as with postoperative pain in the recovery room as rated on a NRS [20]. Skin conductance has also shown a response to fentanyl. Unlike skin conductance, neither heart rate nor systolic blood pressure has demonstrated this degree of correlation with NRS scores or responsive to fentanyl [21, 22]. Skin conductance has poor predictability in comparison to pain scale self-reporting, however [22].

Skin conductance reliability is also limited by the effects of medications including anticholinergics and alpha$_2$ agonists and the impact psychological states can have on sympathetic tone. It is not also useful in differentiating among mild, moderate, and severe pain, and measure of mean skin conductance can be highly variable as it is influenced by electrode placement [23].

The pupillary dilation reflex (PDR), a sympathetic reflex that dilates the pupil in response to noxious stimuli, has been used to assess the analgesic component during balanced general anesthesia [24]. PDR has been used to assess pain and monitor analgesia in healthy volunteers, surgical patients, and children, and opioid administration has been shown to reduce PDR in a dose-dependent manner [25]. It is important to note that unlike many other assessment tools, PDR is a measurement of the level of analgesia (pain elicited by stimulation) rather than a measurement of pain [26]. While further study is needed, PDR could be used as a method of monitoring analgesia in those patients who are unable to communicate, those that fear addiction or are afraid to appear weak, as well as in those suspected of being drug seekers [26].

Conclusion

For those patients who are capable of self-reflection and reporting of pain, current assessment tools are useful for initial pain assessment as well as monitoring of analgesic affects. Modified assessment tools that incorporate behavioral and physiologic signs have been developed to address patients unable to self-report. However, further study is needed to continue to address the challenge of monitoring analgesia in general and, in particular, for those patients that are typically encountered in the acute postoperative, pediatric, and ICU settings in light of the common difficulties related to communication in these patient populations. Current areas of study to address this include skin conductance and the pupillary dilation reflex.

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Neuromonitoring During Spine Surgery

32

Sean A. Flesch, William H. Levis Jr., and Nabil J. Azar

Introduction

Intraoperative neurodiagnostic testing (IONM) for spine procedures as we know it today developed out of initial research in the late 1970s, with middle to late latency somatosensory cortical potentials. Intraoperative EEGs during carotid endarterectomy and surgical epilepsy procedures are considered to be the initial precursors of these more modern IONM modalities. The application for spine surgeries, specifically scoliosis procedures, was identified early on as a way to avoid potential surgical complications and morbidity associated with wake-up testing. This accelerated the acceptance of IONM in the 1980s and supported growing innovation in different modalities such as short-latency somatosensory evoked potentials (SSEPs), D-wave monitoring, neurogenic motor evoked potentials, and the now standard transcranial electrical motor evoked potentials (TCeMEPs). Current available IONM modalities offer a more polished, targeted, and specific set of data which allows more accurate interpretation by specially trained physicians (Fig. 32.1).

Intraoperative neuromonitoring (IONM) has been widely accepted and used in spine surgeries to alert surgeons of potential neural compromise in a real-time manner. The usefulness of IONM is amplified when routinely applied in acute care environments. Patients undergoing post-traumatic injury spinal surgery often present with complicated and progressing neurologic deficits, leading surgical procedures to be more challenging and delicate. In these cases, IONM adds a depth of data to the surgical team that may be previously unknown or unobtainable. Maintaining excellent communication between the monitoring, surgical, and anesthesia teams is essential in accurately interpreting and synthesizing this data.

Common IONM applications for spine surgeries cover routine neurosurgical procedures such as single- or multiple-level spinal fusions and intervertebral disc operations. In acute care environments such as traumatic spinal injury, vertebral fractures, or unstable spine injuries, IONM can provide more critical data in patients who have not received a clear preoperative, clinical evaluation or who have been unresponsive or sedated upon arrival at the hospital. IONM can be very beneficial to the surgical team especially during more

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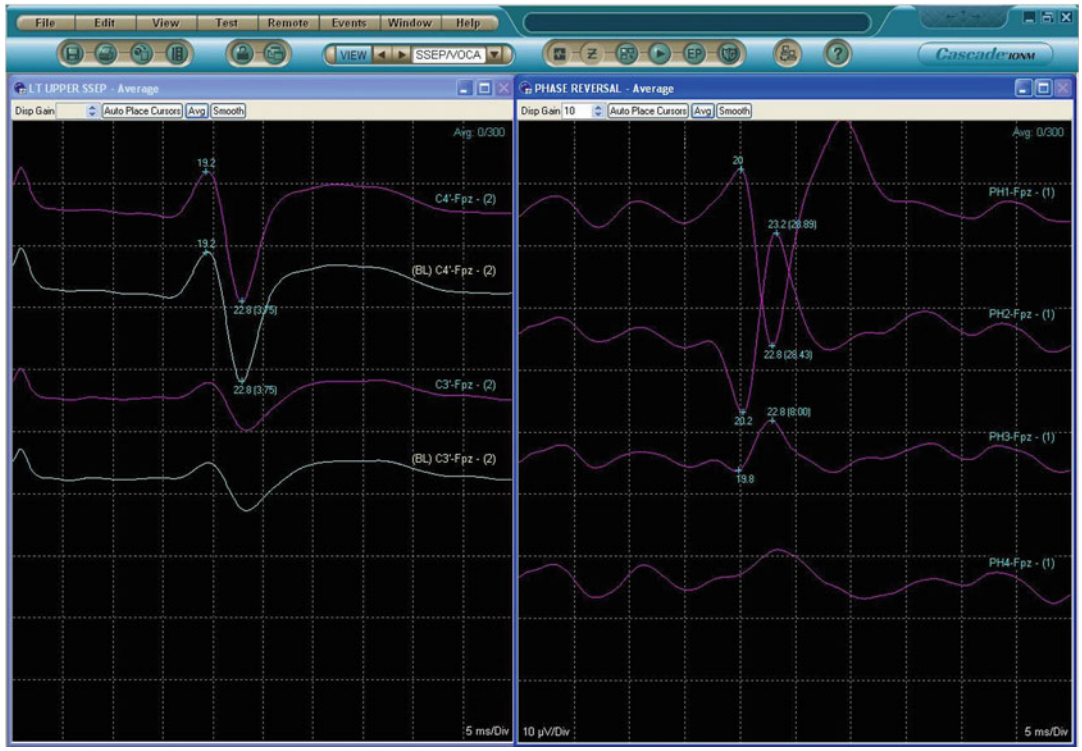

Fig. 32.1 Direct cortically recorded SSEP responses displaying a "phase reversal" at the central sulcus

complex multi-level spinal surgeries which may include fusion, decompression, or total spine reconstruction, can be very beneficial to the surgical team. While no substitute for a thorough presurgical workup, IONM can provide detailed functional information on neural integrity throughout presurgical and surgical manipulation.

Business

The success of an IONM program in routine or acute care settings requires a strong commitment and continued investment from the hospital administration, especially in finances, support, and technology. The relationship of the IONM technologist to interpreting neurologist carries with it a complex medical-legal liability. This unique relationship dictates a process of business model evaluation that best fits the need of a medical institution. Currently, there are two prevailing models for intraoperative neurodiagnostic group practices, each having their own place within the demands of different institutions and their needs.

The most frequently encountered model is the contractor or outsourced model in which a hospital contracts the service group to provide the technical IONM services, with or without the physician interpretation. This model is well utilized in smaller regional hospitals where the volume of acute spinal surgeries is low and the facility typically performs more routine, less complex procedures. This approach is also well suited in regions where several other smaller groups are interested in similar services. Some key benefits to the contractor-based model include:

- Access to highly qualified and specialized technologists and physicians
- Freedom from the cost of continuing education (rapidly evolving specialty)
- Transfer of a portion of the liability on to a third party
- Control of costs in relation to the frequency of utilization

- Competitive pricing and cost control due to competition from other groups

The contractor-based model can also come with some significant drawbacks, which include:

- Poor on demand/short notice availability of services in emergent situations
- Lack of control in turnover or quality of technologists and physicians
- Reduced profits on high margin procedures
- Delay in obtaining testing reports from outside physicians

The second and model is the hospital-based, also known as the "in-house," system. In hospital-based systems, IONM studies are performed by hospital employees and interpretation is performed by internal or contracted physicians. This model is well utilized in larger hospitals with larger volume of complex or emergent procedures. This model can also succeed in smaller medical facilities in which the care location is the regional centralized medical care hub. As with the contractor model, this system has key benefits, which include:

- Improved control over quality and turnover of technologists
- Additional income opportunity by direct billing of studies
- Improved and more consistent rapport and accessibility between the physicians and technologists
- Flexibility in scheduling and providing prompt service for emergent cases

The hospital-based model comes with some drawbacks, including:

- Cost and responsibility of monitoring equipment and continuing education
- Internalizing the liability associated with the technologist and interpreting physician
- Access to internal physician capable of accurate and timely interpretation

Regardless of the model a particular medical facility chooses, the challenges surrounding staffing IONM for an acute care setting are daunting. The availability of competent certified technologists and experienced interpreting physicians is limited. To date, there are less than 1,600 technologists with a professional certification (CNIM issued by ABRET) specializing in IONM testing in the United States. The number of qualified neurologists for interpretation of IONM data is also limited but growing with time. There is a current trend to expand neurophysiology education in university hospitals to include greater exposure to IONM.

Equipment

The usefulness of IONM during the surgical procedure is only as good as the quality of the data acquired and the reading physician's interpretation. To facilitate and improve accuracy, time spent researching hardware options that best fit the dynamics of the personnel is worth the investment. IONM equipment, like most medical equipment, is very costly. In today's dollars, cost expectations range from $25,000 to $65,000 per workstation. Several manufacturers provide vastly different levels of functionality and specificity demanding a thorough inquiry into each model available. The equipment selected needs to maintain high levels of dependability, ease of use, and longevity.

The expectations for response times in acute care are short. The technologist should have rapid access to study templates and montages designed for specific situations. There is often little time to program custom templates in an acute care environment. If a template must be altered due to unique circumstances, the modification of the software should be simple, uncluttered, and rapid. The presence of a front-end database and centralized server to support rapid access to templates improves software usability.

IONM equipment consists of two primary workstations. The technologist operates the acquisition equipment positioned in the operating room that collects and stores the data. The reading physician operates the viewing workstation located either on-site or in a distant location connected to the acquisition equipment over a secured network. The acquisition and the interpretation stations should integrate seamlessly and should present little difficulty or troubleshooting for the users. Connection issues due to network failures can potentially

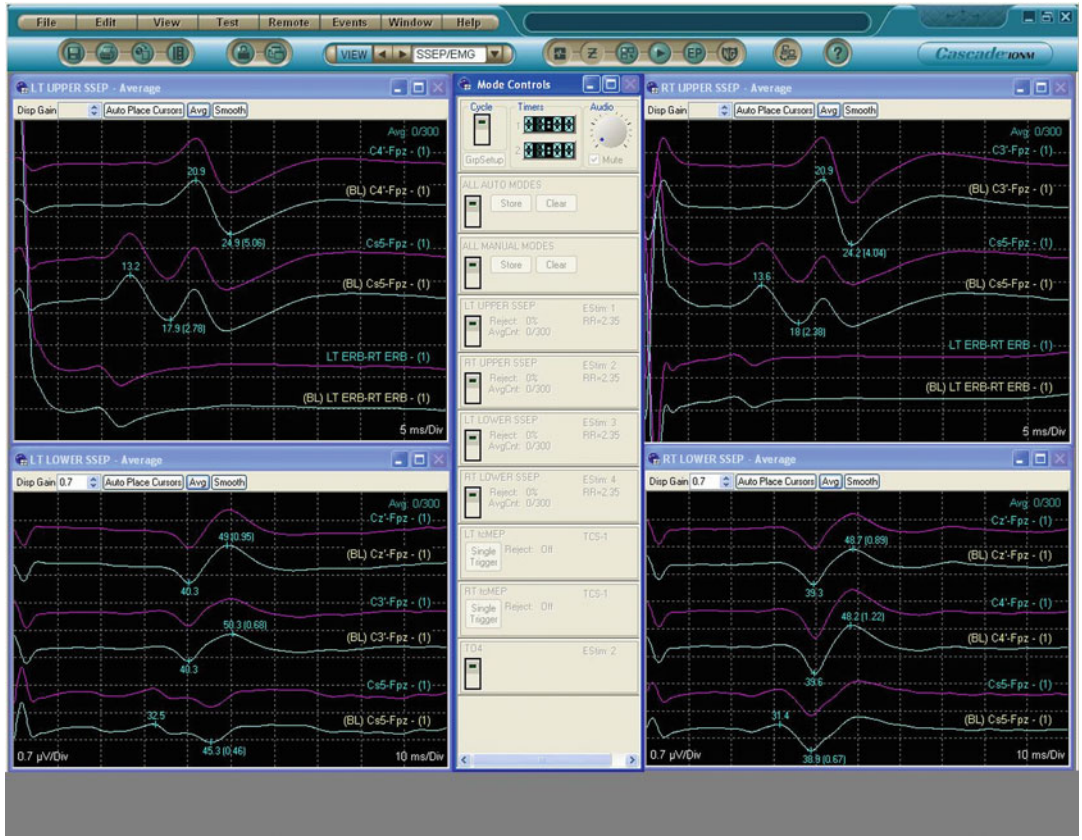

Fig. 32.2 Bilateral upper and lower extremity SSEP responses obtained by stimulating the median and posterior tibial nerves

eliminate the usefulness of IONM and erode the confidence of the surgeon. The central processing units (CPUs) as well as amplifiers and other peripherals should be well built and able to take significant abuse over long periods of time. Successful IONM operations include supportive, knowledgeable, and responsive sales representatives and IT personnel.

Test Modalities

The most frequently used testing modality in IONM is SSEPs. Typical performance of this test begins with stimulation of select nerves in the distal extremities, most commonly median or ulnar nerves for the upper extremities and posterior tibial or common peroneal nerves for the lower extremities. The recording electrodes are placed on the scalp where the waveforms are recorded, amplified, and averaged. The supramaximal electrical stimulation causes an area of depolarization at the nerve membrane and elicits an action potential to propagate along the nerve pathway, mainly along the large-diameter dorsal columns. This impulse is recorded at different levels of the somatosensory pathway being peripheral or central. This multilevel pathway tracking can help identify specific regions of injury or aid in diagnosing neural compromise. The action potential ascends in the dorsal column pathway, enters the brain stem where it decussates, and then terminates in the postcentral gyrus of the cortex (Fig. 32.2).

Recording data from the cortex presents its own set of challenges in the application of the anesthetic regimen, troubleshooting technical issues, and tracing fluctuations. Limiting the usage of inhalational anesthetic agents during SSEP recording will mitigate the depressive

effects of the agents on SSEP responses [1]. Other intravenous agents can also depress the ability to record from the cortex; however, much higher doses are required to significantly impact the quality of the testing. The degree to which the anesthetic regimen is held at a steady state is a strong contributing factor to successful interpretation of intraoperative SSEPs in any procedure. Data collection can further be limited by technical issues complicated by other electrical devices used by the anesthesia team. IONM equipment is very sensitive to electromagnetic fields caused by several devices such as fluid warmers, ECG systems, and poorly maintained operative beds. This electrical "noise" can sometimes hamper interpretation when it is unable to be resolved.

Another IONM testing modality that is commonly paired with SSEPs is TCeMEPs. The combination of these two modalities provides more clarity to the functional integrity of the spinal cord pathways. While SSEPs track the ascending sensory pathways of the dorsal portion of the spinal cord, TCeMEPs track the descending motor pathways of the ventral and lateral spinal cord. TCeMEP pathways carry action potentials from the motor cortex down the anterior and lateral spinal cord to reach the neuromuscular junction which produces a muscle contraction. This contraction is recorded by subdermal electrodes placed in designated muscles in the bilateral upper and lower extremities. TCeMEPs are stimulated transcranially using anodal stimulation. The stimulation is delivered in trains of four to nine pulses producing several volleys of direct and indirect waves traveling down the spinal cord. These multiple waves are required at the lower motor neuron to reach summation, thus propagating the action potential to the muscle. The successful usage of TCeMEPs will include substantial patient movement during stimulation. Coordination with the surgeon is required to prevent unintended injury during the procedure. A bite block is required to prevent potential buccal injury.

Similar to SSEP recording, TCeMEPs carry their own anesthetic restrictions and specific considerations. The depressive effect of inhalational anesthetic agents that inhibits successful recording of SSEPs also inhibits the successful stimulation of TCeMEPs. The use of particular anesthetic agents and its dosing and effect is often a point of controversy among anesthetic and neurodiagnostic professionals. The ideal testing parameters for TCeMEPs require the use of total intravenous anesthesia (TIVA) [1]. This approach provides an ideal testing situation for both SSEPs and TCeMEPs. A balanced anesthetic approach including inhalational agents at low concentrations can also be used effectively in many patient populations. Successful recording of TCeMEP muscle response also requires no muscle relaxants.

TCeMEPs may be contraindicated in patients with skull defects, in patients implanted with electrical devices such as deep brain stimulators or pacemakers, and in patients with poorly controlled seizures. TCeMEPs may also carry significant risks in children less than 2 years of age [2, 3]. It is recommended that a semirigid bite block be placed to avoid tongue lacerations or damage to the respiratory tubing [2, 3] (Fig. 32.3).

While SSEPs and TCeMEPs help provide comprehensive intraoperative data for the care of acute spinal surgeries, both tests fall short of providing detailed information on peripheral nerves [4]. Electromyography (EMG) is a modality that can fit this role by evaluating the spinal root integrity via indirect recording from the muscles. This is particularly beneficial during lumbar spine procedures. SSEPs and TCeMEPs can only provide information via the pathways stimulated. EMG is a way to detect possible injury or irritation in the neural tissue. EMGs also add valuable information to cervical procedures when they involve significant spinal angle adjustment or involve work on the vertebral foramen. EMG can be recorded spontaneously with broad coverage dependent on the spinal level. EMG studies can also be time locked and stimulated to examine specific levels or pedicle integrity. Unlike SSEPs and TCeMEPs, EMG has a rather simple anesthetic restriction. Since the cerebral cortex is not involved, the only limitation is the use of neuromuscular blocking agents. If the neurodiagnostic technologist is able to reliably check the level of blockade with train-of-four (TOF) testing,

Fig. 32.3 Bilateral TCeMEP responses recorded from the abductor pollicis brevis, abductor digiti minimi, tibialis anterior, gastrocnemius, and abductor hallucis

blockade can be administered at induction to aid in intubation and exposure. The blockade is then allowed to metabolize and the integrity of the testing is not compromised.

Procedures

The application of SSEPs, TCeMEPs, and EMG can aid in a variety of acute spinal procedures depending on the spinal level, complexity of the correction, and preoperative neurologic status. Acute cervical spine injuries present an excellent opportunity to utilize these tools in very dynamic ways. A common method for the treatment of an acute cervical spine injury includes spinal fusion. This procedure can be reached from the anterior, posterior, or sometimes both anterior/posterior approaches. In acute care settings, the utilization of prepositional baseline responses can help aid the surgeon in establishing the general baseline health of the cervical cord. Postpositional baselines confirm that the patient is in a safe position and that no additional iatrogenic trauma was inflicted during positioning [5, 6].

Anterior approach cervical fusions typically involve the removal of the intervertebral disc and its replacement with either a bone graft that will grow to fuse the spine or an artificial disc. Regardless of the technique used, an implant is typically inserted into the intervertebral space to maintain adequate alignment of the vertebra.

IONM can aid in the detection of possible damage to the anterior cord, compression of the posterior cord, or stretching of the nerve roots [7].

In posterior cervical procedures, the positioning of the patient for surgery is further complicated due to the patient's prone positioning. The presence of an acute injury magnifies these positioning challenges. It is imperative that the monitoring team maintain excellent communication with the surgeon during the movement of the patient to prone position. The surgeon can use the data to fine-tune the final positioning of the patient's head and neck to maximize both safety and eventual line of sight. In posterior approach cervical fusions, the intervertebral disc is removed and a bone graft or strut is placed between the anterior bodies while avoiding the exposed spinal cord. Posterior fusions are fixated by a series of screws placed in the vertebra and connected by contoured rods. The IONM data provided to the surgeon during the instrumentation phase of the procedure is beneficial in optimizing the positioning of the hardware in the bony structures.

Similarly to cervical procedures, lumbar fusions can also be performed anteriorly or posteriorly. New implant technology allows surgeons to approach lumbar fixation from a lateral approach by utilizing triggered EMG [10]. In all of these approaches, IONM can provide valuable data. Anterior approach lumbar fusions typically include extensive exposures by general surgeons or thoracic specialists. Once the spine is exposed, the procedure continues with the removal and then replacement of disc and vertebral segments. Anterior graft placement presents potential risks to both the nerve roots by changing the position of the vertebral foramen as well as compression of the anterior roots of the spinal canal [8]. Anterior lumbar fixation can include plates to secure the fixation that work in concert with hardware also placed posteriorly.

EMG can also support posterior and lateral approach fusions. The utilization of EMG during these procedures can detect a range of possible issues including positional compression of substantial neural or vascular structures and irritation or retraction of the many nerve roots in the surgical field [12]. The use of triggered EMG testing for pedicle screw placement integrity provides confirmation of operative x-rays. Lateral fusions provide the benefits of the screw and rod stabilization with the added benefit of maintaining the integrity of the spinal support muscles [9]. EMG is typically used in these procedures to stimulate the iliopsoas muscle in an attempt to avoid compromise of the femoral/genitofemoral nerve [10, 13]. This is one example of a procedure, among growing list of neurologic and orthopedic procedures, which requires electroneurodiagnostic participation to perform.

Conclusion

Electroneurodiagnostic testing is helpful and is often required for comprehensive completion of select procedures in acute care medicine. Discovery of new and exciting applications for intraoperative neurodiagnostic testing is currently being explored. While the discipline has seen accelerated growth in the last 30 years, the outcome-based research has lagged behind [11]. There is a demonstrated need for more evidence-based guidelines in the application of many newer IONM techniques as evident in recent expert panels [6]. Neurodiagnostic technologists are working closely with surgeons and neuroscience researchers to develop protocols to accompany the growing ways in which IONM can be utilized. Until these guidelines become more pervasive in the literature, the utility of the information provided to the surgeon remains largely a function of the technologists' neuroanatomical knowledge and the surgical familiarity with neurodiagnostic testing.

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Closed-Loop Anesthesia Based on Neuromonitoring

33

Ngai Liu, El Medhi Hafiani, and Morgan Le Guen

Introduction

A closed-loop controller is defined as a system wherein a controller monitors one or more system variables and adjusts one or more interventions to maintain a setpoint (Table 33.1). In most settings, such as with the delivery of anesthesia, the clinician himself/herself constitutes a closed-loop controller (Fig. 33.1): the patient output is monitored in the form of vital signs, and these parameters are used to titrate interventions by the practitioner. In fact, all our therapeutic actions are by definition a closed-loop system with the particularity that a human controller closes the loop. The consequences of a human controller are that monitoring and actions are intermittent and irregular. The incorporation of an automated controller into a decision support system not only helps relieve the practitioner of repetitive tasks but also provides perfectly reproducible action. The best example is the automated control of implantable pacemakers that makes decisions without the need for manual validation. Despite an increasing number of clinical studies demonstrating the benefits of controllers, the administration of anesthetic agents remains manual, and the only tool marketed for automated administration of propofol has been developed for non-anesthesiologists [1].

Principles of a Closed-Loop Controller

The benefit of an automated controller is to obtain precise control of the variable with continuous analysis and frequent changes in anesthetic drug concentrations. Thus, the drug infusion is related to the specific needs of each patient, taking into account inter- or intraindividual dynamic variability. Within anesthesiology, automated continuous titration of the hypnotic drug guided by electrocortical activity has been demonstrated to improve the anesthesia stability and avoid both over- and underdosing episodes [2]. Table 33.1 summarizes the engineering control terminology [3]. Different algorithms can be used to perform automated titration:

- The most used type of controller is the *proportional-integral-derivative* (PID) controller. This controller calculates the difference between the measured output and the setpoint to adjust input value.

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Table 33.1 Definitions of engineering control terminology

Input	The variable entered into a function that modifies the output (the drug administered for which the effect is measured using a sensor)
Output	The end result of the input (the consequence of drug adjustment measured by a sensor)
Open loop	The input is not determined by the output (the decision to adjust the amount of drug is performed without knowledge of the drug effect)
Closed loop	The input is determined by the output measured by a sensor (the drug adjustment is related to the error)
Setpoint	Preset value that the control system is supposed to target
Error	Difference between the setpoint and the measured value

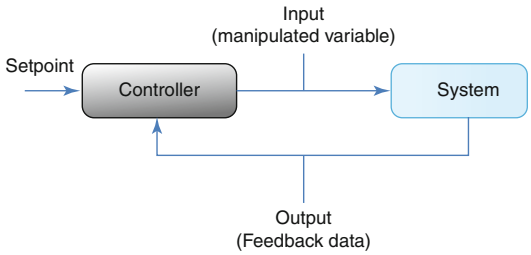

Fig. 33.1 Generic closed-loop scheme

- The *artificial neural network controller* is an adaptive control algorithm with a dynamic learning strategy.
- The *model-based controller* approximates or simulates the target system and predicts the observed response. This approach has been abandoned in favor of a Bayesian approach that optimizes the model.
- The *rule-based controller* uses a set of instructions to perform its actions.
- A *fuzzy logic controller* is a system wherein the logical values true or false are not necessarily accurate but may be affected to some degree of truth. This system requires testing because of the possible arbitrariness within sets.

All these algorithms can be combined (cascade structure) to create a specific controller. The "in silico" evaluation of the controllers is one step, but the relevance of a controller can only be assessed by clinical studies.

Clinical Studies of Automated Titration

Several studies have reported automated propofol administration guided by the Bispectral Index (BIS). Table 33.2 summarizes the clinical studies published since 1998. More than 1,940 patients have been anesthetized with an automated titration of propofol, mainly by a PID controller. Since 2006 some controllers have been used to allow induction of anesthesia (see Table 33.2), and others have been used for more complex patients (e.g., ASA physical status III and IV) [6, 10, 11, 15, 16, 18–20, 22]. The automated titration of propofol has been demonstrated to improve hemodynamic stability in patients scheduled for elective cardiac surgery with cardiopulmonary bypass, as well as reduce the total propofol and vasopressor consumption [15].

Several studies have shown that isoflurane can be administered automatically through a specific device [23], but the prototype was abandoned. Isoflurane can be injected directly into the ventilator circuit, but regulation also depends on the manual adjustment of fresh gas flow [24]. Finally, these studies demonstrated that the electrocortical activity measured by the BIS is a measure of the depth of hypnosis, allowing the automated titration of hypnotics.

Multiple Controllers

General anesthesia is a dynamic balance between hypnosis, analgesia, and muscle relaxation. Currently, several prototypes for the automated titration of propofol are available (see Table 33.2). The clinical relevance of automated administration of neuromuscular blocking agents is limited since the introduction of a specific antidote [25]. However, a study has demonstrated the feasibility of combining automated titration of propofol and mivacurium [21].

Table 33.2 Clinical studies of automated administration

Study	Algorithm	Surgery	Ind	Duration (min)	Analgesia	*N*
Mortier et al. [4]	Model-based	Orthopedic	M	28.8 ± 13.3	Spinal	10
Morley et al. [5]	PID	Gynecologic/general	M	87 [35–164]	Mixture propofol/ alfentanil	30
Leslie et al. [6]	PID	Colonoscopy	M	19 [7–50]	None	16
Struys et al. [7]	Model-based	Gynecologic	M	110	Remifentanil fixed	10
Absalom et al. [8]	PID	Orthopedic	M	72 [40–80]	Epidural	10
Absalom and Kenny [9]	PID	Body surface	M	27.5 [12–86]	Remifentanil fixed	20
Liu et al. [10]	PID	General, gynecologic, urologic, orthopedic, thoracic	Auto	136 ± 86	Remifentanil variable	83
Liu et al. [11]	PID	Lung transplantation	Auto	343 ± 108	Remifentanil ± epidural	20
Puri et al. [12]	PID	Urologic, general, orthopedic	Auto	97 [41–298]	Fentanyl fixed	20
Haddad et al. [13]	Neural network	No cardiac surgery	Auto		Sufentanil or fentanyl	7
De Smet et al. [14]	Bayesian-based	Gynecologic/sedation	Auto	17 ± 3	Alfentanil bolus	20
Agarwal et al. [15]	PID	Cardiac	Auto	357 ± 103	Fentanyl	19
Hegde et al. [16]	PID	Pheochromocytoma laparoscopy	Auto	75 [49–255]	Epidural and fentanyl	13
Méndez et al. [17]	PID		M		Remifentanil	15
Hemmerling et al. [18]	Rule-based	General, thoracic, urologic, orthopedic	M	143 ± 57	Fentanyl bolus	20
Liu et al. [19]	PID	General, gynecologic, urologic, orthopedic, thoracic, cardiac	Auto	140 ± 78	Auto remifentanil	83
Besch et al. [20]	PID	General, gynecologic, urologic, orthopedic, thoracic, cardiac	Auto	150	Auto remifentanil	1,494
Janda et al. [21]	Fuzzy and PID	General, orthopedic	M	129 ± 69	Remifentanil fixed auto mivacurium	20
Liu et al. [22]	PID M-Entropy	General, gynecologic, urologic	Auto	208 [151–311]	Auto remifentanil	30

Abbreviations: *Ind* induction of general anesthesia, *PID* proportional-integral-derivative, *Auto* automated, *M* manual, *N* number of patients

The first automated administration of alfentanil guided by electrocortical activity was published 20 years ago [26]. A study reported that a mixture of propofol and alfentanil in the same syringe can be administered automatically using the BIS [5]. Alfentanil administration can be guided by invasive blood pressure changes [27], but hemodynamic changes lack specificity to measure depth of analgesia during surgical procedures.

One group has developed a PID controller for automated propofol infusion [10]. After this first

controller, the investigators implemented a second controller allowing the automated titration of remifentanil which was also guided by BIS. The principle of this controller was based on the assumption that rapid BIS increase is likely secondary to noxious stimulation and is related to a deficit of antinociception – not to a deficit of the hypnotic component. The controller first administers remifentanil if the error is small and administers remifentanil and propofol when the error is higher. This controller has been validated by a randomized controlled study including 196 patients [19]. The confirmation of the feasibility of the paradigm was confirmed by a study involving 1,494 patients [20].

More recently, a new controller guided by the M-Entropy monitor has been developed. The monitor calculates two parameters – "State Entropy" which is the measure of the irregularity of frontal cortical electrophysiological activity and "Response Entropy." The difference between "Response and State Entropy" represents the activity of facial electromyography which is a surrogate measure to quantify the deficit in antinociception. The controller allows the automated titration of propofol and remifentanil during induction and maintenance of general anesthesia [22].

A prototype named McSleepy allows the simultaneous infusion of propofol guided by BIS, remifentanil guided by a hemodynamic score, and mivacurium guided by a neuromuscular blockade monitor [28].

Conclusion

Published studies have reported the clinical relevance and the technical performance of automated administration of anesthetic agents. Automated administration of intravenous agents outperforms manual control for this repetitive task, but drug administration is only one task of the patient care in acute care environments. The presence of a clinician remains essential to maintain cardiopulmonary homeostasis. However, the introduction of automated systems in the clinical setting will become a reality and will modify existing practice.

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Target-Controlled Infusions

34

Loren A. Hemachandra

Introduction

Target-controlled infusions (TCI) are infusion systems that use a computer controller to achieve and maintain a therapeutic drug level by modifying the infusion rate over time. They seek to mimic and even improve upon the titration that an anesthesiologist would provide, maintaining the patient in a stable plane of anesthesia while allowing the anesthesiologist to focus on other aspects of care.

A TCI system uses a drug-specific pharmacokinetic model as the foundation for its algorithm. It allows patient-specific data to be entered (e.g., age, weight, gender) so that the model better reflects the actual patient. Using this model, the system will estimate the volume in the patient's central compartment, as well as the overall volume of distribution for the drug. At the start of the case, the TCI will calculate the volume of drug necessary to reach a therapeutic level within the central compartment and will bolus that amount [1]. The system will then continually estimate the elimination of the drug (metabolism, excretion, etc.), as well as the expected redistribution from the central compartment. The infusion of the drug is titrated to the sum of the amount being eliminated plus the amount being redistributed, thus maintaining the central compartment at the therapeutic level.

No patient will exactly mirror the model, so every patient will have drug concentrations that vary from the predicted values. A muscular person and an obese person may have the same age, weight, gender, and BMI, but how a drug distributes in the body would vary significantly. To the degree that the patient's physiology varies from the model, systemic concentrations of the drug will also vary. As long as the variance is not large and the therapeutic window of the drug is not small, the patient's actual drug concentrations will remain within the therapeutic window and the patient will receive the desired clinical effect.

Target-controlled infusions are classified as "open loop" or "closed loop." An open-loop system administers infusion based solely on its pharmacokinetic model. Closed-loop systems start with a pharmacokinetic model for the patient but modify its algorithm based upon intraoperative feedback. This helps correct for the variability in pharmacokinetic and/or pharmacodynamic response that exists among patients.

Some TCI maintain distinct notions of the concentrations in the plasma as well as in the drug's site of effect (often the brain). After a bolus of a drug, it takes time for the drug to mix within the blood volume. Drug then diffuses to the effect site proportional to the gradient between the plasma and the effect site. These TCI systems recognize that delay and allow the user to specify the desired concentration either in the

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plasma or at the effect site. Specifying the concentration in the plasma will leave the effect site with somewhat lower concentrations until the two compartments reach equilibrium. Specifying the concentration for the effect site will have the plasma concentration initially exceed the target concentration, bringing the effect site to the desired concentration more rapidly.

Target-controlled infusions can be used for a wide range of agents, including analgesics, hypnotics, paralytics, and even inhalational anesthetics. Each type of agent presents unique difficulties of design, and extensive research is ongoing to find the optimal pharmacokinetic and pharmacodynamic models. Propofol is a commonly used drug with target-controlled infusions, and we will use it for examples throughout this chapter. Target-controlled infusions are prevalent throughout much of Europe and Asia; regulatory concerns have slowed their introduction in the United States [2].

Open-Loop TCI Systems

Open-loop systems deliver an infusion designed to achieve a target drug concentration based solely upon a pharmacokinetic model for the patient. The efficacy of the infusion in an open-loop system is dependent on the accuracy of the pharmacokinetic model. Propofol is generally modeled with a three-compartment model: a central compartment (blood vessels and vessel-rich tissue), a compartment into which the drug diffuses rapidly, and a compartment into which the drug diffuses slowly [3]. The rate at which drug will diffuse from the central compartment to a peripheral compartment at a given time is a function of the relative concentrations in those compartments, as well as the rate of perfusion of the peripheral tissue and its affinity for propofol. As the concentration in the peripheral compartments increases, the rate at which propofol redistributes from the central compartment is expected to decrease. The open-loop TCI will automatically decrease its infusion over time, matching the expected decline in redistribution from the central compartment.

There are many factors that impact how a drug distributes through the body. Some are taken into account in a TCI system in deriving its model for the patient; others are not. Children have larger volumes of distribution (per kilogram) and geriatric patients have a smaller volume of the central compartment [3]. These differences can have a significant impact on the appropriate initial bolus of a drug. There are differences in body fat percentage between the genders, and that difference affects the rate at which a drug may redistribute to peripheral compartments. Impaired cardiac output will slow the rate of mixing within the blood volume, as well as slow the rise in concentration at the effect site. Impaired liver or kidney function may decrease metabolism or excretion of the drug, leading to an erroneously high infusion rate. Hypoalbuminemia may lead to a greater than expected unbound fraction of drug, leading to increased effect. No system takes all these patient factors into account, and so the accuracy of the model will vary by the degree to which the patient has such pathologies.

Multiple pharmacokinetic models have been proposed for propofol. Two well-described models are the Marsh model [4] and the Schnider model [5]. Each model was mathematically derived by administering propofol to a set of research volunteers and measuring the concentrations over time [3]. The Marsh model does not factor in age, so it may be inaccurate in the elderly. The Schnider study included a heterogeneous group of volunteers (men and women, a range of weights, and a range of adult ages) and uses these factors to tailor the model to the patient's characteristics. In practice, the Marsh model calculates a larger central compartment than the Schnider model, leading to a larger initial bolus. Thus, the Marsh model may use more propofol but may also achieve clinical effects sooner [6]. One study showed that use of the Marsh model not only achieved a precise level of sedation more rapidly but that the Marsh prediction of effect-site sedation correlated better with BIS [7].

An early open-loop TCI system was the Diprifusor module, developed during the 1990s [8–10]. It was based upon the 3-compartment pharmacokinetic model described by Marsh. Diprifusor was incorporated into multiple commercially available infusion pumps. The success of

Diprifusor, and of TCI pumps in general, is shown by the fact that "more than 10,000 Diprifusors have been introduced to over 25 countries" and millions of propofol anesthetics have been delivered by TCI [11].

Closed-Loop TCI Systems

Closed-loop TCI systems start with a drug-specific pharmacokinetic model for the patient and initially deliver drug based upon that model. As the anesthetic proceeds, patient data is gathered and fed back into the system, and this is used to modify the system's algorithm. This "closes the loop," providing feedback to the system and allowing it to fine-tune its model to the individual patient.

Feedback can be used to alter either the pharmacokinetic or pharmacodynamic model for the patient. Plasma drug concentrations can be used by the system to aid titration of the drug. This feedback, showing how prior drug administration impacted plasma concentrations over time, allows the system to adjust its estimates for the volume in the various compartments, the rate of transfer between compartments, as well as the rate of elimination/metabolism of the drug. Using this information, the system can rapidly hone in on the target concentration and can then calculate the appropriate maintenance infusion to maintain that target concentration.

Some closed-loop systems incorporate feedback pertaining to the drug's effect. These systems start with an initial target drug concentration but modify the target based upon how the patient responds to the delivered agent. A wide variety of measurements have been used for feedback in closed-loop systems. Closed-loop propofol infusions have been titrated using EEG and evoked potentials as measures of depth of anesthesia [6]. Closed-loop phenylephrine infusions have been studied to maintain arterial pressure during spinal anesthesia [12]. Vital signs (oxygen saturation, heart rate, blood pressure, respiratory rate, end-tidal CO_2) have been used to titrate propofol to maintain moderate sedation [6]. Sensors for muscle movement or electromyography have been used to maintain neuromuscular blockade at a constant level [13]. Blood pressure and heart rate have been used to maintain an optimal level of analgesia [6].

Advantages of Target-Controlled Infusions

Many potential benefits of target-controlled infusions have been hypothesized, and further potential benefits are continually being investigated.

Manual-controlled infusions have an anesthesiologist guessing an appropriate initial bolus or maintenance rate, often leading to too much or too little medication [1]. By doing the complex calculations within its model for the current patient, TCI systems can precisely tailor these doses, potentially leading to greater stability of drug concentration. Target-controlled infusion systems can use also use its pharmacokinetic model to predict time to emergence. These predictions have been shown to be reasonably accurate, though they do not offer significant advantages for expert users of propofol in shorter surgical procedures [14].

Benefits of TCI delivering analgesics have also been published. For fiberoptic bronchoscopy in an intensive care setting, a remifentanil target-controlled infusion provided global comfort with minimal cough [15]. A remifentanil TCI also was used to prevent cough during emergence from nasal surgery [16].

The Cochrane Collaboration evaluated many advantages of TCI reported in the literature. The one benefit that was consistently found across the studies was that "fewer interventions were required by the anaesthetist during the use of TCI compared with" manually controlled infusions [17]. This frees the anesthesiologist to focus on other aspects of patient care.

Potential Risks of Target-Controlled Infusions

Target-controlled infusions are only accurate to the degree that their pharmacokinetic model represents the patient. Even in closed-loop systems,

where feedback allows the model to be tailored to patient effect, the TCI is still dependent upon the initial pharmacokinetic model to determine the initial bolus and infusion rate. Variation of the patient from the "norm" can lead to over- or under-sedation, over- or under-relaxation, and inadequate or excessive analgesia. Many variables can impact the accuracy of the pharmacokinetic model: the sizes of the compartments, the relative perfusion of those areas, cardiac output and the rate of perfusion, the potential protein binding of the drug, or the metabolism of the drug (and possible shifting of the metabolism if other drugs are given).

Morbidly obese patients have pharmacokinetics that varies significantly from their thin counterparts. The original Schnider model, for example, incorporated a formula to calculate lean body mass, but that formula fails in severely obese patients [3]. Use of a target-controlled system in these patients might lead to inappropriate dosing of propofol. Since the morbidly obese is an increasingly large subgroup, studies have evaluated how to adjust target concentrations so that the target-controlled infusion systems can be used in morbidly obese patients [18]. More recent TCI systems make modifications to their models to better accommodate morbidly obese patients, and research will show how well these systems now perform.

Patients with cardiovascular impairment, diabetes, renal failure, or hepatic failure similarly have pharmacokinetics that can be significantly shifted from the norm. Without customized pharmacokinetic models or further research to guide how to use automated infusions in these patients, the use of target-controlled infusions may be ill-advised. The miscalculation for people with shifted pharmacokinetics is especially dangerous when delivering drugs that have a small therapeutic window.

Some patients have both abnormal pharmacokinetics and pharmacodynamics. Consider, for example, chronic opioid users. They have shifted pharmacokinetics, since they metabolize opioid at a greater rate; thus, they would require a greater than expected infusion rate to maintain a target plasma concentration. These patients also have shifted pharmacodynamics, since their tolerance may necessitate a higher than expected target concentration to achieve the desired level of analgesia. Use of an automated infusion system with these patients must be undertaken with care, diligently evaluating the patient to ensure that the infusion is generating the desired outcome.

Types of Agents for Target-Controlled Infusion Systems

The most commonly hypnotic used in TCI systems (and the hypnotic that can be used with commercially available systems) is propofol. It can be used for mild-to-moderate sedation, as well as inducing and maintaining general anesthesia. Each of these uses has its own challenges. For general anesthesia, too little propofol risks intraoperative recall, but too much propofol may lead to hemodynamic compromise or prolonged emergence. For sedation, a patient may not tolerate the procedure if given too little propofol, but too much propofol may risk respiratory compromise. Sedation may be especially challenging for an automated system in procedures that have brief periods of intense stimulation; adequate propofol to cover the stimulating period may lead to apnea when that stimulation disappears.

Both open-loop and closed-loop TCI systems have been designed for the administration of propofol. Diprifusor, described infra, is an example of an open-loop system available outside the United States. There is a closed-loop sedation system that has been under consideration by the US Food and Drug Administration (FDA). SEDASYS system is a closed-loop propofol infusion system for the maintenance of minimal-to-moderate sedation [19]. SEDASYS is intended for American Society of Anesthesiologists (ASA) physical status I or II patients at least 18 years of age undergoing colonoscopy or esophagogastroduodenoscopy procedures. The ASA provided written comments to the FDA regarding the SEDASYS system expressing concern, among other things, about the limitations of oxygen saturation and end-tidal CO_2 measurements for detecting respiratory depression, as well as the inability of SEDASYS to prevent or manage loss of consciousness [20]. The FDA initially rejected

the application for SEDASYS. But after reconsideration, Ethicon Endo-Surgery, Inc. (a division of Johnson & Johnson) announced in May 2013 that the FDA had granted premarket approval (PMA) for SEDASYS [19].

Research that fine-tunes our understanding of pharmacokinetics and pharmacodynamics continues. As an example, a study used a TCI system to calculate propofol clearance with respect to age and gender [21]. It found that propofol clearance in males changes little with increasing age; young female patients have higher propofol clearance than males but that it decreases steadily with increasing age. The better our understanding of the pharmacokinetics of propofol, the more accurate our TCI models will become.

Neuromuscular blockade is an ideal target for a closed-loop target-controlled infusion. Vecuronium, for example, can maintain the level of blockade with an infusion at a constant rate, but one does not know, a priori, what that rate should be [6]. A closed-loop TCI can bolus to try to achieve the desired level of blockade and then use electromyography feedback to fine-tune the infusion to maintain that level of blockade. To work correctly, the TCI must take into account the delay between administration of a bolus and its effect. After a non-depolarizer is bolused, there will be a delay before onset of paralysis, and the system must not erroneously think it has underdosed because of this delay. Statistical models have been evaluated that allow "high stability" in maintaining neuromuscular blockade [22]. In the long run, the marketplace will determine whether the benefit of a TCI for paralysis is worth the increased cost of a "smart" infuser.

Sufentanil, remifentanil, and alfentanil are among the analgesics that have been delivered via target-controlled infusions. Combinations of drugs are also being delivered in TCI systems. Propofol/remifentanil and propofol/sufentanil can be titrated, either combined or individually. The analgesia provided by the opioid lowers the amount of propofol required, possibly speeding recovery at the end of surgery while also promoting a smooth emergence. Computer-controlled rate adjustment has even been studied for inhalational agents. Every anesthesiologist is familiar with manually adjusting isoflurane to maintain a desired end-tidal concentration. While it is not an infusion, the multi-compartment simulation used in TCI systems could model the redistribution of inhalational agent within the body and thus could guide automation of inspired concentrations. The system might be able to more rapidly bring the effect site to steady state without overshooting and then would facilitate maintaining the desired depth of anesthesia. And since the system maintains a notion of how much agent has accumulated in the various compartments of the body, it could potentially estimate the time until emergence (i.e., it could estimate the time until the central compartment would get down to a specified concentration). Anesthesiologists could use this information to help time when to turn off the inhalational agent.

