Chapter 6
Transforming Monitoring and Improving Care with Variability-Derived Clinical Decision Support

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6.1 Introduction

Monitoring of patients with existing or impending critical illness routinely involves the recording of multiple waveforms, including electrocardiography, oxygen saturation, capnography, chest impedance and arterial blood pressure, with continuous display of vital signs such as heart rate, oxygen saturation, respiratory rate and systolic/diastolic blood pressure. Although waveform data is sampled hundreds of times per second, vital signs are commonly charted once per hour, as changes in vital signs are meaningfully evaluated over hours to track response to interventions or gauge clinical trajectory. Clinical improvement or deterioration is evaluated by change in vital signs over hours to days; infection is detected with fever or laboratory tests, and clinical intuition plays a significant role.

Utilizing the currently untapped information contained in waveform data has the potential to reduce the diagnostic and prognostic uncertainty inherent in critical care, even when patients are managed by trained intensivists. This uncertainty results in delayed diagnosis, unnecessary or inappropriate therapy and increased complications, mortality and cost of care. In fact, studies have shown that the most expensive patients are those with indeterminate outcomes [1, 2]. For example, late diagnosis of infection and the cost of treating sepsis represent a large burden on the healthcare system [3]. Similarly, uncertainty in determining optimal timing of extubation in mechanically ventilated patients can harm patients and waste resources [4]. The care of patients with serious acute illness and the demand for ICU services are expected to increase by 40% in the year 2026 compared to 2011 [5, 6].

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J. P. Sturmberg (ed.), *Putting Systems and Complexity Sciences Into Practice*,
https://doi.org/10.1007/978-3-319-73636-5_6

Heart rate variability (HRV) and respiratory rate variability (RRV) time series derived from the continuous physiological waveforms help characterize the degree and complexity of the patterns of the inter-beat and inter-breath interval time series. Decreased variability is associated with age and illness and correlates with illness severity, indicating reduced adaptability and/or increased stress. Alterations in HRV have been associated with sepsis and septic shock [7–9]. HRV monitoring provides early detection of infection in neutropenic patients and determines severity of illness in critically ill patients [10, 11]. Respiratory rate variability (RRV) is also altered in association with critical illness, with a reduction in RRV during organ failure [12] and restrictive lung disease [13]. Reduced RRV has also been evaluated as a marker of increased stress during weaning from mechanical ventilation [14]. Reduced RRV is also statistically associated with and predictive of extubation failure [15, 16].

In the following, we outline our current approach to utilize information buried in the variability of inter-beat and inter-breath intervals routinely monitored at the bedside, transforming the information into clinical decision support that reduces uncertainty, standardizes approach and improves quality and efficiency of care.

6.2 Our Approach

Combining waveform-based variability analysis with predictive modelling, we can enhance timely clinical decision-making at the bedside by providing probabilistic prediction of upcoming clinical events. In order to produce a practical, useable and clinically relevant decision support, we focus on unsolved clinical problems, where altered variability is associated with a well-defined clinical outcome, tied to a decision that the healthcare team has to make. Conditions are then optimal to utilize variability analysis and predictive modelling.

6.2.1 Data Collection

The vital signs of patients are often monitored continuously and used to derive alarms and run predictive analytics or simply to get a quick feedback on patients' status. On the other hand, while routinely displayed, physiologic waveform data such as ECG is rarely recorded for more than a few days or made available for additional offline analyses. Collected waveforms may be used to track vital signs precisely and continuously but also enable the derivation of predictive analytics based on patterns of variation in heart rate, respiratory rate or blood pressure, which in turn can help identify patients at higher risk of a negative outcome. At present, there is no standard method to extract waveform data from bedside monitors or ambulatory physiological devices. Waveform capture solutions depend on the brand and model of the equipment and have varied technical requirements and costs. Setting up waveform data acquisition at clinical institutions is usually not trivial and requires a diverse range of clinical and technical stakeholders.

Research studies involving multiple sites face the additional challenge of harmonizing the waveform data coming from very different systems. The choice of data repository, database and file formats as well as developing software for easily reviewing large amounts of clinical data and physiological recordings should be considered carefully for each study.

