Intensive Care Med (2005) 31:1161–1167
DOI 10.1007/s00134-005-2729-7

CLINICAL COMMENTARY

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Normalizing physiological variables in acute illness: five reasons for caution

Received: 6 February 2005
Accepted: 21 June 2005
Published online: 26 July 2005

B.P.K. is funded by the Canadian Institutes of Health Research and the Ontario Ministry of Science and Technology.

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Introduction

Acute illness is accompanied by the development of abnormal physiology. The development and severity of illness, as well as recovery, is paralleled by changes in the physiological variables that clinicians commonly monitor. Several factors may prompt clinicians to address and treat the variables in isolation from addressing the underlying disease. This article explores why clinicians may target and attempt to normalize abnormal physiological variables and identifies five reasons why such an approach can be hazardous.

Physiological parameters and illness

The evolution of many illnesses usually follows predictable patterns. For example, septic shock, an acute syndrome that is perhaps emblematic of critical care medicine and has a high mortality, commonly follows a foreseeable trajectory from localized to generalized infection, progressive hemodynamic deterioration, multiple organ dysfunction and, in over 30% of patients, death [1]. The cardiovascular changes associated with this syndrome typically include tachycardia and decreased blood pressure and usually an increase in cardiac output.

There are several reasons why clinicians monitor and attempt to correct such physiological variables in the acutely ill. First, in some highly specific situations this approach appears to work. Indeed, although seriously questioned [2, 3], randomized controlled clinical trials have suggested improvement in survival associated with rigorous control of plasma glucose in postoperative adult cardiac surgical patients [4] or more rapid resuscitation of patients with recently diagnosed septic shock [1]. Second, traditionally physiology has been the basis for assessment and treatment in critically ill patients, where monitoring directs how therapy is applied [5]. Although ongoing developments of molecular medicine and evidence-based medicine may alter how patients are treated in the future, the "physiological" approach, i.e., treatment based on physiological monitoring, has been a cornerstone of teaching in critical care medicine for decades [6]. Third, the extent to which physiological variables differ from normal values indicates how ill the patient is. This is important because clinicians know well that disease severity is an important indicator of ultimate outcome, and the assessment of severity is largely based on the degree to which the measured variables (e.g., perturbations of the cardiovascular, respiratory, and acid-base systems) differ from normal values. Indeed such impressions have been validated by numerous scoring systems that incorporate the extent of physiological derangement and predict outcomes

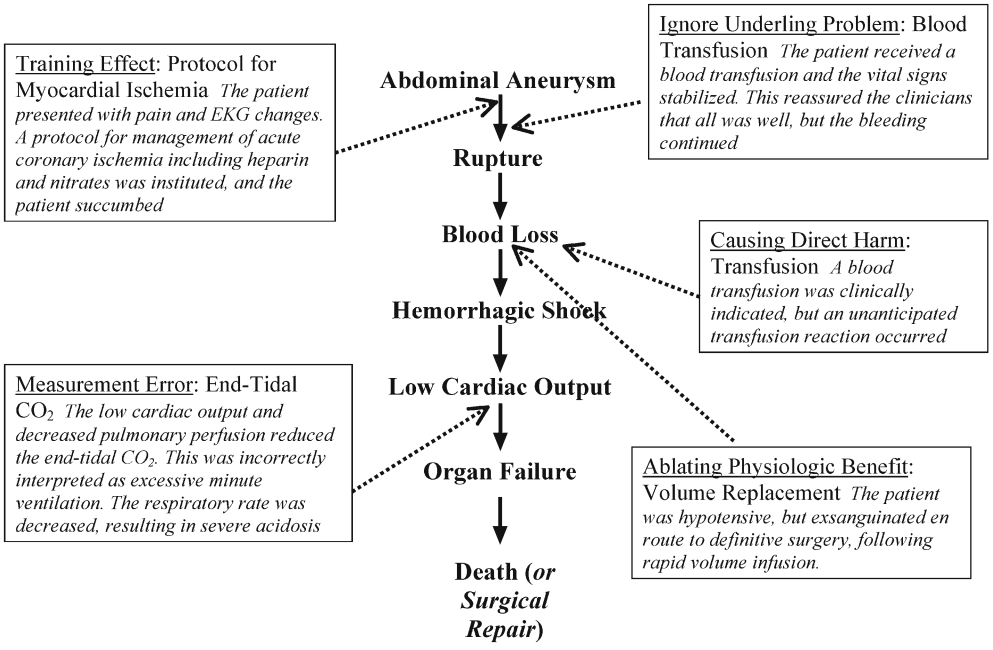

Fig. 1 An example of an acute illness state: hemorrhagic shock resulting from a ruptured abdominal aortic aneurysm. This flowchart illustrates how, using the five identified erroneous approaches, clinicians may intervene but direct therapy inappropriately