Target-Controlled Infusions in Pediatric Populations

The differences between children and adults are many. Children have greater volume of distribution per kilogram than adults. Children have greater clearance. Children may have slightly lower sensitivity to propofol (in terms of how it affects BIS) [23]. But even within the pediatric population, pharmacokinetics and pharmacodynamics can differ significantly based upon age [3]. Multiple models have been proposed for propofol infusion in pediatric populations, and these models must account for those differences. Two well-studied models are the Kataria and the Paedfusor models, each with differing age and weight requirements [3]. A study comparing eight pediatric propofol pharmacokinetic models in healthy patients with ages 3–26 months found that they "differed markedly during the different stages of propofol administration" [24]. Most underestimated the child's volume of distribution leading to larger initial boluses, but still most models were found to work well with the children in the study. Many studies have been published, and extensive research continues for the optimal strategies for administering target-controlled infusions in the pediatric population.

Conclusion

Target-controlled infusions automate the process of infusion initiation and maintenance. Open-loop systems seek to rapidly bring a patient's drug concentration to target levels and maintain that level based upon a standardized model tailored to patient characteristics. Closed-loop systems initiate drug delivery based upon a standardized model but fine-tune the algorithm based upon patient response. On appropriate patients, target-controlled infusions offer a convenient way to maintain depth of anesthesia while minimizing the interventions required by the anesthesiologist. Since infusions are based upon standardized models derived from "normal" patients, using target-controlled infusions on patients with significant pathophysiology can lead to over-delivery or under-delivery of medication. Commercial target-controlled infusion systems have long been available in Europe and Asia but have been delayed in the United States because of regulatory concerns. Recent premarket approval for a closed-loop propofol infusion system indicates that target-controlled infusions may soon become available in the United States as well.

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Part V

Metabolic Monitoring

Glucometrics and Measuring Blood Glucose in Critically Ill Patients

35

Gregory E. Evans, Donald Crabtree, and Liza M. Weavind

Introduction

"Diabetes of stress," the dysregulation of glucose homeostasis in critically ill patients, is well known to providers who work in the acute care environments and critical care settings. The extent to which this is an adaptive response to stress is unknown. The hyperglycemia of critical illness, irrespective of previously diagnosed diabetes, is secondary to increased gluconeogenesis and increased peripheral insulin resistance [1]. In times of stress and illness, glucose uptake is increased in insulin-independent tissues such as the brain, red blood cells, and wounds; the survival advantage of this increased uptake is undetermined. Conversely, the negative effects of hyperglycemia include a more pronounced systemic inflammatory response to endotoxin and the formation of superoxide free radicals which impact endothelial and other cell functions. Hyperglycemia and poor glycemic control have been associated with increased morbidity and mortality in critically ill patients.

In 2001 Van den Berghe and colleagues published a sentinel trial which demonstrated that tight glycemic control (blood glucose concentration between 80 and 110 mg/dL) resulted in absolute reductions in ICU and hospital mortality of 3.4 and 3.7 %, respectively, for cardiac surgical ICU patients [2]. The results of this trial led to widespread integration of tight glycemic control or intensive insulin therapy (IIT) into various practice guidelines and quality of care indices for critically ill patients. There have been several subsequent studies, which demonstrated a lack of benefit with tight glucose control and an increased frequency of hypoglycemic episodes and associated poor outcomes [3, 4]. In 2009 a multicenter randomized trial comparing "tight glucose control" to "conventional glucose control" (144–180 mg/dL) demonstrated a higher mortality among the more tightly controlled patients. The odds ratio for mortality at 90 days was 1.14 in the intense glucose control group [5]. Considering that hyperglycemia and hypoglycemia can both significantly affect clinical outcome, the precision and accuracy of blood glucose measurements are vital. This highlights the importance for clinicians to understand the accuracy and

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methodology used to obtain these measurements to guide clinical practice at the bedside of critically ill patients.

Methods for Measuring Blood Glucose Levels

There are three commonly used methods of measuring blood glucose in the clinical setting:

- Point-of-care glucose meter (POC)
- Arterial blood gas measurements
- Central laboratory testing (CLM)

These meters measure whole blood glucose based on an enzymatic reaction and a detector. In POC devices, the enzyme portion subsists in a dehydrated state on the disposable strip of the glucose meter and the whole blood interacts with the enzymatic portion of the strip, the product of which can be detected by the meter. In the central laboratory, an enzyme specific for a glucose substrate is immobilized between two membrane layers, polycarbonate and cellulose acetate. The substrate is oxidized as it enters the enzyme layer, producing hydrogen peroxide, which passes through cellulose acetate to a platinum electrode where the hydrogen peroxide is oxidized. The resulting current is proportional to the concentration of the substrate. The three principal enzymatic reactions utilized for the measurement of glucose are glucose oxidase and glucose dehydrogenase which are primarily used for POC devices while hexokinase is primarily used for central laboratory analyzers [6].

Enzymatic Reactions

Glucose Oxidase

In 1928 an enzyme that converted glucose to gluconic acid in the presence of dissolved oxygen and flavin adenine dinucleotide coenzyme was discovered. This enzyme was later named glucose oxidase [7]. The glucose oxidase reaction is most specific for beta D-glucose, which accounts for only 64 % of glucose in the blood. Therefore, extended incubation time or the inclusion of an additional enzyme is required to measure both alpha and beta D-glucose. This reaction also yields hydrogen peroxide which is coupled with a reduced form of dye and the dye changes color as it is oxidized. It is this color change that can be measured [8]. Newer devices utilizing the glucose oxidase reaction are amperometric, with the detection of ions in a solution based on electrical current or changes in electrical current. This measurement quantifies glucose measurement according to the magnitude of the current generated by the reaction, which has a higher degree of accuracy than a color change.

Glucose Dehydrogenase

Glucose dehydrogenase converts the glucose of the whole blood sample to gluconolactone. This reaction results in the release of an electron that reacts with a coenzyme electron acceptor. The amount of coenzyme with an accepted electron is proportionate to the glucose concentration. Following the reaction between the electron and coenzyme an electrical current is generated which is proportional to the glucose concentration in the blood sample [9]. There are several POC monitors that utilize the enzyme glucose dehydrogenase to determine blood glucose.

Hexokinase

The most widely used enzymatic method of measuring serum blood glucose in central laboratory analyzers involves hexokinase [10]. In the presence of hexokinase, magnesium, ATP, and glucose are phosphorylated to glucose-6-phosphate which is oxidized to 6-phosphogluconate yielding NADPH. The amount of NADPH yielded from this reaction is directly proportional to the amount of glucose sampled. The NADPH level is then measured by its absorbance of light [11, 12].

Specific Devices

Point-of-Care Glucose Meter

The first point-of-care meter was developed in 1970 by Anton H. Clemens, and it was intended to be used by physicians in the clinic setting to

measure blood glucose level [13]. The idea of self-monitoring blood glucose levels with a glucose meter was later developed by Richard K. Bernstein [14]. In addition to outpatient use, through the years glucose meters have become a tool for inpatient glucose monitoring and management. The reason for this is cost, convenience, and efficiency with testing blood glucose with a glucose meter being significantly cheaper than using the central laboratory ($0.98 compared to $6.68 for a central laboratory analysis) [15, 16]; immediate availability of results and only a blood volume of 10 μL is needed for a sample compared to the tubes used by central laboratory analyzers [17].

Glucose meter measure blood glucose by using any of the three enzymatic methods described previously in this chapter. Similar to blood gas analyzers, a whole blood sample is measured and the results are mathematically adjusted to correlate with central laboratory results. The benefit of glucose meter is the option to utilized arterial, capillary, or venous blood. Additional benefits include the requirement of a significantly smaller whole blood sample and a more rapid return of results compared to blood gas analyzers. Although glucose meter are used in the ICU and other acute care environments, it is clearly stated by the FDA and manufacturers that glucose meter are not designed for utilization in the ICU.

i-Stat

i-Stat is a point-of-care blood analyzer produced by Abbott Laboratories. i-Stat analyzer systems consist of handheld analyzers and single-use cartridges. The i-Stat analyzer is capable of measuring sodium, potassium, chloride, ionized calcium, hematocrit, glucose, creatinine, pH, partial pressure of oxygen, and partial pressure of carbon dioxide in whole blood. Within the blood sample, oxidation of glucose, catalyzed by the enzyme glucose oxidase, produces hydrogen peroxide. The hydrogen peroxide produced is oxidized at the electrode to generate a current which is proportional to the sample glucose concentration. The reference ranges of i-Stat are comparable to the reference ranges of standard laboratory methods [18, 19].

Blood Gas Analysis

Most blood gas analyzers measure whole blood glucose using the glucose oxidase enzymatic reaction. Approximately 100 μL of whole blood is analyzed yielding results in approximately 2 min. Unlike central laboratory serum analyzers, blood gas analyzers measure whole blood samples and the results must be mathematically adjusted to correlate with central laboratory results. Glucose measurements from blood gas analyzers are more accurate than glucose meters and are considered a suitable alternative to central laboratory serum glucose measurements [20].

Central Laboratory Testing (CLM)

The majority of CLM testing is done using the hexokinase or glucose oxidase enzyme. CLM is the gold standard for the measurement of serum blood glucose. By centrifugation the serum is isolated and the glucose content of only the serum is measured. The accuracy of central laboratory analyzers is tightly regulated and must meet the standards determined by Clinical Laboratory Improvement Amendment of 1988 (CLIA 88) [21]. Although the accuracy of CLM is excellent, the utilization of CLM for solely measuring serum glucose is limited due to longer processing time compared to i-Stat, glucose meter, and blood gas serum glucose measurements.

Accuracy Standards

Regulatory control over glucose measurement devices, including central laboratory and point-of-care (POC) devices, is maintained by the FDA. For glucose meters the FDA uses accuracy criteria created by the International Organization of Standardization (ISO), though there is not currently an internationally accepted reference method for the determination of serum blood glucose concentration. The current standards are that “95 % of the individual glucose results shall fall within 15 mg/dL of the results of the manufacturer’s measurement procedure at glucose concentrations <75 mg/dL and within 20 % at glucose concentrations greater than 75 mg/dL” [22].

Table 35.1 Variables that affect serum glucose measurement

Variable	Glucose oxidase	Glucose dehydrogenase
Whole blood	Decrease	Decrease
Arterial blood	Increase	Increase
Capillary blood	Increase	Increase
Postprandial state	Increase	Increase
Anemia	Increase	Increase
Hypoxemia	Increase	No effect
Supplemental oxygen	Decrease	No effect
Acidemia	Decrease	No effect
Alkalemia	Increase	No effect
Hypothermia	Increase	Variable effect
Hypotension	Increase	Variable effect
Acetaminophen	Decrease	Increase
Dopamine	No effect	Decrease
Mannitol	Increase	No effect

Adapted from Ha et al. [50]

The accuracy of blood gas and central laboratory analyzers used in the United States is based on the Clinical Laboratory Improvement Amendment of 1988 (CLIA 88) [23]. Blood gas analyzers have been shown to have accuracy similar to central laboratory analyzers [24, 25]. The accuracy of central laboratory glucose analyzers is based on a frozen serum standards from National Institute of Standards and Technology (NIST) with glucose concentration determined by isotope dilution mass spectrometry.

The FDA requires that all POC glucose meters perform satisfactorily with user variability. The accuracy data released by manufacturers is typically obtained from testing under ideal conditions using trained technicians or highly selected patients [26]. In addition based on the FDA criteria for accuracy, five percent of measured readings can be outside of the mandatory range.

Factors Affecting Accuracy of Measurements of Blood Glucose (Table 35.1)

1. The concentration of fasting whole blood glucose is 12–15 % lower than the glucose concentration in serum. This difference in glucose concentration is the most significant difference between central laboratory and glucose meter values. Central laboratory analyzers centrifuge the whole blood sample to obtain the serum which is analyzed. POC glucose meters vary in their method of analysis. Glucose meters take a fixed volume of whole blood, lyses the cells, and analyze the amount of glucose. Alternatively, using absorbent pads they separate the cellular portion of a sample from the serum which reacts with the enzymatic reagents. It is recommended that plasma-based glucose results from POC glucose meters are used so the values will most closely match that of a laboratory method [27]. POC glucose meters that sample whole blood must be mathematically corrected to plasma to account for this difference. Therefore, central laboratory analyzers measure plasma glucose, while POC glucose meters measure whole blood glucose but are calibrated to yield a plasma glucose measurement with the exception of HemoCue, which yields whole blood glucose levels [28].
2. The source of the blood for glucose measurement is an important factor with regard to assessing accuracy. In the fasting and non-fasting state, the capillary blood glucose concentration is higher than a venous sample. This difference in blood glucose concentration ranges from 2 to 70 mg/dL with the larger discrepancy occurring following a glucose load. Arterial blood samples have a greater glucose concentration than capillary blood sample [29–31].
3. Both glucose oxidase and glucose dehydrogenase enzyme methods of detecting glucose have inherent challenges with accuracy and interference. Glucose oxidase is highly dependent on the presence of oxygen, and elevated oxygen tension can depress serum glucose measurement, while low oxygen tension will have the reverse effect. In contrast glucose dehydrogenase with the coenzyme pyrroloquinoline quinone is not dependent on oxygen tension but is susceptible to interference by other biochemical reactions such as with galactose, mannose, xylose, and ribose [32]. Specific medical therapies, such as peritoneal dialysis with osmotic agent icodextrin, can

case an inaccurately high serum blood glucose measurement because of absorption and metabolism of this agent [33, 34]. Elevated levels of serum urea and uric acid, also seen in patients with renal failure, can reduce the accuracy of glucose dehydrogenase-based POC glucose monitors [35, 36].

4. Appropriate user knowledge and education is essential as 91–97 % of overall inaccuracies are operator-dependent [11, 37, 38]. The common reasons for measurement errors include mechanical stress on the strips, unclean site for testing, unclean meters, clotted specimen, and inadequate amount of blood sample [6]. Glucose oxidase meters can overestimate glucose at elevated altitudes and low temperatures. Glucose dehydrogenase meter results become unpredictable when test strips are exposed to increased humidity [39].
5. Patient factors in acute care environments may also increase the inaccuracy of POC glucose monitoring as medical confounders affect POC glucose meter readings. For this reason the FDA informs manufacturers that "critically ill patients (e.g., those with severe hypotension or shock, hyperglycemic-hyperosmolar state, hypoxia, severe dehydration, diabetic ketoacidosis) should not be tested with POC glucose meters because inaccurate results may occur" [11, 40]. In the setting of hypotension, there is poor tissue perfusion, blood stagnation, and increased glucose uptake secondary to ongoing tissue metabolism, thus enhancing discrepancies between capillary and venous blood glucose levels. It has also been found that electromagnetic interference from medical equipment causes medical device performance degradation which may lead to erroneous blood glucose measurements [41]. As mentioned previously patients that have elevated oxygen tension, like those receiving supplemental oxygen, may have falsely depressed serum glucose levels for glucose oxidase meters. Conversely, hypoxia can erroneously elevate serum blood glucose levels. In patients with hyperlipidemia the high concentration of lipids in the blood may interfere with the results [42]. Glucose levels can also be underestimated in patients with polycythemia [43]. Error in measure can occur when hematocrit is below 35 % or above 55 % [44]. Finally, low pH (<6.95) erroneously reduces serum blood glucose levels, while high pH erroneously increases serum blood glucose levels for glucose oxidase meters [45].
6. There are several drugs that interfere with serum blood glucose measurements. *Acetaminophen*, *ascorbic acid*, *dopamine*, and *mannitol* have been noted to significantly interfere with glucose oxidase meter serum glucose measurements; because of the peroxide reduction, detection method is utilized. *Dopamine* is known to also interfere with the serum blood glucose results of glucose dehydrogenase meters.
7. The ongoing glycolysis in a whole blood sample secondary to the metabolism of erythrocytes and leukocytes leads to a decrease of glucose concentration in a sample at a rate of 5–7 % per hour [46, 47]. Thus whole blood must be separated (serum from cells) within 30 min for laboratory analysis to be an accurate comparison with whole blood analysis on a glucose meter.

Cost Analysis

The role of point-of-care tests in facilitating the management of patients is well established. The data ascertained from the analysis of blood gases comprises approximately 43 % of the information utilized by clinicians to make a clinical decision [48]. Point-of-care tests such as glucose meters provide information to clinicians in real time which allows more rapid intervention by the clinician. If the costs of labor are assumed fixed, then the cost of analysis utilizing i-Stat, central laboratory, and in-unit blood gas analyzers is $4.00, $1.38, and $1.33, respectively. When the costs of labor are taken into consideration, the cost of analysis utilizing i-Stat, central laboratory, and in-unit blood gas analyzers is $6.68, $6.68, and $3.65, respectively [15].

Conclusion

Monitoring and management of blood glucose is an essential component of clinical care in acute care environments and a recorded quality metric for many ICUs. When considering which type of monitoring to use, one must consider the accuracy, cost, and timing of the results. Both point-of-care and central laboratories have strengths and weaknesses depending on current needs. Point-of-care is fast and cheaper when compared to central laboratories but has lower level of accuracy [49]. Regarding current accuracy standards, there is no single device utilized today that meets the FDA's most stringent accuracy standards, although there are some promising technologies on the horizon [50]. Given the allowable accuracy range of point-of-care devices, any borderline measurement should be verified against a predetermined standard in any given care area such as blood gas or central laboratories. Due to the inaccuracy of current point-of-care devices and the multiple comorbidities of the ICU patient, one can make two deductions: (1) if a "tight" glucose management strategy is to be employed, then central laboratories or blood gas should be used for glucose monitoring due to accuracy, and (2) if cost and timing force the clinician to use point-of-care for monitoring, the "looser" glucose strategy should probably be utilized with any borderline measurements immediately verified against blood gas or central laboratories.

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Noninvasive Hemoglobin Monitoring

36

Valerie Begnoche and Michael O'Reilly

Numerous methods are available to measure the hemoglobin concentration of blood. Until recently, however, all these methods required an invasive sample for analysis, contributing to iatrogenic anemia in hospitalized patients and exposing health care providers to needlestick injuries and blood-borne pathogens. Additionally, phlebotomy and analysis of blood, even when done at the bedside with bench top analyzers or point-of-care devices, is time-consuming, is subject to sampling errors, and only provides intermittent measurements. For these reasons, there is significant interest in the development of noninvasive technologies for hemoglobin measurement.

There are several devices that claim to measure hemoglobin noninvasively. Because the technology is new and rapidly evolving, it is likely the technology and the evidence supporting its use will have changed significantly by the time this book is printed. Following is a review of what is known at this time.

There currently are at least four commercially available devices that measure hemoglobin noninvasively, those being SpHb measurement with Pulse CO-Oximetry (Masimo Corp), the Pronto-7 (Masimo Corp), the OrSense NBM-200MP, and the haemospect (MBR Optical Systems). The only noninvasive hemoglobin devices with FDA clearance for use in the United States are Pulse CO-Oximetry devices and the Pronto-7. The other devices are marketed in other parts of the world (Table 36.1). Of the four devices only one, the Pulse CO-Oximetry, manufactured by Masimo Corporation, is designed to provide continuous data. The Pulse CO-Oximetry was also the first noninvasive hemoglobin measurement device available in the US market. The principles of operation for the Pulse CO-Oximetry are similar to those for conventional pulse oximetry in that both are based on the Beer-Lambert law which states that when light of a given wavelength passes through a substance, some of the light is absorbed (absorbance) and some passes through the substance (transmittance). The absorbance is proportional to the path length through the sample and the concentration of the sample. If the path length and the molar absorptivity, also called the extinction coefficient, are known and the absorbance is measured, the concentration of the substance can be deduced. The pulse oximetry sensor is comprised of light-emitting diodes (LEDs) that shine two wavelengths of light through the sensor site (typically the finger), and a detector that detects the amount of each wavelength is absorbed by the tissue to estimate the percent of oxygenated hemoglobin. Pulse CO-Oximetry, on the other hand, utilizes seven or

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Table 36.1 Commercially available noninvasive hemoglobin devices

Device	Technology	Availability as of Nov 2012
Pulse CO-Oximetry (e.g., Pronto, Radical-7) (Masimo Corp.)	Multiple wavelength Pulse CO-Oximetry	FDA cleared, CE marked
Pronto-7 (Masimo Corp.)	Rainbow 4D spectrophotometry	FDA cleared, CE marked
OrSense (e.g., MBM200)	Occlusion spectroscopy	CE marked
Haemospect	Transcutaneous reflection spectroscopy	CE marked

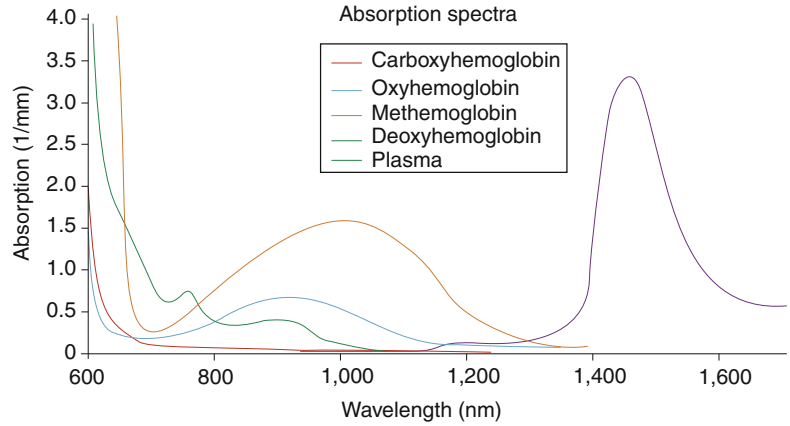

Fig. 36.1 Pulse CO-Oximetry uses multiple wavelengths of light to distinguish between different species of hemoglobin

more wavelengths of light to provide estimations of total hemoglobin (called SpHb) and the dyshemoglobins, carboxyhemoglobin (called SpCO) and methemoglobin (called SpMet) (Fig. 36.1). The initial evaluation of the agreement of SpHb to laboratory measurement of hemoglobin was conducted in 20 healthy volunteers undergoing hemodilution (Fig. 36.2). Macknet and colleagues [1] removed 500 mL of blood from each subject and replaced it with a rapid crystalloid infusion to reduce the hemoglobin concentration while taking serial arterial blood samples and continuously monitoring SpHb with Pulse CO-Oximetry. Blood samples were analyzed with laboratory CO-Oximetry. The bias and precision (1 standard deviation of the bias) for the 165 laboratory measurements and 335 simultaneous SpHb measurements were 0.15 ± 0.92 g/dL. These results were encouraging because they demonstrated the accuracy of SpHb to be similar or better to those found for other invasive methodologies such as point-of-care spectrophotometric devices [2–5]. The first published clinical evaluation of continuous SpHb monitoring was conducted by Miller and colleagues in 20 patients undergoing spine surgery [6]. Seventy-eight arterial blood samples analyzed with a hematology analyzer (reference device) were compared to simultaneous SpHb measurements and a point-of-care spectrophotometric analyzer. The bias and precision of SpHb measurements compared to the reference device were 0.26 ± 1.8 g/dL, which showed significant variability in SpHb accuracy compared to the previous study. Miller et al. noted that accuracy of SpHb increased and variability decreased when perfusion index, a numerical value reflecting perfusion at the sensor site, was higher and concluded that SpHb could have been frequently used to guide clinical decisions in some patients but may not be accurate enough in others. In a similar study conducted in 29 patients undergoing complex spine surgery, Berkow et al. [7] reported bias and precision of 0.3 and 1.0 g/dL for 186 data pairs when SpHb was compared to a CO-Oximetry reference device, confirming the accuracy reported by Macknet et al. Since these initial evaluations, numerous studies have evaluated the absolute

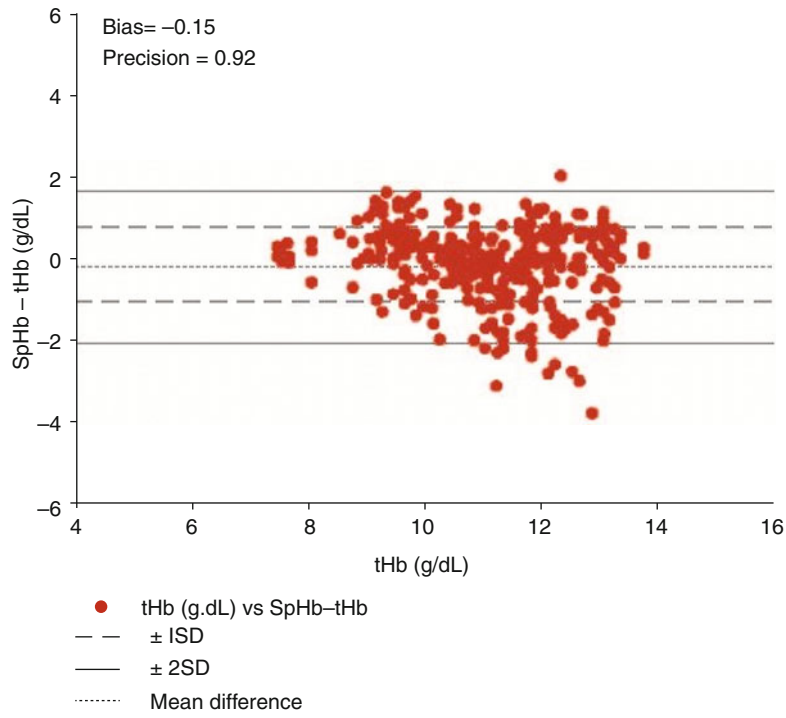

Fig. 36.2 A Bland-Altman plot of 165 hemoglobin values as determined by CO-Oximetry (tHb) versus 335 simultaneous noninvasive hemoglobin values (SpHb) collected from 20 subjects undergoing hemodilution, with mean hemoglobin difference (SpHb, tHb) and standard deviation shown by *dashed* (1 SD) and *solid* (2 SDs) *lines* (Reprinted with permission from Macknet et al. [1])

and trend accuracy of SpHb compared to various reference devices in surgery [8–13] including obstetric surgery [14, 15], in the ICU [5, 13, 16], in the emergency department [17–19], and in remote field settings [20, 21]. The reported bias has ranged from 0 to around 1 g/dL and precision has ranged from 0.5 to over 1.5 g/dL using different versions of the technology and different reference analyzers. In order to address the issue of variable in SpHb accuracy due to the reference device, Frasca and colleagues [5] studied 62 intensive care unit patients, comparing simultaneous SpHb values and 471 blood samples analyzed by a spectrophotometric point-of-care device and a satellite laboratory CO-Oximetry to a laboratory hematology analyzer (reference device). The bias and limits of agreement were 0.0 ± 1.0 g/dL for SpHb, 0.3 ± 1.3 g/dL for spectrophotometric point-of-care device, and 0.9 ± 0.6 for the satellite CO-Oximetry compared to the reference device, demonstrating not only the relative accuracy of SpHb but also significant differences between invasive methodologies.

Regardless of the point-to-point accuracy, most studies that evaluated trending have found that changes in laboratory measurements were significantly correlated with changes in SpHb [7, 8, 10, 11], suggesting that SpHb may be a reliable monitor for trending hemoglobin to detect sudden drops and to prevent unnecessary transfusions or over-transfusion. A preliminary randomized controlled trial that investigated the effect of SpHb monitoring on transfusion practices during orthopedic surgery found that blood transfusion frequency decreased from 4.5 to 0.6 % in patients monitored with SpHb compared to patients who received standard care with no difference in postoperative transfusion rates or 30-day complication rates [22].

Perhaps because SpHb has been commercially available since 2008, there are numerous studies attesting to its accuracy and clinical utility. There is far less clinical evidence for the other three noninvasive hemoglobin devices, the Masimo Pronto-7, the OrSense NBM-200MP, and the haemospect.

The Pronto-7 device relies on multi-wavelength, spectrophotometric technology similar to Masimo's other Pulse CO-Oximetry devices except that it is designed for spot check measurements only (does

not provide continuous data) and uses different proprietary algorithms to estimate hemoglobin. Like Pulse CO-Oximetry, the Pronto-7 provides oxygen saturation values (SpO_2), pulse rate, and perfusion index but is not able to measure other hemoglobin species such as carboxyhemoglobin and methemoglobin like the Pulse CO-Oximetry. Gayat et al. [18] tested the accuracy of the Pronto-7 compared to a laboratory hematology analyzer in 270 emergency room patients and found a bias and precision of 0.56 ± 1.2 g/dL. The Pronto-7 also had acceptable repeatability of measurements with a within-subject coefficient of variation of 3.5 % compared to 1.3 % for the hematology analyzer reference device. Additionally, when patients were assessed for pain and anxiety associated with the hemoglobin test, they reported significantly lower pain and anxiety associated with the noninvasive test compared to the invasive blood sampling.

The OrSense NBM-200MP measures hemoglobin via a ring-shaped pneumatic sensor that intermittently squeezes the base of the finger to occlude blood flow similar to a blood pressure cuff. The sensor measures the differential light absorption before and after the occlusion to determine hemoglobin concentration using a proprietary technology referred to as occlusion spectroscopy. Like the Pronto-7, the OrSense device provides intermittent measurements rather than continuous data and therefore may be more appropriate for spot-checking rather than trending. When the OrSense NBM200 was tested in a population of pregnant women, bias and precision was found to be 0.1 ± 0.86 g/dL when 126 readings were compared to venous blood samples analyzed with a hematology analyzer [23]. Gayat et al. [18] assessed the performance of the NBM200MP in 297 emergency department patients and reported bias and precision of 0.21 ± 1.6 g/dL, showing it to have a smaller bias but larger standard deviation than the other noninvasive device tested, the Pronto-7 (Fig. 36.3). Like with the Pronto-7, patients reported less pain and anxiety associated with the NBM200MP compared to the invasive reference method.

The haemospect (formerly called the Mediscan 2000) is a point-of-care device that uses a handheld, pen-like probe that is placed on the forearm of the patient. The haemospect probe emits halogen white light through silica fibers onto the skin and underlying tissues and measures the wavelength of the light reflected back through a process referred to as transcutaneous reflection spectroscopy. An early version of the device was tested for hemoglobin measurements compared to a hematology analyzer in healthy preterm infants [24]. Eighty-five data pairs were obtained. The haemospect compared to the reference device had a small bias and an error of less than 5 %. In a follow-up study conducted in 80 neonates [25], from which 313 spectroscopic measurements were recorded, the bias was around 0 and the standard deviation was 0.6 g/dL. When the haemospect device was field-tested for anemia screening in western Guatemala [21], it was only able to obtain readings in 70 of 80 tests on the palm and 60 of 80 tests on the forearm, but otherwise had a strong positive correlation to the venous blood test ($r = 0.94$ for palm and 0.90 for forearm).

A common flaw of studies assessing the accuracy of new technologies like noninvasive hemoglobin measurement is the failure to account for the sources of measurement variation introduced by the study methods and reference device. Preanalytic errors may include poor sampling technique and handling, inadequate sample, improper mixing, and using multiple sources of blood (capillary, venous, and arterial), which vary in hemoglobin concentration [26, 27]. Errors may also result from the improper use of the noninvasive devices, such as the wrong size or type of sensor or the senor improperly applied. Each of the devices has specific directions for use which must be followed in order to achieve an accurate result. Analytic errors may include using the reference device outside of calibration or using multiple devices as the reference. Gehring et al. [28] showed that the hemoglobin values from the same blood sample analyzed on two identical devices from five different CO-Oximetry manufacturers had an average standard deviation of 0.5 g/dL with the highest standard deviation at 1.2 g/dL. Hemoglobin values consistently differ within and between the various hemoglobin measurement

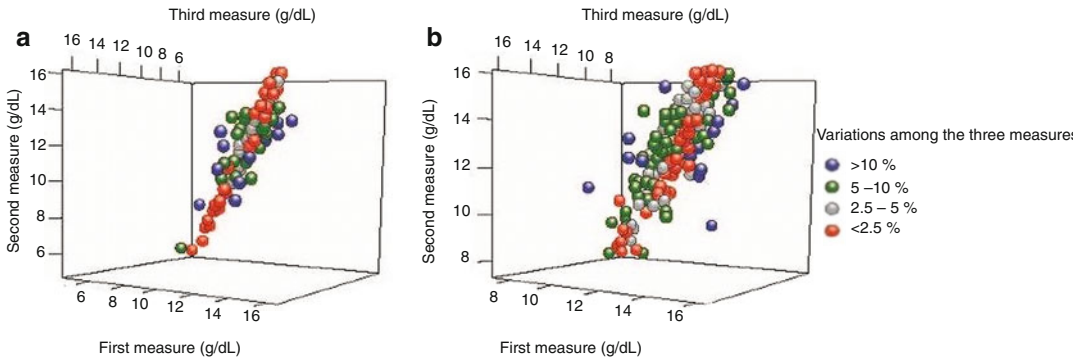

Fig. 36.3 Three-dimensional representation of the variability of the measures obtained with the two monitors. Results for the Pronto-7 are displayed on the panel (**a**) and for the OrSense on the panel (**b**). The coordinates of each point are the three consecutive measures. The graphical representation shows that the OrSense monitor seems to be associated with a higher variability compared to the Pronto-7. This is confirmed by the fact that variations among the three consecutive measurements was lower than 2.5 % in 71 % of the cases when using the Pronto-7 monitor but only in 47 % of the cases when using the OrSense monitor

methods due to the sources of variation inherent to each method. This calls into question the use of the term "accurate" versus "agreement" when comparing one method to another. The use of difference reference methods, sampling techniques, and sources of blood makes it problematic to compare results between studies as well. Few comparison studies have used the international gold standard reference method for hemoglobin measurement, the cyanmethemoglobin assay [29], because it is labor-intensive, expensive, and requires the use of toxic chemicals.

Scientific innovations and continuing improvements in existing technologies have vastly expanded noninvasive patient monitoring in the past decade. Both intermittent spot check measurements and continuous monitoring of total hemoglobin can now been accomplished noninvasively, improving patient safety and comfort. Although invasive measurements may still be necessary to confirm some noninvasive values, continuous monitoring of total hemoglobin concentration has the potential to detect sudden changes in hemoglobin due to occult bleeding and prevent unnecessary transfusions or overtransfusions, both of which increase health care costs and patient morbidity.

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Monitoring of O_2 Uptake and CO_2 Elimination During Anesthesia and Surgery

37

Peter H. Breen and Abraham Rosenbaum

Introduction

In some areas of medicine, metabolic monitoring and interpretation are advanced. For example, in the critical care medicine unit, pulmonary uptake of oxygen ($\dot{V}_{O_2}$) and elimination of carbon dioxide ($\dot{V}_{CO_2}$) are used to ensure adequate tissue metabolism and drive nutrition therapy. In the exercise physiology environment, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are measured during treadmill or bicycle exercise to determine exercise capacity and tolerance and to specifically determine the anaerobic threshold (AT), the point at which metabolic demands require the addition of anaerobic metabolism to aerobic metabolism. In both of these environments, there are mature measurement modalities to determine airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.

In contrast, there is a dearth of knowledge in the anesthesia community about tissue metabolism, and the relationship between tissue $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ and indirect calorimetry, the estimation of these parameters by measurement of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Metabolic monitoring during anesthesia is mostly confined to two areas: First, the inspired O_2 fraction ($F_{I_{O_2}}$) is monitored to preclude the delivery of a hypoxic gas mixture to the patient. Second, the tidal P_{CO_2} (capnogram) is monitored to ensure a patent airway and to estimate the alveolar P_{CO_2} ($P_{A_{CO_2}}$) by the end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) [1], with little thought to the relationship that $P_{A_{CO_2}}$ is proportional to the ratio of tissue $\dot{V}_{CO_2}$ production and alveolar ventilation ($\dot{V}_A$) [2, 3]. Malignant hyperthermia, with acute and significant increase in production of tissue $\dot{V}_{CO_2}$ is a gross example of how the increased $P_{ET_{CO_2}}$ (given no increase in $\dot{V}_A$) represents the increase in tissue metabolism [1, 2, 4].

We believe that the main reason for the lack of understanding of indirect calorimetry during anesthesia is that the accurate measurement of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are challenging in the rebreathing anesthesia ventilation circle circuit. As a consequence, there are few if no measurement devices for indirect calorimetry in the operating room. This is quite remarkable considering the breadth of anesthesia monitoring technologies available to us during anesthesia. The anesthesia machine, ventilator, standard monitors, and advanced monitors (including modalities such as transesophageal echocardiography and cardiac output estimation from arterial pressure waveforms) represent monitoring technologies that cost into the six figures. Yet, we do not routinely monitor the most essential parameter of tissue wellness, which is the maintenance of

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normal aerobic tissue metabolism as evidenced by normal tissue $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and the calculated respiratory quotient ($RQ = \dot{V}_{CO_2} / \dot{V}_{O_2}$).

We believe that the anesthesiologist should be interested in the measurement of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ for three major reasons: First, airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ may quickly and noninvasively detect non-steady-state perturbations that frequently occur during anesthesia and surgery [2]. For example, an abrupt decrease in cardiac output ($\dot{Q}_T$) and venous return causes an acute decrease in $P_{ET_{CO_2}}$ and airway $\dot{V}_{CO_2}$ (and $\dot{V}_{O_2}$). Second, airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ may provide first detection of onset of anaerobic lactic acid metabolism during anesthesia and surgery [5–7]. Third, we believe that there is a relationship between values of tissue $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ and the level of anesthesia depth.

Some of the basic technologies required to measure airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the operating room are already available to us, such as the measurement of airway flow ($\dot{V}$) and the measurement of O_2 and CO_2 gas fractions (F_{O_2} and F_{CO_2}) by sidestream sampling. To the extent that we can develop measurement technologies that accurately measure indirect calorimetry during anesthesia and surgery, then these monitors of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ will be available to all patients undergoing anesthesia, will be inexpensive, will be completely noninvasive, and will pose no risk to the patient (excepting misinterpretation of data).

In this short chapter, we briefly present our approach to the engineering technologies, interpretation, and future potential of the measurement of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and RQ during anesthesia and surgery. The interested reader is referred to the cited references for in-depth analysis and comparison to the literature.

Pitfalls in the Measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ During Anesthesia

Pulmonary O_2 update is given by

$$\dot{V}_{O_2} = \dot{V}_I \cdot F_{I_{O_2}} - \dot{V}_E \cdot FE_{O_2} \qquad (37.1)$$

where $\dot{V}_I$ and $\dot{V}_E$ are the inspired and expired minute volumes and $F_{I_{O_2}}$ and FE_{O_2} are the inspired and mixed expired O_2 fractions [6, 8, 9]. For $\dot{V}_{O_2}$, separate measurement of both $\dot{V}_I$ and $\dot{V}_E$ leads to substantial error because $\dot{V}_{O_2}$ is a small number calculated as the difference of two large values (inspired $\dot{V}_{O_2}$ and expired $\dot{V}_{O_2}$) [9]. To accurately measure this difference, most airway flowmeters lack sufficient precision and zero stability, and the extra volume in expired gas, due to increased warmth and added humidity compared to inspired gas, must be measured [9]. To address these problems in the critical care and exercise physiology arenas, the Haldane transformation is utilized, which invokes the conservation of the inert gas nitrogen during steady state ($\dot{V}_I \cdot F_{I_{N_2}} = \dot{V}_E \cdot FE_{N_2}$). By solving for $\dot{V}I$ and substitution into Eq. 37.1,

$$\dot{V}_{O_2} = \dot{V}_E \left(F_{I_{O_2}} \cdot FE_{N_2} / F_{I_{N_2}} - FE_{O2} \right). \qquad (37.2)$$

$\dot{V}_{CO_2}$ is derived in a similar fashion [10, 11]. Nitrogen fractions are usually determined by subtraction of F_{O_2} and F_{CO_2} from unity [9], assuming that no other gas species (such as anesthesia gases) are present.

In the critical care medicine unit, $\dot{V}_{O_2}$ is easily determined by an exhaled $\dot{V}$ measurement, a mixed collection of expired gas from the patient (e.g., Datex Deltatrac II Metabolic Monitor; Datex Instrumentarium, Helsinki, Finland [7, 8]) or from the expiratory port of the open circuit non-rebreathing ventilator and by a measurement of $F_{I_{O_2}}$. During anesthesia, the measurement challenges become immense because the mostly rebreathing circle anesthesia circuit returns most of the last exhalation (minus the CO_2 removed by the absorber) to form the next inspiration [6, 12]. Then, there is no way to collect mixed expired gas fractions. Furthermore, gas temperature and humidity are greater in expired than inspired gas and can change significantly during the course of ventilation during anesthesia [13]. Errors in humidity and temperature can significantly affect the determination of inspired and expired volumes and thus cause errors in the measurement of $\dot{V}_{O_2}$ [9].

Our Approach to Measure $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ During Anesthesia

Bymixer-Flow Measurements

The key challenge is how to measure mixed expired gas concentrations in the anesthesia circle circuit.

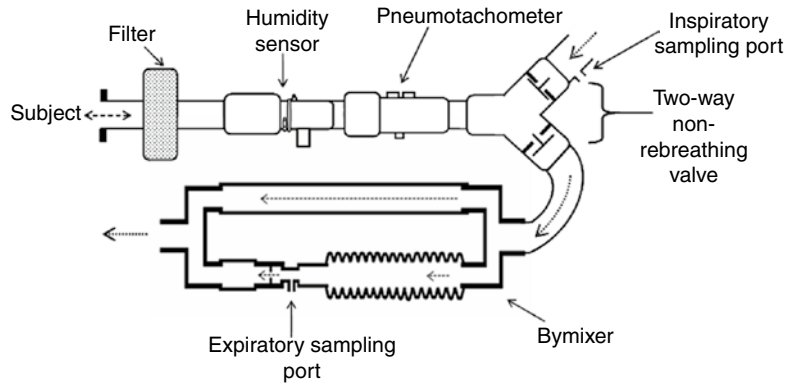

Fig. 37.1 Bymixer used in the specially designed indirect calorimetry apparatus to measure airway O_2 uptake ($\dot{V}_{O_2}$) and CO_2 elimination ($\dot{V}_{CO_2}$) in spontaneously breathing awake patients. The patient breathed through the filter (to prevent contamination), the fast response temperature and humidity sensor (for STPD correction), the pneumotachometer cuvette (to measure gas flow), and the non-rebreathing valve. This valve connected the inspiratory arm inlet and the expiratory arm outlet (incorporating the bymixer). The non-rebreathing valve is depicted during the expiratory phase (Reprinted with permission from Rosenbaum and Breen [14])

To this end, we have invented and developed an implementation of the bymixer (US Patent #7,793,659) [6–8, 14–16], an in-line flow-averaging hydraulic gas mixer (Fig. 37.1). The bymixer diverts a constant proportion of the main flow (upper channel) through an adjustable mixing chamber (bottom channel) which then returns to the main flow. Then, gas sampled from the mixing chamber provides flow-averaged mixed gas fractions. Changes in the size of the mixing chamber and of the resistor (that controls the proportion of bypass flow) determine the response time of the bymixer. The resistor is located immediately downstream (to the left) of the expiratory sampling port (see Fig. 37.1). The bymixer can be easily interpolated into the expiration limb of the anesthesia circle circuit (Fig. 37.2) [6]. We have demonstrated that inspired gas concentrations can vary significantly during inspiration in the circle circuit. Accordingly, we also interpose a bymixer in the inspiratory limb of the anesthesia circle circuit. The bymixers, coupled with an accurate flow sensor at the airway opening or on the expiration limb of the circle circuit, generate accurate bymixer-flow measurements of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. We have also developed a spontaneous ventilation apparatus [7] that incorporates the bymixer-flow apparatus, appropriate for measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in awake breathing patients (see Fig. 37.1).

Breath-by-Breath Measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$

An alternate approach to determine mixed expired and inspired gas fractions is to accurately measure flow with respect to time at the airway opening while simultaneously measuring the F_{O_2} and F_{CO_2} of the gas flow. Using CO_2 as an example, at every time interval, dt (usually 5–10 ms), $\dot{V}(t)\ F_{CO_2}(t)\mathrm{d}t$ is the small volume of CO_2 that has entered or exited the airway. The integration of this term over one breath will yield the overall V_{CO_2} per breath [10, 12, 17, 18]. Since the gas fractions are measured by sidestream sampling at the airway opening through a long tube to a measurement bench (with inherent transport and response delays [1, 4, 17–19]), the temporal synchronization of the flow and gas fraction signals is mandatory and challenging [17], especially for $\dot{V}_{CO_2}$. Furthermore, gas volumes must be corrected to standard temperature and pressure dry (STPD) by the values measured by the fast response airway humidity and temperature sensor [9, 11] (see next paragraph). To date, breath-by-breath devices, such as the Datex-Ohmeda M-COVX Airway Module (GE Healthcare, Madison, WI), may have inaccuracy [6, 20] and are not commonly used in the anesthesia environment.