6.2.2 Variability/Complexity Assessment

Physiological waveforms acquired from a patient are processed through a software engine, which we have termed Continuous Individualized Multiorgan Variability Analysis (CIMVA). CIMVA performs a series of automated algorithms that process the waveform files into a comprehensive multivariate characterization of the quality of the waveform and the event time series (i.e. consecutive inter-beat and inter-breath intervals over time) and the calculated measures of degree and complexity of variability.

The first step is to translate the waveform into a time series of physiological events. For example, individual heartbeats are identified from an ECG waveform, using commonly used algorithms and fiducial points (e.g. peaks of the P, R or T waves). We form time series of time intervals, such as R-peak to R-peak intervals (RRI). Similarly, a time series of inter-breath intervals (IBI) can be derived from a capnogram (CO2 waveform). A thorough automated assessment is performed on the quality of the underlying physiological waveform signal and derived physiological events time series. Movement artefacts, noise, disconnections and saturations are identified on the waveforms. A signal quality index is determined on a beat-by-beat or breath-by-breath basis, using continuity and morphology analyses. In addition, the times series of physiological events (RRI, IBI) are filtered to exclude non-sinus beats, abnormally shaped breaths and nonphysiologically plausible data.

Using the cleaned time series of events, the signal complexity and degree of variability are assessed. This is performed through a moving window analysis, whereby a window of fixed duration (or fixed number of events) is shifted in time across the entire duration of the event time series. A comprehensive set of variability metrics are calculated within each window. Variability measures include measures characterizing the statistical properties (e.g. standard deviation, RMSSD), the informational complexity (e.g. entropy measures), the pattern variations across time scales (e.g. fractal measures, power law exponents) or the energy contained in the signal (e.g. spectral measures). Each technique provides a unique perspective on the data; no single technique offers a definitive characterization of biologic signals, and thus investigators agree a plurality of techniques offers the most complete evaluation [17–19]. This analysis is performed iteratively and repetitively, measuring variability over time intervals (e.g. 5 min for HRV, 15 min for RRV), then tracked over time. Nonstationarities (i.e. rapid underlying trends, spikes) are assessed and removed. Only high-quality variability estimates are used in subsequent processing steps. This automated high-quality comprehensive variability analysis forms a multivariate representation of variability and signal complexity tracked over time.

6.2.3 Predictive Modelling

Predictive modelling is ideally suited to translate multivariate variability into clinically relevant information. To do so, we identify clinical outcomes statistically associated with altered variability and perform observational clinical research measuring variability and outcomes for multiple patients. Outcomes are categorized, such as extubation outcomes (e.g. failed extubation requiring re-intubation vs. successful), the presence or absence of infection or rapid vs. slow death after withdrawal of life-sustaining therapy (which determines eligibility for donation of organs after cardiac death); and the dataset is typically separated into patients who develop the outcome and patients who do not.

Several strategies are available to develop a prediction tool that estimates the likelihood of a patient developing the outcome of interest. First, a set of relevant features is determined that will be fed to one of the several possible multivariate statistical techniques such as logistic regression, k-nearest neighbour analysis, decision trees, support vector machines, neural networks and so on. Relevant input features are determined through a priori expert knowledge or a feature selection process whereby the discriminative power of each feature is assessed on a subset of patients (training set), based on a predetermined performance metric (e.g. prediction accuracy). Considered features include the set of variability measures as well as relevant clinical parameters (e.g. tidal volume, gender, comorbidities, risks scores, etc.) and/or laboratory data. In addition, separate predictive models can be derived for variability measures and clinical or laboratory parameters and the models later combined, through fusion or decision scores via appropriate weighting or using a Bayesian framework. This may result in a more efficient model and improved prediction when features are recorded at different time intervals (e.g. daily scores).

The development and performance assessment of the multivariate statistical techniques is carried out with a cross-validation scheme, whereby the dataset is separated into training and validation sets for model and feature selection, and an unseen testing set for an unbiased estimate of the performance and generalizability on future datasets. Finally, performance evaluation of predictive models is based on receiver operating characteristic (ROC)-derived metrics (i.e. area under the curve, sensitivity, specificity, and positive predictive value and negative predictive value), as well as time-dependent metrics (i.e. time-stamped endpoints) for tracking patient improvement or deterioration prior to or post-outcome. The output of the predictive model is a probability of developing the outcome and can, for example, be presented to clinicians in the form of a continuously updated fold increase in risk to facilitate timely clinical decision-making.