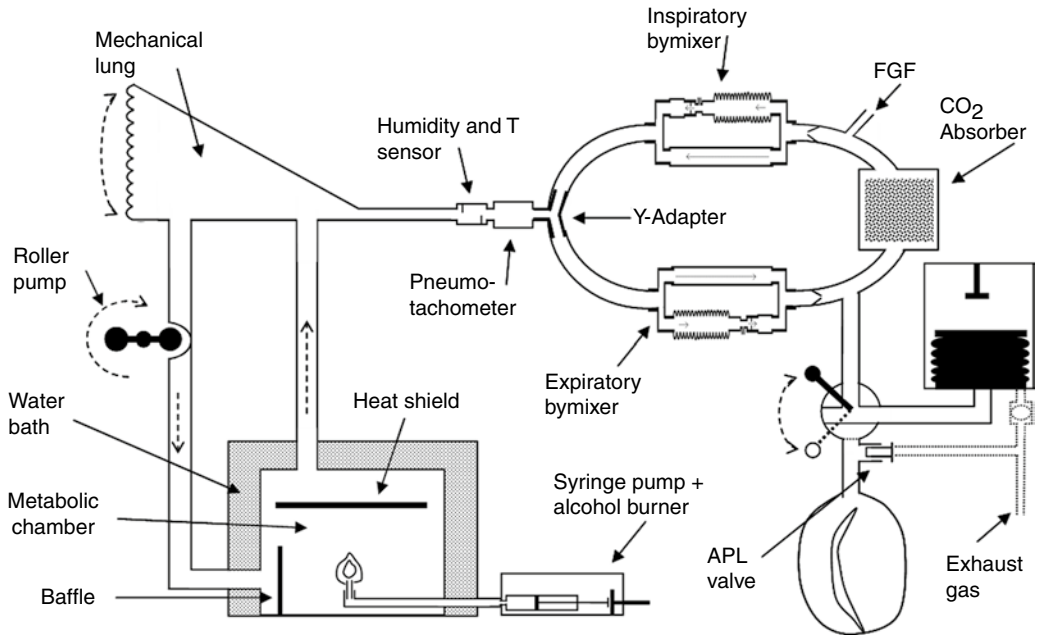

Fig. 37.2 Validation of the bymixer-flow measurement in the anesthesia semi-closed circle circuit by the metabolic lung simulator. Bymixers (in-line mixing chambers) were placed on both the inspiratory and expiratory limbs. *T* temperature, *FGF* fresh gas flow, *APL* adjustable pressure limiting (With kind permission from Springer Science + Business Media: Rosenbaum et al. [6])

Correction for Humidity and Temperature

To address the different and changing values of inspired and expired humidity and temperature (*T*) [13], we have invented and developed a fast response airway sensor of humidity and *T* (US Patent #6,014,890) (Fig. 37.3) [5, 21]. A dry thermocouple (label B) rapidly measures changes in gas *T* (dry *T*). A wet thermocouple (label A) measures humidity by the psychrometry principle, whereby evaporation of water cools the wet thermocouple below the dry *T*. The addition of the airway humidity and *T* sensor significantly improves the bymixer-flow (Haldane principle) measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ [5–8]. For breath-by-breath measurements or when $\dot{V}_I$ and $\dot{V}_E$ are each measured in the bymixer-flow method, then determinations of inspired and expired *T* and humidity are mandatory; otherwise humidity and *T* errors in the measurement of the large inspired and expired volumes become amplified in their difference (small volume of V_{O_2} per breath) [4, 9, 11, 17].

Validation of the Bymixer-Flow Measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$

To validate the bymixer-flow measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, we developed a metabolic lung simulator (MLS) (see Fig. 37.2) [22]. A mechanical lung is connected by a circular circuit to a metabolic chamber. A precision infusion pump meters pure ethanol into the metabolic combustion chamber to generate precise and variable values of reference $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Two roller pumps circulate gas between the mechanical lung and the metabolic chamber. The ventilation circuit (incorporating the inspired and expired limb bymixers, the airway flow sensor, and the fast response humidity and *T* sensor) is attached to the mechanical lung [6–9]. Figure 37.2 depicts the circle anesthesia circuit attached to the MLS [6]. Accordingly, the MLS provides calibrated and adjustable values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ over a wide range of ventilatory parameters.

Figure 37.4 demonstrates the excellent correlation of bymixer-flow measurements of airway $\dot{V}_{O_2}$

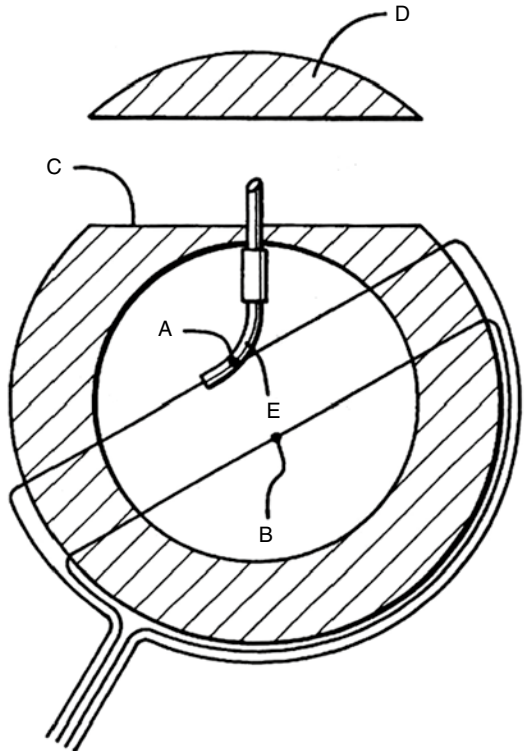

Fig. 37.3 Axial cross-section view of the humidity sensor (US Patent #6,014,890). Two tiny thermometers (copper-constantin thermocouples) (*A*, *B*) were mounted across the lumen of the common airway adapter (*C*). A water reservoir (*D*) supplied a continuous flow of water through dialysate tubing (*E*) to maintain a water envelope around thermocouple A to measure wet temperature (*T*). The other dry thermocouple (B) measured the gas *T*. With a decrease of the relative humidity (RH) of gas flowing through the airway adapter, evaporation from the wet thermocouple decreased wet *T* below dry *T* (psychrometry principle) (Reprinted from Breen [21])

and $\dot{V}_{CO_2}$ compared with the stoichiometric values with an anesthesia circle circuit (see Fig. 37.2) [6]. Limits of agreement analysis generated percent errors (mean ± 1.96 SD) of 2.5 ± 9.8 % for $\dot{V}_{O_2}$ and −1.2 ± 7.2 % for $\dot{V}_{CO_2}$. Using the MLS, we found similar excellent validation of bymixer-flow measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during ventilation with the open non-rebreathing ventilation circuit [5, 8] and during ventilation with the spontaneous breathing apparatus for awake patients (see Fig. 37.1) [7]. There is no gold standard reference measurement of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ for patients under anesthesia ventilated with the anesthesia circle circuit. Accordingly, the rigorous validation of the bymixer-flow system measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ against the MLS was mandatory. The MLS also encompasses basic features of mammalian gas kinetics ("central lung connected by $\dot{Q}_T$ and venous return to peripheral metabolism") [22], which allows the bench testing of non-steady-state perturbations (e.g., abrupt decrease in roller pump "$\dot{Q}_T$").

Clinical Rationale to Measure $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ During Anesthesia

We believe that there are at least three main areas of clinical interest for the measurements of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during anesthesia and surgery.

Non-Steady-State Gas Kinetics During Anesthesia

There are many acute perturbations during anesthesia and surgery that cause immediate changes in airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. For example, during an experimental abrupt decrease in cardiac output ($\dot{Q}_T$) (Fig. 37.5) [3, 23], the airway $\dot{V}_{CO_2}$ and $P_{ET_{CO_2}}$ decrease because the decrease in venous return reduces CO_2 delivery from the peripheral tissues to the lung. The lung functions as a mixing chamber in which $P_{A_{CO_2}}$ decreases because CO_2 delivery from tissues to lung decreases while the level of minute ventilation remains constant. At the same time, the simultaneous reduction in pulmonary perfusion pressure (due to reduction in $\dot{Q}_T$) increases the amount of high alveolar ventilation-to-perfusion ($\dot{V}_A / \dot{Q}$) lung units [1, 4]. The exhalation from high $\dot{V}_A / \dot{Q}$ lung units contains less CO_2 which dilutes $P_{ET_{CO_2}}$ below $P_{A_{CO_2}}$ [23–25]. The respective oxygen variables behave in an analogous fashion [2, 11, 26]. If the reduction in $\dot{Q}_T$ is sustained, the recovery of airway $\dot{V}_{O_2}$ is faster than the recovery of $\dot{V}_{CO_2}$, because the peripheral stores of CO_2 in the body are much greater than the stores of O_2.

We have developed a numerical analysis model of mammalian gas kinetics during

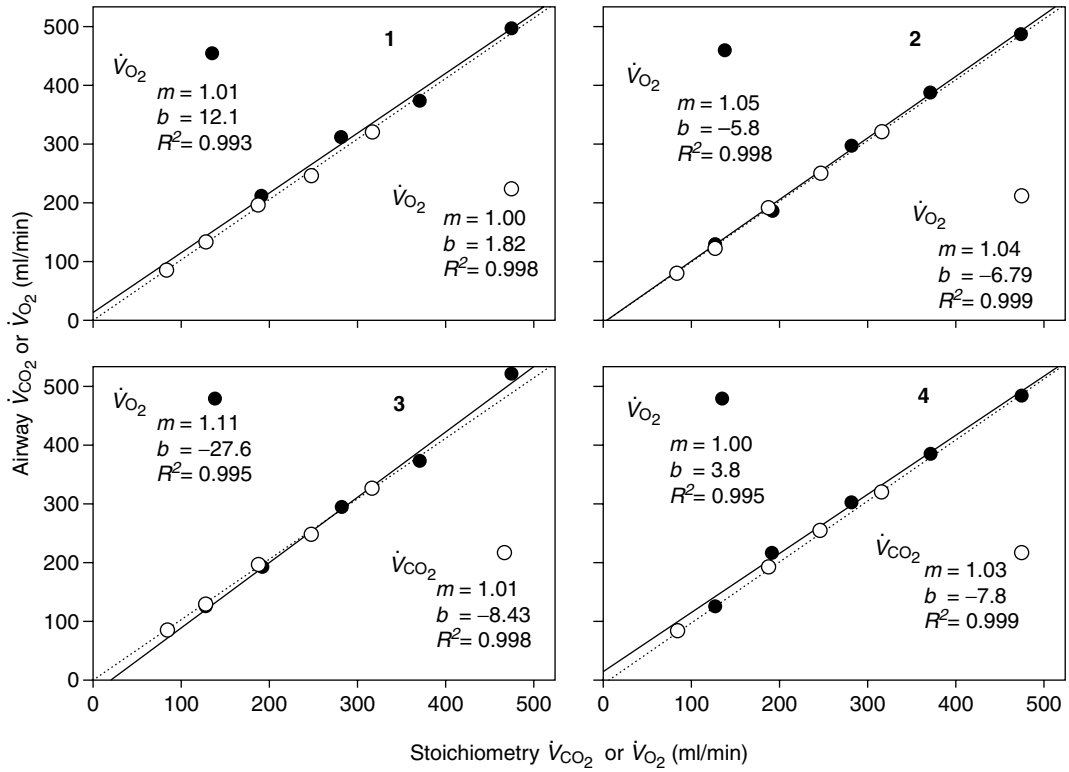

Fig. 37.4 Circle anesthesia circuit. Linear regression of bymixer-flow measurements of CO_2 elimination ($\dot{V}_{CO_2}$, *open circles*, and *dotted lines*) and O_2 uptake ($\dot{V}_{O_2}$, *solid circles*, and *lines*) versus the stoichiometric values generated by metered ethanol combustion in the metabolic lung simulator (MLS). Each panel (1-4) is a separate experiment. *m* slope, *b* Y intercept, and R^2 coefficient of determination (Reprinted with permission from Rosenbaum and Breen [14])

non-steady state [23], which encompasses a five-compartment lung model spanning the clinical range of $\dot{V}_A/\dot{Q}$ abnormalities (pulmonary shunt, low $\dot{V}_A/\dot{Q}$ or venous admixture, normal lung, high $\dot{V}_A/\dot{Q}$, and infinite $\dot{V}_A/\dot{Q}$ or alveolar dead space). The central lung compartment is connected to the peripheral tissue compartment through $\dot{Q}_T$ and venous return. Figure 37.6 displays model data for the effects of abrupt and sustained decrease in $\dot{Q}_T$ similar to the preceding paragraph. This gas kinetics model has been useful to elucidate mechanisms underlying observed data, to test new hypotheses, and to conduct virtual experiments that cannot be studied in patients or are too difficult to control in experimental animals.

The interested reader is referred to other studies that involve acute perturbations that acutely affect airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, including application of positive end-expiratory pressure (PEEP) [18, 24, 27, 28], onset of pulmonary embolism [29], relief of pulmonary embolism [25], onset of combined carbon monoxide and cyanide poisoning [11, 30, 31], bronchial flap-valve obstruction [26, 32], and leaking inspiration valve in the circle circuit [33]. Better understanding of how airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ change during these acute perturbations should be able to help the clinician with early and non-invasive detection, diagnosis, and management of these conditions. Some non-steady-state principles are already seeping into clinical medicine. For example, the best index of return of spontaneous circulation during cardiopulmonary resuscitation is an increase in $P_{ET_{CO_2}}$ (representing the increase in CO_2 transport from the peripheral tissues to the lung as venous return and $\dot{Q}_T$ increase) [1, 3].

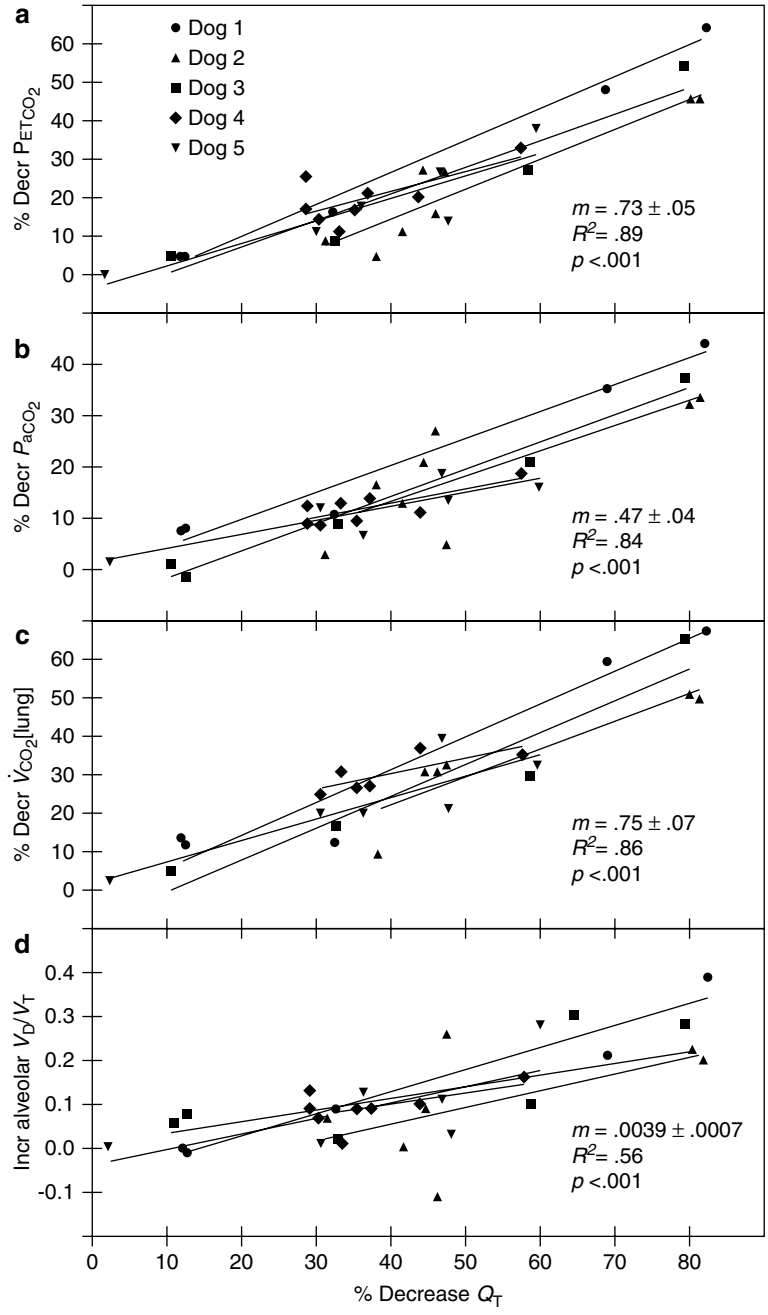

Fig. 37.5 Effects of 32 vena cava balloon inflation sequences in five anesthetized dogs to decrease cardiac output ($\dot{Q}_T$). During each balloon inflation sequence, the *y*-axis variable is correlated against the percent decrease in $\dot{Q}_T$. Panel (**a**) percent decrease in end-tidal P_{CO_2} ($P_{ET_{CO_2}}$). (**b**) Percent decrease in arterial P_{CO_2} (Pa_{CO_2}). (**c**) Percent decrease in pulmonary $\dot{V}_{CO_2}$ ($\dot{V}_{CO_2}[lung]$). (**d**) Arithmetic increase in alveolar dead space/tidal volume ratio (V_d/V_t). The linear regression line for each dog is shown. *m* average (±SD) slope for five dogs, R^2 coefficient of determination (Reprinted with permission from Isserles and Breen [3])

Can Indirect Calorimetry First Detect Onset of Anaerobic Lactic Acidosis?

During exercise physiology testing, as workload increases (treadmill or bicycle ergometer), aerobic metabolism increases and airway $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ rise together. Then, the plot of $\dot{V}_{CO_2}$ versus $\dot{V}_{O_2}$ generates a straight line of slope equal to $RQ = \left(\dot{V}_{CO_2} / \dot{V}_{O_2}\right)$ (Fig. 37.7) [34]. At a point on the line called the anaerobic threshold (AT), further exercise demand requires the addition of anaerobic metabolism, which generates more $\dot{V}_{CO_2}$ and the slope of the line and RQ increases [11].

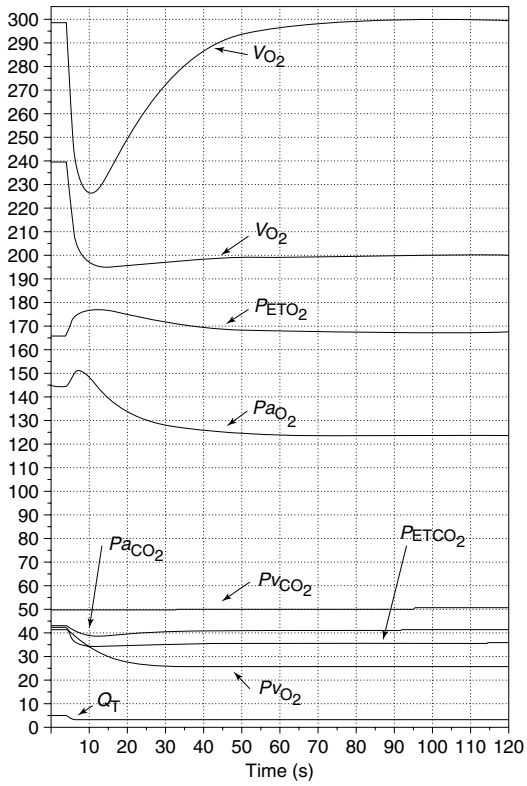

Fig. 37.6 Numerical analysis model of non-steady-state gas kinetics, showing the effects of an abrupt reduction in cardiac output ($\dot{Q}_T$) from 5 to 2.5 L/min. Length of *y*-axis is 120 s. $\dot{V}_{O_2}$, pulmonary O_2 uptake (ml/min); $\dot{V}_{CO_2}$, pulmonary CO_2 elimination (ml/min); $P_{ET_{O_2}}$, end-tidal P_{O_2}; Pa_{O_2}, arterial P_{O_2}; $P_{\bar{v}_{CO_2}}$, mixed venous P_{CO_2}; Pa_{CO_2}, arterial P_{CO_2}; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; and $P_{\bar{v}_{O_2}}$, mixed venous P_{O_2} (all partial pressures, *P*, are in mmHg) (Reprinted from Breen)

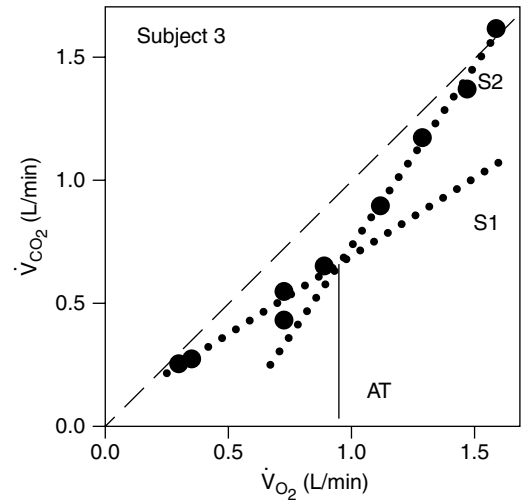

Fig. 37.7 Bymixer-flow measurements (see Fig. 37.1) of pulmonary CO_2 elimination ($\dot{V}_{CO_2}$) plotted against O_2 uptake ($\dot{V}_{O_2}$) in an untrained subject during increasing exercise load. *S1* and *S2* are linear regression lines. The anaerobic threshold (*AT*) is the $\dot{V}_{O_2}$ when the slope of $\dot{V}_{CO_2} / \dot{V}_{O_2}$ increases (Reprinted from Rosenbaum and Breen [35])

Of course, patients under anesthesia and surgery are not exercising. In fact, early data (see below) suggests a reduction in airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ under anesthesia. Thus, when patients under anesthesia and surgery suffer from anaerobic lactic acidosis, there must be regional and/or global hypoperfusion of tissues [35].

In a study modeling regional hypoperfusion of tissues, we measured bymixer-flow $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in three anesthetized patients before and after release of a leg tourniquet during orthopedic surgery [36]. We hypothesized that tourniquet inflation and leg ischemia would cause regional anaerobic lactic acidosis. Upon tourniquet release, we expected airway $\dot{V}_{CO_2}$ and $\mathrm{RQ}\left(\dot{V}_{CO_2} / \dot{V}_{O_2}\right)$ to increase. Upon tourniquet release, there were abrupt increases in $\dot{V}_{O_2}$ (35±6 %) and $\dot{V}_{CO_2}$ (28±14 %) in all patients. *RQ did not increase* because the increase in $\dot{V}_{O_2}$ was greater than the increase in $\dot{V}_{CO_2}$. After tourniquet release, the increase in airway $\dot{V}_{O_2}$ represented the increased O_2 consumption of the ischemic tissue, enhanced by the shift of the oxyhemoglobin dissociation curve to the right and vasodilatation in the tissues. The recovery (decrease) of $\dot{V}_{O_2}$ towards the pre-tourniquet release value occurred in about 5 min. The recovery of $\dot{V}_{CO_2}$ was much slower because of buffering by blood and the higher tissue storage of CO_2 [29].

Another study examined global hypoperfusion of tissues. Currently, the presence of anaerobic lactic acidosis under surgery is assessed by intermittent arterial blood gas analysis and calculation of the base deficit (BD, difference between the calculated HCO_3 concentration and the normal value of 24 mM/L after the blood P_{CO_2} has been algorithmically tonometered to its normal value of 40 mmHg) [37]. We have conducted preliminary studies in three anesthetized patients undergoing long liver surgeries (about 500 min) [38].

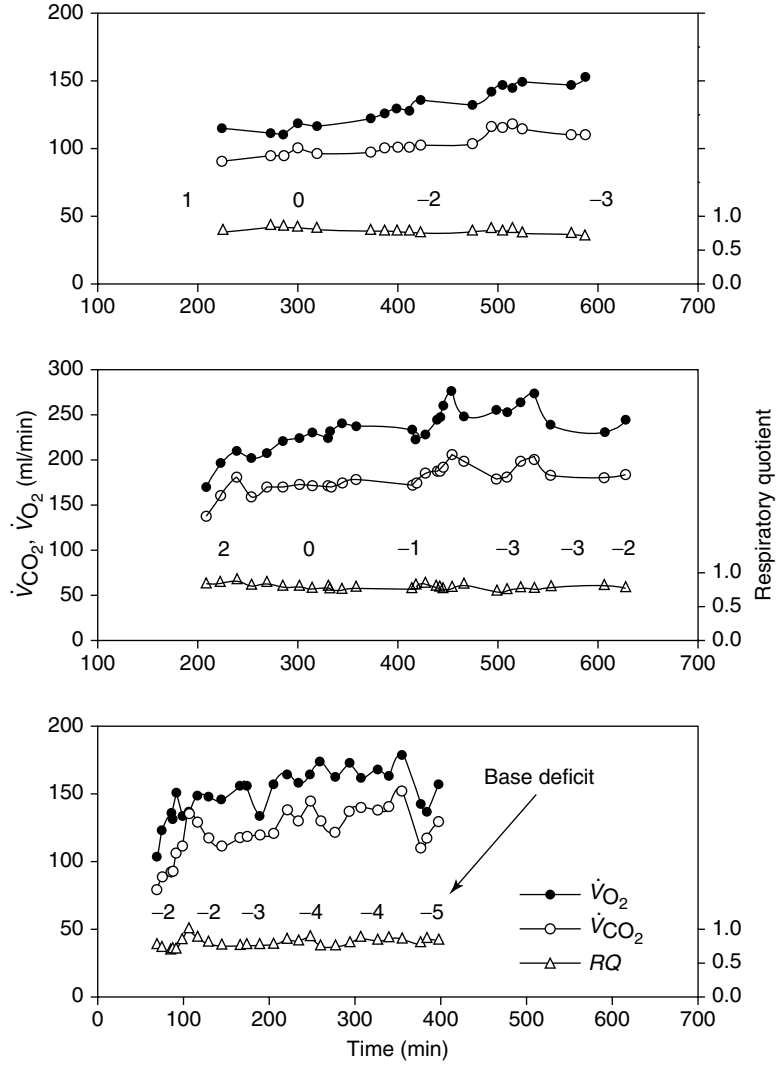

Fig. 37.8 Bymixer-flow measurements of pulmonary O_2 uptake ($\dot{V}_{O_2}$) and CO_2 elimination ($\dot{V}_{CO_2}$) and respiratory quotient ($RQ = \dot{V}_{CO_2} / \dot{V}_{O_2}$) in three anesthetized patients undergoing long liver surgeries. Base deficit (*BD*) is determined from intermittent arterial blood gas analyses (Reprinted from Beroukhim et al. [39])

BD grew more negative by 4–5 mM/L. Normally, the increase in BD suggests hypovolemia, tissue hypoperfusion, and metabolic lactic acidosis, and the primary anesthesia team delivered continuous fluid resuscitation. To our surprise, simultaneous bymixer-flow measurements of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ did not decrease (and even increased) and the RQ did not increase but remained relatively constant (0.72–0.85) (Fig. 37.8) [38]. These are first data, we believe, strongly suggesting that noninvasive measurements of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ can quickly and noninvasively confirm euvolemia and normal tissue aerobic metabolism despite the development of significant base deficit and can prevent needless fluid administration (including blood products). Other mechanisms for the measurement of base deficit in these patients must be sought, including the possible development of hyperchloremic metabolic acidosis. Further studies are planned to delineate the relationships between anaerobic lactic acidosis and airway measurements of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and RQ [30, 31], including the possibility, in a preoperative assessment, to estimate perioperative risk by identifying the anaerobic threshold (AT) during exercise [7].

Effect of Anesthesia on Tissue Metabolism, as Measured by Airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$

Using the bymixer-flow measurement system, we have measured $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ before and after induction of anesthesia [39]. Average (±SD) $\dot{V}_{O_2}$ pre- and post-induction were 3.5 ± 0.7 and 2.1 ± 0.5 ml/kg/min, respectively (40.1 % decrease, $p < 0.05$). Average $\dot{V}_{CO_2}$ pre- and post-induction were 3.1 ± 1.0 and 1.8 ± 0.4 ml/kg/min, respectively (40.6 % decrease, $p < 0.05$). Over anesthesia induction, the respiratory exchange ratio (RER = airway $\dot{V}_{CO_2} / \dot{V}_{O_2}$) remained stable (0.87 ± 0.15). These dramatic decreases (about 40 %) in airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were sustained throughout the post-induction period until surgical incision. The sustained decreases in airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ and the constant RER support a reduction in metabolic rate rather than a decrease in $\dot{Q}_T$. We plan further studies to delineate the relationships among anesthesia depth and tissue metabolism as measured by airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Other factors that can affect tissue metabolism must be considered, including the degree of surgical stimulation and the level (if any) of neuromuscular blockade [17].

Conclusion

As detailed in the three numbered sections above, we believe that the bymixer-flow measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ (and the calculated value, $RQ = \dot{V}_{CO_2} / \dot{V}_{O_2}$) may noninvasively and quickly detect non-steady-state perturbations (such as an abrupt decrease in cardiac output) during anesthesia and surgery and may offer a window into the state of metabolism and tissue wellness. We plan to test the hypothesis that indirect calorimetry measurements of airway $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ will help diagnose and drive treatment of these pathophysiology perturbations and improve patient outcome.

For example, one implementation of goal-directed fluid management is to administer fluid volume to maintain the stroke volume variation (SVV, the decrease in stroke volume induced by increased thoracic pressure during mechanical ventilation) less than 13 %. But is this increase in cardiac output what the patient needs? Perhaps the "goals" of goal-directed fluid management should be reconsidered. We hypothesize that a better endpoint may be airway measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ which can estimate the global level of tissue metabolism and can specifically seek an increase in the RQ, which might reflect onset of anaerobic lactic acidosis.

We suggest that the current developments to measure indirect calorimetry during anesthesia may have parallels to the development of pulse oximetry. Development of pulse oximetry has epitomized the maximal extraction of patient information from a noninvasive measurement, which now includes measurements of methemoglobin, carboxyhemoglobin, and hemoglobin, as well as indices of peripheral tissue perfusion. In a similar fashion, we predict that airway measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ will provide the "missing link" to metabolic monitoring during anesthesia. As researchers and clinicians gain more experience with these indirect calorimetry data, we believe that other clinical physiologic and pathophysiologic relationships will be discovered.

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Gastric Tonometry

38

William T. Costello

Introduction

The care of the critically ill patient calls for the integration of complex monitors and interventions in pursuit of a common goal: the prevention or reversal of tissue ischemia. Gastric tonometry is the indirect measurement of gastric intramucosal pH (pHim), abnormalities in which may provide insight into the degree of splanchnic tissue ischemia [1]. Tissue ischemia occurs most frequently when an illness or injury leads to an imbalance between oxygen delivery (DO_2) and oxygen consumption (VO_2). A majority of commonly used DO_2 monitors measure global DO_2 through the assessment of cardiac output and some measure of hemoglobin oxygenation. This approach provides limited insight into the heterogonous distribution of DO_2. Complications may result from tissue ischemia in specific at-risk capillary beds, for instance, and this may not be reflected in the global assessment of DO_2. In addition, many of these technologies are expensive, invasive, and associated with a significant risk of injury or infection. Gastric tonometry is an inexpensive, minimally invasive monitor of tissue oxygenation in an anatomical location with high risk for complications associated with tissue ischemia.

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Background

Animal studies dating back to the early 1980s indicated that preservation of global DO_2 did not reliably prevent splanchnic tissue hypoxia in the setting of acute hypovolemia [2, 3]. This was attributed to regional regulation of the splanchnic vasculature. In these studies, gastric mucosal pH was decreased, despite what would have been considered adequate volume resuscitation, as indicated by normal heart rate, blood pressure, central venous pressure, cardiac output, and calculated DO_2. This finding was also observed early human studies [1, 4–7]. Many have postulated that splanchnic tissue ischemia, when unmonitored and often inadequately treated, may lead to bacterial translocation into the bloodstream and subsequently to sepsis syndromes.

Equipment

The equipment necessary to measure pHim is relatively inexpensive and noninvasive compared to other common ICU monitors. A nasogastric (NG) tube is placed in the mid-gastric position with a silicone balloon, permeable to CO_2, located at the tip. The balloon is filled with normal saline, and samples are drawn at the proximal end. The sample is analyzed for CO_2 tension by a standard arterial blood gas analyzer. Alternatively, the balloon can be filled with air, and the pCO_2 analyzed semi-continuously by infrared spectroscopy. The calculation of pHim also requires the ability to

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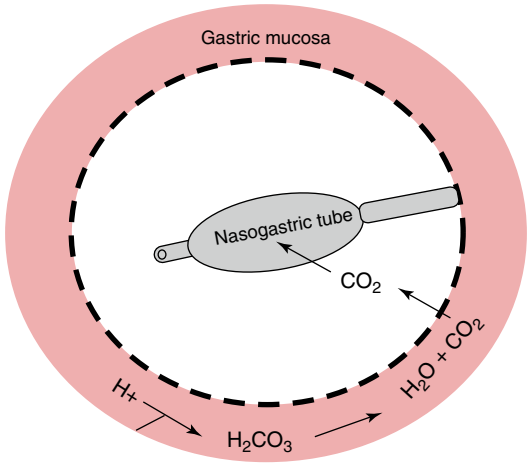

Fig. 38.1 Nasogastric tube equipped with balloon permeable to CO_2 positioned in the gastric lumen. CO_2 created from H+buffering by carbonic acid in diffuses into the balloon. Samples drawn are used to calculate pHim

measure arterial HCO_3^-, which is most commonly accomplished by arterial blood gas analysis (Fig. 38.1).

Interpretation

Determination of pHim is based on the assumption that CO_2 in the stomach lumen is the result of HCO_3^- buffering in the intraluminal serum, as represented in the equation $H^2 + HCO_{3-} \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$. The CO_2 then diffuses freely into the balloon-tipped catheter, while the HCO_3^- is carried by the mucosal capillaries into the serum. The Henderson-Hasselbalch acid/base equation is applied, using the pCO_2 value from the sample and arterial HCO_3^- as follows:

$$\text{pHim} = \log\left[\text{HCO}_3^-\right](\text{arterial}) / 0.03 \times \text{pCO}_2\,(\text{gastric})$$

A pHim value of 7.35 or greater is considered normal, while an acidic pH of less than that is associated with inadequate regional DO_2. This assumes that CO_2 and arterial HCO_3^- equilibrate freely across the gastric mucosal epithelium and that there is no additional creation of CO_2 in the gastric lumen from the interaction between secreted H^+ and exogenous HCO_3^-. The impact of this confounding factor can be limited through the use of an H2-receptor blocker, such as ranitidine [4].

Safety

Gastric tonometry monitors are safe compared to other measurements of tissue ischemia. NG tubes are commonly placed in critically ill patients for the administration of enteral nutrition and medications, as well as for the prevention of aspiration in mechanically ventilated patients. The rate of complications is low, ranging from 0.3 to 8 % [8], and most complications are minor, though reports of fatal complications associated with NG tube placement do exist. No published data exists currently on the specific rate of NG tubes equipped with a balloon for pHim monitoring.

Since the calculation of pHim requires the simultaneous measurement of serum HCO_3^-, special care should be taken to limit the number of unnecessary blood draws. The mere presence of an arterial cannula has been shown to lead to anemia in the ICU [9].

Compared to more frequently utilized hemodynamic monitors, such as arterial and pulmonary artery catheters, and transesophageal echocardiography, gastric tonometry is relatively noninvasive. Misinterpretation of the tonometric data likely poses the greatest risk to the patient, but no published study has shown an increase in morbidity or mortality associated with this modality.

Prognostic Value

Multiple studies have shown prognostic value in the use of gastric tonometry in the critically ill. In 1993, Maynard et al. studied 83 patients admitted to the ICU with a mean APACHE II score of 20.9 using gastric tonometry. Initial pHim value was statistically more sensitive for predicting death than arterial pH, lactate concentration, calculated DO_2, base excess, mean arterial pressure, and heart rate, and pHim at 24 h was the only statistically

significant independent predictor of mortality [1]. This has also been validated in critically ill trauma patients [5].

Guide for Resuscitation

The evidence for the use of gastric tonometry as a guide for therapy is significantly weaker. Gutierrez, et al. demonstrated a significant improvement in the 28 day mortality for the subgroup of patients admitted to the ICU with a pHim >7.35 when resuscitation was guided by gastric tonometry. No significant difference was observed between the gastric tonometry and control groups if the admission pHim was <7.35 [6]. Multiple follow-up studies have been done comparing the outcomes for critically ill patients whose resuscitations were targeted at the correction of pHim [10–12]. No statistically significant difference was observed in any of these studies; though the ability to predict outcomes based on early low pHim was observed repeatedly. Levy et al. observed that septic shock patients treated with epinephrine were more likely to develop a low pHim when hypotension was treated with epinephrine vs. a combination of norepinephrine and dobutamine [13]. They concluded that this potentially represented a higher risk for splanchnic ischemia with epinephrine infusion in septic shock. Intraoperatively, gastric tonometry has been used to evaluate and compare the type of volume resuscitation used, where a balanced salt solution was shown to preserve a normal pHim better than resuscitation with normal saline [14].

Conclusion

Gastric tonometry offers information on the adequacy of oxygen delivery in a tissue bed known to be at high risk for ischemia in critically ill patients. This information is not reliably obtained or extrapolated from any other commonly used monitors of DO_2. It has been shown to provide pertinent prognostic information in numerous patient populations, in association with a relatively low cost, both in terms of equipment as well as in the addition of risk to the patient, suggesting value beyond the numerical data. Studies have yet to show that gastric tonometry can be used as an independent guide to improve individual patient outcomes, a finding shared with nearly all other monitors used in these same populations. When applied appropriately, gastric tonometry has the potential to be a valuable addition to the care of critically ill patients.

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Temperature Monitoring

39

Adam B. King and Jesse M. Ehrenfeld

Introduction

Hypothermia is a common iatrogenic complication in acute care environments due to environmental exposure, illness, and the effects of anesthesia or other drugs. For example, during surgery the prevalence of hypothermia is estimated at 50–70 % [1]. Unintended hypothermia is associated with a number of notable adverse events. Intraoperatively, hypothermia may cause increased blood loss and can contribute to increased transfusion requirements [2], prolonged neuromuscular blockade, and increased cardiac morbidity [3]. In the postoperative period, perioperative hypothermia can lead to prolonged recovery in the postanesthesia care unit (PACU) and postoperative shivering, in addition to the aforementioned increased cardiac risk. Iatrogenic consequences can continue to affect the patient in the recovery period as well as unintended perioperative hypothermia is associated with longer surgical wound healing times and increased wound infections. Most medical specialty societies, including The American Society of Anesthesiologists, recommend temperature monitoring when clinically significant changes in body temperature are intended, anticipated, or suspected in an acute care environment [4].

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Normal Body Temperature

Normal body temperature is considered to be 36.8 °C with a normal range between 36.2 and 37.5 °C [5]. There is a diurnal variation in body temperature with a low point early in the morning and a peak in the evening. The sympathetic and parasympathetic nervous work in concert to maintain core body temperature within this typical range as shown in Fig. 39.1. Hypothermia is defined as an oral temperature less than 36 °C. Hyperthermia is defined by a core temperature greater than 38 °C.

Body temperature is thought to be closely regulated by set point theory using a central thermostat. Thermal receptors are located throughout the body. Cold signals are transmitted using small, thinly myelinated Aδ fibers. These Aδ fibers are also responsible for transmission of pressure and nociceptive information. They are involved in the first, sharp pain transmission and sensation of cold. Warm signals are transmitted using small, unmyelinated C fibers. C fibers also transmit nociceptive information but are involved in second pain sensation that is burning in nature. All of these afferent temperature signals converge

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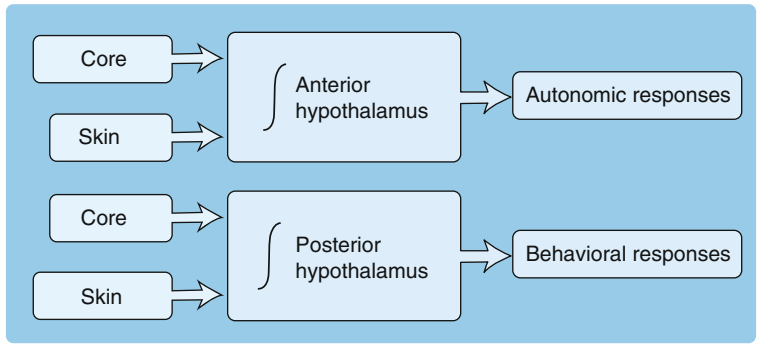

Fig. 39.1 Skin and core temperature contributions to central thermoregulatory control. Core temperatures contribute approximately 80 % to the control of autonomic thermoregulatory responses; mean skin temperature contributes the remaining 20 %. Changes in core temperature are, thus, far more important than those in skin temperature; however, skin temperatures change far more than core temperature and remain important. In contrast to autonomic thermoregulatory responses, which are integrated in the anterior hypothalamus, behavioral responses (e.g., putting on a sweater, opening a window) are integrated largely in the posterior hypothalamus and are determined largely by skin temperature (Reproduced from Sessler et al. [31]; kind permission from Springer Science+Business Media BV)

in the spinothalamic tracts of the anterior spinal cord where they travel to the hypothalamus. The preoptic area of the hypothalamus is believed to be the coordinator of temperature regulation in the brain [6].

In response to hypothermia, cutaneous vasoconstriction occurs which is regulated by the sympathetic nervous system. As a protective mechanism, shivering begins to occur as the body's core temperature continues to decrease. Shivering increases the body's metabolic heat production by an impressive 200–500 % [7].

On the opposite end of the spectrum, the body has also developed innate responses to hyperthermia. An increase in core temperature leads to two different but integrated autonomic responses. The first is sweating and the second is vasodilation of the cutaneous blood vessels. These two mechanisms work in concert to promote heat loss from the surface of the body.

Methods of Heat Transfer

There are four mechanisms of heat transfer across a temperature gradient: *conduction*, *convection*, *evaporation*, and *radiation*. The most common source of heat loss is through radiant heat losses. Radiant heat exchange is a function of surface area. This becomes especially important to take into consideration in the field of pediatrics. Compared to adults, infants have a high surface area to body mass ratio, which makes them particularly vulnerable to radiant heat losses.

The second most common cause of heat loss is through convective losses. Convective losses involve the movement of molecules from a warm to cool area. It is dependent on a temperature differential; an example of this phenomenon is the wind chill effect.

The other two mechanisms of heat transfer are evaporative and conduction. Evaporative heat loss is particularly important during long surgeries with exposed viscera. This causes water to be lost to the surrounding environment. Conduction involves the transfer of heat through direct contact. This can be used to our advantage through the use of heating and cooling blankets.

Effects of Anesthesia on Temperature Regulation

After induction of general anesthesia, unless intentionally intervened upon, a core temperature decrease of 1 °C can occur within the first 40 min. This is thought to occur secondary to peripheral vasodilation leading to heat loss in the extremities [8]. Additionally, during the time period after induction, the patient is usually uncovered and

Table 39.1 Temperature monitoring sites

Temperature monitoring sites	
Core	Peripheral
Pulmonary artery catheter	Skin
Tympanic membrane	Rectal
Esophageal	Bladder
Nasopharyngeal	Axillary

exposed to the cold ambient temperature of the operating room. The combination of these two factors leads to inadvertent hypothermia shortly after induction. In addition, general anesthesia inhibits the ability of the hypothalamus to regulate body temperature.

Intraoperative hyperthermia usually is due to overwarming of the patient. However, more serious causes of hyperthermia such as malignant hyperthermia, mismatched blood transfusions, or an infectious etiology must be considered. Due to the risk for significant morbidity or mortality should these sources of intraoperative hyperthermia go unrecognized, monitoring for hyperthermia is just as important as monitoring for hypothermia.

Temperature Monitoring Devices

There are multiple devices and anatomic sites available for perioperative temperature monitoring. Measurement of core temperature is the best indicator of body temperature. Accurate measurement of temperature is of utmost importance because it may lead to early recognition of hypothermia or even hyperthermia. Most devices used currently are thermistors and thermocouples. See Table 39.1 for temperature monitoring sites.

Thermistors are temperature sensitive thermoconductors. Thermocouples measure the current generated when different metals are joined. Both have been adapted to clinical practice for the measurement of temperature. Additionally, infrared sensors can also be used to detect temperature. Infrared sensors sense the infrared energy emitted from a surface at all temperatures above absolute zero.

Core Temperature Monitors

The pulmonary artery catheter is considered the gold standard for measurement of core body temperature. However, due to the high cost and invasiveness of placement of the catheter, they are reserved for patients that would otherwise require them for hemodynamic monitoring.

Esophageal temperature can be monitored using a thermocouple or thermistor that is incorporated as part of an esophageal stethoscope. It reflects core temperature in a more cost-effective and less invasive method than the pulmonary artery catheter. The optimal position is approximately 45 cm measured from the nose in adults [3]. In addition, they should be positioned at the point of maximal heart sounds for maximum accuracy [9].

Due to their proximity to the brain, nasopharyngeal temperature probes reflect brain and core temperature with reasonable accuracy. Interestingly, in a study of patients undergoing cardiopulmonary bypass, nasopharyngeal temperature was more accurate at reflecting brain temperature during rewarming than cooling [10]. This was thought to be because rewarming is a slower process than cooling.

Tympanic membrane temperatures may be measured using thermocouples or thermistors manually placed against the tympanic membrane. While less invasive than some other core temperature monitoring techniques, this can be uncomfortable in awake patients and even proves at times difficult in patients who are not. Tympanic membrane temperatures can also be taken using an infrared sensor. However, these thermometers usually get directed at a shallow part of the ear canal and do not provide an accurate measurement of core temperature [11]. However, tympanic membrane temperatures can accurately reflect core temperatures if taken correctly.

Peripheral Temperature Monitors

Skin temperature monitors can be used to estimate core body temperature. However, because of the differential between core and peripheral

blood flow, skin temperatures tend to underestimate core temperature. These monitors are also affected by changes in ambient temperatures. Thermoregulatory changes in vasomotor tone leads to cutaneous vasoconstriction, a reduction in skin blood flow and reduction in skin temperature. Additionally, skin and rectal temperatures are unreliable in detecting temperature changes during malignant hyperthermia in swine [12]. One must take this propensity to underestimate core temperature into account when using these peripheral temperature monitors in clinical practice.

Axillary temperature can be an accurate estimate of core temperature. However, the probe must be placed over the axillary artery and the arm must be abducted at all times to maximize precision [13]. This can be a definite drawback to the axillary temperature probe, as maintaining the position of the probe can prove difficult.

Bladder temperature can be measured using a Foley catheter with an attached thermistor or thermocouple. Bladder temperature can give an accurate representation of core temperature. However, during times of low urine output or during surgeries involving the lower abdomen, the accuracy of this site may decrease.

Rectal temperature can be measured by insertion of a thermistor or thermocouple into the rectum. Rectal temperatures are affected by the presence of stool and bacteria in the rectal vault [14]. These confounders tend to cause rectal temperatures to overestimate the true core temperature.

Skin, bladder, rectal, and axillary temperature monitoring can give a reasonable estimate of core body temperature in certain appropriate clinical scenarios. However, if rapid changes in temperature are anticipated, a more accurate measurement of core temperature might be of benefit and preferred to maximize outcomes.

Complications of Hypothermia

Hypothermia affects multiple organ systems within the body and has been shown to correlate with increased mortality rates in trauma patients [15, 16]. This has been further confirmed by a review of 100 noncardiac surgical patients that found that postoperative hypothermia was associated with an increase in mortality [17].

Hypothermia affects the cardiovascular system in multiple different ways. It predisposes the heart to arrhythmias, notably ventricular fibrillation. There is an increase in systemic vascular resistance and therefore afterload with hyperthermia, which increases the work of the heart. One notable study found that the incidence of myocardial ischemia is increased in patients undergoing revascularization of the lower extremity when they experience perioperative hypothermia [18]. The study ultimately concluded that perioperative hypothermia was an independent risk factor for myocardial ischemia. Frank et al. showed that norepinephrine levels were 1.5 times higher than controls in patients with perioperative hypothermia than those who maintained normothermia [19]. Interestingly, these patients also had increased systolic, diastolic, and mean arterial blood pressures upon arrival to the postanesthetic care unit. Frank et al. proposed that the increase in norepinephrine concentrations in hypothermia patients could be responsible for the increase in perioperative myocardial ischemia [19].

Oxygen consumption and whole body metabolic rates are decreased with decreasing temperature. Additionally, there is a leftward shift of the oxyhemoglobin curve with a decrease in body temperature. This shift decreases the amount of oxygen that is off loaded from hemoglobin in the tissues. The decrease in oxygen demand is usually greater than the decrease in supply cause by the shift in the oxyhemoglobin curve. Oxygen consumption decreases about 7 % per °C that core temperature decreases. This can be used to the patient's advantage during cerebral or myocardial ischemia. Induced hypothermia after cardiac arrest has been shown to improve outcomes in select patients [20, 21]. In addition, core temperatures of 18 °C are used during aortic arch surgery to provide cerebral protection [22].

As temperature decreases, there is a prolongation of the prothrombin and partial thromboplastin times. This in addition, the platelet dysfunction caused by decreases in core temperature can lead to coagulopathy [7].

There is triple incidence of wound infections in patients experiencing intraoperative hypothermia [23]. This is thought to occur because of vasoconstriction caused by the decrease in core temperature. This vasoconstriction leads to a decrease in subcutaneous oxygen tension, which has been associated with increased wound infections [24]. A second reason for the increase in wound infection rates is that hypothermia impairs T-cell-mediated antibody production and oxidative bacterial killing by neutrophils [25, 26].

The above complications can lead to significant morbidity. In addition, to these complications, there are also minor complications that can arise. The pharmacology of drugs changes during hypothermia. The duration of action of vecuronium is more than doubled in patients experiencing core hypothermia [27]. Hypothermia also decreases the minimum alveolar concentration of volatile anesthetics by 5 % per °C below normal body temperature [28]. Mild hypothermia is associated with postoperative thermal discomfort and can delay discharge from the PACU [29, 30]. This can lead to a significant increase in hospital costs and decreased operating room efficiency.

Conclusion

Temperature is tightly controlled by the body's autonomic regulatory system to optimize its function from the cellular to organ system level. Derangements in temperature, be it hypothermia or hyperthermia, can cause significant harm and thus needs to be monitored closely. Loss of heat most commonly occurs via radiant and convective losses. Excessive temperature is usually the result of rewarming but can be a red flag for a more ominous condition such as malignant hyperthermia or infection. A number of devices and anatomic locations are available for monitoring purposes, but those reliably reporting core temperature remain standard for cases in which temperature fluctuations are anticipated. Normothermia should be maintained unless otherwise indicated to minimize the impact of temperature derangements on the perioperative well-being of patients.

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Part VI

Other Forms of Monitoring in the Acute Care Environment

Point-of-Care Coagulation Monitoring

40

Michael T. Ganter and Christoph K. Hofer

Introduction

Blood coagulation is a complex, sensitive, and tightly regulated physiological network of interacting cells, proteins, and cofactors [1, 2]. If deranged, it may dramatically influence a patient's outcome. A comprehensive understanding of perioperative hemostasis and its monitoring is a prerequisite for physicians working with patients at risk for major bleeding and thrombosis. The coagulation system represents a delicate balance of forces supporting coagulation (coagulation, antifibrinolysis) and forces inhibiting coagulation (anticoagulation, fibrinolysis). The distinctive challenge for the perioperative physician is to readily assess and judge both sides of this balance, provide an individualized and goal-directed therapy, and maintain homeostasis [3, 4].

Besides patients' medical history, clinical presentation, and routine laboratory-based coagulation tests, bedside coagulation analyses (point-of-care, POC) are increasingly being used to monitor blood coagulation and guide hemostatic therapy. POC coagulation analyzers may overcome several limitations of routine laboratory-based coagulation tests (i.e., PT/INR, PTT) and platelet count. Blood analyzed at the bedside allows for faster turnaround times. The coagulation status is assessed in whole blood (not plasma) and the plasmatic coagulation system interacts with platelets and red and white blood cells. If platelets are assessed, not only their number (quantity) but also their function (quality) will be tested. Furthermore, in certain devices, clot development can be visually displayed in real time and the coagulation analysis can be performed at the patient's temperature. POC coagulation analyzers, however, still assess blood coagulation in vitro in a cuvette: most analyzers measure coagulation under static conditions (no flow) and the cuvettes are not endothelialized. Therefore, results obtained from in vitro POC tests never reflect all aspects of hemostasis and must be carefully interpreted after considering the clinical conditions (e.g., overt microvascular bleeding in the surgical site) [5, 6].

There are several methods available to analyze blood coagulation at the bedside. According to their main objective and function, POC coagulation analyzers can be categorized into devices focusing on the analysis of:

- *Primary* (*cellular*) *hemostasis*, *mainly platelet function*. Tests analyzing primary hemostasis measure platelet count and function as well as von Willebrand factor (vWF) activity.
- *Secondary* (*plasmatic*) *hemostasis*. These bedside tests are being used to monitor

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anticoagulant therapy. Examples include the activated clotting time (ACT), whole blood PT/INR, and heparin management devices.

- *Entire hemostasis, from initial thrombin generation to maximum clot formation up to fibrinolysis*. Viscoelastic coagulation monitoring devices like TEG (Haemonetics Corp., formerly Haemoscope Corp., Braintree, MA), ROTEM (Tem International GmbH, formerly Pentapharm GmbH, Munich, Germany), and Sonoclot (Sonoclot Coagulation & Platelet Function Analyzer, Sienco Inc., Arvada, CO) assess the hemostatic system globally, analyzing primary and secondary hemostasis, clot strengths, and fibrinolysis.

POC Monitoring of Primary (Cellular) Hemostasis

Primary hemostasis plays a central role in the pathogenesis of arterial thromboembolic disease [7]. An increasing number of patients are on antiplatelet medication, such as cyclooxygenase-1 (COX-1) inhibitors, P2Y receptor (for binding adenosine diphosphate, ADP) antagonists, and glycoprotein (GP) IIb/IIIa receptor blockade (Fig. 40.1). In these patients, knowledge of residual platelet function (PF) is highly warranted in order to maintain an optimal balance between platelet function and inhibition (i.e., bleeding and thrombosis). Traditional assays, such as light transmission aggregometry (LTA; also called turbidimetric platelet aggregometry), are still considered clinical gold standards of PF testing. LTA is one of the most widely used tests to identify and diagnose specific PF defects. However, conventional LTA is labor-intensive, is costly, and requires a high degree of experience and expertise to perform and interpret. Additionally, platelets are tested under low shear conditions in platelet rich plasma, an in vitro setting that is different from in vivo primary hemostasis. Clinical medicine warrants more and more rapid, accurate, and reliable tests, simple to operate at the bedside, and availability 24/7. Over the last 20 years, several POC devices have been developed to measure PF that fulfill the above criteria

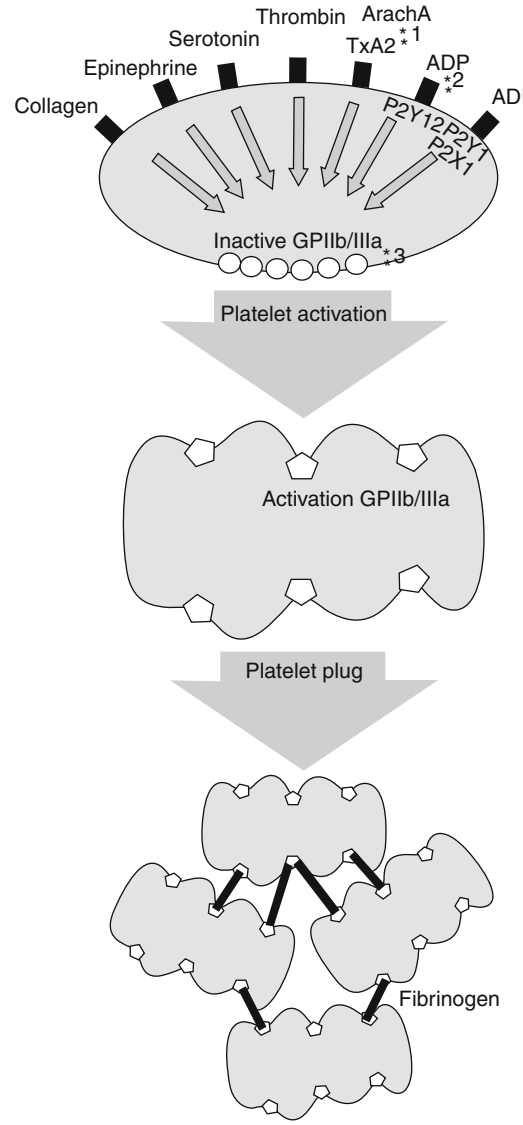

Fig. 40.1 Platelet activation and aggregation. Multiple pathways are implicated in platelet activation and aggregation. Some pathways can be therapeutically blocked in certain patients at risk for thromboembolic disease, e.g., thromboxane pathway (*1* aspirin), ADP pathway (*2* clopidogrel, prasugrel), and GPIIb/IIIa activation and interaction with fibrinogen (*3* abciximab, eptifibatide). Besides specific activating pathways (agonist-receptor binding; see Figure) and downstream signaling, platelets may become unspecifically activated by abnormal flow conditions, e.g., severe arterial stenosis (high shear stress) or artificial surfaces. Finally, as a result of initial activation, platelets change their shape and release dense and alpha granules (multiple activators, cytokines, chemokines), further activating themselves (amplification) and others

at least in part, allowing their use in routine clinical practice [6]. Limitations of all techniques have to be considered [8].

Whole Blood Impedance Platelet Aggregometry

Multiplate (Verum Diagnostica GmbH, Munich, Germany) is a widely used platelet aggregometer and represents significant progress in platelet aggregometry. The technique avoids several methodological problems of the original LTA, especially by using whole blood, disposable test cuvettes, commercially available test reagents, and an automated pipetting system. Furthermore, Multiplate assays have a high sensitivity in detecting effects of acetylsalicylic acid (aspirin), ADP antagonists, and GPIIb/IIIa inhibitors on platelets.

The working principle of Multiplate is based on two silver-coated conductive copper electrodes immersed into whole blood and the ability of activated platelets to adhere to the electrode surface. Each test cuvette consists of two pairs of electrodes allowing duplicate measurements simultaneously. The instrument continuously measures the change of electrical impedance, being proportional to the amount of platelets attached to the electrodes. The measured values are transformed to arbitrary aggregation units (AU), plotted against the time (Fig. 40.2). Three parameters are provided: aggregation units (AU), velocity (AU/min), and area under the aggregation curve (AUC), whereas AUC has the highest diagnostic power. Multiplate has five channels and parallel testing can be done at the same time. As for other techniques, different activators are commercially available: arachidonic acid (sensitive to aspirin, NSAID, GPIIb/IIIa antagonists), ADP with/without prostaglandin E1 (sensitive to P2Y and GPIIb/IIIa antagonists), TRAP-6 (thrombin receptor activating peptide, sensitive to GPIIb/IIIa antagonists), collagen (sensitive to aspirin, GPIIb/IIIa antagonists), and ristocetin (sensitive to Bernard-Soulier syndrome, severe von Willebrand's disease, aspirin) [9].

Multiplate has some limitations: test results are not independent of the actual platelet number and running the tests is time-consuming and complex and requires serial pipetting. Additionally, as with other platelet function tests, a resting time of 30 min after blood sampling is recommended before running the tests, which may impede immediate detection of platelet dysfunction in emergency cases.

VerifyNow/Ultegra

The VerifyNow Analyzer (Accumetrics, San Diego, CA) is an optical platelet aggregometer, and the technique was initially distributed as Ultegra Rapid Platelet Function Analyzer (RPFA). Activated platelets stick to fibrinogen-coated beads and aggregate with a consecutive increase in light transmission (Fig. 40.3). Variation of light absorbance over time is displayed as platelet aggregation units. Early clinical investigations yielded conflicting results and the assay has been modified to the VerifyNow assay, now detecting effects of acetylsalicylic acid and ADP and GPIIb/IIIa antagonists. This assay has been used to determine clopidogrel response in clinical trials and its results correlated well with those of platelet aggregometry [10].

VerifyNow tests are easy to perform, use small sample volumes, and do not require pipetting. The absence of flow conditions and the scarce consistency over time in the identification of aspirin-resistant individuals are limitations of this assay.

Platelet Function Analyzer

The INNOVANCE PFA-200 System, formerly PFA-100 (Siemens, Marburg, Germany), has been clinically introduced in 1985 by Katzer and Born as a screening test for inherent and acquired platelet disorders as well as von Willebrand's disease. Citrated whole blood is aspirated at high shear rates through a capillary with a membrane-coated microaperture: collagen and either epinephrine (COL-EPI) or ADP (COL-ADP). Recently, another test cartridge has been introduced, the PFA-P2Y (ADP and

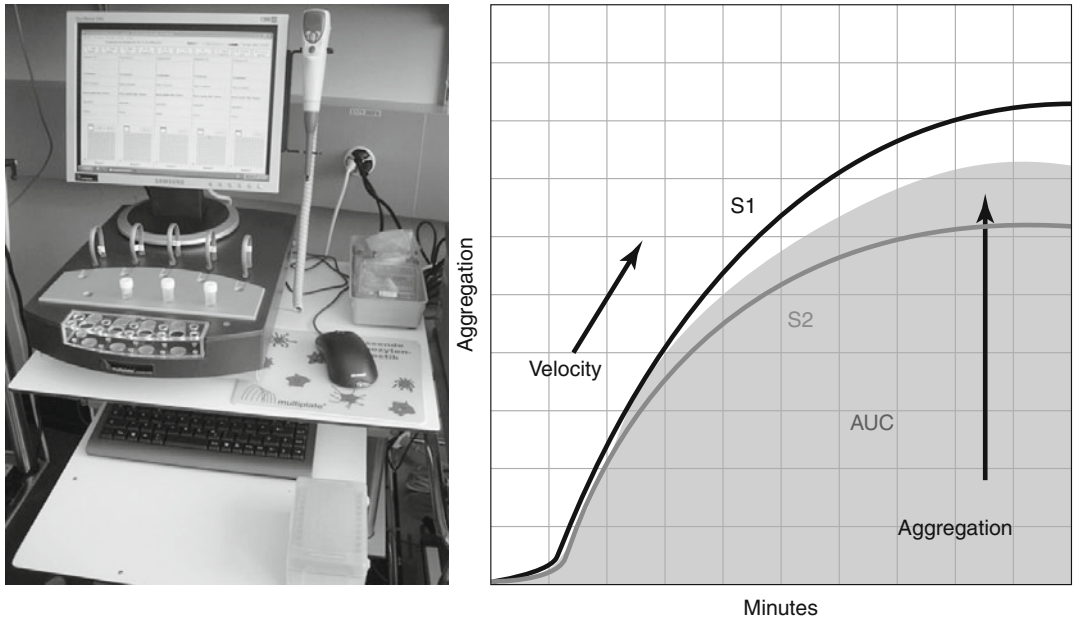

Fig. 40.2 Whole blood impedance platelet aggregometry (Multiplate). Impedance values are transformed to arbitrary aggregation units (AU), plotted against the time. In one cartridge, measurements are done in duplicates (*S1*, *S2*). The following parameters representing platelet function are provided (after averaging the duplicate results): maximum aggregation (AU), velocity of aggregation (AU/min), and area under the aggregation curve (*AUC*)

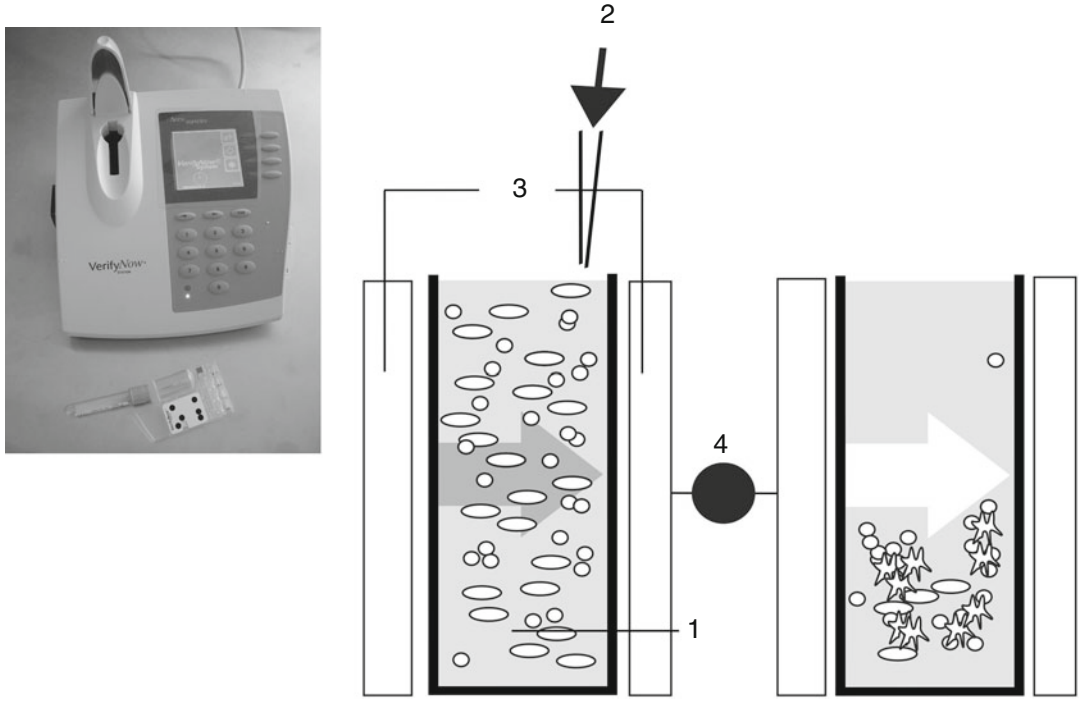

Fig. 40.3 Optical platelet aggregometry (VerifyNow). Platelets are activated and start to aggregate with fibrinogen-coated beads. Thereby, light transmission increases, which will be measured by the light detector. Activated platelets attach to fibrinogen-coated beads (*1*), platelet agonist (*2*), light source and detector measuring light transmission (*3*), and operating unit, transforming optical to electrical signal (*4*)

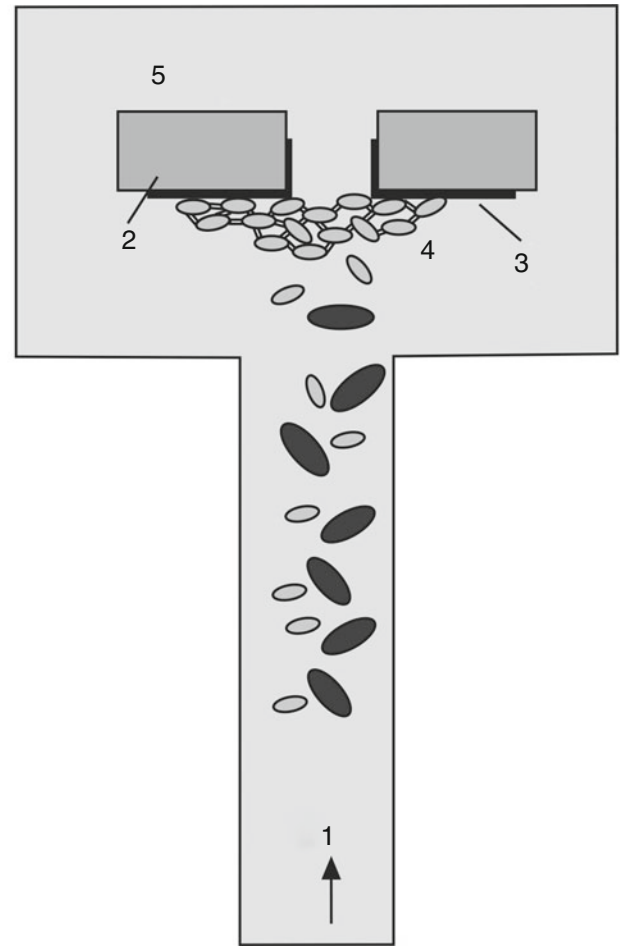

Fig. 40.4 Platelet function analyzer (PFA-100, PFA-200). Citrated whole blood is aspirated at high shear rates through a capillary (*1*) with a membrane-coated microaperture (*2*). The membrane may be coated with collagen and epinephrine (COL-EPI) or adenosine diphosphate (COL-ADP, PFA-P2Y) to activate platelets (*3*). The closure time is the time taken for activated platelets to occlude the membrane (*4*) in the cartridge (*5*)

prostaglandin E1), to assess the clinical effectiveness of ADP antagonists. Both shear stress and platelet agonists lead to attachment, activation, and aggregation of platelets forming a plug occluding this microaperture (Fig. 40.4). The time taken to occlude the aperture is known as closure time (CT) and is a function of platelet number and reactivity, von Willebrand factor activity, and hematocrit (inverse correlation of CT with Hct). The main advantages of this assay are that it does not require fibrin formation, provides rapid results, and is particularly useful in the diagnosis of von Willebrand's disease and overall platelet dysfunction. However, to get valid results, a hematocrit ≥30 % and platelet count ≥100,000/μL are required. Additionally, citrate concentration, blood type, and leukocyte count may interfere with its accuracy. Whereas early reports suggested a high sensitivity for detection of acetylsalicylic acid by prolonged PFA-100 COL-EPI closure time in association with normal values for COL-ADP, more recent investigations could not consistently confirm these results [11]. Taken together, PFA-100/200 has a high negative predictive value, i.e., primary hemostasis is functioning normally (with some exceptions: primary secretion defects, storage pool disease, mild von Willebrand's disease) if

CT is in normal range. However, formal and more specific platelet aggregation testing is required to establish the underlying cause if CT is abnormal.

Modified Thrombelastography: Platelet Mapping

Since conventional TEG/ROTEM are not sensitive to targeted pharmacological platelet inhibition, a more sophisticated test has been recently developed for TEG to specifically determine platelet function in presence of antiplatelet therapy (modified TEG, platelet mapping). Briefly, the maximal hemostatic activity of the blood specimen is first measured by a kaolin-activated whole blood sample. Then, further measurements are performed in the presence of heparin to eliminate thrombin activity: reptilase and factor XIII (activator F) generate a cross-linked fibrin clot to isolate the fibrin contribution to the clot strength. The contribution of the ADP or TxA2 receptors to the clot formation is provided by the addition of the appropriate agonists, ADP, or arachidonic acid. The results of these different tests are then compared to each other and the platelet function calculated.

Platelet mapping seems to be a suitable procedure for the assessment of all three classes of antiplatelet agents, but at present, the sensitivity and specificity compared to laboratory platelet aggregometry have not been determined in detail. Additionally, the reagents are expensive, multiple channels are required to run the tests, and well-trained personnel are required for optimal performance, limiting its use as POC procedure [12].

Platelet-Activated Clotting Time

Platelet-activated clotting time (PACT; HemoSTATUS, Medtronic HemoTec, Inc., Parker, CA) is a modified whole blood-activated clotting time test (ACT) adjoining platelet activation factor (PAF) to the reagent mixture for detection of platelet responsiveness by shortening of the kaolin-activated clotting time in whole blood samples. Until now, few studies investigating the correlation to clinical bleeding in patients undergoing cardiac surgery have been performed and their results were controversial.

ICHOR/Plateletworks System

This platelet count ratio assay from Helena Laboratories (Beaumont, TX) simply compares whole blood platelet count in a control EDTA blood sample with the platelet count in a similar sample that has been exposed to a platelet activator. In patients without platelet dysfunction or antiplatelet drug treatment, the presence of the agonist reduces platelet counts close to zero, due to aggregation of most of the platelets. The findings of recent studies indicate that adding the agonist ADP to the test sample appears useful for the assessment of both P2Y(12) inhibitors (clopidogrel, prasugrel) and GPIIb/IIIa antagonists. Minimal sample preparation and whole blood processing are advantages of this assay. The main disadvantage, however, is the lack of sufficient investigations.

Impact Cone and Plate(Let) Analyzer

The Impact Cone and Plate(let) Analyzer (CPA, DiaMed, Israel) tests whole blood platelet adhesion and aggregation under artificial flow conditions. A small amount of whole blood is exposed to a uniform shear in a spinning cone and platelet adhesion to the polystyrene wells is automatically analyzed by an inbuilt microscope. The quantity of moistening of the surface of the plates (surface covering) depends on platelet function, fibrinogen, von Willebrand factor levels, and the bioavailability of GPIb and GPIIb/IIIa receptors. The test duration is less than 6 min. The addition of arachidonic acid and ADP to the test specimens may assess the effect of acetylsalicylic acid and ADP antagonists on platelets. The Impact Analyzer is a simple and rapid whole blood platelet analyzer requiring small sample volumes. However, test results are dependent on platelet count and hematocrit and only limited published data are available on its clinical performance [6].

POC Monitoring of Secondary (Plasmatic) Hemostasis

Activated Clotting Time

Originally described by Hattersley in 1966, ACT reflects the amount of time to form a clot after contact activation of coagulation. The ACT is a functional coagulation test of the intrinsic clotting pathway and has been developed for guiding unfractioned heparin-induced anticoagulation at the bedside, particularly during cardiac surgery, extracorporeal membrane oxygenation (ECMO), and coronary interventions [13].

Several ACT instruments are commercially available and ACT measurements can be performed using different coagulation activators, each with unique characteristics and various interactions. Results from different ACT tests cannot be used interchangeably. This variability highlights the importance of establishing appropriate instrument-specific and locally adjusted reference values for monitoring anticoagulation [14].

ACT monitoring of heparinization is not without limitations, and its use has been criticized because of significant variability and the poor correlation with plasma heparin concentrations during cardiopulmonary bypass (CPB) [15]. It has been suggested that many factors—patient, operator, and equipment—can alter ACT. Therefore, ACT prolongation during CPB is not necessarily caused by heparin administration alone and may be associated with patient hypothermia, inadequacy of specimen warming, hemodilution, quantitative and qualitative platelet abnormalities, or administration of antifibrinolytic therapy. Furthermore, low factor XII levels, which are found in patients with sepsis and patients undergoing renal replacement therapy, may lead to "falsely" high ACT values without clinical relevance [13].

Heparin Concentration Measurement

Because of the limitations of ACT estimating plasma levels of heparin, POC devices have been developed to more accurately measure heparin concentration. The most studied device is the Hepcon HMS Plus Hemostasis Management System (Medtronic, Minneapolis, MN). It calculates heparin doses before initiation of CPB by performing a heparin dose response, measuring heparin concentrations, and calculating protamine doses based on residual heparin levels. A number of clinical studies report that Hepcon-guided anticoagulation results in higher total heparin but lower protamine doses than conventional management and may thereby decrease the activation of the coagulation and inflammatory cascade. Results are provided readily; however, higher costs, more complex handling, greater dimensions, and lack of large studies showing benefit on patients' outcome have limited its widespread use [16].

Monitoring Oral Anticoagulants

Several POC-INR coagulation devices have been developed to measure the effects of oral anticoagulants and to provide modified prothrombin time (PT)/INR values. No vein puncture is required (capillary blood samples) and test results are readily available for clinical use, particularly during phases of rapid changes in the coagulatory state. Most devices use electrochemical or optical clot detection [17].

POC Monitoring of the Entire Coagulation Process

TEG, ROTEM, and Sonoclot measure the clot's physical property under low shear conditions and graphically display the changes in viscoelasticity of the blood sample after initiating the coagulation cascade. In contrast to routine laboratory coagulation analyses, all phases of the developing and resolving a clot are displayed, including lysis, hyperfibrinolysis, and hypercoagulability.

Thrombelastography and Rotational Thrombelastometry

Thrombelastography is a method to study the entire coagulation potential of a single whole blood specimen and was first described by

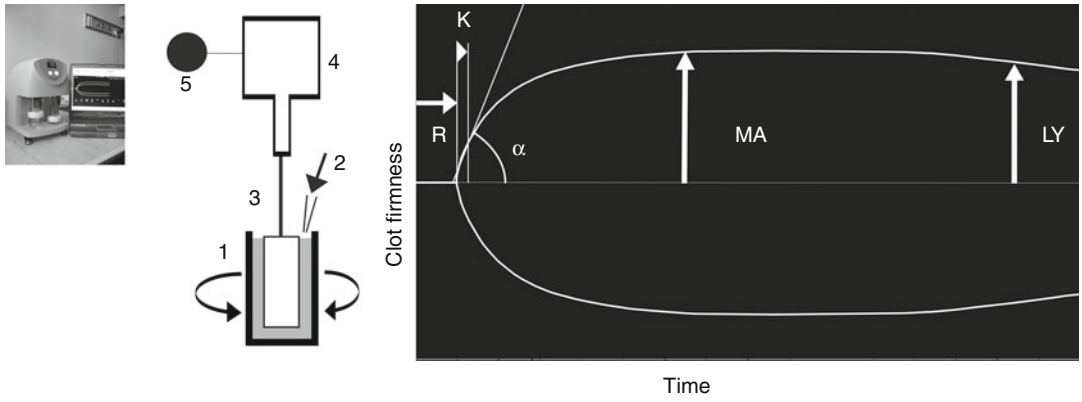

Fig. 40.5 Thrombelastography (TEG). Working principle: Rotating cup with blood sample (*1*), coagulation activator (*2*), pin and torsion wire (*3*), electromechanical transducer (*4*), and data processing unit (*5*). TEG tracing: *R* reaction time, *K* kinetics, *α* slope between r and k, *MA* maximum amplitude, *LY* lysis

Hartert in 1948 [18]. Because thrombelastography assesses the viscoelastic properties of blood, it is sensitive to all interacting cellular and plasmatic components. After starting the analysis, the thrombelastograph measures and graphically displays all stages of the coagulation process: the time until initial fibrin formation, the kinetics of fibrin formation and clot development, the ultimate strength and stability of the clot, as well as the clot lysis. In the earlier literature, the terms thrombelastography, thrombelastograph, and TEG have been used generically. However, in 1996, these terms became a registered trademark of Haemonetics Corp. (formerly Haemoscope Corp.), and from that time on, TEG has been employed to describe the proprietary 2-channel coagulation analyzer by Haemonetics Corp. only. Alternatively, Tem International GmbH (formerly Pentapharm GmbH) introduced a modified 4-channel coagulation analyzer in the year 2000 using the terminology rotational thrombelastometry, ROTEM.

In TEG, whole blood is added to a heated cuvette at a set temperature, typically 37 °C. A disposable pin connected to a torsion wire is suspended in the blood sample and the cup is oscillated through an angle of 4°45′ (rotation cycle 10 s; Fig. 40.5). As the blood sample starts to clot, fibrin strands connect and couple the cup with the pin and the rotation of the cup is getting transmitted to the pin. The rotation movement of the pin is converted by a mechanical–electrical transducer to an electrical signal, finally being displayed as the typical TEG tracing (see Fig. 40.5).

ROTEM technology avoids some limitations of traditional TEG and offers some advantages: measurements are less susceptible to mechanical shocks, four samples (TEG only two) can be run at the same time, and pipetting is made easier by providing an electronic pipette. In ROTEM, the disposable pin (not the cup) rotates back and forth 4°75′ (Fig. 40.6). The rotating pin is stabilized by a high precision ball bearing system. Signal transmission is carried out via an optical detector system (not the torsion wire). The exact position of the pin is detected by reflection of light on a small, embedded mirror on the shaft of the pin. Data obtained from the reflected light is then being processed and graphically displayed (see Fig. 40.6).

Although TEG and ROTEM tracings look similar, the nomenclature and reference ranges are not comparable (Table 40.1). Both systems use different materials (ROTEM cups and pins are composed of a plastic with greater surface charge resulting in greater contact activation compared to cups and pins used in TEG) and different proprietary formulas of coagulation activators (composition, concentration). For example, if the same blood specimen is analyzed by TEG and ROTEM with their proprietary intrinsic

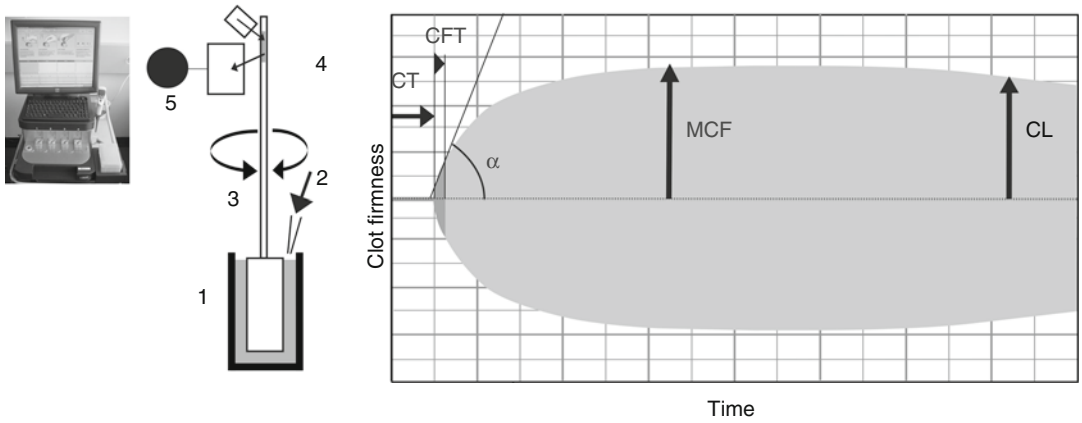

Fig. 40.6 Rotational thrombelastometry (ROTEM). Working principle: Stationary cuvette with blood (*1*), coagulation activator added by automated pipette (*2*), rotating pin stabilized by a high precision ball bearing system (*3*), electromechanical signal detection via light source and mirror mounted on the shaft of the pin (*4*), and data processing unit (*5*). *ROTEM tracing*: *CT* clotting time, *CFT* clot formation time, *α* slope of tangent at 2 mm amplitude, *MCF* maximal clot firmness, *CL* clot lysis

Table 40.1 Measured parameters and reference values for thrombelastography (TEG) and rotational thrombelastometry (ROTEM)

Parameter	TEG	ROTEM
Clotting time (period to 2 mm amplitude)	*R* (reaction time)	CT (clotting time)
	N (nWB, kaolin) 4–8 min	N (cWB, inTEM) 137–246 s
	N (cWB, kaolin) 3–8 min	N (cWB, exTEM) 42–74 s
Clot kinetics (period from 2 to 20 mm amplitude)	*K* (kinetics)	CFT (clot formation time)
	N (nWB, kaolin) 1–4 min	N (cWB, inTEM) 40–100 s
	N (cWB, kaolin) 1–3 min	N (cWB, exTEM) 46–148 s
Clot strengthening (alpha angle)	*α* (slope between *R* and *K*)	*α* (slope of tangent at 2 mm amplitude)
	N (nWB, kaolin) 47–74°	N (cWB, inTEM) 71–82°
	N (cWB, kaolin) 55–78°	N (cWB, exTEM) 63–81°
Clot strength at set time (amplitude)	A30, A60	A5, A10, A20
Maximum clot strength	MA (maximum amplitude)	MCF (maximum clot firmness)
	N (nWB, kaolin) 55–73 mm	N (cWB, inTEM) 52–72 mm
	N (cWB, kaolin) 51–69 mm	N (cWB, exTEM) 49–71 mm
		N (cWB, fibTEM) 9–25 mm
Clot elasticity	G	MCE (maximum clot elasticity)
Clot lysis at set time	LY30, LY60	CL30, CL60

Coagulation tests: intrinsic contact activation (kaolin; inTEM = partial thromboplastin phospholipids), extrinsic activation (exTEM = recombinant tissue factor), functional fibrinogen (fibTEM = tissue factor plus platelet inhibitor cytochalasin D). Reference values depend on coagulation activator, blood sampling technique, other pre-analytical factors, and studied population (see text) [5]

Abbreviations: *N* normal values, *nWB* native whole blood, *cWB* citrated and recalcified whole blood samples

coagulation activator, i.e., kaolin or inTEM reagent (partial thromboplastin phospholipids), respectively, the results obtained with both systems are significantly different [19]. TEG and ROTEM cannot be used interchangeably, and treatment algorithms have to be specifically adapted for each device [20].

In the perioperative setting, most coagulation analyses are done in citrated whole blood that is recalcified and specifically activated to reduce

variability and running time. Several commercial reagents are available and contain different coagulation activators, heparin neutralizers, platelet blockers, or antifibrinolytics to answer specific questions on the current coagulation status [5]. Thereby, blood samples can be extrinsically (tissue factor; e.g., exTEM reagent) and intrinsically (contact activator; e.g., inTEM reagent) activated. To determine functionality and levels of fibrinogen, reagents incorporate platelet inhibitors (e.g., cytochalasin D in fibTEM reagent). This concept has been proven to work and a good correlation of this modified MA/MCF with levels of fibrinogen measured in the laboratory has been shown, even in children [21, 22]. Finally, by adding an antifibrinolytic drug to the activating reagent (e.g., aprotinin in apTEM), the test provides information on the current fibrinolytic state (especially when compared to a test run without antifibrinolytics) and may help guide antifibrinolytic therapy [23].

The repeatability of measurements by both devices has shown to be acceptable, provided they are performed exactly as outlined in the user's manuals [5].

Sonoclot Coagulation & Platelet Function Analyzer

The Sonoclot Analyzer was introduced in 1975 by von Kaulla et al. and measures viscoelastic properties of a blood sample [24]. A hollow, oscillating probe is immersed into the blood and change in impedance to movement imposed by the developing clot is measured (Fig. 40.7). Different cuvettes with different coagulation activators and inhibitors are commercially available. Normal values for tests run by the Sonoclot Analyzer depend largely on the type of sample (whole blood vs. plasma; native vs. citrated sample), cuvette, and activator used [5].

The Sonoclot Analyzer provides information on the entire hemostasis process both in a qualitative graph, known as the Sonoclot Signature (see Fig. 40.7), and as quantitative results: the activated clotting time (ACT), the clot rate (CR), and the platelet function (PF). The ACT is the time in seconds from activation of the sample until fibrin formation. This onset of clot formation is defined as a certain upward deflection of the Sonoclot Signature and is detected automatically by the machine. Sonoclot's ACT corresponds to conventional ACT, provided that cuvettes containing a high concentration of typical activators (celite, kaolin) are used. The CR, expressed in units/min, is the maximum slope of the Sonoclot Signature during initial fibrin polymerization and clot development. PF is reflected by the timing and quality of the clot retraction. PF is a calculated value, derived by an automated numeric integration of changes in the Sonoclot Signature after fibrin formation has completed. To obtain reliable results for PF, cuvettes containing glass beads for specific platelet activation (gbACT+) should be used. The nominal range of values for the PF goes from 0, representing no PF (no clot retraction and flat Sonoclot Signature after fibrin formation), to approximately 5, representing strong PF (clot retraction occurs sooner and is very strong, with clearly defined, sharp peaks in the Sonoclot Signature after fibrin formation) [25].

Indications of POC Coagulation Monitoring

Patients with significant blood loss and those at risk for major hemorrhage or thrombosis require real-time POC coagulation monitoring to adequately assess hemostasis and individually guide targeted therapy. The modern practice of coagulation management is based on the concept of goal-directed and goal-specific therapy. Maintaining an adequate coagulation status is essential besides preserving sufficient blood volume and oxygen-carrying capacity [3, 4].

Guiding Procoagulants and Antifibrinolytics

Patients with massive hemorrhage develop an acquired coagulopathy due to intravascular volume resuscitation combined with absolute and

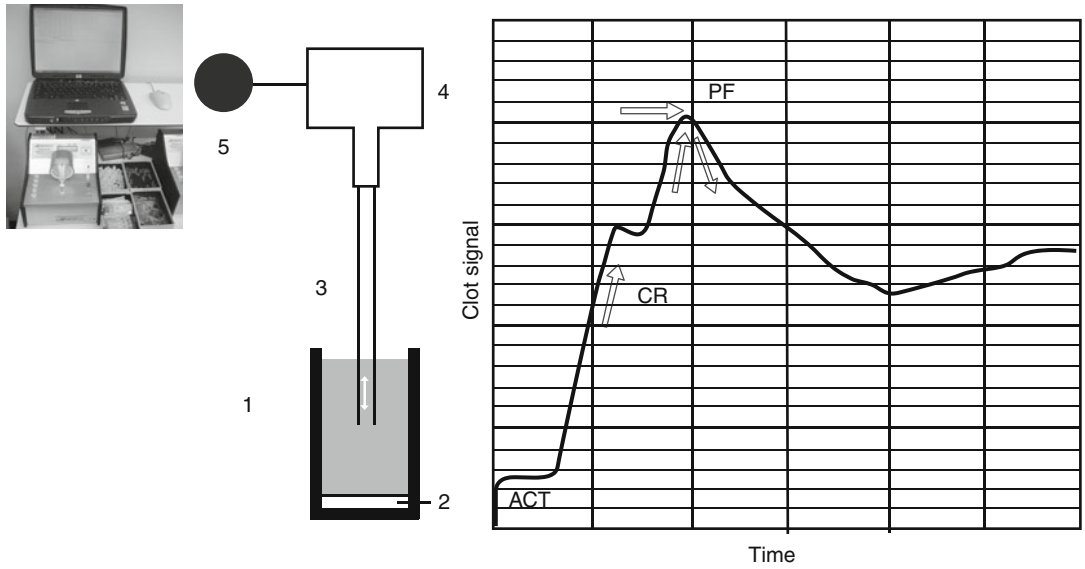

Fig. 40.7 Sonoclot Coagulation and Platelet Function Analyzer. Working principle: Blood sample in cuvette (*1*) containing specific coagulation activator (*2*), disposable plastic probe (*3*) oscillating in blood sample mounted on electromechanical transducer head (*4*), and data processing unit (*5*). Sonoclot Signature: *ACT* activated clotting time, *CR* clot rate, *PF* platelet function

functional loss of their coagulation potential. Fibrinogen is the first coagulation factor to decrease to critically low levels in acquired bleeding. It is the substrate to form a clot and required for platelet aggregation and establishment of a fibrin network [26]. If depleted, specific supplementation of fibrinogen is mandatory for rescue and maintenance of hemostatic function [27, 28]. Several guidelines like the updated European trauma treatment guidelines recommend replacing fibrinogen early, and in the last few years, this has become standard of care in many European centers [29]. However, there is still a debate on how fibrinogen levels should be assessed and monitored, what the critical threshold for fibrinogen substitution should be, and what target levels should be achieved [28]. At the bedside, functional fibrinogen levels can be analyzed with TEG, ROTEM, and Sonoclot measuring clot strength in presence of a platelet GPIIb/IIIa inhibitor (Table 40.2) or by assessing Sonoclot's CR [21]. It is recommended to keep fibrinogen levels >1.5–2.0 g/L, which corresponds to MCF levels greater than 8–10 mm in a fibTEM test [29, 30]. Factor XIII is required for full functionality of fibrinogen because factor XIII cross-links fibrin and stabilizes the clot. Major bleeding and/or extensive surgery may lead to acquired factor XIII deficiency that has been associated with increased bleeding. Therefore, it is recommended to keep factor XIII in normal range [31]. Since viscoelastic POC coagulation monitoring devices assess the entire coagulation process, they are additionally used (in combination with bedside tests measuring primary and secondary hemostasis only) to guide therapy with other coagulation factors (e.g., prothrombin complex concentrate, fresh frozen plasma), platelets, and antifibrinolytics. Specific algorithms on how to interpret measured parameters and on when to start a specific and targeted procoagulant or antifibrinolytic therapy have been published recently [30, 32, 33]. In patients with unknown life-threatening bleeding, POC devices may further detect presence of anticoagulants like heparin (e.g., heparinase-ACT, hepTEM) or Coumadin (e.g., POC-INR). Thereby, anticoagulant therapy can be diagnosed readily at the bedside and corrected individually according to clinical needs.