6.3 Example of a Clinical Application: Weaning and Variability Evaluation (WAVE)

Expeditious, safe extubation is vitally important in the care of intensive care unit (ICU) patients as prolonged mechanical ventilation harms patients, and failed extubation (i.e. re-intubation within 48 h) is associated with increased morbidity, mortality and costs [4, 20–22]. Absence of elevation of the respiratory frequency to tidal volume ratio (f/VT) or rapid shallow breathing index (RSBI<105) during a spontaneous breathing trial (SBT) is the current standard indicator that extubation will be successful [23, 24]. Despite this practice, several studies document an extubation failure rate of 15% [23, 25, 26], suggesting that the RSBI, the most objective measurement available, has only limited value in predicting successful extubation after an SBT [24].

Several small studies have demonstrated that reduced heart or respiratory rate variability (HRV or RRV) during SBTs is associated with extubation failure [27–30]. In a large, multicentre (12 sites), prospective observational study, we enrolled 721 patients and collected information during spontaneous breathing trials including physiologic measures, ECG, capnograms and extubation outcomes [15].

A large set of HRV and RRV metrics were derived using CIMVA software. Repeated randomized subsampling with training, validation and testing sets were used to derive and compare an ensemble of logistic regression models. An optimal predictive model utilizing five RRV metrics during the last SBT prior to extubation was derived, which outperformed other commonly used measures such as RSBI and vital signs or clinical judgement. The output from this model was a probability of extubation failure (WAVE score) or equivalently a fold increase in risk, which in turn could help physicians stratify patients more efficiently.

The previous work of the WAVE study was seminal to the development of the clinical decision support software, Extubation Advisor™. Extubation Advisor™ was developed to deliver a comprehensive assessment of the risk of extubation failure to clinicians at the bedside. A key set of clinically relevant information is gathered from the respiratory therapist at the bedside via an electronic form, and a report is generated, which summarizes the patient condition during an SBT as well as his/her risk of extubation failure. The components of this standardized report were determined via a mixture of best clinical practices available in the literature as well as feedback from targeted clinical users and include patient information, SBT information and parameters, vitals, extubation readiness checklist, respiratory therapist impression and risk of extubation failure.

Great care must be taken to ensure that a clinical prediction tool does not negatively disrupt the established clinical workflow. The identification of all stakeholders that are anticipated to be impacted by the tool is critical at an early stage. Furthermore, actively engaging healthcare staff, technical and research teams and patients/family can greatly help identifying a relevant, impactful clinical problem, focusing on metrics relevant to the problem as well as providing feedback on user interface and efficient deployment of the predictive tool.

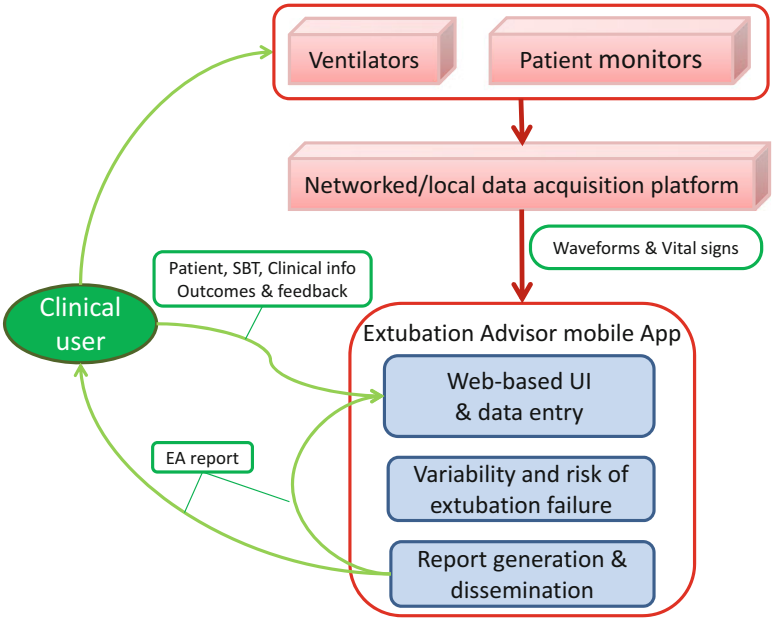

Fig. 6.1 High-level flow diagram of Extubation Advisor™

Figure 6.1 shows an example of integration of the extubation failure prediction tool based on the WAVE study.