Table 40.2 Commonly used commercially available tests for viscoelastic point-of-care coagulation devices

Assay	Activator *Inhibitor*	Proposed indication
Thrombelastograph hemostasis system (TEG)		
Kaolin test	Kaolin	Overall coagulation assessment and platelet function
Heparinase test	Kaolin + *Heparinase*	Specific detection of heparin (modified kaolin test adding heparinase to inactivate present heparin)
FF (functional fibrinogen) test	TF + *Abciximab*	Assessment of functional fibrinogen levels
Platelet mapping	ADP + *Arachidonic acid*	Platelet function, monitoring antiplatelet therapy (aspirin, ADP and GPIIb/IIIa inhibitors)
Native test	None	Nonactivated assay Also used to run custom hemostasis tests
Rotational thrombelastometry (ROTEM)		
exTEM	Recombinant TF + *Heparin inhibitor* (*hexadimethrine*)	Extrinsic pathway; fast assessment of clot formation and fibrinolysis
inTEM	Contact activator	Intrinsic pathway; assessment of clot formation and fibrin polymerization
fibTEM	exTEM + *Cytochalasin D*	Assessment of functional fibrinogen levels
apTEM	TF + *Aprotinin*	Fibrinolytic pathway; fast detection of fibrinolysis when used together with exTEM
hepTEM	Contact activator + *Heparinase*	Specific detection of heparin (modified inTEM test adding heparinase to inactivate present heparin)
naTEM	None	Nonactivated assay Also used to run custom hemostasis tests
Sonoclot Coagulation & Platelet Function Analyzer		
SonACT	Celite	High-dose heparin management
kACT	Kaolin	High-dose heparin management
gbACT+	Glass beads	Overall coagulation and platelet function assessment
H-gbACT+	Glass beads + *Heparinase*	Overall coagulation and platelet function assessment in presence of heparin; detection of heparin
Native	None	Nonactivated assay Also used to run custom hemostasis tests

Abbreviations: *ACT* activated clotting time, *TF* tissue factor, *ADP* adenosine diphosphate, *GPIIb/IIIa* glycoprotein IIb/IIIa receptor

Guiding Anticoagulants

The complex process of full anticoagulation with heparin, e.g., for cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO), reversal with protamine, and post-interventional hemostasis therapy, requires careful and accurate bedside coagulation monitoring. Besides guiding heparin anticoagulation with ACT measurements, it has been shown that advanced POC coagulation monitoring may reduce allogeneic blood transfusion, save costs, and improve outcome [33–35].

Recognized risk factors for thrombosis are generally related to one or more elements of Virchow's triad (stasis, vessel injury, and hypercoagulability). Major surgery has been shown to induce a postoperative hypercoagulable state and this hypercoagulability has been implicated in the pathogenesis of postoperative thrombotic complications, including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, and vascular graft thrombosis. Identifying hypercoagulability with conventional non-viscoelastic laboratory

tests is difficult unless fibrinogen concentration or platelet count is markedly increased. However, hypercoagulability is easily being diagnosed by viscoelastic POC coagulation analyzers (short R/CT time and the increased MA/MCF exceeding 65–70 mm) and specific anticoagulant treatment can be initiated.

Conclusion

Hemostasis is a complicated, vital system to our body. Normal blood coagulation exists when procoagulant and anticoagulant forces are in balance. Clinically relevant phenotypes of hemostasis, bleeding and thrombosis, occur immediately if the system is no longer in equilibrium. Patients with major bleeding and those at risk for thrombosis require real-time POC coagulation monitoring in combination with clearly defined algorithms to adequately assess hemostasis and individually guide targeted therapy. Thereby, unnecessary and blind administration of anti- and procoagulant substances can be avoided, resulting in reduced allogeneic blood transfusions. Ultimately, costs are saved and overall patients' outcomes are likely to be improved [3, 4, 32, 33, 36].

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Pediatric Monitoring

41

Thomas M. Romanelli

Introduction

The American Society of Anesthesiologists requires the same basic monitoring standards for pediatric as well as adult surgical patients [1]. Pediatric monitoring is not limited to electronic devices, but includes the audiovisual, acoustic, and proprioceptive capabilities of the anesthesia provider to enhance situational awareness. Clinically appropriate monitoring begins at the time of patient transport to the operating room, with continuous observation of the child's chest wall expansion and color and observation of abnormal respiratory efforts such as stridor. Differences in age and maturity level and the presence of developmental delay will make some patients resistant to the application of standard preinduction ASA monitors because of fear and anxiety. A controlled inhalation induction with visual confirmation of adequate inspiratory depth, appropriate skin and mucosal membrane color, and the absence of physical evidence of airway obstruction (i.e., suprasternal retractions, paradoxical diaphragmatic motion, a sense of abnormal compliance while managing the anesthesia circuit reservoir bag) is broadly considered to be an acceptable practice, with the immediate application of all remaining basic monitors to be completed at the earliest convenient opportunity.

All pediatric patients should be monitored with pulse oximetry, capnography, ECG, and temperature, and age-appropriate alarm limits should be programmed accordingly. Additional monitors may be required, and the anesthetic plan should address anticipated surgical conditions, duration, and probability of significant blood loss. An overview of the various monitoring modalities is provided in Table 41.1, but does not constitute a complete list. Potential issues may arise with the application and/or insertion of pediatric monitors, especially when patients possess extreme ranges of body mass. Premature infants pose a multitude of challenges even for basic monitoring, and these device limitations and potential methods for mitigation of corresponding inaccuracies will be discussed.

Noninvasive, Nonelectronic Monitoring

Audiovisual and Acoustic Inspection

The anesthesia provider must maintain appropriate vigilance of the pediatric patient and incorporate his/her sensory capabilities with the additional data provided by the standard electronic monitoring paradigm [2]. Observation of chest wall excursion (with appropriate depth and symmetry), preservation of normal mucosal and nail bed color, and the continued presence of

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Table 41.1 Pediatric monitors

Noninvasive, nonelectronic
Audiovisual and acoustic inspection
(Clinician senses and precordial stethoscope)
Proprioceptive feedback
Noninvasive, electronic
Oximetry
Capnography
ECG
Blood pressure (oscillometric)
Temperature
Invasive or noninvasive, electronic, surgery-specific
Arterial catheters
Central venous catheters
Cardiac output monitors
Near-infrared spectroscopy
Depth of anesthesia (processed EEG)

brisk capillary refill are all important facets to multidimensional monitoring. The experienced pediatric anesthesia care provider is capable of detecting relatively subtle changes in such variables and can rapidly reconcile this information with the data provided by standard electronic monitors. Intermittent examination of the surgical field can provide timely information concerning hemorrhage, evolving fluid shifts, potential compression of major organs, and/or vasculature with surgical instruments or possibly the surgeon proper (i.e., as when a surgeon's hand rests upon an infant's leg and obstructs distal blood flow to an ipsilateral oximeter). The physiologic reserves of the infant and premature neonate are extremely limited, and such visual cues may alert the provider to developing issues before standard electronic alarms are activated.

The use of a precordial stethoscope is a simple, inexpensive, and risk-free method to monitor general cardiorespiratory function [3]. The precordial device may be utilized in circumstances where an esophageal stethoscope cannot (i.e., laser airway procedures). Despite the general reliability of this monitor, its use among pediatric providers remains inconsistent [4, 5]. The application of a precordial stethoscope to the third or fourth intercostal space at the left sternal border permits the continuous evaluation of heart tones and breath sounds. A decrease in the intensity of heart tones correlates with diminished cardiac output and may be among the first signs of inhalational agent overdose. However, this technique remains a qualitative method, and such changes may not be appreciated until cardiac output has decreased by as much as 50 % [6].

The precordial stethoscope has other potential limitations. Its ability to accurately transmit sound may be affected due to the use of various connecting materials, tubing length, and the presence of distracting ambient sounds in the OR environment. Misinterpretation of transmitted sounds may lead a provider to develop a false level of confidence concerning endotracheal tube position, which may lead to a delay in diagnosis of esophageal intubation [7–9]. An obvious limitation is the fact that when applied to the left sternal border, the precordial stethoscope cannot be relied upon to diagnose endobronchial intubation. Several modifications to the basic precordial model have been described that enhance its accuracy and capabilities but at the cost of simplicity, expense, and time required to obtain clinical competency [10–13].

Despite its limitations, the precordial stethoscope remains a useful tool to augment the anesthesia provider's awareness during the conduct of pediatric surgery. It is the author's position, based upon the accumulated clinical experience acquired in multiple environments, that the additional monitoring input from this device is most useful for patients less than 3 months of age and during the transitional periods of induction, emergence, and PACU transport.

Proprioceptive Feedback

The performance of an intermittent hands-on physical examination, especially when surgical drapes obstruct easy access to the patient's airway, will also supplement the clinician's audiovisual acuity. Palpation of peripheral pulses, gross assessment of skin temperature, the sensation of abnormal airflow, and the smell of inhalational agent consistent with an inadequate airway seal are all derived from focused physical contact with the patient.

Noninvasive, Electronic Monitoring

A recent analysis of the ASA Closed Claims database has shown that the widespread adoption of pulse oximetry and capnography for pediatric monitoring has been the largest contributor to a reduction in adverse events resulting from inadequate oxygenation and ventilation [14]. Pediatric cardiac arrest in healthy children (ASA physical class 1–2) is the direct consequence of respiratory failure in 20 % of cases [15]. Despite such progress in limiting morbidity and mortality, there remains significant liability surrounding respiratory events that are not considered preventable by standard respiratory monitors (e.g., aspiration of gastric contents). There has also been an increase in the proportion of claims submitted on behalf of patients less than 3 years of age, which probably reflect changes in demographic trends among pediatric surgical candidates (i.e., increasing frequency of neonatal surgical procedures) [16].

Oximetry

Standard oximeters apply an algorithmic analysis to two wavelengths of measured light (660 and 940 nm) in order to derive an estimation of arterial saturation (SpO_2). Neonates possess relatively large fractions of hemoglobin F and transition to typical hemoglobin A proportions during the first 3–6 months of life. Since the absorption spectra of fetal and adult hemoglobin are similar, standard oximeters retain appropriate accuracy [17]. A number of prospective, single-blind studies have described the evidence supporting current national recommendations regarding the use of oximetry for the identification and prevention of major hypoxic events among the pediatric population [18, 19].

Baseline variability in the sensor accuracy is a practical consequence of the different proprietary algorithms (which modulate signal processing) and the specific microprocessors utilized by various medical device manufacturers. Oximetry is accurate within a range of ±2 % for saturations >90 %, but this range may increase as saturations decline below 90 % [20]. Additional error may be seen in small children secondary to the lack of adequate contact surface area or alignment with the active probe elements. When misaligned, the emitted light is projected tangentially towards the detector without effective penetration through an arterial bed (known as "penumbra effect" or "optical shunting") [21]. It is often most efficient to use wraparound devices on the hands and feet of neonates and infants <3 kg and cover the probe with non-reflective material to insulate the sensor from ambient light. The presence of burns, trauma, and congenital anomalies (i.e., phocomelia) may prevent application of oximetric sensors to traditional locations. Many unconventional locations (tongue, buccal mucosa, etc.) are suitable and provide accurate data with minimal modification of the probe [22, 23]. The pediatric provider should recognize the situational need and potential advantage of centrally placed oximeters, as there is evidence that such monitors will reflect saturation changes earlier than distally located probes [24].

Neonates and infants may present with elements of persistent transitional circulation (i.e., physiologic shunts such as patent foramen ovale or ductus arteriosus) with abnormal pulmonary blood flow patterns. Oximetric signals may differ depending upon the location of the probe. Measurements obtained from the right hand or ear represent pre-ductal saturations and correlate reasonably well with cerebral circulation. In those patients with complex congenital cardiac pathophysiology, simultaneous monitoring of pre-ductal and post-ductal values may be useful [25]. Differences of >10 % between the two probes are consistent with marked pulmonary hypertension and subsequent right-to-left shunting. Monitoring trend changes in such values can alert the provider to consider appropriate ventilation adjustments or vasoactive agent therapies to compensate for abnormal pulmonary blood flow.

Other potential sources of oximetric error include the presence of intravascular dyes, motion artifacts, and inadequate peripheral perfusion. All contrast dyes produce reductions in measured SpO_2 since they absorb light within a spectra range similar to hemoglobin. Bilirubin's

Table 41.2 Comparison of sidestream versus mainstream capnographs

Sidestream	Mainstream
Gas drawn from breathing circuit (~200 mL/min)	Negligible volumes sampled
Fine-bore sampling tubing attaches to filter	Tube with "window" inserted into circuit
Disposable patient connections	Patient connectors may be autoclaved
Small and lightweight	Larger device; may bend unsupported circuits
Lag time = few seconds	Lag time = few milliseconds
High fresh gas flows relative to minute ventilation may dilute sample and reduce $ETCO_2$ display	Same limitation; distal sampling not possible
Distal sampling from endotracheal tube corrects this flow effect	

Modified from Bell and Limb [17]

light absorption properties also overlap those of hemoglobin, but hyperbilirubinemia-induced oximetric changes have not been demonstrated to be clinically significant [26]. Motion artifacts affect the signal-to-noise ratio and drive SpO_2 downward, producing falsely low values. Hypovolemia, hypothermia, and cardiogenic shock all contribute to low perfusion states, and the vasoconstriction observed with such conditions limits the dynamic range of arterial pulsations. In one pediatric study, a skin temperature of <30 °C was the strongest predictor of oximetric error [27].

The conversion of the pulsatile component of absorption into an electrical signal displayed as a continuous plethysmograph may serve as an indicator of the adequacy of tissue perfusion at the site (where strong beat-to-beat signal variation represents intact distal blood flow). Furthermore, the extent of arterial pulse wave variation observed with positive-pressure ventilation may serve as an indirect monitor of intravascular volume status (i.e., with larger variations representative of greater degrees of intravascular hypovolemia) [28]. The clinical utility of this plethysmographic feature must still be validated by additional studies.

Next-generation oximeters incorporate more advanced technologies to address current limitations and add new features. So-called "rainbow" oximeters now measure up to eight wavelengths which can accurately measure saturations even in the presence of abnormal hemoglobin species [29]. Read-through-motion techniques represent advanced electronic filtering designed to detect pulsatile flows despite motion or low perfusion states. Quantification of the plethysmographic signal may provide clinically useful measurements of distal perfusion.

Despite such useful features, it remains unclear whether the use of advanced oximeters will significantly improve patient safety. Oximetric data should always be reconciled in light of dynamic clinical conditions and evolving pathophysiology. The anesthesia provider should be closely attuned to the pitch of the oximeter, and the baseline volume level adjusted so that it is audible to all operating room personnel.

Capnography

Confirmation of airway patency and adequate ventilation is the primary purpose for continuous monitoring of end-tidal carbon dioxide ($ETCO_2$). Most capnographs apply infrared spectroscopy to exhaled gas obtained via mainstream or sidestream sampling. These sampling methods have advantages and disadvantages as noted in Table 41.2.

A visible waveform may still be erroneous as demonstrated with the initial readings obtained after esophageal intubation. False-positive results in this condition represent the residual CO_2 that was

insufflated into the gastrum by aggressive mask ventilation, but this artifact usually disappears within five to six breaths. Likewise, an endotracheal tube incorrectly positioned just above the larynx continues to be at risk for dislodgement, but may still register near-normal values on the capnograph. In a spontaneously breathing patient false negatives are associated with cardiac arrest or inadequate pulmonary blood flow, and if severe enough, bronchospasm will prevent appropriate gas exchange despite proper endotracheal tube location.

Capnography remains the most clinically useful estimate of the patient's true arterial CO_2, and continuous monitoring allows the provider to avoid the potential detrimental effects of hypercarbia (increased ICP and pulmonary vasoconstriction) and hypocarbia (cerebral vasoconstriction). The difference between these two values is generally small in healthy adult patients (3–5 mmHg), but may increase in the pediatric population. In infants and neonates in particular, the endotracheal tube length, Y-piece connectors, passive humidifiers, and elbows produce relative increases in dead-space volume with subsequent underestimation of arterial CO_2. This effect can be further magnified in micro-preemies (neonates <800 g) and such patients remain a higher risk for being hypoventilated with resultant hypercarbia [30]. Multiple techniques have been employed to limit such inaccuracies and include small-volume ETT connectors, endotracheal tubes with a distally positioned sampling lumen, and limited volume humidifiers that are inserted into the circuit proximal to the sampling line [31–33].

Capnography remains clinically applicable even for those patients without an ETT. The adequacy of ventilation can still be assessed with mask ventilation or spontaneous breathing via nasal cannula despite the relative increase in anatomic dead space. The application of a Salter-style nasal cannula (which provides a more accurate $ETCO_2$ sampling location) is an accepted practice for procedural sedation, which has experienced tremendous growth in pediatric off-site locations during the last decade [34].

As with any device, potential mechanical failures may occur with capnography. Misaligned connections or cracks in the sampling tubing ports may entrain room air with subsequent effects upon measured $ETCO_2$ accuracy. Obstruction of the sampling port by oropharyngeal secretions or accumulated condensation that may occur with extended-duration procedures will either decrease $ETCO_2$ measurements or eliminate them altogether. The provider should always be prepared with a standard or precordial stethoscope as an immediate backup monitor.

Electrocardiogram

The pediatric patient usually does not possess ischemic heart disease necessitating electrocardiography (ECG), but ECG monitoring remains essential as an assessment tool for heart rate and rhythm. Cardiac output in neonates and infants is dependent upon heart rate, since they lack the capacity to effectively increase stroke volume. In the setting of an inhalation induction, the onset of relative bradycardia (100 beats per minute) as demonstrated by the ECG is usually indicative of volatile agent overdose. Titration of inhaled gases and administration of anticholinergics will mitigate this event.

In the newborn, right and left ventricular wall thickness is similar and may present as right axis deviation with right ventricular hypertrophy on the ECG. Normal growth brings an appropriate increase in left ventricle muscle mass until a typical adult pattern is achieved by the age of 2 or 3 years. Lead II provides the most useful information for the healthy pediatric patient, as the prominent P waves assist rhythm recognition. The addition of lead V_5 is most applicable for extended-duration procedures in which ECG changes caused by electrolyte shifts or cumulative blood loss may be observed. Dual-lead ECG monitoring is essential for those patients with known arrhythmias (e.g., Wolff-Parkinson-White) or older children who have benefited from the repair of complex cardiac anomalies. In the latter case, the initial ECG tracings may appear grossly abnormal due to the altered intracardiac architecture and its effect on conduction pathways; continuous monitoring and observation of *changes in baseline trends* are clinically relevant.

Table 41.3 Appropriate sizing of pediatric blood pressure cuffs

Bladder width	Bladder length
Should cover 66–75 % of upper arm Recommended values: Neonate: 3 cm Infant: 5 cm Small child: 6 cm Large child: 9 cm	Minimum of 40 % the measured circumference of the upper arm; 80 % considered ideal
If the applied cuff is too small, NIBP will be erroneously high; for cuffs too large, the reverse is true	

Modified from Bell and Limb [17]
Abbreviation: *NIBP* noninvasive blood pressure

Blood Pressure

The typical, noninvasive blood pressure device is an automated oscillotonometer, which compares the oscillation variability from two sequential cardiac cycles to derive systolic, diastolic, and mean arterial pressures. This technique permits rapid and accurate (±9 mmHg) measurements, provided that the bladder length and width are appropriately sized for the patient (Table 41.3). All devices should have a preset adult, pediatric, and neonatal mode which limits inflation pressures and prevents bruising or peripheral nerve injury in infants and small children.

Inaccurate measurements are often the result of motion artifacts, arrhythmias, or the inadvertent external compression of the blood pressure cuff by operating room personnel or equipment. Current recommendations for blood pressure cuff sizing and the pediatric blood pressure nomogram are based upon values utilizing measurements from the upper extremity [35]. Infants and small children present additional challenges since easy access to the upper extremity may not be possible, or in cases where trauma or burns preclude the use of traditional blood pressure cuff locations. In such circumstances, it has become a common practice to measure blood pressure via the calf in infants and neonates. However, there is a paucity of literature describing the presence or absence of statistically significant differences in measured values between the arm and calf, and none of which demonstrate a definitive change in long-term outcomes [36–38].

Temperature

Accurate temperature monitoring is important for neonates and infants because of the disproportionate relationship between body mass and surface area which predisposes to hypothermia. Infants exposed to cool environments have limited compensatory mechanisms (vasoconstriction and brown fat thermogenesis) which can be quickly overwhelmed. Systemic vasodilation that occurs following an inhalation induction with potent, volatile agents exacerbates radiant heat loss in these patients. The OR room thermostat is perhaps an underappreciated monitor, but the adjustment of ambient temperature from 30 to 33 °C may help mitigate large temperature swings during the induction period. Once the procedure is begun and the patient is covered by surgical drapes, the thermostat may be adjusted for OR personnel comfort.

Core temperature measurement via esophageal, rectal, or nasopharyngeal vectors is accurate and simple provided the monitors are placed at an appropriate depth. The thermistor probes should be positioned in the mid-esophagus, 2–5 cm into the rectum, and (for a nasopharyngeal probe) a depth equivalent to the measured distance between the nares and tragus, respectively. Although there may be minor accuracy differences between the temperature locations, for most surgical procedures, these variations are not likely to be clinically significant [39].

Forced-air warming devices such as the Bair Hugger (Arizant Healthcare, Inc., 10393 West 70th Street, Eden Prairie MN, USA) have proven effective in limiting radiant heat losses, particularly its pediatric "underbody" variant that provides large surface area coverage. When used appropriately with continuous core temperature monitoring, the risk of patient injury is quite low. However, adjustment of preset temperatures may be required for neonates and infants since extended-duration procedures are associated with a higher risk of iatrogenic hyperthermia [40].

Noninvasive or Invasive, Electronic: Surgery-Specific

The following section will describe the operating principles of a number of advanced monitors, their potential limitations, and applicability to pediatric care.

Arterial Blood Pressure

One of the most common sites for arterial access in neonates is the umbilical artery, because it is easily identified in the delivery suite and provides accurate blood pressure measurements and opportunities for serial sampling [41]. Typically, a 3.5-Fr catheter is passed (depth of insertion derived from a weight-based formula) after obtaining hemostatic control of the umbilical stump and dilating the artery so that the distal tip is above the diaphragm ("high position") or at the level of the third lumbar vertebral body ("low position"). Emboli, vascular injury, and renal artery thrombosis have been observed with umbilical artery catheters, but the overall complication rate is low [42].

Other sites for cannulation include the radial, dorsalis pedis, posterior tibial, femoral, or axillary arteries, and typical catheter sizes used for this procedure are 24 or 22 g. Regardless of the site selected, care must be taken to avoid bubbles, volume overload, and potential vascular injury. Typical transducer sets that utilize high-pressure bags are inappropriate for neonatal use and should be replaced by infusion pumps that deliver a saline solution at the rate of 1 mL/h to maintain line patency. Manual flushing is potentially dangerous, and even a 1-mL flush may be sufficient to deliver residual bubbles as far back as the vertebral artery.

The normal transmission of the arterial pulse results in a distal amplification of the systolic pressure, gradual attenuation of the dicrotic notch, and general preservation of diastolic and mean pressures. A more detailed interpretation of the waveform enhances its clinical utility (Fig. 41.1). A strong, upward slope of the waveform is consistent with preserved myocardial contractility, whereas a dampened slope suggests impairment. The dicrotic notch in infants is normally located in the upper half of the waveform, but can appear in the lower third of the descending waveform when there is decreased peripheral vascular resistance, a condition observed with patent ductus arteriosus and left-to-right shunting into the pulmonary vascular bed. Also, patients with intravascular depletion will exhibit a greater degree of respiratory variation while receiving positive-pressure ventilation [43].

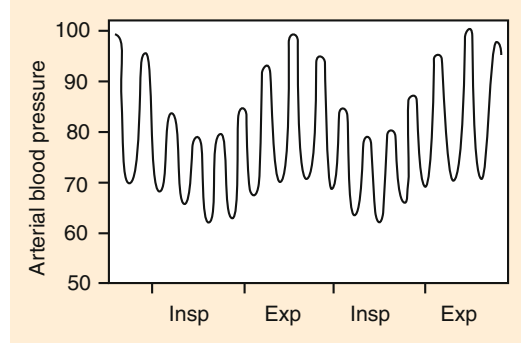

Fig. 41.1 Systemic arterial pressure showing pulsus paradoxus of 20 mmHg. Pulsus paradoxus is said to occur when there is a decrease in systolic pressure over 10 mmHg during inspiration. In cardiac tamponade, reduction in stroke volume occurs, and pulse pressure is usually less than 40 mmHg. In spontaneous breathing, there is an increase in venous return to the right heart during inspiration because of the decrease in intrathoracic pressure, causing distention of the right ventricle. The right ventricle cannot expand its free wall because of the fixed pericardial volume. Therefore, bulging of the interventricular septum occurs, compromising left ventricular filling. Pulsus paradoxus results because of this further reduction in left ventricular stroke volume during inspiration. The changes seen in pulsus paradoxus are an exaggeration of the normal changes seen during respiration. Paradox is easily measured directly from a tracing from an intra-arterial blood pressure line (Reproduced from Woodcock et al. [55]; kind permission from Springer Science + Business Media B.V)

Aside from technical difficulties in obtaining arterial access in neonates and infants, the mechanical limitations of transducer systems and their effect on interpretation of waveforms should be considered. Where feasible, a short-length catheter that has the largest possible diameter is

inserted and connected to noncompliant tubing with limited connections and stopcocks to preserve pressure wave transmission. The author utilizes one proximal stopcock for serial sampling and one distal stopcock for flushing and syringe-pump attachment. Visual inspection to ensure a bubble-free fluid line is essential. Periodic low-volume flushing and readjustment to right atrial or brain level will help minimize potential clotting and transducer drift. Over- or under-dampening may be addressed in those monitors that offer frequency modulation functions [44].

Central Venous Pressure

When necessary, the umbilical vein may be cannulated and the catheter tip advanced blindly through the ductus venosus and into the inferior vena cava and right atrium. Although the ductus venosus usually remains patent for the first 3–5 days of life, it is possible for the catheter to be misdirected into the hepatic vein system with the potential risk of portal vein thrombosis and liver necrosis. Radiographic confirmation of appropriate catheter positioning is essential.

Central venous access is appropriate for pediatric patients who are scheduled for procedures associated with large fluid shifts or hemorrhage, who may require potent vasoactive medication administration, or whose peripheral vasculature has been depleted of reasonable access options (the notorious "difficult stick"). The internal jugular, subclavian, and femoral veins have all been used successfully, and the application of ultrasound guidance technologies to facilitate central venous cannulation has become the standard of care. There are a number of methods to confirm correct positioning and include chest radiographs, echocardiography, ECG-guided insertions, and weight-based formulas [45, 46].

In healthy pediatric patients, the A, C, and V waveforms correspond to increased atrial pressure during right atrial contraction, upward tricuspid valve motion during early ventricular contraction, and diastolic filling against a closed tricuspid valve. Atrial fibrillation and supraventricular tachycardia will be marked by the loss of A waves and an increased V wave prominence because the AV valves are being pushed into partially emptied atria. Atrioventricular dissociation will display prominent A waves ("canon waves") and is representative of atrial contraction against a closed tricuspid valve. In patients with tricuspid regurgitation, the C wave and its corresponding X-descent will be replaced with a large positive wave representing retrograde blood flow through an incompetent valve; central venous pressure in this circumstance will be falsely high (Fig. 41.2).

Cardiac Output Monitoring

There are a number of devices suitable for pediatric use that will determine cardiac output. A more recent method introduced into some aspects of pediatric critical care is pulse-induced contour cardiac output, or PiCCO (PULSION Medical Systems AG, Munich, Germany). This device requires an internal jugular or subclavian central line and a femoral or brachial arterial catheter equipped with a thermistor. A premeasured cold saline injectate is administered and disperses thermally and volumetrically throughout the pulmonary and cardiac intravascular space. Upon reaching the thermistor, temperature differentials generate a dissipation curve to which the Stewart-Hamilton equation is applied to calculate cardiac output (Q).

The principle of contour analysis is based upon the assumption that the area described by the peak-to-peak interval of the arterial waveform is proportional to stroke volume. Therefore, cardiac output may be calculated by deriving the product of stroke volume and heart rate. In a given individual, aortic impedance remains a variable which must be periodically measured with the standard transpulmonary cold thermodilution technique to ensure system calibration. There appears to be good correlation of derived cardiac values obtained from PiCCO with those of traditional pulmonary artery catheters [47].

PiCCO has the potential to provide more hemodynamic data than the classic pulmonary artery catheter. Left heart failure, sepsis, trauma, and burns may alter membrane permeability,

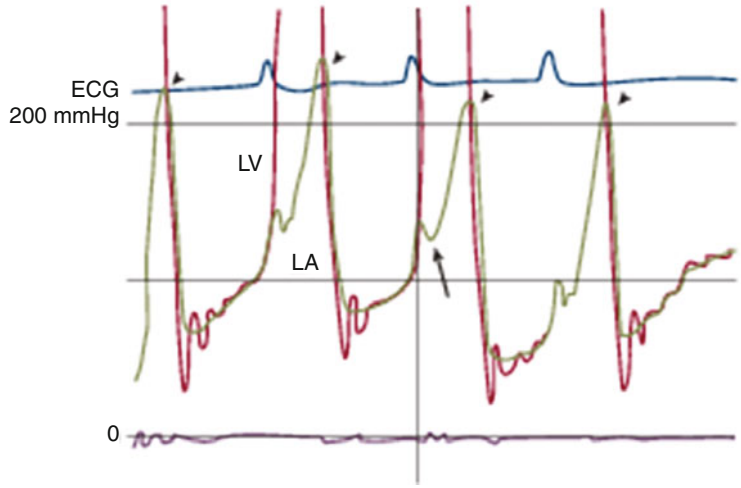

Fig. 41.2 The "V" wave of mitral regurgitation. This tracing shows a large left atrial "V" wave (*arrowheads*) occurring at the end of systole in a patient with atrial fibrillation. Following the "V" wave, there is a rapid fall in left atrial (*LA*) pressure, along the course of the declining left ventricular (*LV*) pressure. In diastole, LA and LV pressures are equalized. The *arrow* indicates a "C" wave deflection. Giant "V" waves are defined by a more than 10 mmHg increase above the mean pressure. They are not pathognomonic of mitral regurgitation and are typically blunted in patients with a large and compliant left atrium (Reproduced from O'Gara P [56]; kind permission from Springer Science + Business Media B.V)

plasma oncotic pressures, and the integrity of endothelial junctions, which results in the accumulation of interstitial and alveolar pulmonary fluids. This extravascular lung water (EVLW) is one of the derived parameters offered by PiCCO and may serve as an indicator of the severity of lung injury and potential mortality [48].

The device has some limitations. It is more invasive than a transesophageal Doppler but also provides more information if calibrated correctly. The PiCCO may also give erroneous data in the presence of intracardiac shunts.

Near-Infrared Spectroscopy

The Somanetics INVOS system (Somanetics, Inc., Troy, MI, USA) is a noninvasive monitor of brain tissue oxygenation that analyzes the absorption spectra of 2–4 wavelengths of infrared light at 700–1,000 nm. The derived value represents regional cerebral oxygenation (rSO_2) and monitors this trend over time. Since rSO_2 represents the balance between cerebral oxygen consumption and delivery, this value may be influenced by many variables. A number of animal models have delineated a minimum rSO_2 that correlates with progressive ischemic brain injury [49, 50]. In general, most clinicians accept that an absolute decline of >20 % from baseline levels or a rSO_2 reading of 45–50 % is an indicator for appropriate clinical interventions to restore cerebral oxygen metabolism. This threshold is supported by new-onset MRI lesions detected after pediatric cardiac surgery [51].

A recent literature review supports the use of NIRS technology as a reliable cerebral oxygenation monitor whose clinical utility in several pediatric settings is still expanding [52]. However, there are no published, prospective studies delineating long-term clinical outcome differences.

Depth of Anesthesia

Several devices offer EEG signal processing (often enhanced by proprietary variants of Fourier

transformation) to derive a single value correlating to the patient's depth of sedation. The Bispectral Index (BIS) Monitor (Aspect Medical Systems, Natick, MA) uses a range of 0–100; 0 is equivalent to an isoelectric EEG, and 90–100 represents an awake state in infants and children [53].

However, there appears to be significant individual variability which limits the utility of BIS as an indicator of anesthetic depth and a tool to assess the risk of awareness. The choice of anesthetic agents may alter the effective range of BIS readings [54]. The device is also sensitive to motion artifacts, the use of electrocautery, and EMG impulses. It remains unclear if BIS and similar devices offer improved pediatric outcomes, especially for those patient subsets with preexisting neurological deficits.

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Fetal Monitoring

42

Matthew V. Buck and Michael G. Richardson

Intrapartum Fetal Hypoxemia and Neurologic Injury

Electronic fetal heart rate monitoring (EFM), also known as tococardiography, was introduced in the 1960s. It rapidly proliferated in clinical practice as a promising solution to the problems of peripartum neonatal mortality and neurological morbidity, including cerebral palsy (CP). EFM was anticipated to help identify the onset of birth asphyxia, thought to be the primary cause of these adverse neonatal outcomes, and to facilitate immediate obstetric intervention [1]. Numerous lines of evidence have subsequently cast doubt on the causal role of perinatal hypoxia in poor neonatal neurologic outcomes. For example, decades of widespread EFM use has resulted in a dramatic fivefold increase in cesarean deliveries based on EFM indications, yet no accompanying decline in CP rates (approximately 2–3/1,000 births) [2, 3]. Furthermore, the prevalence of CP in highly developed countries has remained comparable to that in less developed countries where emergent cesarean delivery based on EFM data is limited or absent [3]. It is now thought that CP may result primarily from antenatal developmental events, and when associated with ominous perinatal fetal heart rate (FHR) patterns, the latter may merely reflect the presence of that preexisting developmental abnormality [2]. On the other hand, EFM may reduce the incidence of early neonatal seizures [4, 5] and mortality [4]. Although intrapartum hypoxia-ischemia may be causative in only a small minority of CP cases among non-anomalous term neonates (10–14 %) [3, 6], it appears to play a role nonetheless [6, 7]. Of note, several common acute catastrophic events (abruption, uterine rupture, cord accidents, amniotic fluid embolism) and other obstetric complications (e.g., preeclampsia) are often accompanied by ominous EFM patterns and may contribute to hypoxic-ischemic encephalopathy (HIE) [3, 7].

Although the exact role of peripartum hypoxic ischemia in neonatal neurologic outcomes remains unclear, the detection of intrapartum hypoxia remains an important goal in modern obstetric practice, and EFM remains the current standard for detection, despite significant limitations (see below). Initially used to monitor high-risk pregnancies, EFM is now used in the vast majority of all deliveries. Because of EFM's prominent role in the obstetrician's peripartum management decisions and assumptions about fetal well-being, this chapter focuses primarily on this modality.

Technical and Clinical Aspects

Cremer reported the first-recorded fetal electrocardiogram (fECG) in 1906 [8]. Early EFM utilized electrodes applied to the maternal abdomen

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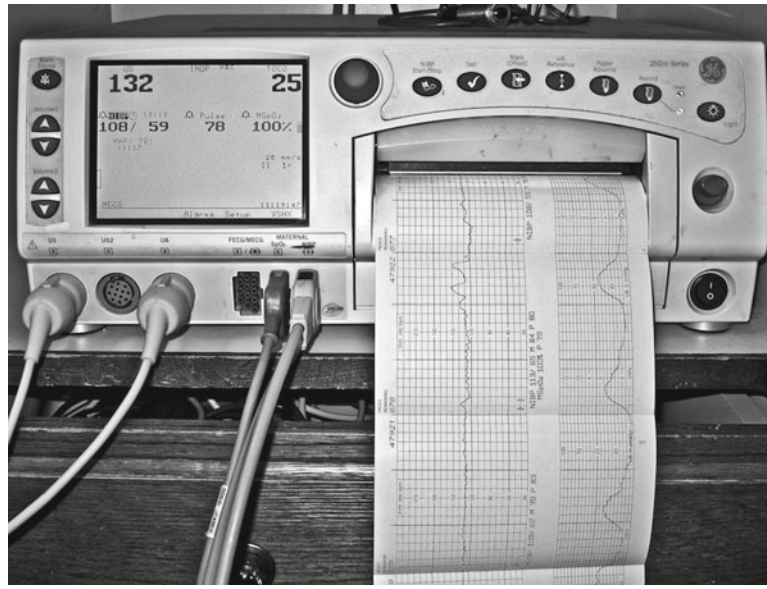

Fig. 42.1 Fetal/maternal monitor. Inputs include two channels for external fetal Doppler (US, US2), one for either external tocodynamometer or intrauterine pressure catheter (UA), fetal scalp electrode or maternal electrocardiogram (FECG/MECG), maternal pulse oximetry (SpO_2), and automated maternal oscillometric blood pressure (NIBP). Continuous real-time numerical data are displayed on the electronic screen, while a paper recorder captures the fetal heart rate and uterine contraction pattern tracings, plus maternal numerical physiologic data (blood pressure, pulse rate, pulse oximetry)

to record fECG and calculated FHR from R-R intervals [9]. Measurements were difficult during labor, owing to fetal movement and confounding maternal ECG signals. Advancements in technology and the advent of the fetal scalp electrode [8, 9] made routine EFM feasible, and commercially available EFM began to replace intermittent auscultation of fetal heart tones using the fetoscope by the late 1960s and early 1970s. The development of Doppler ultrasound technology and microprocessor autocorrelation (separation of fetal heart contraction signals from fetal motion artifact) made possible the reliable and sensitive FHR detection capabilities of maternal/fetal monitors used today.

Modern monitors include several inputs—one or two channels for fetal Doppler ultrasound input, one for recording uterine contractions, and one for either fetal or maternal ECG input. Most monitors also integrate maternal physiologic inputs (SpO_2, NIBP, HR) (Fig. 42.1). Outputs typically include (1) the device's electronic monitoring screen (numerical FHR, uterine contractions, and maternal physiologic data), (2) audio output (fetal heart rates, maternal pulse oximetry), (3) a paper printer, (4) VGA output for bedside video display, and (5) digital output. The latter allows for interface with clinical information systems, which capture and archive integrated physiologic, clinical, and census data for large numbers of patients on the maternal unit. Such systems can deliver live monitoring data for multiple patients to multiple clinical workstation computers (Fig. 42.2) and feature automated alarm algorithms and capabilities for sophisticated review of stored data.

FHR input to the fetal/maternal monitor is most commonly delivered by an external Doppler transducer (Fig. 42.3) applied to the surface of the parturient's abdomen and directed at the fetal heart (Fig. 42.4). Alternatively, a spiral ECG electrode (Fig. 42.5) is inserted into the fetal scalp surface skin providing direct ECG input for highly accurate beat-to-beat measurement of the R-R interval and calculation of FHR and enabling more complex monitoring modalities (see STAN,

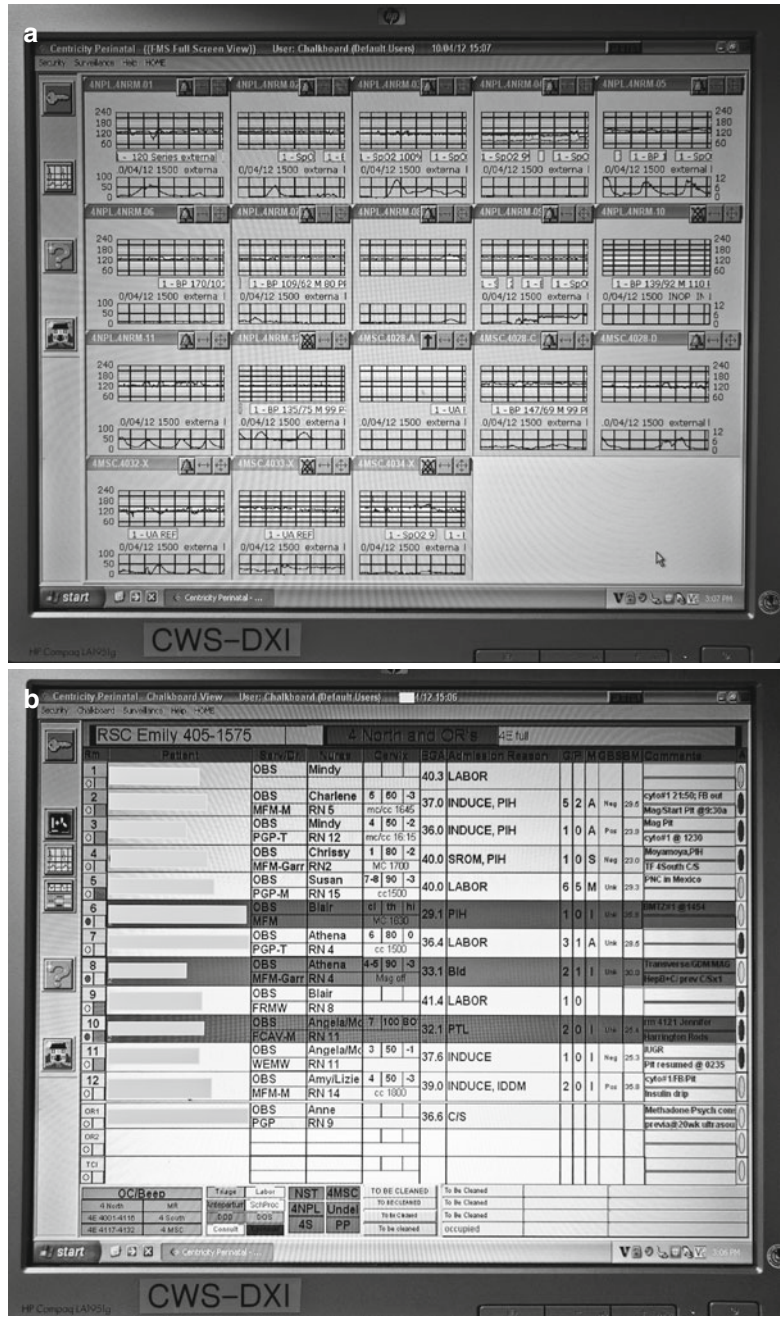

Fig. 42.2 (**a**, **b**) Clinical information system software receives, organizes, displays, and archives monitoring input from multiple patients

below). FHR patterns are interpreted in relationship to uterine contractions. To record the latter, an external tocodynamometer serves as the most common source of input (see Fig. 42.3). This noninvasive pressure transducer is strapped onto the parturient's abdomen over the uterine fundus (see Fig. 42.4). Uterine contractions increase the abdominal circumferential distance, increasing transduced pressure. Only the timing and frequency of contractions, not contraction strength, can be inferred from the resulting qualitative recording. Insertion of an internal intrauterine pressure catheter (IUPC) (Fig. 42.6) permits quantitative assessment of uterine contraction

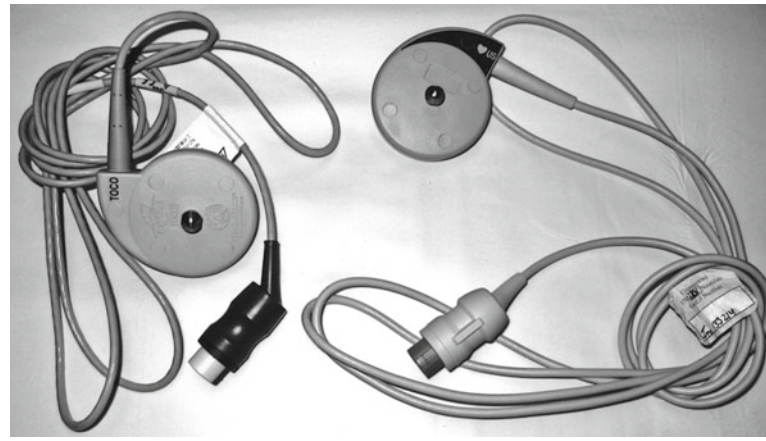

Fig. 42.3 External monitors include tocodynamometer pressure transducer (*left*) and fetal heart rate Doppler monitor (*right*)

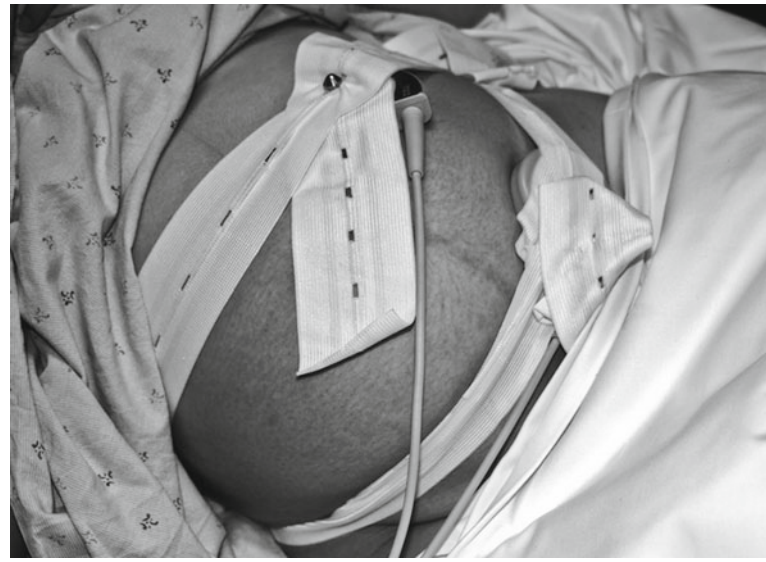

Fig. 42.4 External monitors applied to the gravid abdomen with circumferential elastic straps

strength, useful in more precisely guiding titration of uterotonic drugs during labor induction or augmentation. Intrauterine pressure is either transduced directly at the tip by an integrated transducer or is conducted through the length of the IUPC device to a pressure transducer located at the distal end of the monitoring cable that connects the IUPC device to the monitor. In addition to monitoring IUP, the device has a multi-orifice port that conducts amniotic fluid upon correct insertion into the uterus and which can be used to infuse saline during amnioinfusion procedures (see Fig. 42.6).

Benefits of external monitors are that they may be applied and removed intermittently, are completely noninvasive, and provide adequate and reliable information under most circumstances. However, factors such as obesity or fetal prematurity may affect signal quality of external monitors. The internal monitors confer benefits of direct, quantitative, and reliable measurement of ECG and IUP, which may facilitate peripartum obstetric management in certain circumstances. Although IUPC and FSE technical improvements have improved safety and accuracy, application of FSE does require rupture of membranes and presentation of the vertex, while IUPC requires adequate cervical dilation for insertion. Both devices have some contraindications (e.g., chorioamnionitis, placenta previa, other bleeding complications).

Wireless telemetric EFM has recently been introduced (GE Mini Telemetry System), eliminating cable connections to the fetal/maternal monitor, allowing greater mobility in labor (e.g., walking), and even monitoring during labor aqua-therapy. The lightweight (under six pounds) portable transmitter has three input ports—FHR ultrasound transducer, external tocodynamometer or IUPC, and maternal or fetal ECG. Output signals are transmitted to a receiver connected to the maternal/fetal monitor.

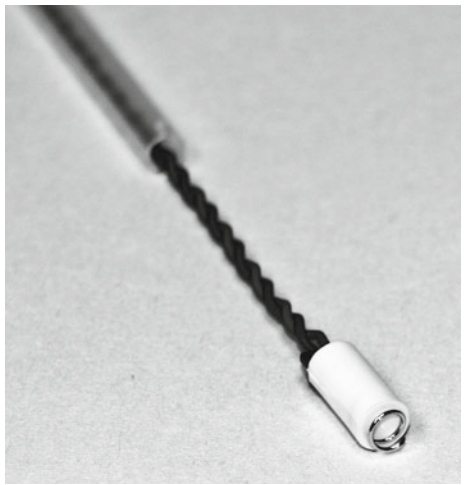

Fig. 42.5 Fetal scalp electrode, showing sharp tip that affixes the spiral wire electrode to the fetal presenting part

EFM as a Screening Test: The Problem of Unnecessary Cesarean Deliveries

The contemporary approach to introducing new therapies or diagnostic tests involves evaluation of effectiveness, safety, risk, and costs. Application of screening tests or programs to large populations with low prevalence of disease may generate a high rate of false-positive results, which may then trigger a cascade of additional interventions (further testing or therapy) along with their own complications and adverse psychological consequences for healthy individuals. For these reasons, requirements for screening programs must be especially stringent [10]. Unfortunately, the introduction of EFM preceded this contemporary rigorous approach by several decades, and EFM rapidly gained widespread acceptance as a screening program (rather than a diagnostic test reserved for specific indications) in the clinical obstetric realm [11]. This practice continues despite ample evidence that EFM increases cesarean delivery rates without

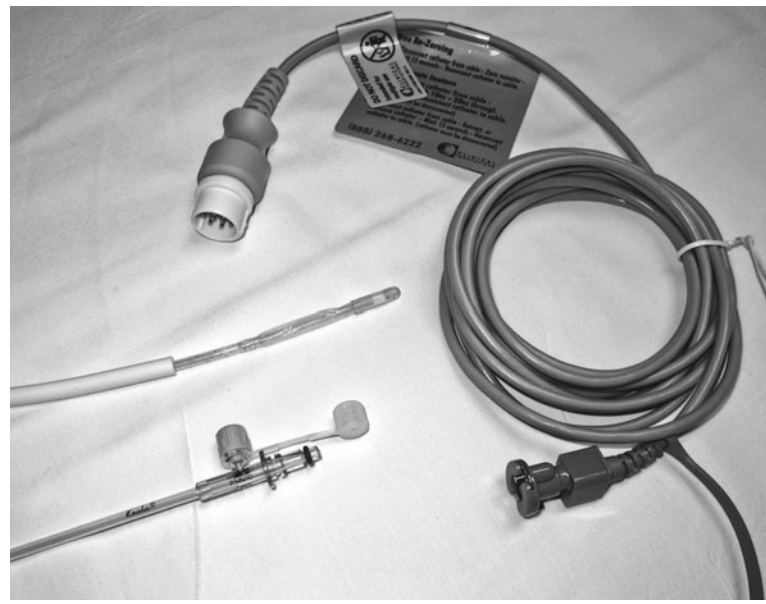

Fig. 42.6 Internal uterine pressure catheter, or IUPC (*left*), including the intrauterine pressure port and a balloon to keep the catheter in place (*middle left*) and the proximal catheter port (*lower left*). The latter is connected to the distal end of the cable (*lower right*) containing a pressure transducer. The proximal end of the cable (*top left*) is connected to the fetal/maternal monitor. Some IUPCs are designed with the pressure transducer embedded in the tip of the device

demonstrable neonatal outcome benefit [5]. This is thought to reflect widespread application of a test with poor validity to a population with low prevalence of fetal jeopardy [11]. The Royal College of Obstetrics and Gynecology (RCOG) and the British National Institute of Clinical Excellence recommend reserving intrapartum continuous EFM for high-risk, not low-risk, pregnancies [12]. ACOG considers continuous EFM equivalent to intermittent fetal auscultation (IFA) in uncomplicated pregnancies but falls short of recommending preference for the latter [13]. Despite lack of benefit and potential adverse consequences, continuous EFM continues to enjoy widespread use as a screening modality (versus indicated diagnostic test) in the United States [13]. Its persistence is likely due to a combination of overriding medical and legal fear of poor neonatal outcomes, underappreciated maternal consequences of unnecessary surgery, and inappropriately overstated beliefs about EFM's contribution to its high negative predictive value (more a function of low prevalence of fetal jeopardy, rather than low likelihood ratio for a negative test) [11, 14].

Toward Standardization of Interpretation

Instead of attempting to curb EFM's routine use and restricting it to specific indications [11], recent efforts have targeted improving EFM's diagnostic performance. One persistent weakness of EFM is poor inter- and intra-observer FHR waveform interpretation reliability, owing to its subjective nature [14]. The first consensus on standardized, unambiguous definitions for FHR evaluation did not appear until 1997 [15] and was endorsed by the American College of Obstetricians and Gynecologists (ACOG). The statement was limited to recommendations for defining FHR characteristics, with the goals of promoting greater "evidence-based clinical management of fetal compromise" and of enhancing research on assessment of EFM's predictive value [16]. Subsequently, EFM interpretation classification schemes and intrapartum intervention responses were developed and proposed in the United Kingdom and Canada [16]. In 2008, a second US consensus statement clarified and revised the 1997 nomenclature (Table 42.1) and proposed a standard 3-tiered classification system for FHR tracings (Table 42.2) [16]. Because FHR tracings are interpreted in relation to uterine contraction activity, clarification regarding the latter was included—frequency (number per 10-min window, averaged over 30 min) is characterized as either normal (≤5/10 min) or tachysystole (>5/10 min). The 2008 statement included a dozen key assumptions and factors common to EFM interpretation—subjective elements of interpretation (visual; emphasis on patterns; context-dependence); the temporally dynamic nature of FHR patterns; additional terminology/characteristics (e.g., baseline, periodic, episodic; gradual, abrupt; abandonment of short-/long-term and beat-to-beat variability qualifiers); and elements of full EFM description. Key concepts regarding interpretation standardization were emphasized (e.g., the reliability of moderate FHR variability or FHR accelerations, in predicting absence of fetal metabolic acidemia, and the unreliability of their absence in predicting presence of fetal acidemia). The statement noted the paucity of research on EFM during the intervening decade despite the "high penetrance of this technology in obstetric practice" and urged intensification of high-quality research efforts targeting priority areas—indeterminate FHR patterns; duration of patterns on outcomes; the interaction between uterine activity, EFM, and outcomes; EFM education programs; computerized interpretation systems; EFM and outcomes databases; and EFM adjunct technologies (e.g., STAN).

Toward Standardization of Intrapartum Management

In addition to uniformity of definitions and interpretation, evolution toward a more consistent, evidence-based management framework is currently advocated [16–18]. ACOG has integrated the three-tiered EFM category scheme into a standardized management algorithm,

Table 42.1 Definitions and characteristics recommended by the American College of Obstetricians and Gynecologists to describe fetal heart rate patterns

Baseline	Mean heart rate, rounded to nearest 5 bpm
	Measured in 10-min window, excluding accelerations/decelerations, and periods of marked variability (>25 bpm)
	Requires ≥2 min of identifiable baseline segment (not necessarily contiguous)
	Quantified as rate (bpm)
	<110: "bradycardia"; 110–160: "Normal"; >160: "tachycardia"
Variability	Fluctuations, irregular in amplitude and frequency
	Measured in 10-min window, excluding accelerations/decelerations, and periods of marked variability (>25 bpm)
	Quantified as amplitude range (trough-to-peak; bpm)
	Undetectable: "absent"; ≤5: "minimal"; 6–25: "moderate"; ≥25: "marked"
Acceleration	Visually apparent increase
	Magnitude: amplitude from baseline to peak (bpm)
	Duration: from beginning to return to baseline (min and sec)
	Abrupt increase, ≥15 bpm, lasting ≥15 s (≥10 bpm ≥10 s before 32 week EGA)
	Peak amplitude occurs <30 s after onset
	Peak amplitude occurs <30 s after onset
	Duration ≥2 min, ≤10 min: "prolonged acceleration"
	Duration ≥10 min: "baseline change"
Decelerations	Visually apparent decrease
	Magnitude: amplitude from baseline to nadir (bpm)
	Duration: from beginning to return to baseline (min and sec)
	"Intermittent" (occur with <50 % of uterine contractions) vs. "recurrent" (≥50 %)
	Grading systems based on depth, absolute nadir, and duration have been proposed, but predictive value is unclear
Early	Usually symmetrical; gradual (onset to nadir ≥30 s) decrease and return
	FHR nadir coincides with peak of uterine contraction
	Often, the onset, nadir, end coincide with beginning, peak, end of uterine contraction
Late	Usually symmetrical; gradual (onset to nadir ≥30 s) decrease and return
	FHR nadir occurs *after* peak of uterine contraction
	Usually, the onset, nadir, and end all occur after the beginning, peak, and end of uterine contraction, respectively
Variable	Abrupt decrease (onset to nadir <30 s); ≥15 bpm, lasting ≥ 15 s and < 2 min
	If occurring with uterine contractions, onset, depth, and duration often vary with successive contractions
	May be accompanied by other characteristics of uncertain significance (e.g., slow FHR return after contraction end; biphasic decelerations; tachycardia after decelerations, accelerations preceding and/or following ["shoulders," "overshoots,"], FHR fluctuations in deceleration trough)
Prolonged	≥ 15 bpm, lasting ≥2 min, <10 min (≥ 10 min: baseline change)
Sinusoidal	Visually apparent, smooth, sine wavelike undulating pattern in baseline
	Cycle frequency of 3–5/min, persisting ≥20 min

Modified from Macones et al. [16]

including intrauterine resuscitation measures recommended for category II and III EFM tracings [17]. It is assumed that most category III tracings, as well as some category II tracings, reflect fetal metabolic acidosis, a consequence of insufficient fetal oxygen delivery. The goal of intrauterine resuscitation measures administered in response to category II or III tracings is to augment fetal oxygen delivery to alleviate hypoxia-ischemia [18, 19]. Specific resuscitative measures address

Table 42.2 Three-tier interpretation system recommended by the American College of Obstetricians and Gynecologists to classify fetal heart rate patterns, along with recommended intervention responses

Category	Criteria	Interpretation (at time of observation)	Action
I	All must be present	Normal	Routine monitoring
	Normal baseline (110–160) Moderate variability Absent late or variable decelerations Early decelerations and accelerations may be present or absent	Strongly predictive of normal fetal acid–base status	No specific action
II	All EFM tracings not categorized as category I or III[b]	Indeterminate	Continue surveillance and reevaluate, considering entire clinical context, and administer intrauterine resuscitation measures
		Not predictive of abnormal fetal acid–base status Inadequate evidence to classify as Cat I or III	If accelerations, or moderate variability → continue surveillance
			If accelerations absent, or absent/minimal variability, and no improvement, consider delivery
III	Either	Abnormal	Prompt evaluation
	Absent variability *and* any of one of recurrent late decelerations, variable decelerations, or bradycardia	Predictive of abnormal fetal acid–base status	Prepare for delivery and attempt to resolve abnormal EFM pattern (intrauterine resuscitation to improve fetal oxygen delivery)
	Sinusoidal pattern		If unresolved, consider prompt delivery

Modified from Macones et al. [16]

[a]Examples of category II tracings: bradycardia without absent variability; tachycardia; minimal or marked variability; absent variability without recurrent decelerations; absence of induced accelerations after fetal stimulation; recurrent variable decelerations plus minimal or moderate variability; prolonged deceleration; recurrent late decelerations with moderate variability; and variable decelerations with other characteristics [slow return to baseline; "shoulders"]

the potential pathophysiologic basis of the problem and are understood when linked to the numerous steps in the oxygen pathway from environment to fetus (Table 42.3). Miller and Miller [18] have proposed physiology-based "basic principles" of EFM interpretation—(1) significant FHR decelerations reflect interruption oxygen transfer, (2) moderate variability and/or accelerations preclude fetal metabolic acidemia, and (3) neurologic injury caused by fetal hypoxemia does not occur until progression to significant fetal metabolic acidosis. They hypothesize that enhanced safety is achievable by combining these "factually accurate principles," standardized EFM practices, and a structured, simplified management and intervention algorithm. It remains to be determined whether this simplified algorithmic approach will be accepted into clinical practice, much less produce the improvements in outcomes that are intended.

Further study and modification of this approach to improving EFM performance and standardizing intervention can be anticipated. A notable concern regarding the three-tier classification scheme is that the intermediate category II tracings comprise the bulk of fetal EFM tracings and are accompanied by the greatest uncertainty regarding fetal condition. Parer and Ikeda have proposed a five-tier system, based on 134 different permutations of rigidly defined FHR characteristics, and reflecting increasing levels of fetal acidemia risk [20]. Each level of the framework is linked to a specific management proposal, escalating in a manner appropriate to fetal risk. The intermediate levels emphasize escalating surveillance, assessment, in utero

Table 42.3 Physiologic rationale integrating connecting oxygen transfer pathway steps, presumed barriers, and problem-specific interventions to improve gas transfer

O_2 pathway step	Underlying physiology	Barriers/problems	Remedy (consider relevant specific interventions)
Environment	FiO_2	Hypoxemic environment	Augment FiO_2 (supplemental O_2 by facemask or mechanical ventilation)
→ Maternal lungs	Ventilation	Hypoventilation or apnea. Causes	Augment maternal ventilation
		Obstruction	Ensure airway patency (e.g., swelling; bronchospasm; trauma; foreign body)
		Strength	Manage/antagonize weakness (e.g., Ca^{++} for Mg^{++} toxicity; assist ventilation for high spinal or unconsciousness)
		Ventilatory drive (CO_2 responsiveness)	Augment/manage CO_2 drive (verbal command; naloxone for opioid toxicity)
→ Maternal blood	Gas exchange	V/Q mismatch; shunt (including atelectasis)	Alveolar recruitment (treat pulmonary edema; treat bronchospasm; mechanical ventilation; incentive inspirometry)
	Oxygen-hemoglobin interaction	Anemia; preeclampsia (P_{50} shift 30 → 24 mmHg)	Increase hemoglobin concentration (transfusion)
→ Left heart	Pulmonary circulation	Diminished pulmonary blood flow	Augment pulmonary blood flow (IVF, vasoconstrictors; consider maternal shunt)
→ Maternal systemic circulation	Maternal cardiac output	Diminished CO	Augment cardiac output (vasoconstrictors; IV fluid)
→ Uterine arteries	Uterine artery blood flow	1. Systemic hypotension	1. Augment CO or SVR (LUD to relieve IVC compression; vasopressor; IVF)
		2. Aortic compression	2. LUD to relieve aortic compression
		3. High resistance	3. Relax uterus (cease uterotonic; administer tocolytic)
→ Intervillous space	Low resistance	Excessive uterine tone	Relax uterus (cease uterotonic; administer tocolytic)
→ Fetal blood	Gas exchange surface area	Reduced surface area (e.g., abruption), or barrier to exchange (e.g., placental senescence)	n/a [no known interventions available]
→ Fetal circulation	Umbilical cord	Cord compression or insufficiency	Alleviate compression → reposition mother; amnioinfusion

Modified from Miller and Miller [18]
Abbreviations: *FiO_2* inspired O_2 fraction, *IVF* intravenous fluid, *CO* cardiac output, *SVR* systemic vascular resistance, *LUD* left uterine displacement

resuscitation, and preparation for potential surgical intervention. Despite the complexity of their classification scheme, they observed moderate to substantial interpretation agreement between experts and comparable results using a computerized interpretation program [21]. Compared to the three-tier classification system, sensitivity for identifying acidemic fetuses may be greater using the five-tier system [22]. The latter has recently been formally proposed for use in Japan [23].

Alternative and Adjunct Modalities

The early recognition of EFM limitations in solving the CP problem prompted a search for alternative or complementary fetal monitoring and assessment modalities. *Fetal scalp blood pH sampling* was introduced in the 1960s as an adjunct to help assess equivocal EFM patterns, to serve as "the final arbiter of fetal condition in the presence of abnormal intrapartum FHR patterns"

and to reduce unnecessary cesarean delivery [24]. Conflicting reports in the 1980s regarding scalp blood sampling's usefulness, lack of guidance or consensus regarding its role, and simultaneous advances in EFR interpretation resulted in the gradual phasing out of this modality by the end of the twentieth century [24]. Fetal scalp pH has remained popular outside the U.S., and lactate sampling may be a useful alternative [25]. *Reflectance pulse oximetry* was developed in early 2000s, as a promising fetal assessment adjunct. Its clinical usefulness and acceptance has been slowed by technical limitations and poor predictive accuracy [26–28]. Subsequent studies, including a NICHD trial [29], failed to demonstrate benefit and have relegated this modality to research until further refinements are developed and clinical usefulness is established.

Fetal ST segment analysis (*STAN*), requiring application of a fetal scalp electrode to capture the fECG, is being actively studied as a potential enhancement to EFM. Preliminary developmental work in mammalian fetal models during mid-1970s through early 1980s established increased T-wave amplitude relative to QRS amplitude (T/QRS ratio) as a marker for fetal anaerobic metabolism during graded asphyxia. These fECG changes were observed to occur simultaneously with somatosensory-evoked EEG responses and to precede asphyxia-induced cardiovascular compromise in fetal mammalian studies [30]. Correlation between fECG ST segment changes and other physiologic evidence of anaerobic metabolism (specifically that of mammalian fetal myocardium) was subsequently confirmed. Recording system improvements were made and promising observational clinical study results in humans were published in the 1980s [30]. This led to two randomized clinical trials (RCTs) in the 1990s comparing EFM versus EFM + STAN [31, 32], which demonstrated both reduced fetal metabolic acidosis and reduced operative delivery for non-reassuring EFM. Follow-up of neonates revealed a reduction in encephalopathy [33]. Benefits from combined FHR + STAN monitoring have not been as dramatic in subsequent prospective trials [34]. A single institution, 7-year, prospective, cohort study of nearly 13,000 term pregnancies in Sweden demonstrated a significant reduction in fetal metabolic acidosis, while operative delivery rates remained stable and STAN monitoring increased from 28 to 70 % [35]. A recent meta-analysis of the five RCTs to date failed to demonstrate improved perinatal outcomes, other than reduced operative vaginal delivery rates, and this reduction was very small (13.6 % vs. 15.2 %) [36]. Despite inclusion of over 15,000 pregnancies, the studies are underpowered to make conclusions on important but rare outcomes of interest (encephalopathy; death). Amidst growing clinical use of STAN monitoring in some European countries, health authorities in Sweden issued a recommendation that, lacking sufficient evidence for maternal and neonatal benefit, STAN should be limited to research protocols [37]. This recommendation remains controversial [38]. Clinical use of STAN in the United States has trailed and patiently awaits conclusion of a large ongoing NICHD trial designed to better determine if and how STAN may serve to advance neonatal outcomes (ClinicalTrials.gov identifier: NCT01131260).

Finally, coming full circle, there has been renewed interested in intermittent fetal auscultation as a monitoring modality for low-risk parturients. Proponents acknowledge the need for staff skill development and continuous presence, definition, and identification of "low risk" and a protocol for moving to EFM when indicated [14, 18].

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Ultrasound

43

Rajnish K. Gupta and Clifford Bowens Jr.

Ultrasound machines have become smaller and more affordable over the last decade, thereby increasing their utility for the anesthesia provider. Ultrasounds are now used for vascular access, regional anesthesia, echocardiography, chronic pain procedures, and diagnostic procedures such as pneumothorax evaluation. These new, smaller machines provide the flexibility of larger more expensive ultrasound devices but are more portable and user friendly. However, without an understanding of the physics and mechanics of ultrasound, the provider can become confused and frustrated with the device.

The key components of the ultrasound machine are the computer/CPU, the transducer probe, and the display. The sequence of events in acquiring an ultrasound image includes application of the transducer to the skin surface, transmission of pulses of ultrasound signal into the tissue, reflection of the signal from tissue structures, reception of the signal by the transducer probe, processing of all the returning signals into a composite image, and display of the image on the monitor. Each of these steps involves multiple variables and considerations when using an ultrasound (Fig. 43.1).

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Sound

Sound waves are mechanical energy that is transmitted as pressure waves through a material medium. Sound waves cannot exist in a vacuum, since they require the movement of molecules or particles to propagate. These pressure waves are a series of alternating **compression** and **rarefaction** zones where the particles in the matter are densely packed together then pulled farther apart, respectively. This alternating pattern is typically depicted as a wave.

Frequency and Wavelength

Frequency is the number of waves per second transmitted by the ultrasound transducer. Frequency is usually described in terms of Hertz (Hz), which is defined as cycles/second. Megahertz (MHz) are the number of million cycles/second generated by the ultrasound. Most modern ultrasound machines can generate frequencies between 2 and 15 MHz depending on which ultrasound transducer is used.

Frequency (f) and **wavelength** (λ) are inverse properties of each other. The wavelength is the distance between two waves and is calculated by the ratio of the velocity (c) to the frequency.

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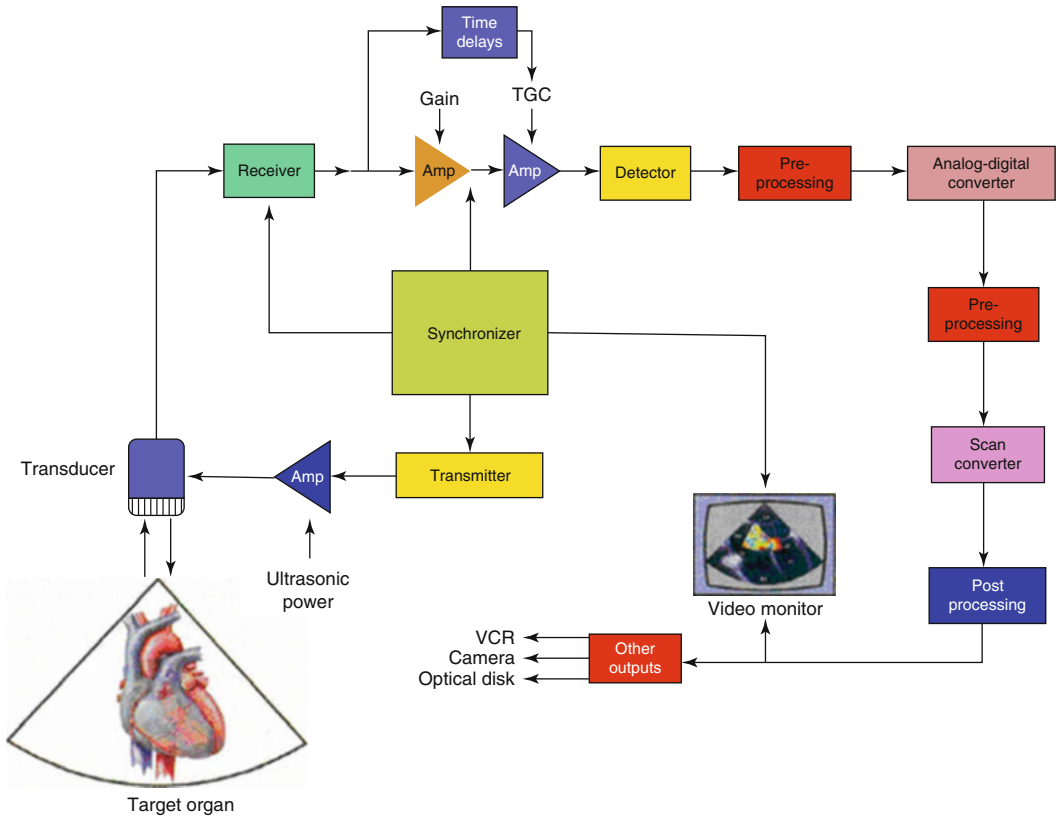

Fig. 43.1 A basic block diagram of the essential ultrasound system components that are required to generate, transmit, receive, process, and display two-dimensional echocardiographic images. *AMP* amplifier, *TGC* time-gain compensation, *VCR* video cassette recorder (Reproduced with permission from Savage RM, Aronson S. Comprehensive textbook of intraoperative transesophageal echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 52)

Therefore, the higher the frequency is, the shorter the wavelength.

$$\lambda = c / f$$

In ultrasonography, a higher-frequency signal (shorter wavelength) provides the capacity for higher resolution images. The ability to distinguish two adjacent structures as separate entities is defined as **resolution**. If the distance between two entities is greater than the wavelength of the transmitted ultrasound signal, then the ultrasound can resolve these as separate items. If the distance between these two objects is smaller than the wavelength of the ultrasound signal, then ultrasound will not be able to distinguish between the objects (Fig. 43.2).

The consequence of a higher-frequency signal is the loss of signal strength and penetration, referred to as signal **attenuation** (Fig. 43.3). Since the ultrasound beam reflects off more objects, less of the signal is available to transmit deeper into the tissue. A low-frequency signal has a longer wavelength and will continue to have enough power to penetrate deeper into tissue without attenuation. However, a lower-frequency signal does not have the same resolution as a higher-frequency signal. This is a significant trade-off when deciding which frequency setting and ultrasound transducer to use (Fig. 43.4)

Piezoelectric Crystal

Piezoelectric crystals are embedded in the ultrasound transducer (Fig. 43.5). These are pressure-electric crystals, typically made of quartz, that

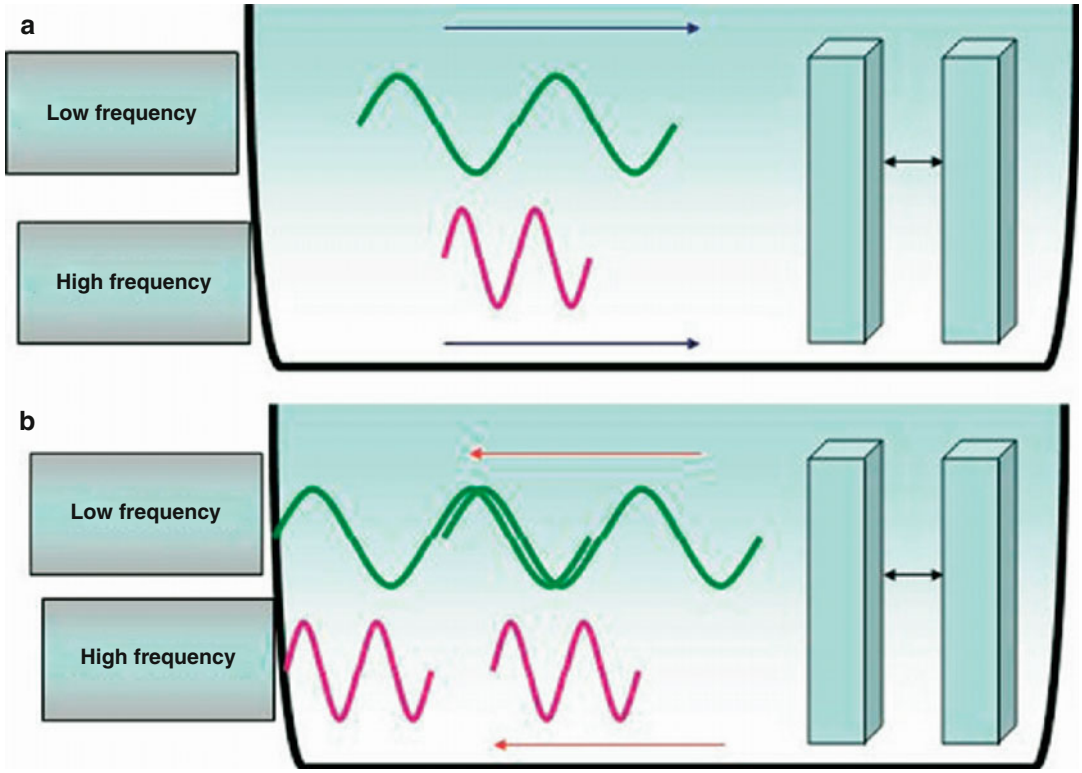

Fig. 43.2 Axial resolution is the ability to discern objects in line with the axis of the ultrasound beam. The axial resolution of an ultrasound wave is dependent upon wavelength (λ), frequency (f), and the speed of ultrasound in tissue (c). In human tissue $c = 1{,}540$ m/s, and, therefore, $\lambda = c/f$. Axial resolution is roughly described as one-half of the pulse length in millimeters. (**a**) A low-frequency and a high-frequency pulse (2-cycle pulse, which is equal to 2 λ) propagating toward two rectangular objects. (**b**) The waves returning toward the probe following the reflection off the objects. The blue arrows depict the ultrasound pulse traveling toward the two objects, and the *red arrows* depict the ultrasound traveling back toward the transducer. The lower-frequency ultrasound has a wavelength that is larger than the distance between the objects (indicated by *black arrows*). Therefore, the returning signal from both objects will overlap; therefore, the probe will interpret this signal as a single object. The higher-frequency pulse discerns two separate objects because the wavelength is much shorter than the distance between the two objects and the returning waves will not overlap (Reproduced with permission from Sites BD, Brull R, Chan VWS, Spence BC, Gallagher J, Beach ML, et al. Artifacts and pitfall errors associated with ultrasound-guided regional anesthesia. Part I: understanding the basic principles of ultrasound physics and machine operations. Reg Anesth Pain Med. 2007;32(5):412–8)

respond to both mechanical and electrical stimulation. When an electrical stimulus or current is applied to the crystals, they change shape rapidly and create vibrations. Based on the type and size of crystal, these vibrations can be emitted in a variety of frequencies within the ultrasonic spectrum. These vibrations are then filtered and focused by the ultrasound transducer itself and transmitted into the tissue. Conversely, when these crystals receive a mechanical stress (returning ultrasound signal), they also emit an electrical current. Therefore, when sound waves reflect back to the ultrasound transducer, they cause mechanical deformation of the piezoelectric crystals, which generates electrical signals that the CPU in the ultrasound machine translates into visual images.

Transducer Probes

Ultrasound transducer probes come in a variety of shapes and sizes with various functions. For most purposes, large or small linear or curvilinear probes are used; however, there are specialized probes as well. Small linear "hockey stick"

probes are used for very small structures, such as in pediatrics. Transthoracic and transesophageal probes are used for echocardiography. Transvaginal probes are utilized for fetal ultrasound in obstetrics.

All probes have the ability to produce a range of ultrasound frequencies. However, the large curvilinear transducers typically produce a lower-frequency range (e.g., 2–5 MHz) to allow for deeper penetration of the ultrasound signal. The small linear probes typically produce a higher-frequency range (e.g., 12–15 MHz) to allow for greater resolution of shallow structures. Appropriate probe selection depends on the planned procedure and the type of anatomy to be scanned.

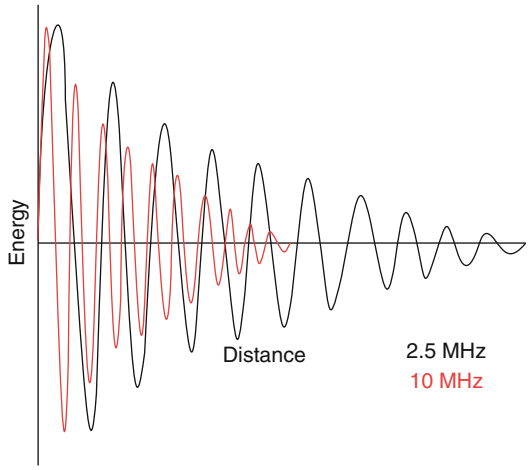

Fig. 43.3 Attenuation. Attenuation is estimated as $\alpha \times f \times$ path length, where f is the frequency of the ultrasound wave and α is the attenuation coefficient. Notice the lower-frequency wave (2.5 MHz) has less attenuation at a given distance when compared with the 10-MHz wave. Thus, the 2.5-MHz wave is able to penetrate the tissue more efficiently than the 10-MHz wave (Reproduced with permission from Sites BD, Brull R, Chan VWS, Spence BC, Gallagher J, Beach ML, et al. Artifacts and pitfall errors associated with ultrasound-guided regional anesthesia. Part I: understanding the basic principles of ultrasound physics and machine operations. Reg Anesth Pain Med. 2007;32(5):412–8)

Transmit/Receive

The ultrasound transducer, controlled by the computer's CPU, sends out pulses of ultrasound signal via the piezoelectric crystals in rapid succession. These pulses transmit through body tissue and interact with it in a variety of ways. Some of the signal is reflected back to the ultrasound transducer. This reflected signal causes mechanical changes in the piezoelectric crystals, which then receive the signal and transmit the electrical results back to the CPU for processing. Therefore, the crystals are constantly transmitting and receiving ultrasound signal during real-time sonography.

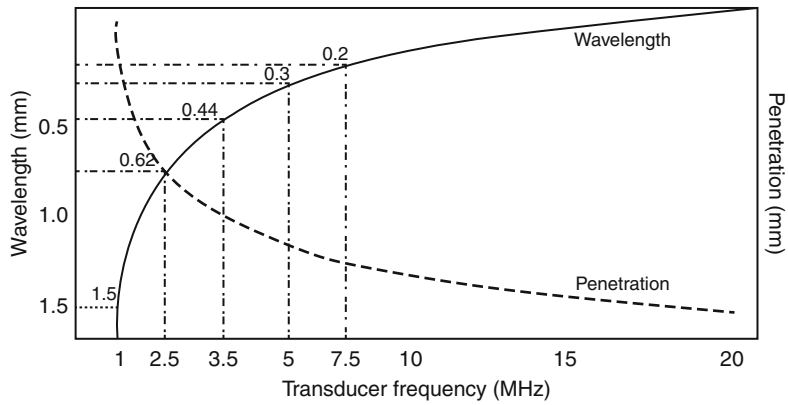

Fig. 43.4 Graph of transducer frequency (horizontal axis) versus wavelength (*solid line*) and penetration (*dotted line*) of the ultrasound signal in soft tissue. Although higher-frequency transducers (shorter wavelength) offer improved axial, lateral, and temporal resolution, the depth of penetration is greater with lower frequencies (longer wavelengths) and thus may permit better visualization of distant structures in the image scan. *mm* millimeters, *cm* centimeters, *MHz* megahertz (Reproduced with permission from Sarti A, Lorini FL. Echocardiography for intensivists. New York: Springer; 2012)

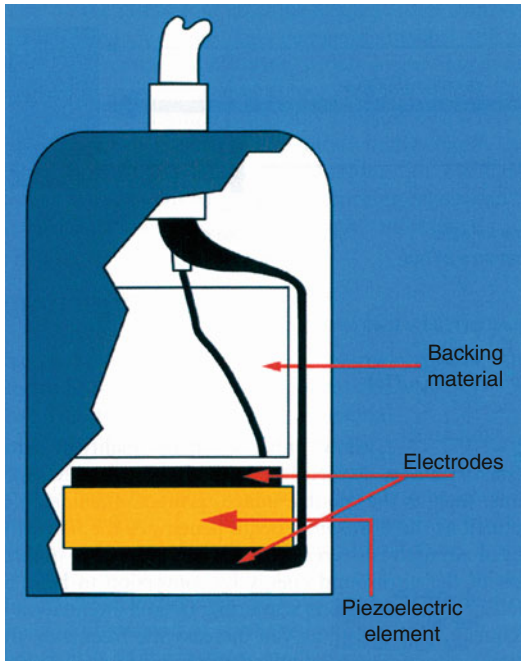

Fig. 43.5 Piezoelectric plate construction. An electrical charge results when a cut plate of quartz crystal is subjected to ultrasonic mechanical stress. Conversely, the piezoelectric plate vibrates, producing ultrasonic sound waves, when it is subjected to an alternating electrical current (Reproduced with permission from Savage RM, Aronson S. Comprehensive textbook of intraoperative transesophageal echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 5)

Skin Contact

Ultrasound waves are transmitted between 2- to 15-MHz frequency range. This type of wave signal does not travel well through air, so maintaining good contact with conductive medium on the skin is critical for allowing the entire signal to transmit into the body tissue. Usually ultrasound gel is used for this purpose. However, any gel-like substance can be used, such as sterile lubricant gel. When using a transducer probe cover, gel must be applied between the probe and the cover and also between the cover and the skin to prevent air from getting in between. Some newer ultrasound probe covers have adhesive contact for the transducer surface that eliminates the air between the transducer probe and the probe cover. Gel is still used between the probe cover and the skin to facilitate the conduction.

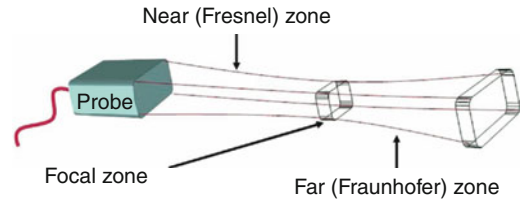

Fig. 43.6 Characteristics of an ultrasound beam. The focal zone is where the ultrasound beam width is narrowest and demarcates the near zone (Fresnel zone) from the far zone (Fraunhofer zone). It is also the area of the best lateral resolution because the beam width is the narrowest at this location. Once the beam extends beyond the focal zone, lateral resolution begins to deteriorate due to divergence. This figure represents a prototypical electronically focused ultrasound beam (Reproduced with permission from Sites BD, Brull R, Chan VWS, Spence BC, Gallagher J, Beach ML, et al. Artifacts and pitfall errors associated with ultrasound-guided regional anesthesia. Part I: understanding the basic principles of ultrasound physics and machine operations. Reg Anesth Pain Med. 2007;32(5):412–8)

Focus

The ultrasound beam that is emitted from the transducer is actually a compilation of multiple beams from separate piezoelectric crystals. As these separate signal beams travel from the ultrasound probe, an acoustic lens is used to focus them into one area (Fig. 43.6). Distal to this focal point, the beams diverge. The area of the ultrasound image where the beams are closest is referred to as the **focal zone**. In the focal zone, there is the least amount of visual distortion in the ultrasound image (Fig. 43.7). Traditionally, the focal zone is adjusted electronically on the ultrasound machine to be located at the depth of interest in the body. The zone of more dispersed ultrasound beams closer to the ultrasound probe (shallower in the image) is referred to as the **Fresnel zone**. The zone farther from the focal zone (deeper in the image) is the **Fraunhofer zone**.

Reflection

Sound waves that are transmitted from the transducer encounter various densities of tissue as they travel through the body. The density of each tissue affects the velocity (c) of sound traveling

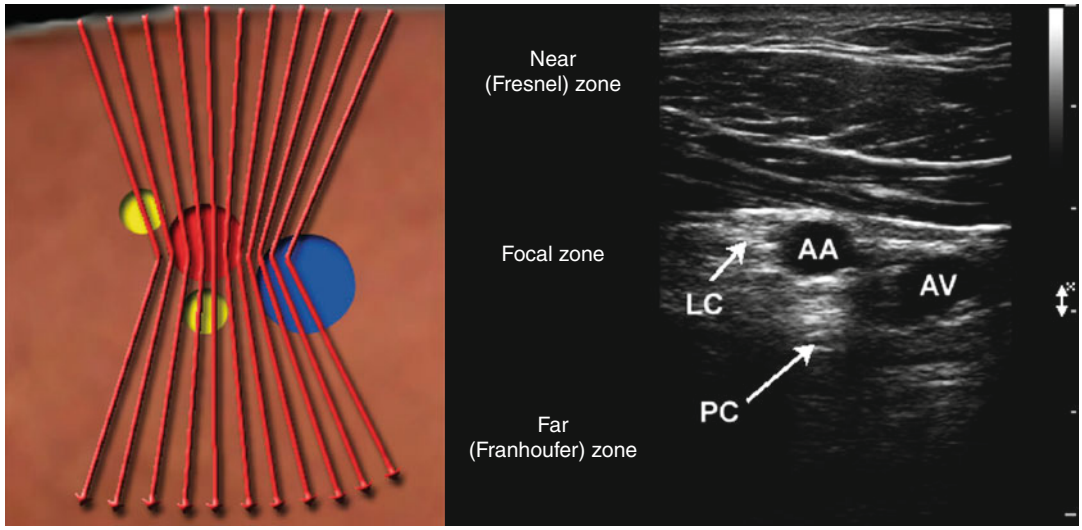

Fig. 43.7 The focal zone is the point where the beam is narrowest. Lateral resolution is optimal in this zone, before beam divergence. Lateral resolution refers to the ability of the US machine to correctly display two objects lying at the same depth as separate structures (Reproduced with permission from Brull R, Macfarlane AJR, Tse CCH. Practical knobology for ultrasound-guided regional anesthesia. Reg Anesth Pain Med. 2010;35(2 Suppl):S71)

through that tissue. This relationship is referred to as **acoustic impedance**. When a sound wave encounters a change in the density of material (a change in the acoustic impedance), part of the wave is reflected back as an echo. When there is a larger difference in acoustic impendence between two materials (greater acoustic mismatch), a larger echo wave is reflected back and the attenuated remaining wave continues on. Gases and solids generate a huge acoustic mismatch, so this interface creates a large reflected wave (bright structure) with very little wave transmitting past it (dark shadow). However, interfaces with liquids, such as blood vessels, offer little impedance to acoustic transmission, so they appear black (no reflected waves) on the ultrasound image, and the tissue behind the vessel is seen clearly since very little signal attenuation occurred.

Gain

Gain is the visual volume control of the ultrasound image. Raising the gain increases the amplitude of the returning ultrasound signal. As the received signal returns to the ultrasound transducer and is processed by the CPU, it is displayed as a point with a relative brightness value. This brightness value is established by the strength of the returning signal. By increasing the overall gain of the ultrasound, you can increase the brightness value of all the points simultaneously and equally. This brightens the image. Increasing and decreasing the gain can be useful to accommodate for variability in the ambient room lighting to allow the operator to view the structures on the screen properly.

However, there are pitfalls to adjusting the gain. Most of the received signal represents true structures; however, some of it represents noise or artifact. By increasing the overall gain, the amplitude of the noise increases as well, potentially making an artifact appear as a true structure. Conversely, decreasing the gain significantly can make a true structure invisible to the operator. The optimal amount of gain is one that minimizes artifact, but enhances true structures. This optimal gain varies according to the ambient light in the room, since the operator's eyes will adjust to that ambient light and will perceive brightness differently in a bright room versus a dark one.