A typical workflow for Extubation Advisor™ would be as follows:

- An intubated and mechanically ventilated patient is scheduled for a spontaneous breathing trial (SBT). The patient is connected to a bedside monitor displaying ECG, CO2 and other relevant waveforms. A respiratory therapist (RT) logs on to the Extubation Advisor™ application on a tablet or mobile device. The RT inputs patient/admission information, completes an SBT checklist and starts the trial. During the SBT, the waveform data is continuously acquired via the bedside monitor or the ventilator using a hospital-based data acquisition platform or mobile data acquisition device attached to the ventilator.
- After the SBT is complete, Extubation Advisor™ requests the portions of waveforms and vital signs data (if available) corresponding to the SBT, proceeds to clean and assess the quality of the data, computes variability metrics and generates a score summarizing the risk of extubation failure. Extubation Advisor™ also generates an interactive report for the RT to view on a mobile platform and a PDF version that can be dispatched to interested parties. The attending physician and RT examine the report along with other clinical information and determine whether to proceed with extubation or not.

- Finally, the extubation information and outcome are entered via the EA user interface 48 h post-extubation for post-analysis of the performance of the model and future improvements.

6.4 Conclusions

In this paper, we presented a systematic approach to highlight how to systematically derive relevant decision support tools from well-defined clinical questions to bedside implementation. Focusing on the weaning process in mechanically ventilated ICU patients as an example, we showed that by assessing the complexity and variability of often unused physiological waveforms commonly acquired at the bedside, combined with easily obtainable clinical data, we could provide a timely standardized report of the risk of extubation failure. A possible integration of this Extubation Advisor™ tool in clinical processes and workflow was also highlighted.

Stemming from a desire to extract useful information from physiological signals as surrogate "sensors" of the human body, we quickly realized that often used single summary parameters were inadequate for making timely decisions on complex health problems. Instead, we noted that complex behaviours similar to what could be observed in health systems have been addressed in other fields such as chaos theory, network theory, fluid dynamics, etc. with a range of tools and methods, each tool presenting a slightly different insight into the complex problem.

We believe it is also important to view our understanding of physiological signal complexity in the wider context of cellular, metabolic, macroscopic and population interactions, where complex interactions similarly occur. The complexity science umbrella of methods and applications is broad, and valuable insights can be gained by sharing and pooling knowledge from its various subdisciplines.

The Journey

The framework presented in this paper offers a practical approach for utilizing variability as a window into the integrity of the complex system that is the human body.

Major challenges in critical care are related to complex illnesses such as multiple organ dysfunction syndrome, yet until two decades ago, most approaches relied on analytical approaches, focusing on individual immunologic mechanisms and assuming linear relationships. The failures of these reductionist models prompted us, and others, to reframe the host response to major insults as a complex nonlinear system, whereby nonlinear interactions between interconnected organ systems contribute to the emergence of complex properties, which individual parts of the

system do not otherwise exhibit. This represented a profound shift in our approach but also opened the door to a great amount of new and exciting techniques from nonlinear dynamics, including variability analysis.

We embraced variability analysis as a natural toolkit to characterize the emergent properties of a complex system, following earlier works from Glass and Mackey [31] and Goldberger and West [32], among others. We embarked on a comprehensive exploration of a wide range of linear and nonlinear variability metrics, working on physiological signals from multiple organ systems (ECG, CO_2, ABP, etc.), in an effort to characterize different aspects of the underlying system dynamics of the systemic host response.

After many years using this rich complex science toolkit, we are slowly working towards individualized variability directed intervention, where therapeutic approaches are tailored to a patient based on his/her own patterns of variability and systemic host response.

Take-Home Message

- There is much untapped potential in routinely collected yet discarded clinical waveform data (e.g. electrocardiogram, capnography)
- The complexity and degree of variability of heart and respiratory rate measured from waveforms and their changes over time are linked to a variety of ill health states
- Predictive models using clinical data and variability of physiological signals can provide key decision insights to the clinical team
- A systematic approach is described to ensure that the clinical problem answered by a decision support tool is well-defined and relevant to clinical practice and that its development and implementation is beneficial to clinicians and integrates with clinical workflows

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