Gain can be selectively adjusted as well. This is referred to as **time-gain compensation** (TGC).

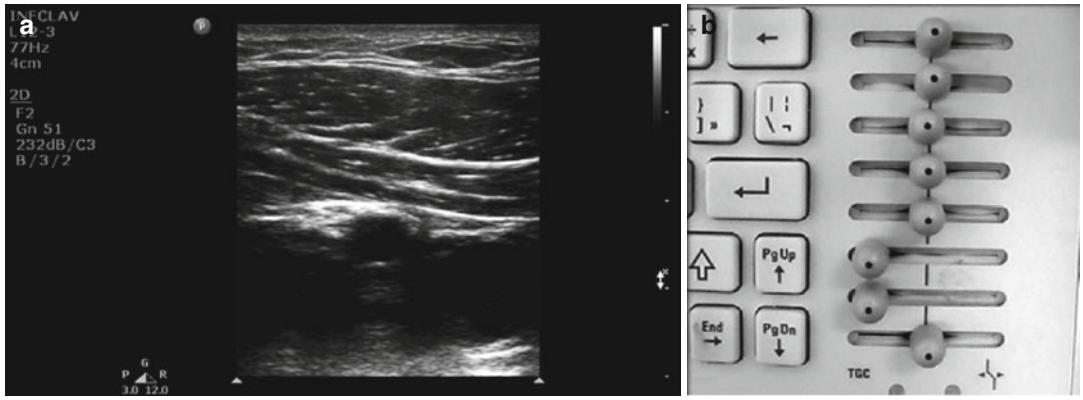

Fig. 43.8 Incorrect TGC setting. (**a**) The hypoechoic band in the middle of the image makes it difficult to identify the posterior cord. This is because the TGC dial corresponding to this depth of the field is turned down (**b**), creating a band of undergain (Reproduced with permission from Brull R, Macfarlane AJR, Tse CCH. Practical knobology for ultrasound-guided regional anesthesia. Reg Anesth Pain Med. 2010; 35(2 Suppl):S71)

Time-gain compensation may be available in varying degrees of granularity, depending on the equipment. The CPU maps the returning signal points on the screen by knowing the time that a signal pulse was sent out and how long it took to return to the transducer. The strength of the returning signal is translated as the brightness. The time it took is represented as the position that point is displayed on the screen. Signals that take longer to return are represented as deeper structures, whereas signals that return rapidly are represented as shallower structures. Since the ultrasound CPU is aware of this timing, gain can be adjusted for targeted depths. This is helpful in two ways. Deeper structures tend to have lower signal intensity and so appear darker than shallower structures. This creates an image that fades as it goes deeper. By selectively adjusting the gain for the deeper points, the image can be represented with a more consistent brightness. Alternatively, if the anatomy of interest is at one specific depth in the middle of the image, certain ultrasound machines can enhance the gain of that specific range of depths while keeping the shallower *and* deeper points darker and less noticeable (Fig. 43.8).

Remember, gain adjustments are strictly a computer manipulation of the returning signal to enhance the viewing of the ultrasound image for the operator. Adjusting gain does nothing to truly improve the quality of signal that is being received.

Artifacts

Ultrasound artifacts can reduce the sonographer's ability to utilize this technology effectively for diagnosis and procedures. One of the most common artifacts is a degraded image. **Image degradation** typically involves visible structures that are not real or real structures that are not visible. Causes of image degradation include electrical noise resulting in random extra dots, inappropriately high- or low-gain settings, inadequate transducer to skin contact, bright ambient light with significant screen reflection, and inappropriate probe or frequency selection. Many of these artifacts are correctable by the user.

Acoustic shadowing and **acoustic enhancement** are artifacts that are used to assist in the imaging evaluation process. Dense structures (e.g., bone) typically have a hyperechoic (bright) near edge with a long dark hypoechoic shadow behind them since very little signal strength can pass through dense structures. Structures that are filled with liquid (e.g., cysts) are seen as a hypoechoic with a hyperechoic-enhanced shadow behind them since the sound signal increases in velocity as it passes through liquid. This distinction can help distinguish various structures in the ultrasound image.

Scattering of ultrasound signal when an irregular structure is encountered causes reduced

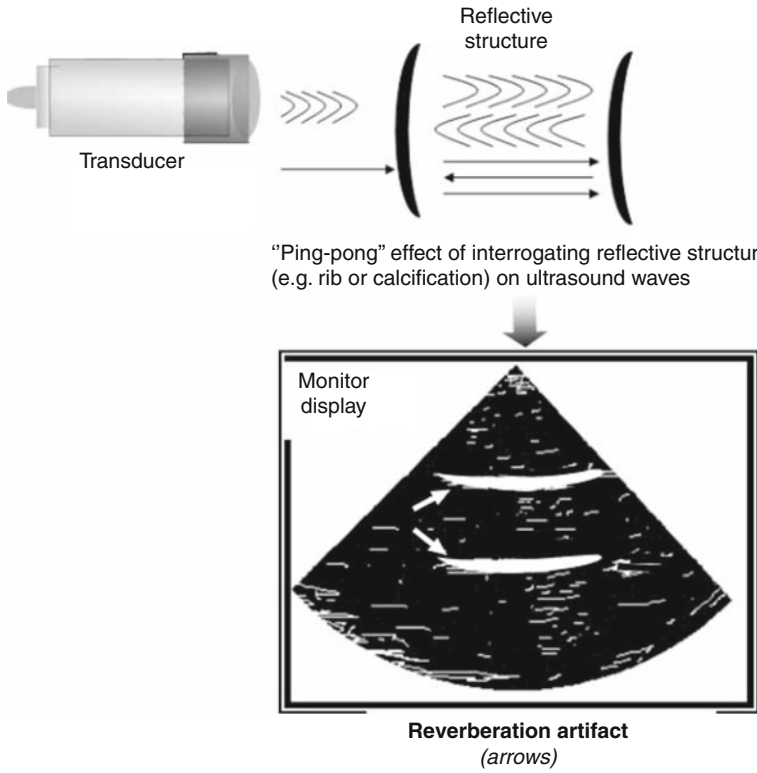

Fig. 43.9 Reverberation artifact, detailed in a stepwise manner. Each number above the needle (*top*) has a corresponding number in the ultrasound screen (*bottom*) to graphically represent the result of different reverberation events. Thus, the probe interprets these later-occurring signals as objects distal to the needle at intervals that are multiples of the needle diameter (Reproduced with permission from Solomon SD. Essential echocardiography: a practical handbook with DVD. New York: Humana Press; 2007)

amounts of wave signal returning back to the transducer probe. This scattered signal energy reduces the amplitude of the reflected wave of the structure itself and decreases the amount of signal that passes through the structure to view deeper tissues. **Signal reverberation** occurs when the reflected signal bounces back down into the tissue one or multiple times before returning to the transducer (Fig. 43.9). This increases the time from the send to receive of that signal and causes the CPU to misinterpret the signal as having reflected off a deeper structure. An example of this is when the ultrasound signal reverberates within a hollow bore needle. The final ultrasound image will show a series of parallel lines deeper than the actual needle, making it difficult to visualize the true needle and the true structures deep to the needle.

Doppler Effect and Color Doppler

The **Doppler effect** is used with ultrasound to evaluate the flow of fluids in the body (i.e., blood vessels). The Doppler shift represents the change in frequency of the reflected wave from the original transmitted frequency when the sound wave hits an object that is moving away or towards the transducer. Using this information, the CPU can determine the direction and velocity of that movement (i.e., flow). **Color Doppler** is the mapping of this direction and velocity information to a standardized set of red and blue coloration to create a visual representation of this flow. The major pitfall in using Color Doppler is not recognizing when color will not be seen even though flow exists. If the sensitivity of the Color

Doppler is set too low, small amounts of flow through tiny blood vessels may not show up with color on the ultrasound image, giving the sonographer incomplete information. Adjusting the sensitivity of the Color Doppler can resolve this issue. In addition, if the flow of fluid is exactly perpendicular to the ultrasound beam, no Doppler shift occurs and therefore no color will be mapped to that structure. Tilting the ultrasound probe in one direction or the other usually solves this second problem.

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Part VII

Information Technologies in the Acute Care Setting

Overview of Electronic Health Records

44

Jonathan P. Wanderer and Jesse M. Ehrenfeld

Introduction

EHRs, EMRs, and HIT

The electronic health record (EHR) has been defined as a longitudinal collection of data specific to individual patients and populations that is maintained electronically [1]. While competing definitions and models of EHRs exist, it is generally accepted that a EHRs are a subset of the data that healthcare organizations collect electronically. EHRs are owned by patients and span episodes of care across different healthcare organizations that will be bridged by the National Health Information Network (NHIN) [2]. They are distinct from the electronic medical record (EMR), which is the healthcare application environment in which the EHR lives. EMRs are owned by healthcare organizations and encompass many components of health information technology (HIT), including computerized physician order entry (CPOE) systems and clinical decision support systems (CDSS) in addition to clinical documentation applications.

There are a number of core components within the EHR, which can be broken down into the individual categories of demographics, medications, allergies, immunizations, laboratory data, radiology reports, vital signs, problem lists, and progress notes. These items together constitute a longitudinal record of current and past medical history for a given patient. An example EMR is shown in Fig. 44.1, and these components will be reviewed in detail.

Demographics

The demographic component of the EHR describes the aspects of each patient that separate him or her from the population as a whole. The characteristics commonly describe by demographic variables are age, gender, race, ethnicity, religious affiliation, sexual orientation, gender identity, and information regarding where a particular patient lives. These features are useful in distinguishing each patient individually but are also useful in interpreting data collected from large numbers of EHRs. Such a collection of data defines the population as a whole and is critical in interpreting result from outcome tracking and research related to quality improvement.

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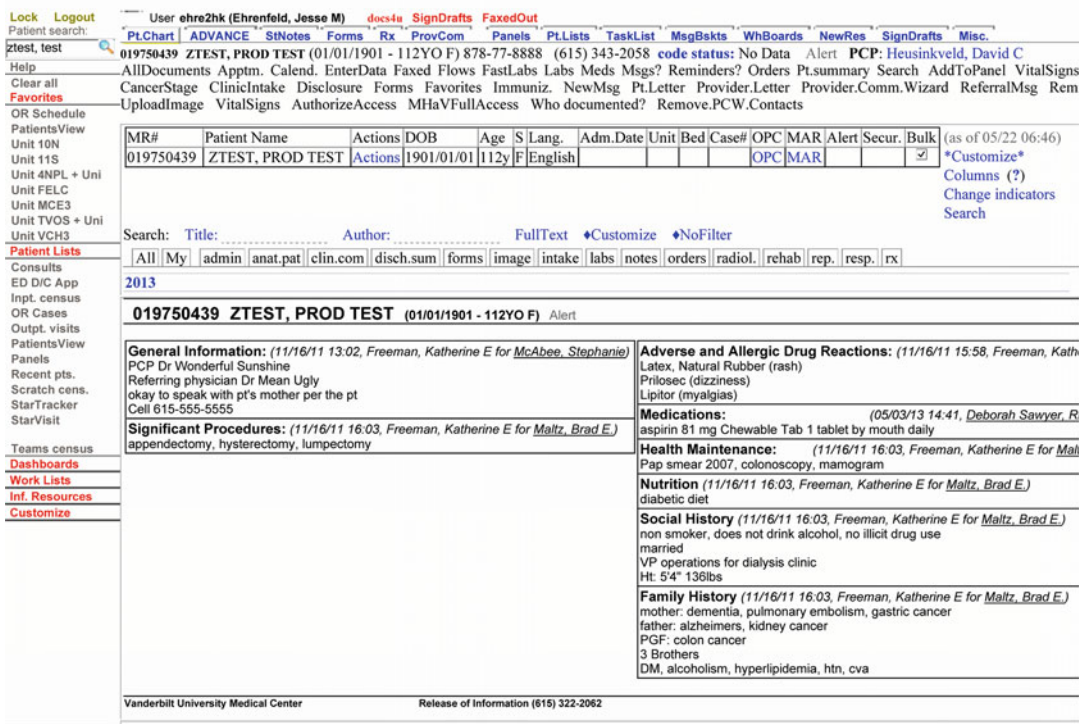

Fig. 44.1 A typical electronic medical record from StarPanel, which was developed at Vanderbilt University (Image courtesy of J.Ehrenfeld)

Medication List

A key feature of any document describing medical history is a list of medications that a patient is presently taking. The core components of a medication list are types of medication, dosages, routes of administration, and frequencies in which the medications are taken. Additional useful details include the prescriber, contact details for the prescriber, the location at which the medication was filled, the date when the prescription was last filled, and the reason that the medication was prescribed. Some medication lists also allow documentation of how the medication is actually used by the patient, if it is taken as prescribed or if the medication has been held for a particular reason (e.g., upcoming surgery). Also helpful within the medication list is a list of past medications or recent changes to medications, which provide a context in which to interpret the current medications and dosages. Medication lists are the basis for medication reconciliation, a process that takes during each clinical encounter (outpatient and inpatient) in which the patient's medication list is reviewed and any medication changes are documented along with the reason for the change. This process has been demonstrated to reduce medication discrepancies with the potential for harm [3].

Allergies

Frequently documented along with the list of medications is the allergy list. This is another critical component of the EHR and has been used to trigger CDSS alerts when medications are ordered to which the patient is allergic or when ordered medications share cross-reactivity with medications to which the patient is allergic. Core components of the allergy list are the type of medication and the reaction caused by administration of the allergy. Additional information frequently stored in the allergy list is the date when each reaction was noted and the certainty of the information provided. These details are helpful in providing context for the information provided and distinguish,

Fig. 44.2 A visualization of laboratory data from the Wandering Data Application showing patient trends over time (Image courtesy of J. Wanderer)

for instance, a recent well-documented, life-threatening anaphylactic reaction from a remote history of a rash that occurred in the patient's childhood. While technically allergies refer to a specific reaction triggered by the immune system, this section of the EHR is often populated by non-allergic drug reactions and common, known side effects to medications. Allergies are checked by healthcare providers at hospital admission and are rechecked as part of safety checklist procedures that have been recently promoted [4]. In addition to CDSS-triggered allergy alerts, electronic allergy lists have also been used to create physical allergy-alert bracelets at the time of hospital admission. Non-medication allergies such as sensitivity to latex are important components of the allergy history and may trigger additional precautions such as an allergy-alert sign placed at the door of a patient's room.

Immunizations

Records of vaccinations that the patient has received constitute the immunization section of the EHR. The key components of this section are the type of vaccine administered, the dosage, and the date of administration. Additional details include the place of administration and any reactions noted. Frequently this part of the EHR will also list surrogates of immunization, such as history of chickenpox or serum antibody titers. These details are critical to the practice of pediatrics and adult medicine alike; CDSS alerts may be triggered by information with this section and have been demonstrated to improve vaccination rates [5]. Travel health clinics and occupational health departments at healthcare organizations also rely on this component of the EHR.

Laboratory Data

The laboratory data found in EHRs are chemistry labs such as electrolyte panels; hematologic labs including blood counts, coagulation studies, and blood bank samples; microbiologic data from cultures; and fluid analyses from urine, the pleural space, or other sources. At a minimum, the data contained are the measured values, reference values, and the date and time that the laboratory data were obtained. For microbiologic data from cultures, these data are updated with each culture observation and the date and time of the updated observation will be included. EHRs frequently include the ability to view these data over time in a graphical fashion (Fig. 44.2), which allows for trends to be identified. Additionally, laboratory

values that are above or below the reference values are often flagged as high or low, respectively, to aid in rapid interpretation of data. Some EHRs include relevant medication data to add context to the laboratory data [6]; however, these data are not standard.

Radiology Reports

The reports available in the radiology section of the EHR include chest x-rays, MRI scans, CT scans, and radiographic studies such as upper and lower gastrointestinal barium studies. The core parts of data for radiology reports are the study performed, the date and time of the study, the interpretation of the study images and the name and credentials of the radiologist who interpreted the study. While the interpretation is typically free text, some progress has been made towards standardizing the formatting of these reports [7]. When a report is not available, EHRs will list these data as pending. Commonly these reports will also contain a mechanism to view the images themselves or via a picture archiving and communication system (PACS). PACS provide storage and access to images from a variety of sources, typically stored in Digital Imaging and Communications in Medicine (DICOM) format.

Vital Signs

Physiological measurements are recorded in EHRs from both office visits as well as hospital admissions. At a minimum, these values include temperature, heart rate, and blood pressure. Additional details recorded are height, weight, pulse oximetry values, and cardiac rhythm. On intensive care units, measurements include those from invasive monitoring devices such as pulmonary artery catheters and intracranial pressure monitors. Often EHRs incorporate a method for plotting these values over time so that trends can be appreciated; where normal trends are inherent in the interpretation of data, such as height and weight in pediatrics, these values are plotted against normal reference curves so that interpreting data is a straightforward task within an EHR [8].

Problem Lists

A key aspect of health management is keeping track of active health issues for each patient. This allows the reader of an EHR to get an overview of the patient's important medical issues without delving into detailed notes. At its core, a problem list is simply an itemized list of health conditions. CDSS are capable of identifying missing items from problem lists based on other EHR, which can lead to improved completeness [9]. More sophisticated problem lists detail the date at which each problem was added and the healthcare provider who added it, allow for tracking of problems over time, and permit linkages to medication and laboratory data. More and more systems now link each problem to a specific International Classification of Diseases (ICD) code, which can aid in data analysis.

Progress Notes

Healthcare provider notes are comprised of narrative medical history data, descriptions of physical examinations, and relevant laboratory, radiologic, medication, allergy, and vital sign data. Semiautomated note creation is possible with EHRs and has been demonstrated to improve the quality of progress notes [10]. A common format for progress notes starts with a subjective narrative and follows with objective data, an assessment, and a care plan; office visit formats for the care plan are typically organized by problem list, while intensive care notes more commonly sort plans by organ system. Each note is concluded by the name and credentials of the individual who composed the note, along with an electronic signature with the date and time that the note was completed. EHRs often have the capability to have interim or preliminary notes available, which can be both viewed by others

and edited by the author. This is particularly helpful in academic centers, where trainees often compose the first draft of a patient note. Once notes are signed and finalized, addition of more information is accomplished by attached an addendum note that is likewise electronically signed and dated.

Outcome Tracking

The predominant use of EHRs is by healthcare providers directly involved in patient care, but the use of data contained within these records can extend across many patients in the form of outcome tracking. By specifying certain desired outcomes, such as a target value for hemoglobin A1C as a long-term marker of glucose levels in diabetics, or CD4 count in HIV positive patients, many patients can be tracked simultaneously and disease registries can be created [11]. These types of features allow outcome outliers to be identified and targeted interventions to be directed appropriately. Outcomes can also be grouped by provider or by healthcare organization, which can be made publically available and used by patients to determine where to receive care. An example of such an effort is in a coronary artery bypass graft registry [12]. As these data become increasingly available, they may play a more prominent role in attracting or discouraging referrals.

Clinical Decision Support Systems

In addition to storing patient health data, EHRs can facilitate the interpretation of these data as well as steer healthcare providers towards recommendations from clinical practice guidelines through the incorporation of CDSS. These systems are designed to help clinicians deliver healthcare by making health knowledge available when and where it is needed. There have been over 100 published examples of these systems, the majority of which have been demonstrated to improve provider performance [13]. To extend the usage case presented above, CDSS have been built that offer recommendations for routine health maintenance for diabetics [14] and have been demonstrated to make modest improvements in glycemic control [13]. As EHRs adoption continues, these systems are likely to play an increasing role in our healthcare system.

Conclusion

EHRs contain many critical components of patients' medical history and are an integral component of the EMR. The core components of an EHR are demographics, medications, allergies, immunizations, laboratory data, radiology reports, vital signs, problem lists, and progress notes. In addition to providing a longitudinal view of a patient's medical history, EHRs facilitate outcome tracking to aid patients and clinicians alike. Importantly, EHRs are a key place where CDSS can be leveraged to bring medical knowledge directly to healthcare providers to guide clinical decisions.

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Benefits and Drawbacks of Health Information Technology

45

Jonathan P. Wanderer and Jesse M. Ehrenfeld

Introduction

Health information technology (HIT) is a term that describes the use of computerized systems in accessing healthcare information by patients, healthcare providers, insurers, and government entities. While the first examples of HIT were described decades ago, the impetus for healthcare systems to broadly adopt HIT can be traced to the Institute of Medicine's 2001 call to place these systems at the center of healthcare redesign to foster quality improvements [1]. HIT is seen as holding the potential to prevent medical errors, reduce costs, decrease paperwork, increase efficiency, improve healthcare quality, and ultimately empower both patients and clinicians. Given the current impact of healthcare on the nation's budget and projections for increased expenditure in the future, the successful implementation of HIT has become a national priority. The importance placed on HIT in improving our nation's healthcare system was reflected in the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009, which allocated $19 billion to encourage adoption of this technology [2]. HIT is the intersection of information technology applied to public health and medicine, providing the ability to measure across a variety of domains and enabling providers to more easily manage population cohorts (Fig. 45.1).

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Benefits

The potential benefits of HIT can be loosely classified into improvements in clinical, operational, and societal outcomes. By providing additional cross-checks and verification steps, errors in patient care can be prevented. HIT can offer providers easy access to the most recent patient care guidelines and provide suggestions when care deviates from those guidelines, which can improve the quality of delivered healthcare. On the operational side, HIT facilitates streamlining office processes such as billing and scheduling and can improve the efficiency of hospital workflows and legibility of healthcare records. At the societal level, HIT simplifies the process of data collection on a population basis for powerful epidemiological research and holds the potential to reduce healthcare costs. There are a number of sources of evidence for each of these benefits.

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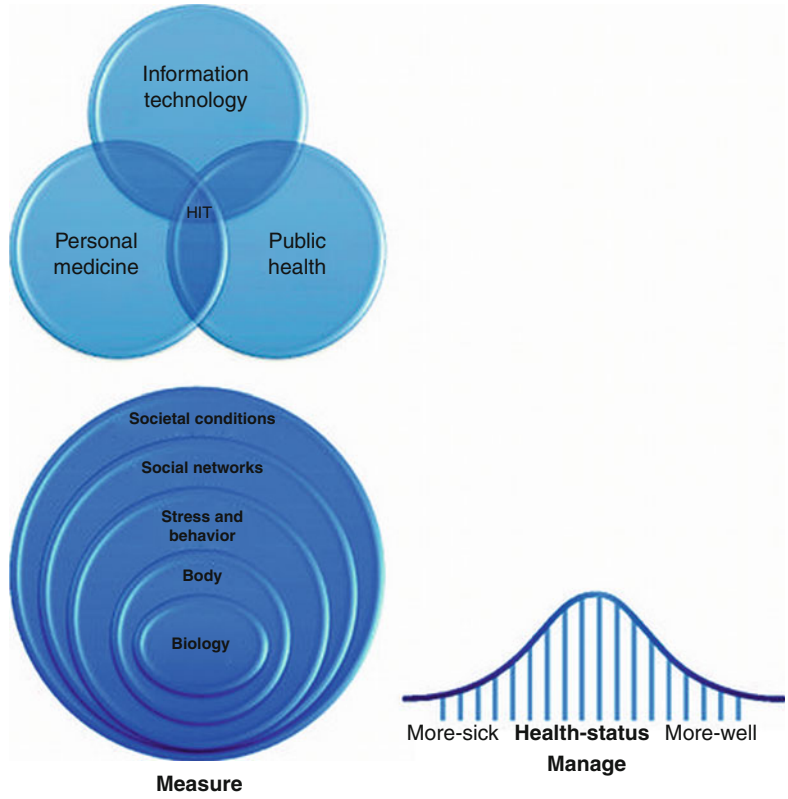

Fig. 45.1 Health information technology (HIT) is the intersection of information technology applied to personal medicine and public health (Reprinted from Schatz and Berlin [28])

Clinical Outcomes

One of the most important components of HIT is the electronic health record (EHR). While paper records are static, EHRs can provide healthcare providers with patient-specific alerts and reminders. A recent study demonstrated that patients of providers who received alerts for HIV-related care were more likely to have appropriate checking of CD4 counts and were more likely to be prescribed AZT, PCP prophylaxis, and vaccinations [3]. Another important part of HIT is computerized provider order entry (CPOE) systems, which can provide drug guidelines, dosage calculation assistance, and drug interaction alerts. Multiple studies have shown a reduction in erroneous drug dosages using these systems [4, 5]. Improvements in achieving the target dosage level have also been reported [6]. Protocol-driven alerts can be integrated into specialty-specific HIT applications such as perioperative information management systems, where they have been used to reduce rates of missed prophylactic antibiotic doses before surgery [7] and improve adherence to postoperative nausea-prevention guidelines [8].

Operational Outcomes

In addition to impacting healthcare delivery through influencing healthcare provider behavior, HIT can improve operations within an institution which in some instances has led to substantial cost reduction. One institution looked at the financial impact of implementing antibiotic management within an EHR. By reducing excess drug dosage, duration and drug-related adverse events, significant cost savings were achieved [9]. Similar systems have been implemented to reduce the number of laboratory tests ordered, which in one outpatient setting has been shown to reduce visit charges by 13 % [10]. At the administrative level, HIT can reduce costs

incurred by needing to pull physical charts and manually code billing diagnoses while improving charge capture. These benefits have been estimated to save up to $86,400 per provider over 5 years [11].

A more difficult to quantify but easily appreciable benefit of an EHR is that clinical notes are typed, rather than handwritten. This also allows notes to be viewed remotely by multiple users simultaneously as virtual charts can be shared readily, while physical charts cannot. These features are useful in facilitating communication between and among healthcare teams, but the same technology is also useful in communication between healthcare providers and patients. Operational efficiency can be gained by automated reminder systems for preventative care. While there are many potential applications, improvements have been demonstrated through sending text message reminders to patients for immunizations [12] and mammography [13]. Integration with pharmacy systems allows for smart medication reminders, which can improve compliance with medication compliance and increase the rate of appropriate medication refills [14].

Societal Outcomes

While it is easy to appreciate the direct benefit to patients from improved quality of care, reduced costs, and enhanced operational efficiency, there are also societal benefits from the adoption of HIT. The underlying functionality that enables patient reminders results in the creation and maintenance of large patient care databases which can be used for research. These databases can directly support large-scale retrospective studies and also help identify patients for possible recruitment into prospective research [15]. This collation of health information also facilitates population health management and has been used to track the spread of communicable disease [16]. The development and growth of healthcare information exchanges will further expand the areas in which HIT can benefit society as a whole.

Drawbacks

Determining the net impact of the adoption of HIT requires understanding the drawbacks to the implementation of these systems which must be weighed against the benefits. There are direct costs of HIT, namely, in the acquisition of software and hardware along with the expenses related to maintaining both over time. Transitioning to HIT typically requires changes in how healthcare providers work, which can lead to transient or permanent productivity loss, as well as workflow disruptions. Provider training and support must also be factored in. Some posit that the costs of provider and end-user training, time away from clinical care, and associated lost clinical revenue are the highest costs related to system implementation. Additionally, while aggregating patient health data can have societal benefits, it also leads to individual privacy concerns which require careful data access controls. Each of these drawbacks deserves consideration.

Acquisition and Maintenance Costs

The costs of obtaining and supporting the necessary hardware and software to implement HIT depend heavily on the size of the practice or hospital adopting the technology, as well as the specific software package selected and features included. Companies that specialize in EHRs also vary in terms of what portion of expenses is charged for the initial outlay versus support costs. Additionally, the cost of importing patient data from paper records or an existing legacy system needs to be considered. On the low end of the cost spectrum are ad-supported cloud computing solutions that are free [17]. Acquisition costs for fully featured EHRs at large academic institutions, by contrast, have ranged up to $700 million [18]. Maintenance costs are similarly variable and depend on the size of the organization and the details of the negotiated contract. Estimates for a five-physician practice in 2011 were $46,659 per physician for the initial year with a yearly maintenance cost of $17,100 [19].

Workflow Disruptions

Conversion from a paper-based system to HIT systems such as EMRs and CPOE necessitates significant changes in healthcare provider workflow. These workflows vary by HIT product, and significant differences have been found in user satisfaction with different products that have the same feature set [20]. Successful implementation of new HIT systems typically involves a careful analysis of provider workflow and customization of existing products to reduce discrepancies with existing workflow. However, by design, HIT systems have workflow modifications in order to implement some of the safety features discussed earlier. When these designs are poorly implemented or not understood, providers may develop workarounds to facilitate their workflow at the expense of the safety features [21]. Additionally, these workflow modifications frequently reduce provider task efficiency.

Productivity Loss

Implementation of HIT requires training for the healthcare providers using the new system, which necessarily involves loss of clinical time. In addition to the costs of training time and the workflow disruptions previously discussed, new workflows may be significantly slower resulting in transient or permanent reductions in productivity. One study examining found an initial increase of 2.2 min per patient visit following CPOE implementation, although this difference was reduced over time ultimately resulting in a reduction of 3.7 min per patient [22]. A recent review of the impact of EHRs on documentation efficiency showed that much depends on the implementation details. Central workstations tend to slow the documentation process, while bedside systems can reduce documentation time. On the whole, EHRs are unlikely to significantly decrease documentation time and in some instances increase it [23].

Privacy Concerns

One of the central features of HIT is assembling patient health data in a central location, whether those data are kept locally at a hospital or physician's office or stored remotely through cloud-based services. This aspect of HIT requires careful attention to the issue of who is able to access those data and what protections exist against unauthorized access. Both patients and healthcare providers alike share concerns about the privacy of health data and a privacy breaches are a constant threat. The HITECH Act which has acted as a catalyst for the adoption of HIT included a provision for four Strategic Health IT Advanced Research Projects (SHARP), one of which was awarded to develop technology to reduce privacy and security risks while increasing public trust [24]. Clearly, this will be an area of continued concern as HIT is increasingly adopted by healthcare organizations.

Potential for Harm

While there are many potential benefits of HIT, realizing these benefits depends upon well-thought-out and executed implementation strategies. Introduction of new technologies can also introduce new problems. CPOE, as previously discussed, can incorporate alerts and cross-checking that can reduce adverse drug events. However, CPOE can also facilitate medication errors. A recent study found 22 types of medication errors that were observed by a majority of physicians at one hospital on a weekly or more frequent basis [25]. A separate study found 79 unintended consequences of CPOE implementation at five sites [26]. In an extreme example, introduction of CPOE system was associated with a significant increase in mortality in a pediatric intensive care unit after delays in medication administration lead to patient harm [27]. A thorough discussion of the factors involved in a successful HIT rollout is beyond the scope of this chapter, but it is evident that there are no one-size-fits-all solutions and that HIT must be

evaluated carefully at the local level before successful adoption is possible.

Conclusion

HIT can be a powerful tool, capable of improving clinical outcomes, reducing cost, lowering barriers to communication, increasing operational efficiency, and facilitating important population-level health research. However, this can come at a substantial cost, both in terms of acquisition and maintenance costs as well as provider time. Wielded poorly, it is also capable of causing measurable harm. Careful institution stewardship of HIT is essential to maximize the benefits of HIT while minimizing the drawbacks.

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Special Case: Perioperative Information Management Systems

46

Allan F. Simpao and Jesse M. Ehrenfeld

From the Paper Anesthesia Record to Perioperative Information Management Systems

In the 1890s, Drs. Cushing and Codman pioneered the use of paper records to document a patient's physiological status during the delivery of anesthesia [1]. While the paper record remained the sole method for intraoperative documentation throughout most of the following century, there was growing recognition in the 1970s and 1980s of a benefit to anesthesia providers in the development of the electronic capture, storage, retrieval, and formatting of preoperative information and intraoperative data [2, 3].

Early efforts to automate anesthetic record keeping include both a mechanical device described by McKesson in 1934 and video recording by Piepenbrink and colleagues in 1990 [4, 5]; neither method proved to be successful [6]. Although computerized documentation of physiological data had been utilized since the 1970s, the first successful implementation of a system employing a direct interface to the clinical monitors in order to capture patient physiological data electronically was likely the Duke Automatic Monitoring Equipment (DAME) system which was developed in the early 1980s [7, 8]. Commercial systems evolved subsequently in sophistication and complexity from simple record-keeping applications to more comprehensive software and hardware solutions with extensive functionality, and the term Perioperative information management Systems (PIMS)—as opposed to ARK, or anesthesia record keeper—was coined and became commonplace [9].

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Anesthesia Functionality of Perioperative Information Management Systems

The core function of PIMS remains the generation of an automated, continuous electronic anesthesia record that captures and documents the patient's intraoperative physiological data (e.g., vital signs) and allows for the manual notation of intraoperative events (e.g., time of intubation, skin incision, drug administration) [10]. The PIMS end-user interface not only allows for continuous access to the ongoing anesthesia record so that the anesthesia provider can use the data in real time during a case, but also is usually designed so that users enter data in a

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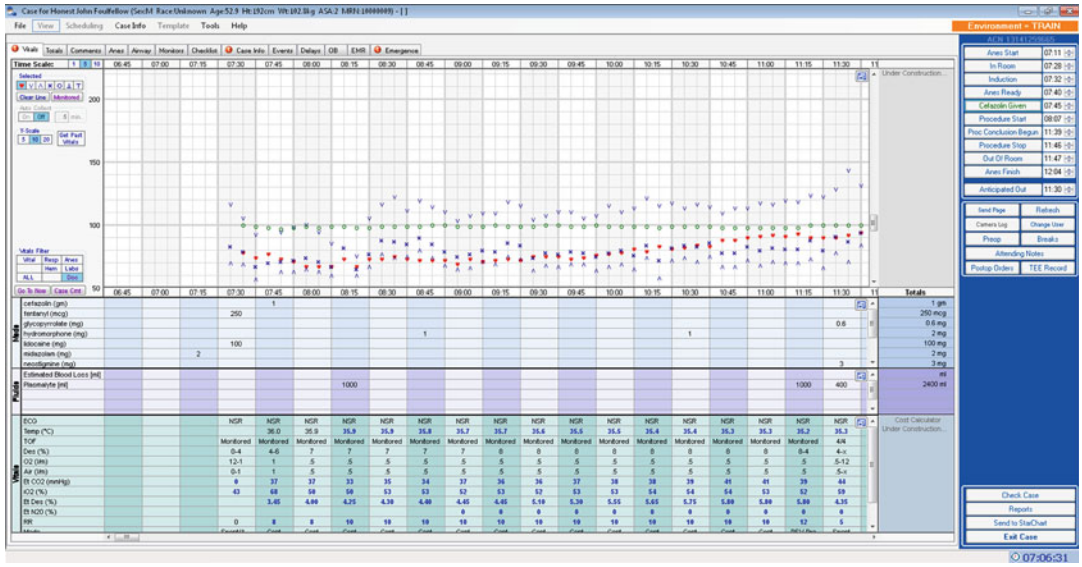

Fig. 46.1 Example of a perioperative information management system user interface (GasChart, developed by Vanderbilt University)

manner that complements their existing work flow (Fig. 46.1). Furthermore, in order to facilitate situational awareness, most PIMS possess an intraoperative interface that highlights critical data elements as they arise. This may occur via mechanisms such as a different color or a larger font to help the user identify key pieces of information quickly [11].

Currently available PIMS exist as either stand-alone products or as components of a hospital's electronic medical record (EMR) system. Both types offer a variety of features to expand their utility beyond automated intraoperative record keeping to enhance other aspects of the perioperative environment. For example, most PIMS offer preoperative patient assessment tools, which range in sophistication from free-text fields for the manual input of patient information to an extensive electronic history-taking questionnaire with customizable algorithms that take into account patient comorbidities as well as the specific procedure [12]. Some PIMS reduce redundant data entry by interfacing with the hospital's electronic health record (EMR) system, so that relevant patient information (e.g., patient's age and allergies) loads automatically into the preoperative assessment and the intraoperative chart [13]. Examples of other preoperative modules include support for preoperative test recommendations based on patient data or the procedure, a browser that allows users to view previous anesthesia records, or web-based forms to permit a user (with valid access credentials) to peruse a patient's preoperative assessment from any computer with Internet connectivity.

Postoperative functionality is also available in most PIMS, with some allowing the user to order pain medication and antiemetics electronically, while others enable continued documentation of the patient's anesthesia record via a PIMS workstation in the postanesthesia care unit (PACU). Comprehensive PIMS reports detailing the patient's intraoperative course may be made available to staff in the PACU or intensive care unit via PIMS or EMR workstations or as a paper printout.

The Benefits and Obstacles Associated with Perioperative Information Management Systems

Table 46.1 lists the areas where PIMS have been noted in the peer-reviewed literature to provide positive benefits to patients, anesthesia departments, and hospital systems.

Table 46.1 Benefits of perioperative information management systems as published in peer-reviewed journals

Improved documentation
More accurate, precise capture of intraoperative data and patient responses to anesthesia
Generate high-resolution, legible anesthetic records that are more easily searched and accessed than paper records
Automatic real-time notification of missing documentation entries
Enhanced legal fortification via unbiased, precise information
Support risk management and quality assurance activities
Improved quality of care
Automatic risk calculation and anesthetic management recommendations
Artificial intelligence to prevent adverse intraoperative events
Facilitate implementation and adherence to departmental protocols
Implement evidence-based medicine (e.g., adherence to clinical guidelines for antibiotic prophylaxis)
Tool to provide point-of-care clinical decision support
Can provide timely clinical feedback to impact clinical behavior
Improved patient safety
Automatic notification of operating room location errors
Development of drug diversion surveillance
Help avoid blood transfusion reactions
Enhance situational awareness
Allows the anesthesia care team to focus on the patient, rather than recording vital signs
Improved operations management
Decrease workload on billing personnel when reviewing anesthesia records
Improve anesthesia department's administrative role in the perioperative setting
Improve staff scheduling
Generate a real-time surgical whiteboard to improve situational awareness
Facilitate reductions in staffing costs
OR modeling for administrative decision support
Facilitates individual anesthesia provider performance tracking
Enables verification of Accreditation Council for Graduate Medical Education case requirements for residents and fellows
Improved cost containment
Decrease anesthesia drug and supply costs and utilization
More accurate accounting of anesthesia supplies and medications
Tool for controlling resource management in the operating room
Improved reimbursement
Enhance anesthesia billing and charge capture
Increase hospital reimbursement
Merge financial systems with clinical documentation to gain efficiencies
Improved clinical research
Enables researchers to rapidly find rare events or specific occurrences across a large number of cases
Helps develop evidence-based medicine guidelines from data sets of empiric clinical practice
Link intraoperative data to outcomes data (e.g., National Surgical Quality Improvement Program
Share data through national research consortiums (e.g., the Multicenter Perioperative Outcomes Group or Anesthesia Quality Institute)

Adapted from Kadry et al. [10] and Ehrenfeld and Rehman [13]

Multiple obstacles have been stated as causes for the limited adoption and implementation of PIMS, including decreased vigilance in the operating room, financial implications of installation and maintenance, reluctance to give up paper records, fear of computers, medicolegal concerns, and resistance to changes in clinical workflow patterns [14–16].

One recent study found no difference in the accuracy of practitioners' recall of patient variables

Type	Consequence level	Level of difficulty
Managerial	Low	Low
Example: Bayesian analysis to predict amount of surgical time remaining		
Process of care	Medium	Medium
Example: surgical care improvement project (SCIP) (antibiotics before incision, normothermia, etc.)		
Outcome based	High	High
Example: Provide risk-adjusted 30 day post-op pain scores after arthoplasty		

Fig. 46.2 The three levels of clinical decision support: managerial, process of care, and outcome

when using computerized or manual entry record-keeping systems, suggesting little impact on vigilance [17]. While the initial outlay of funds for PIMS implementation is significant, the ultimate return on investment depends on the individual institution's specific financial, billing, and management practices [11]. According to a recent literature review, there are four areas by which a PIMS may contribute a positive net return on investment. These areas include (1) more efficient staff scheduling and decreased staff costs, (2) decreased anesthesia drug costs, (3) better charge/billing capture, and (4) increased hospital reimbursement from improved hospital coding [18]. In regard to medicolegal concerns, 24 anesthesia departments reported in a recent survey that there were no cases in which the PIMS hindered the defense process; in fact, the majority of respondents viewed PIMS as valuable for risk management [19].

Perioperative Information Management Systems and Clinical Decision Support

Clinical decision support is a recent advancement in PIMS development and can be grouped into three categories as shown in Fig. 46.2: managerial (e.g., maximizing operating room efficiency and throughput), process of care (e.g., improving adherence to clinical protocols and guidelines), and outcome-based decision support (e.g., facilitating care that leads to better patient outcomes) [20]. Two recent systematic literature reviews suggested that computerized clinical decision support systems can improve practitioner performance and patient care significantly, especially if the decision support is an automated part of clinician workflow and is comprised of recommendations rather than just assessments [21, 22].

Some applications of clinical decision support consist of simple algorithms, such as tools that provided drug-dosing assistance based on weight, or automated reminders utilizing the simplified risk stratification to address postoperative nausea and vomiting [23, 24]. There has been ongoing development of PIMS-based clinical decision support via reminders, alerts, and other notifications in order to modify the behavior of anesthesia practitioners and thereby subsequently improve a variety of perioperative processes, such as correction of operating room location errors [25], billing procedures and quality of documentation [26, 27], addressing intraoperative hypothermia [28], delays in alarm usage after cardiopulmonary bypass [29], and timely administration of

antibiotic prophylaxis [30, 31]. Clinical decision support based on near-real-time interrogation of PIMS data has shown benefits at one institution that include improved beta-blocker compliance, increased billing charge capture of invasive line procedures, and reduced wastage of inhalational anesthetic agents [32].

Some decision support implementations may not improve the status quo due to the nature of the intraoperative event. A recent study explored the use of text messages to send intraoperative hypoxemia alerts to the supervising anesthesiologists of those operating rooms and found that the utility was quite low, as nearly all hypoxemic episodes were resolved prior to the arrival of the anesthesiologist to the operating room [33].

The Utilization of Perioperative Information Management Systems Databases

PIMS generate comprehensive electronic perioperative records that have facilitated clinical research when compared to the alternative, which is a laborious, expensive manual chart review of paper records. Numerous studies have been published using information from PIMS databases. For example, one recent study utilized data acquired from a PIMS to perform detailed analysis of blood component utilization and determined that incorporating this method of data acquisition and analysis into a blood management program could reduce unnecessary transfusions, an outcome that could potentially increase patient safety and reduce costs [34]. Another recent use of PIMS data is by the Anesthesia Quality Institute, which has created the National Anesthesia Clinical Outcomes Registry to automatically capture electronic data specific to anesthesia cases. Data come from a variety of sources, including hospital electronic health care records and PIMS. Per the Institute's leaders, aggregation of this data will allow for calculation of national and cohort-specific benchmarks for anesthesia outcomes of interest. Provision of this data to anesthesia practitioners through periodic private reports will motivate improvements in the quality of care [35].

The quality of the data captured and stored within a PIMS is only as reliable and robust as what end users put into the system. Clear, consistent definitions of specific data elements and events will enable uniform documentation which in turn will facilitate billing, reporting, and increasingly clinical decision support functions. As with many clinical practices, these definitions often vary across and sometimes even within institutions. For example, there are many different definitions of the "induction of anesthesia" (e.g., administration of a hypnotic, provision of anxiolytics, or start of preoxygenation). One recent study found that even when attending anesthesiologists agreed with a research assistant observer that an episode of emesis had occurred, only 38 % of the events were actually recorded in the PIMS by the provider [36].

The Adoption and Implementation of Perioperative Information Management Systems

While numerous studies have shown that PIMS records perioperative physiological data with greater accuracy and reliability when compared to the paper anesthetic record [37–40], adoption of PIMS has been slower than expected in non-academic settings [41]. As of 2006, only an estimated 5 % of US operating rooms had a PIMS installation [42].

Recent legislation that was intended to expand electronic health documentation in the USA will likely accelerate the pace of PIMS adoption [43]. In fact, government and academic practices have been more apt to implement PIMS. One survey reported in 2008 that 44 % of academic centers were planning to implement or had implemented a PIMS, while a more recent survey found that at least 50 % of survey respondents were currently using, installing, planning to install, or searching for a PIMS, with most PIMS adopters consisting of large anesthesiology groups or academic or government settings [44, 45]. In contrast, outside of academic environments, industry data suggested that 90 % or more of anesthesia care providers still used paper-based documentation in 2011 [46].

The Future of Perioperative Information Management Systems

While the paper anesthetic record remains widely used and available documentation method, evidence of the numerous tangible benefits of PIMS continues to accumulate in the peer-reviewed literature. In the future, PIMS should continue to improve in terms of user interface, portability, and interoperability with hospital-wide EMRs. The nationwide push for hospital EMRs should accelerate the implementation of integrated PIMS solutions. Clinical decision support will continue to be developed in more sophisticated and meaningful ways, improving patient care and safe practices.

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Part VIII

New and Emerging Technologies

Intelligent Patient Monitoring and Clinical Decision Making

47

J. Mark Ansermino

Intelligent Patient Monitoring and Clinical Decision Making

Advances in monitoring technology have resulted in the exponential growth of the amount of physiological data collected in many healthcare environments: the operating room, the intensive care unit, the hospital ward, and even at home. This growth in data generation has the potential to enhance clinical decision making. However, human limitations in memory and other cognitive resources must be understood and overcome before the benefits of this rich data source can be realized. This is founded on the premise that improved knowledge (evidence) is the foundation of improved decision making, and more data have the potential to significantly improve knowledge. However, the abundance of data currently presented to anesthesiologists in the operating room, as well as to healthcare providers in other clinical environments, has already led to information overload. This abundance of data exceeds the demonstrated limitation of human short-term memory, which is seven chunks of information [1], leaving much of the data unappreciated. Existing displays are cluttered with excessive amounts of information, do not provide appropriate salience for timely critical information, and do not assist with integration of disparate information into a useful conceptual whole.

There is a compelling argument that advances in patient monitoring have actually increased the probability of human error, through reduction in direct observation of the patient, while adding complexity and false alarms to the healthcare providers' cognitive workload. In addition, monitors may become distracting during a crisis because while monitoring systems may detect abnormalities; current system design neglects to provide information with any degree of data interpretation. Specific cognitive limitations that are at the root of preventable accidents when monitoring patients include the following: imperfect vigilance (especially for context-sensitive information), distraction, data overload, and cognitive resource limitation that may result in task fixation or limited task switching [2]. The technical challenge is to develop systems that enhance both the vigilance and reasoning capabilities of the clinician.

The ability of clinicians to direct attention to important patient information is impeded by competing environmental noise, alarms, social distractions, and the performance of other tasks required of the healthcare provider. These tasks include but are not limited to completion of documentation, drug and fluid administration, and other procedures. Improvement of performance in patient monitoring by healthcare providers is unlikely to be achieved by exhorting them

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to work more carefully. Rather it will require improvement in situational awareness realized with the help of technological solutions such as those applied in the aviation and nuclear power industries [3].

Limitations of Current Patient Monitoring Technologies

Unintelligent Alarms

False alarms due to artifacts are a frequent and highly irritating reality. This high false-positive rate causes alarm fatigue and renders alarms ineffective because they are frequently ignored [4]. Abnormal clinical conditions are currently signaled in one of the two ways: (1) by a primitive alarm that is automatically triggered when a single parameter fluctuates beyond a fixed threshold or (2) by the healthcare provider visually tracking changes to a signal pattern over time. Current alarm systems are based on upper and lower thresholds and are set with the assumption that each parameter (e.g., heart rate, blood pressure) remains within the same range for each patient over time. As physiological rhythms fluctuate and the acceptable range varies for each individual, false alarms are inevitable, especially if the alarm is based on a single parameter. Clinical interventions and artifacts from electrocautery interference and movement exacerbate the false-alarm rate, such that >90 % of alarms currently generated in the clinical environment can be dismissed as insignificant, one-third of these being triggered by artifacts [5]. Responsiveness to alarms diminishes as the frequency of false alarm increases. This high false-positive rate renders alarms ineffective, as they are frequently ignored [6].

Current alerting modalities deployed in physiological monitors err on the side of caution by triggering an alarm each and every time a value could possibly be abnormal. No latitude is given to missing an event. This results in highly sensitive alert triggers with very low specificity. Monitoring prone to false alarms degrades performance significantly more than monitoring prone to missing an event because false alarms degrade both compliance and reliance while missed events only reduce reliance [7]. Some reduction in reliance may be advantageous in keeping the human engaged in patient monitoring. While a highly sensitive alerting scheme can be argued as being safe, from a regulatory perspective, it has a very negative impact on human performance.

Recent highly publicized deaths [8] resulting from the failure of healthcare providers to heed alarms have raised serious concerns about the safety of the traditional threshold-based alarms. The ECRI (Emergency Care Research Institute) has listed alarm fatigue as number 2 on the top 10 health technology hazards [9]. This is based on numerous reports of alarms not being heeded and resulting in patient harm.

Volume and Complexity of Data

Advances in sensor technology have resulted in an exponential growth in the amount of physiological data collected during a typical surgical procedure (>5 MB/h). However, only a small fraction of the physiological data collected during a typical surgical procedure is relayed to the clinician at the bedside using a visual or auditory display. The remainder is unused and discarded. The identification of an abnormal state requires much more than selection of a single correct threshold or development of a perfect filter. Additional information, such as the patient context and the integration of expert knowledge, offers the opportunity to improve detection of abnormal values.

The lack of clinical consensus on acceptable limits of basic physiological measurements (such as blood pressure) highlights the complexity of interpreting the mass of clinical data collected from patients. For example, more than 140 definitions of intraoperative hypotension have been identified based on different measurements (systolic or mean blood pressure), thresholds or thresholds of change in blood pressure, and duration of change and method (invasive or non-invasive) used for measuring blood pressure [10].

While clinicians seem capable of making important clinical decisions based on physiological measurements, the heuristics (rules of thumb) used to make these decisions are poorly understood. Efforts to identify and reproduce the heuristics used by expert clinicians [11] were found to have a very high false-positive event rate and lack clinical utility. This would imply that clinicians are not generally able to accurately describe the heuristics used to make everyday clinical decisions.

Limitations in Clinical Decision Making

Evidence-based healthcare has been widely adopted to reduce clinical practice variation by replacing personal clinical experience as the primary resource for medical decision making. The demonstration of improved outcomes in many clinical scenarios with the use of evidence-based healthcare on larger population studies has highlighted the limitations of individual experience and heuristics in decision making. However, many clinical decisions made by anesthesiologists each day are not based on evidence from clinical trials. This lack of evidence is likely to continue due to the complexity and cost of conducting such investigations. The clinician should still be aware of the numerous pitfalls when using personal heuristics for making clinical decisions. These heuristics are learned during training and from individual experience.

The pioneering work by Tversky and Kahneman identified representativeness, availability, adjustment, and anchoring as key categories of heuristics and bias when making decisions under uncertainty [12]. More than 40 specific biases have been identified [8] (Table 47.1). The adverse anecdote (the bad outcomes one has heard about) is more compelling in clinical decision making than the strongest scientific evidence with the tightest of confidence intervals. This is closely linked to the common clinical practice of worst case scenario avoidance even when the probability of such events occurring is extremely low.

Table 47.1 Failed heuristics, biases, or cognitive dispositions to respond (incomplete list)

Anchoring	Delusions of success
Availability bias	Gamblers fallacy
Adverse antidote	Insensitivity to sample size
Base rate neglect	Hindsight bias
Commission bias	Prior probability bias
Confirmation bias	Regression to the mean

Human Cognitive Limitations

Specific cognitive limitations during anesthesia include imperfect vigilance (especially for context-sensitive information), distractibility, data overload, and cognitive resource limitation that may result in task fixation or suboptimal task switching. When the sustained attention of a clinician is diverted from the monitoring task, change blindness can occur [9]. In addition, the human limitations affecting the simultaneous processing of multiple information sources must be addressed if patient safety is to be further improved. Expert clinicians do not continuously watch the monitor. Typical behavior consists of a 2-s glance at the monitor approximately once per minute [13]. For example, the typical display should be reengineered to display only salient information and be optimized to support this at-a-glance monitoring behavior.

Technological Solutions

In parallel with improved education and training, innovations in technology may reduce the impact of some of the current challenges with clinical monitoring.

Artifact Removal

Despite the fact that modern monitoring devices have incorporated complex denoising functions, artifacts are still a significant challenge for intraoperative physiological monitoring.

The continuous homeostatic control in response to surgery and blood loss is a tightly coupled interaction between the intervention and

the underlying state of the patient. Standard fixed threshold alarms cannot adapt to these changes and lead to a high rate of false alarms. Alarm thresholds that adapt to the individual patient will improve alarm performance [14] but are more complex to define and regulate. Measurement redundancy can also be used to reduce false alarms. Observations of the same physiological event (e.g., heart rate) can be compared between sources such as ECG and pulse oximetry (data fusion) [15] or can be related by a verified equation that is valid during physiological variations. Most real clinical adverse events cause changes in multiple variables. These multivariable changes can be used to differentiate artifacts from true adverse events and to identify adverse events that only manifest subtle variations in individual signals [16]. This integration of information into smart alarms will become even more crucial as the number of monitored parameters increases [17].

Data Integration

The context in which data is collected can provide significant insights for interpretation of physiological measurements. Patient history, clinical setting, drug administration, the phase of anesthesia (induction, maintenance, or recovery), and changes in a variable over time help interpret its value. Tracking the temporal tendencies of physiological variables reflects the dynamics of a patient's condition. These features should be extracted and conveyed to the clinician or translated to semantic inputs for a higher-level inference solution. Visual cues [18] and configurable graphical representations [19] have been shown to improve clinician diagnostic performance. Sensor fusion is another integration solution that aims to combine measurements from multiple sensors to provide more robust estimates of the true levels of the variable than would be possible from a single sensor source, especially in the presence of noise. Combining sensor fusion with clinical knowledge, and historical observations further improves the meaningfulness of a clinically monitored value. Future clinical decision support systems will provide the highest level of data integration as our understanding of how tacit knowledge evolves into explicit knowledge improves, and is used to provide improved real-time advice.

New Sensory Channels

Visual communication remains the predominant method currently used to relay information to the clinician. This communication channel can be significantly enhanced using visual cues and animations. Sonification (transfer of information with the use of sound) is routinely used to augment information transfer of heart rate and oxygen saturation during physiological monitoring. Sonification offers significant potential to deliver additional information during physiological monitoring, especially for maintaining peripheral awareness during other tasks [20]. The sense of touch offers a unique, underutilized resource to communicate information. The effect of different tactile display modalities (vibration and electrical stimulation) at different body locations and the impact of encoding information on the reception process for physiological monitoring have been investigated. An example of a tactile belt for physiological monitoring is shown in Fig. 47.1. The tactile display would seem to offer a new and exciting possibility for the communication of physiological information [21]. Gustatory and olfactory information transfer has yet to be investigated for use in clinical monitoring.

Clinical Decision Support

Computer-based clinical decision support (CDS) is a widely used term for a heterogeneous array of systems that can be classified based on context, knowledge source, method for decision support, method for information delivery, and method of workflow integration [22]. In acute care environments, a CDS could range from a simple screen-based or pager alert to a fully featured expert alert system that incorporates

Fig. 47.1 (**a**, **b**) A tactile belt with smart alerts undergoing clinical evaluation

physiological monitoring, drug administration, and clinical context. Patient-specific reminders are more effective than education and feedback in improving guideline compliance. In a study to assess compliance with guidelines for the prevention of postoperative nausea and vomiting, the introduction of reminders improved compliance from 39 to 79 % [23]. This improvement occurred in all practitioners and declined rapidly when reminders were removed. Reminders have also been evaluated to improve timely prophylactic antibiotic administration [24] and quality of documentation [25, 26]. A more effective strategy to ensure compliance is the use of forcing functions (aspect of a design that prevents the user from taking an action without consciously considering information relevant to that action).

Automation

The optimal solution for reducing information overload and clinician workload would be closed-loop automation (see Chap. 6). The advantage of closed-loop control in anesthesia will come from design and implementation of multivariable control systems that can simultaneously take into account drug interactions, changes in the patient's physiological status, and clinical interventions.

Outside of medicine, the archetypical example of a successful introduction of automated control and intelligent monitoring is represented by cockpit automation and autopilots in the aviation industry. Whereas pilots initially resisted this technology, analysis of commercial jet airplane accidents from 1959 to 2006 shows that while the level of automation in the

cockpit significantly increased, the number of hull losses significantly decreased despite an exponential growth in the number of annual flight departures and flight hours. Although this improvement in safety is due to many factors beyond cockpit automation and intelligent monitoring, these have played a part in this improvement in safety. It is also worth noting that this new technology was introduced without randomized studies to prove its impact on safety. Automation across acute care environments will result in similar safety improvements.

Closed-loop systems can only be put to clinical use if designed to fulfill strict stability and robustness criteria due to the large intra- and inter-patient variability observed in clinical practice. Robust control design theory is the only practical way to meet such criteria, and hybrid systems theory can be used to design verifiably safe systems [27]. Studies of automation in other industries have shown that automation can reduce mental workload but does neither eliminate the vigilance decrement nor replace the operator. The benefits of automation, for both clinicians and patients, require the optimization of human and system performance. Therefore, automated systems in acute care environments will necessitate designs that optimize the performance of the human in the loop.

Conclusion

Physiological monitoring in the future will rely on miniature, wireless sensors to record multiple physiological processes noninvasively. This vast array of data will be integrated to inform clinical decisions but will also necessitate increased automation through closed-loop control, especially for safety enhancement. The integration of technology with human expertise will complement clinician performance by optimizing tasks that humans perform suboptimally, such as extended vigilance. Clinicians (and patients) need an intelligent system to augment vigilance and situation awareness and to aid in decision making to prevent patient harm.

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Robotization

48

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and Shantale Cyr

Introduction

How does the concept of robotization apply to critical care medicine and acute care environments? Etymologically, the word is derived from a play called Rossum's Universal Robots by the Czech writer Karel Čapek; in this play, slaves (i.e., robots) perform all the necessary tasks of daily life to allow humans to leisurely cherish all the beauties of life. If we want to robotize intensive care, critical care medicine, or anesthesia, we need to "convert (a system, for example) to automation by the application of advanced scientific technology" [1]. In order to understand the scope of robotization in medicine, it is important to understand that robotization, or automation, can apply to taking over very simple tasks or highly complex mechanisms by robots. Robotization does also not necessarily mean that the whole procedural process is replaced by robots: there is often a gradual change from solely human tasks or reasoning to a fully automated process without human intervention. The inherent demands on patient safety and quality of care necessitate a slow and gradual implementation of automated processes, continuously verifying that robots can deliver the same quality of care as humans can. The incentive to create robots in medicine is based on their proven track record of precision and absence of fatigue. Critics claim that the absence of intuition is a disadvantage when robots are used; however, intuition can possibly be replaced by sophisticated algorithms which take all possible memories and experiences much more into account than humans can: if intuition is linked to emotion, then the absence of emotion is certainly one of the strengths of robots and not a weakness.

Robotization is the hallmark of our industrial revolution; without robots, our daily life would not be feasible. Robots have been developed since the 1840s, but are still not widely available in medicine. The first robot-assisted surgical procedure used the PUMA 560 robotic surgical arm for a neurosurgical biopsy in 1985. The first use of robots in surgery is documented in 1987, when a laparoscopic robotic cholecystectomy was performed. In 1990 the AESOP system was the first system approved by the Food and Drug Administration (FDA). The da Vinci system was approved by the FDA in 2000 for general endoscopic surgery.

The development of robots is most needed in complex environments where there is an overflow of information, in environments where tasks need to be repeated with the same precision and quality and in areas where fatigue is a constant issue. Studies have demonstrated that quality of care is often impaired by human error, variability of skills,

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Fig. 48.1 (**a**) The InTouch RP-7 robot allows mobile audio-video communication with health-care professionals or patients from a remote location; communication with vital sign or other patient data monitoring systems is possible. (**b**) InTouch work station consisting of computer and joystick for manipulation of the robot

and human fatigue, and acute care environments are subject to these criteria. The concept of automated anesthesia has been described before [2]. However, there is currently no FDA-approved robot available to perform routine tasks in intensive care units, emergency rooms, or operating rooms. Recently, there has been some progress in the area of the use of robots for telemedical applications, with robots making remote hospital visits possible for physicians. In addition, there are some interesting scientific developments to create robots for anesthetic applications. This chapter outlines the concepts and most recent advances in this area, starting with the use of robots in telemedical applications ("telemedical robots") in the intensive care unit. "Robots" will subsequently be divided into "pharmacological robots," which (semi-)automatically administer drugs, and "manual robots," which aid with or replace human gestures.

Telemedical Use of Robots to Allow Remote Patient Visits

The shortage of specialists has led to a limitation of access to high-quality attending physician care especially in acute care areas like the intensive care unit and especially at times beyond normal working hours, evenings, nights, or weekends. "Telepresence robots" have been developed to overcome these problems. One of the predominant robots in that area is the InTouch RP-7 robot (Fig. 48.1a). This robot is a mobile platform that enables the physician to interact through the robot with health-care professionals or patients. It consists of a panoramic visualization system, a drive system, and an interface on a control station. It also features a docking station to which several devices (e.g., electronic stethoscopes, otoscopes, or ultrasound devices) can be connected for further transmission to the physician at the remote-control station. The control station consists of a laptop or desktop computer, camera, headset, joystick, and control software (Fig. 48.1b), thus allowing the physician to control movement of the robot, movement of the video cameras and screens, as well as dual continuing audio-video transmission. Few studies have evaluated the benefit of the implementation of such a system on patient outcome or costs. Vespa et al. [3] undertook a prospective cohort study to test the effectiveness of the telepresence with physicians making rounds in the ICU in response to

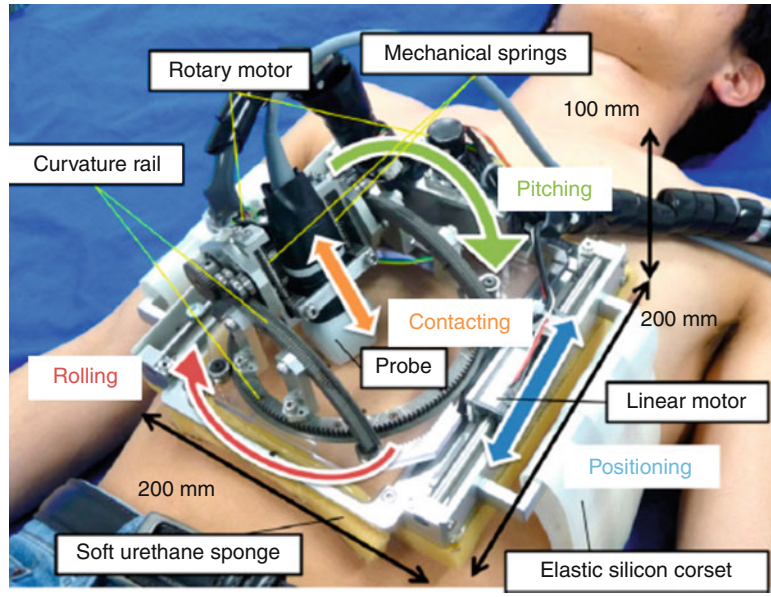

Fig. 48.2 Wearable echocardiography device, strapped on a mannequin that can be remotely controlled by a physician

nursing pages. During a period of 1 year, two physicians used the robotic telepresence device in 640 patients for neurological or neurosurgical problems. The results were compared with 578 matched patients from the years 2003–2004 before implementation of the robotic telepresence system. The use of the robotic system reduced the latency time between face-to-face (direct or via robot screen) contact between the physician and the nurses from 218 to 9 min on average. This leads to a significant reduction in latency to attend to brain ischemia from over 2 h to 8 min and to attend to elevated intracranial pressure from 108 to 11 min. There was also a marked reduction in length of stay in the ICU during the robotic telepresence period which was attributed to its use. The authors concluded that the use of the telerobot allowed rapid – albeit remote – assessment of unstable patients by the attending physician, reduction of length of stay, reduction in hospital costs, and improved efficiency in bed management. In a recent study [4], a telerobotic nighttime multidisciplinary ICU round time was put in place and the ICU nursing satisfaction determined using a standard questionnaire. There was improved satisfaction, based on their perception of ICU physicians being sufficiently available in the ICU, present during acute emergencies and having sufficient time to have questions answered. Despite these encouraging results, robotic telepresence system needs to be improved in terms of user interface and autonomy, reducing the time to "travel" from one room to the next.

Another example of a telerobot (Fig. 48.2) has been presented recently by Ito and colleagues in two publications [5, 6]. A robot was developed to be attached to focused areas of trauma; the wearable echocardiography device can be attached to the specific area (e.g., the abdomen or thorax). In one study [5], the device was attached to four areas of trauma in a mannequin study by nonmedical staff members; the device could be attached correctly within 5 cm of the target area sufficient for a medical doctor to remotely perform an ultrasound exam within 9 min. The possibility of remotely performing an ultrasound exam in patients with blunt trauma might have the capability to establish a diagnosis early, with obvious impact on patient outcome.

Despite robotic telepresence being still in its infancy, early studies already demonstrate a significant impact on quality of care, satisfaction of medical or nonmedical personnel, improved access to care, and possibility to reduce costs significantly.

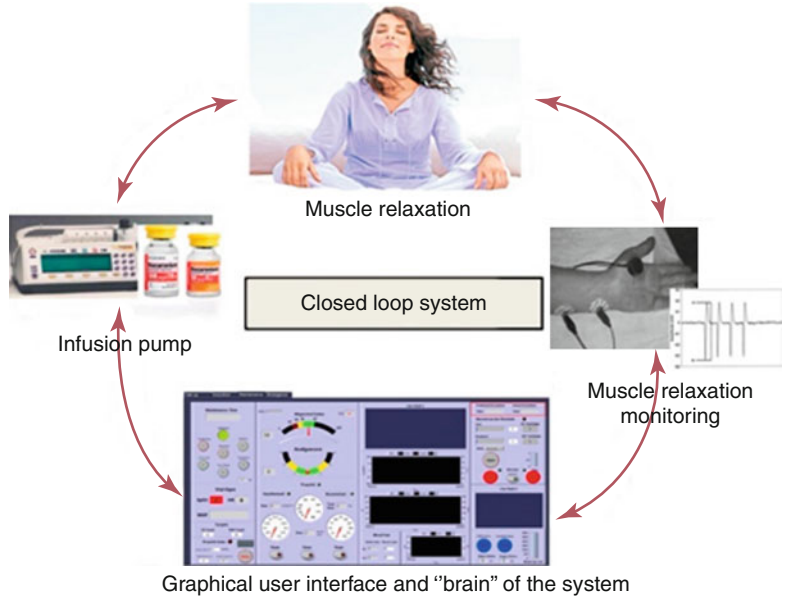

Fig. 48.3 Illustration of a typical closed-loop system, in this case for muscle relaxation

"Pharmacological Robots" for Anesthesia

Pharmacological robots are principally closed-loop systems which are able to titrate anesthetic drugs on their own (see also Chap. 6). Every closed-loop system has three elements: "the brain" (algorithms), one or more target control variables, and one or more drug delivery systems (Fig. 48.3). Feedback loops enable the system to constantly adjust itself to maintain a target without manual input.

The three components of anesthesia are hypnosis, analgesia, and muscle relaxation. A complete pharmacological robot should control all of these, as a recently developed device can: McSleepy [7]. Preliminary clinical results show that McSleepy can in fact deliver general anesthesia, where anesthesia induction, maintenance, and emergence are automatically controlled by the system.

The control variables are bispectral index (BIS) for hypnosis, analgoscore [8] for analgesia, and phonomyography for muscle relaxation. In order to maintain the target BIS value, McSleepy titrates propofol by calculating the BIS error (difference between the target BIS and the actual BIS value). Previous propofol adjustments, the BIS variation (the difference between two consecutive BIS values), and the BIS trend (the difference between the target and the BIS average over the last 5 min) are also considered to maintain the desired depth of hypnosis (the target BIS value can be chosen by the user). The analgoscore [8] is a pain score based on heart rate (HR) and mean arterial pressure (MAP). During anesthesia, painful stimuli are not the only events that can modify HR and MAP. Hypovolemia (an increase in HR without an increase in MAP) and vagal reactions (a decrease in HR with no decrease in MAP) are recognized as such by McSleepy. McSleepy calculates the correct dose of remifentanil, but if changes in HR and MAP are not due to painful stimuli but to hypovolemia or vagal reactions, a fixed minimal remifentanil dose is administered as a safety feature.

Neuromuscular blockade is obtained using rocuronium, which is administered by McSleepy when the TOF ratio is more than 25 %. Additionally, McSleepy includes some safety features to control muscle relaxation: rocuronium boli cannot be repeated within a time interval shorter than 5 min, and no rocuronium boli can be administered within 20 min of the end of surgery. In order to perform safe anesthesia, other safety features are implemented: McSleepy has

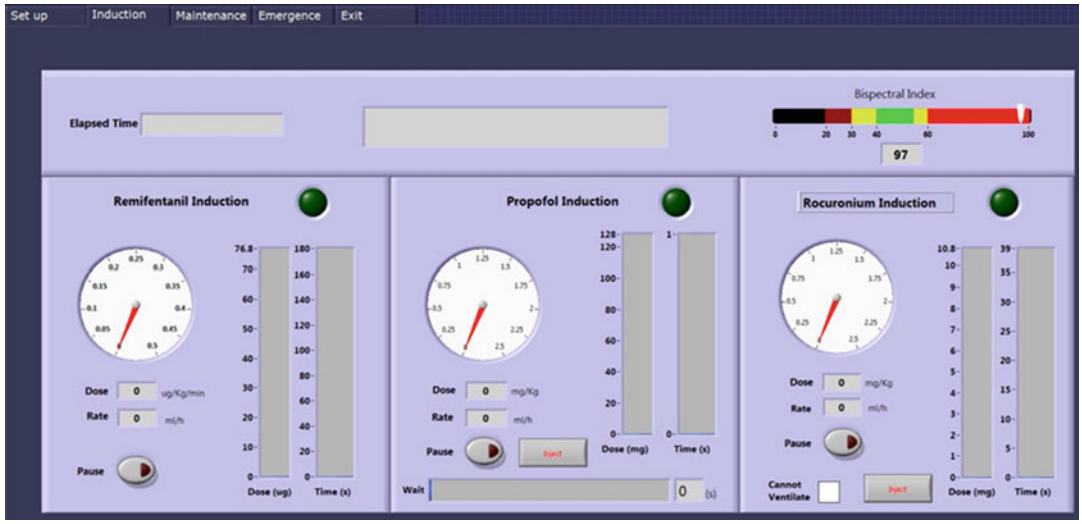

Fig. 48.4 McSleepy is the first pharmacological robot for general anesthesia; illustration of the induction window, which allows users to follow the progress and, if necessary, manually override the robotic induction process

low and high limits for drugs during the maintenance of anesthesia, and, if necessary, the system can be easily overridden manually. There are four windows in the McSleepy interface: a setup window where patient's data and the type of surgery are entered, an induction window (Fig. 48.4) during the induction period, a maintenance window that shows monitoring and live video feeds, and an emergence window at the end of surgery.

There are several precursors of McSleepy, closed-loop systems which are explained in more detail in other chapters. The first one is the CLADS [9], a closed-loop anesthesia delivery system presented in 2007. This system can only control hypnosis; it can be defined as a single-loop system. Every 5 min, CLADS calculates the BIS error. CLADS can carry out induction and maintenance of propofol-induced hypnosis, it performs better than manually administered anesthesia, and it might lead to quicker recovery.

A dual-loop system was presented in 2011 [10]. It is acknowledged as dual because it controls the delivery of two drugs (propofol and remifentanil), but it has only one control variable: the BIS. The controller of the system is a proportional-integral-derivative algorithm. The system is built on the theory that propofol can assure a steady level of hypnosis, but when painful stimuli occur, they induce a cortical activation; as a result, BIS increases. According to the amplitude of the BIS error, the system decides drug adjustments and which drug to adjust.

"Pharmacological Robots" for Sedation

Anesthesia is not the only field where pharmacological robots are developed. In 2011, at the annual meeting of the Society for Technology in Anesthesia (STA), the Hybrid Sedation System (HSS) was presented [11]. It is a new closed-loop system for sedation with spontaneous breathing that incorporates a decision support system (DSS) for critical events. Critical respiratory and hemodynamic events are pointed out through audiovisual alarms by the incorporated DSS. The HSS was used to perform sedation in patients undergoing knee or hip arthroplasty in spinal analgesia and propofol sedation. The system identified more critical events and performed better sedation than manually delivered sedation. Pulse oximetry, capnometry, ECG, noninvasive blood pressure, respiratory rate, and BIS are the components of the HSS monitoring suite. HSS also has an interface which allows anesthesiologists to

enter patient data and the type of surgery and to administer additional propofol boli when needed. The interface also displays vital signs as well as live feeds from the surgical field. The control variables are BIS, peripheral oxygen saturation (SpO2), and respiratory rate.

Another important computer-assisted sedation system is called SEDASYS [12, 13]. The European Union, Canada, and FDA have already approved this system for sedation of low-risk patients. Evading oversedation, ensuring a correct depth of sedation, and conserving spontaneous breathing are the aims of the system. SEDASYS consists of a monitoring suite, an automatic oxygen delivery system, and a mechanical responsiveness monitor. At preset intervals, auditory and tactile stimuli are administered by the responsiveness monitor to verify the depth of sedation. If oversedation is identified, infusion of propofol is instantaneously stopped by SEDASYS, oxygen delivery is increased, and the patient is asked to take a deep breath [13]. The starting infusion rate of propofol is determined by gastroenterologists in relation to patient characteristics. In 2011, results collected while performing propofol sedation via SEDASYS in 489 patients undergoing scheduled esophagogastroduodenoscopy (EGD) and colonoscopy were presented [12]. In the control group, sedation was achieved using benzodiazepine and fentanyl; non-anesthesiologists administered the drugs. SEDASYS delivered better and equally safe sedation. SEDASYS is described to be cost-effective for patients, but patients might be at risk of oversedation and hypoxia [14, 15].

Manual Robots

Manual robots are robots in the stricter sense of the Robotic Institute of America, which defines robots as "reprogrammable, multifunctional manipulators designed to move materials, parts, tools, or other specialized devices through various programmed motions for the performance of a variety of tasks." It further divides robots into four classes, "handling devices with manual control, automated handling devices with predetermined cycles, programmable, servo-controlled robots with continuous of point-to-point trajectories and robots capable of Type C specifications which also acquire information from the environment for intelligent motion." Most robots in medicine, such as surgical robots, are handling devices with manual, often remote, control. There are two areas where robots have been used in very early pilot studies to aid with manual tasks: intubation and the performance of nerve blocks.

Robotic Intubation

Tighe et al. [16] used the da Vinci Surgical System to execute two fiberoptic intubations in simulation (Fig. 48.5a, b). One robotic arm held the video camera, which was placed above the standard airway mannequin. The other robotic arms were used to manipulate grasping instruments of different size whereas the fourth robotic arm held the fiberoptic bronchoscope in place. Two intubations were performed, both orally and nasally, with success in a time of several minutes. Obviously, the use of the da Vinci system for intubation is hardly practical for future routine use; however, it demonstrates the versatility of the surgical robot system. In another study, a specific system was developed for robot-assisted intubation. It consists of a robotic arm with a videolaryngoscope mounted at the end, which can be manipulated using a standard joystick allowing movements in 6° of freedom (Fig. 48.6). The system can be controlled using a so-called intubation cockpit. The cockpit is linked to two or more live video cameras, positioned laterally to the patient's head. It figures visual and acoustic alarms. The Kepler intubation system was successfully tested in a standard airway mannequin [17], showing a reasonable learning curve and very good success rate. In the dummy testing, a semiautomated function can be used: using playback from previous intubations, the robot, once inserted at a specific point of the mouth, performs the intubation itself, without human interaction; it places the videolaryngoscope in such a way that the vocal cords can be visualized – insertion of the

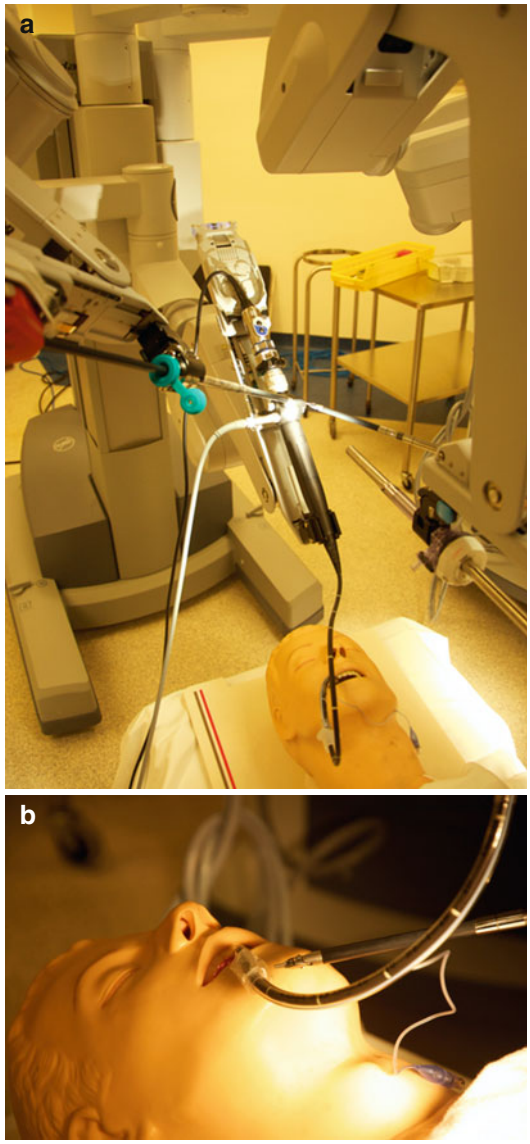

Fig. 48.5 Use of the da Vinci Surgical System to perform intubation in an airway mannequin. (**a**) Overview of system setup; (**b**) Close-up of intubation

endotracheal tube needs just a gentle push of the upper end of the tube and is a non-skilled gesture. This system was also successfully tested in a pilot study in humans [18]: eleven endotracheal intubations were successful; one intubation was not possible because the videolaryngoscope fogged, a common phenomenon when videolaryngoscopes are used, with or without robot.

Manual Robots for Regional Anesthesia

The same group of Tighe et al. [19] used the da Vinci system to perform both a single-shot nerve block and catheter insertion in a phantom model. The ultrasound probe was used to manipulate the nerve block equipment; the robotic arms carried the video camera and the graspers for the block performance. Nerve blocks could be effectuated using this setup; however, the authors noted that the current state of equipment of the da Vinci system was not ideally suited to perform such tasks (Fig. 48.7).

The Magellan system uses the same components as the Kepler intubation system (Fig. 48.8): however, there is specifically designed block cockpit and a custom-made adapter to hold a syringe or needle. This robotic system [20] was tested in 13 human patients. The Magellan can be controlled using three different arm speeds: the high speed, the medium speed to advance the needle towards the skin and the low speed to transverse the skin and advance further towards the targeted nerve area. The nerve is identified using standard ultrasound imaging technique with the possibility to place webcams in different angles (e.g., lateral to the needle insertion site). The researchers performed 16 blocks of the sciatic nerve in the popliteal fossa with 100 % success. Recently, the same group [21] presented a custom-made image recognition software, capable of reliably identifying the center of the sciatic nerve in the popliteal fossa. It also showed that there was an excellent agreement between the detection of the nerve area using the software compared to manual detection by experienced anesthesiologists.

Remotely Controlled Anesthesia and Anesthetic Consulting

Remote-controlled anesthesia was initially concentrated on remote consulting across continents or in rural areas. Recently, the field has moved from teletherapeutic control of propofol administration across the distance of 200 km [22] to

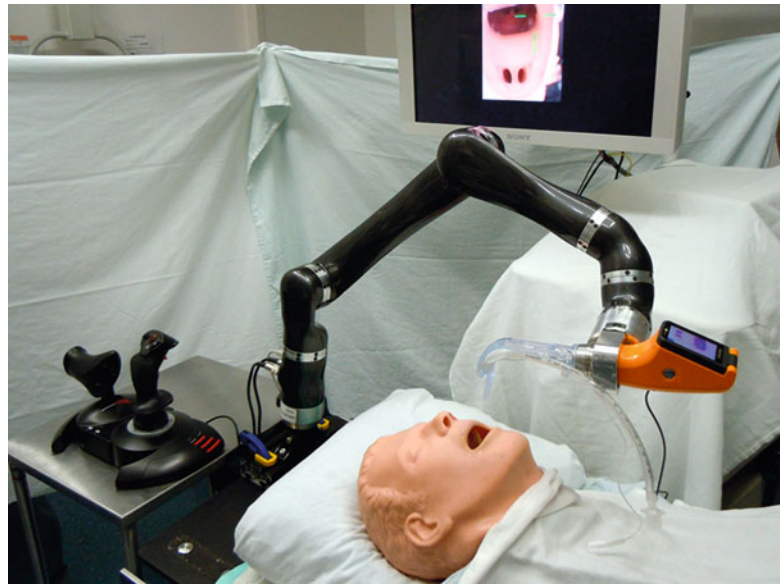

Fig. 48.6 Kepler intubation system consisting of joystick, robotic arm, and videolaryngoscope

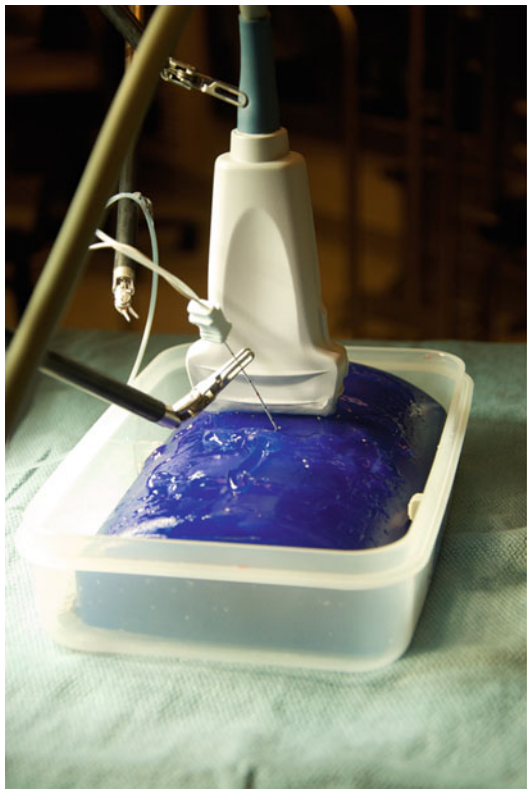

Fig. 48.7 Use of the da Vinci surgical robot for nerve blocks in a phantom

robotic anesthesia delivery across continents [23]. Ihmsen et al. [22] connected two computers from Erlangen to Munich in Germany through a virtual private network. Patients underwent general surgery in Munich with hypnosis provided using total intravenous anesthesia with propofol; using EEG-feedback control, the drug infusion of propofol was calculated in Erlangen and then sent to the patient site computer in Munich in 11 patients. The median performance error of the system was - 4.6 (4.4)% and the median absolute performance error was 18.8 (5.7)%. Remote-controlled propofol anesthesia needed to be continued manually in one patient because the Internet connection broke down. In 2010, the first completely robotic anesthesia was performed as a transcontinental anesthesia with patients undergoing thyroid gland surgery in Pisa, controlled from Montreal [23]. The system consisted of an anesthesia cockpit in Montreal (remote-control center) with a user interface installed on computer that allowed remote control of all anesthetic parameters; in addition, there were four video cameras installed at the patient site recording and continuously transmitting video imaging of videolaryngoscopy at induction, surgical site, ventilator parameters, and vital sign monitoring. Audio-video communication was established using standard high-speed Internet. In this study, even the intubation was guided remotely, with the local operator, an anesthesia resident with little experience with the use of the videolaryngoscope, being assisted by information and commands from the Montreal

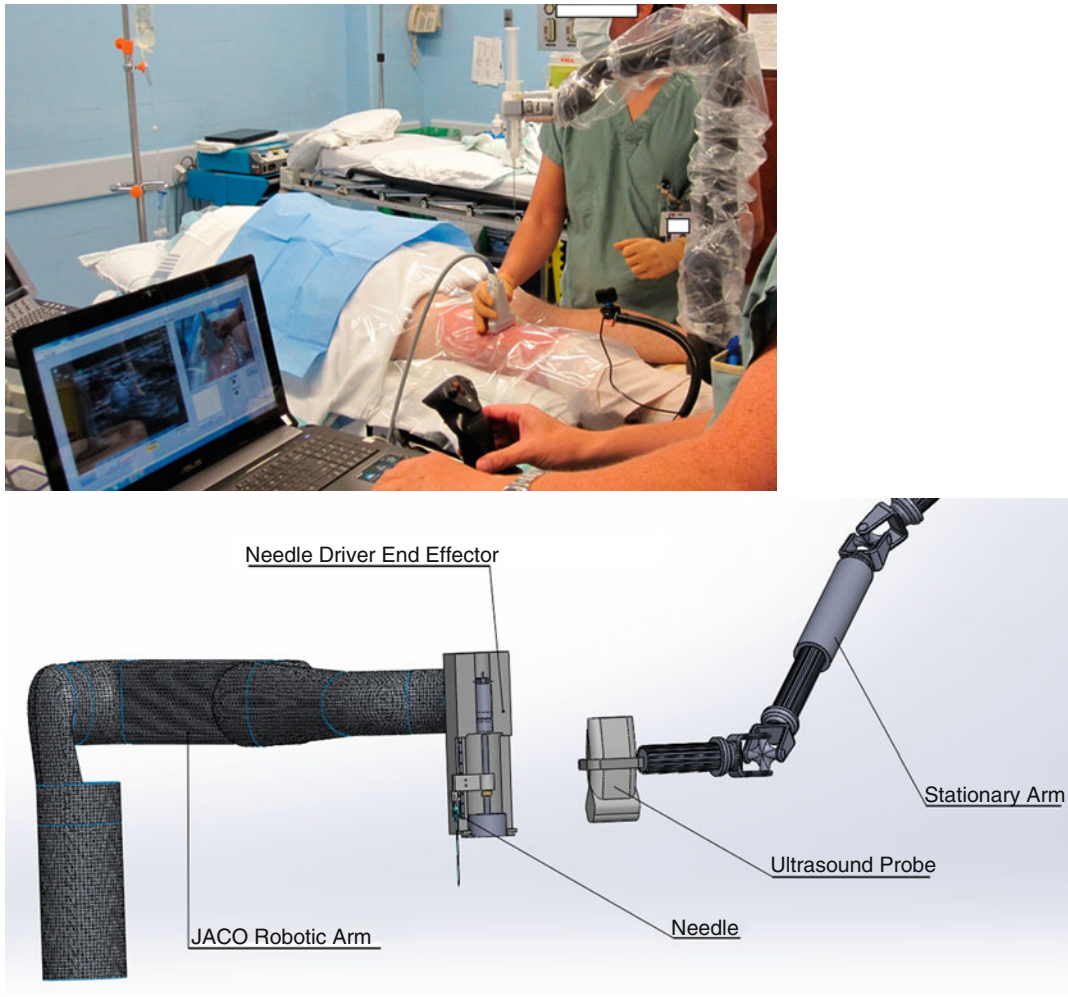

Fig. 48.8 Magellan, a robotic system for performing nerve blocks, consisting of a joystick, a robotic arm, and a custom-made operational software

cockpit. Induction, maintenance, and emergence from anesthesia were remotely controlled via closed-loop general anesthesia using propofol, remifentanil, and rocuronium. This project showed that remote control of all three components of anesthesia – hypnosis, analgesia, and muscle relaxation – is feasible in 20 patients and showed good clinical performance to induce and maintain anesthesia. Even remote preoperative airway assessment was feasible and showed good to excellent agreement with direct assessment at the patient site.

Prior to these two studies, telemedicine in anesthesia was confined to either remote anesthetic monitoring or telemedical consultation. Cone et al. published a case report in 2004 [24], where cholecystectomy was performed in a rural area of the Amazonian rainforest, with the help of remote vital sign and video patient monitoring and attending physicians as consultants in Virginia. Fiadjoe et al. [25] provide even real-time consultation and monitoring for a pediatric liver transplantation performed in India.

Wong et al. [26] presented remote clinical consultations across Ontario performed remotely by anesthetic residents while a nurse at the patient site had direct contact with the patient. The patient's history was taken by the nurse, with the anesthesiologist able to ask additional questions if needed. The local implementation of a digital

stethoscope allowed remote examination of respiratory and cardiovascular system, while the airway was assessed using an "airway camera," operated by the nurse. Based on this pilot study, remote preoperative assessment is now performed routinely via the Northern Ontario Telecommunication Health Network. Obviously, this kind of remote assessment still necessitates the patient coming into a local site and the presence of a nurse.

In order to further robotize preoperative patient assessment and avoid any displacement of the patient for the assessment, a special interface and image recognition software were designed [27]. The performance of the so-called pre-op cockpit was evaluated by the authors in comparison of direct preoperative assessment. The authors determined the Mallampati class, thyromental distance, and the distance of the mouth opening showing overall good agreement; since this assessment was performed remotely using a standard Internet connection and a standard videoconference platform (Skype), it could be performed at the patient's home. The distances are automatically calculated by the cockpit using custom-made image recognition software.

Conclusion

Robots are without fatigue; they are not influenced by emotions and perform in the same way over and over. At present, the most widely used robots in the field of intensive care, emergency care medicine, and anesthesia are "telepresence robots": they are mobile stations that can be operated remotely using a joystick and allow audio-video communication between a physician and the local health-care team and the patient, including remote viewing and recording of locally acquired digitalized patient data, such as vital sign parameters. However, this is a very simple form of robotization. "Pharmacological robots" have evolved from early closed-loop systems to complete systems that allow not only the closed-loop control of all anesthetic parameters but also a broad spectrum of interaction between the robot and the user via easy-to-use, intuitive interfaces. The McSleepy device is such a robot for anesthesia, the HSS or the SEDASYS for sedation. Very recently, attempts have been made to develop robots for manual gestures; these "manual robots" are in the early experimental phases with devices such as the Kepler intubation system or the Magellan system showing promise in early pilot studies. The field of "teleanesthesia" is also developing slowly, from remote preoperative assessment to transcontinental anesthesia delivery.

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