in populations of critically ill adults [7, 8] and children [9]. Fourth, beyond linking the initial degree of physiological derangement with severity of illness at the outset, established data have documented a close association between the sequential changes in physiological abnormalities and prognosis from acute illness [10]. Finally, in the same way that increasing deviation of variables from normal values reflects worsening of disease and poor prognosis, the converse is also true; normalization of abnormal variables parallels disease resolution and may be the principal objective evidence that a patient's condition is improving.

Despite this rationale the approach is imperfect and sometimes has disastrous results. A recent randomized controlled trial of nitric oxide synthase inhibition in septic shock was designed with simple pathophysiological rationale [11]; although the drug was effective in correcting the blood pressure and reversing shock [12], mortality was increased, not decreased [11]. Indeed, more comprehensive consideration, including attention to the critical importance of myocardial function in sepsis, might have predicted such a response [13, 14]. This vivid example illustrates the need for reflection about simplistic physiological rationale vs. demonstration of actual outcome benefit, and the potential for error associated with the former.

Normalization as a therapeutic endpoint

Based on the above considerations it is understandable why clinicians would instinctively focus on attempting to normalize abnormal physiological variables in patients who are acutely ill. Although several studies have demonstrated adverse effects of increasing levels of physiological support to supranormal levels (e.g., oxygen delivery [15], endocrine replacement [16]), clinicians may not appreciate dangers that may be associated with adjustment of variables to normal levels. We outline in this contribution five principles by which targeting and attempting to normalize physiological variables in acutely ill patients can lead to harm. These principles are illustrated by published examples and suggest global approaches for avoidance of such complications. An illustrated outline is provided in Fig. 1, focusing on the potential harm associated with correcting variables in a patient with ruptured abdominal aneurysm.

Ignoring the underlying problem

Classical approaches to treating acute illness involve provision of supportive care while at the same time addressing the primary problem. There are clearly some derangements in physiological variables, for example, severe hypoxemia, which are inherently life-threatening and must therefore be immediately treated. However, the clinician cannot be content with the return of measured variables to normal but must consider the underlying cause of the derangement. Failure to do so can result in significant harm to the patient.

Consider a patient presenting with severe hypovolemic shock from a massive gastrointestinal hemorrhage. Initial management may include fluids, blood products, and potentially vasopressors. It is gratifying to see the blood pressure climb to normal levels with the supportive care. It would be catastrophic, however, if one did not continue with definitive management of the bleeding. Similarly, a

patient with pyonephrosis from an obstructed ureter could develop septic shock and all the physiological derangements that occur with multiorgan dysfunction. The variables can look much better with usual critical care support (e.g., mechanical ventilation, fluids, vasopressors), but the patient is unlikely to improve overall without appropriate abscess drainage. In both situations it is obvious that the management of the patient requires both supportive care in addition to measures directed at the underlying cause.

Consider also each individual parameter monitored in the critical care unit. Derangements in any variable can have a myriad of causes. For example, pulse oximetry may inform the clinician about a potentially important change in a key physiological parameter, oxygen saturation. Desaturation can have any of numerous underlying causes, each requiring specific therapy. Such concerns are reflected in an editorial commentary on the intraoperative use of pulse oximetry wherein Fairley [17] wrote, "As the blindfolded anesthetist walks unknowingly towards the cliff of hypoxia.... the protective hand of the pulse oximeter sentry stops him from falling over the edge. The oximeter will not tell him why.... or the direction back."

Inducing harm

It has long seemed logical to clinicians that in acutely ill patients the restoration of vital functions to normal levels would result in reduced imposition on the physiological reserve and increase the probability, and the rapidity, of recovery [18]. In terms of transfusion of red blood cells, the rationale—representing conventional thinking up to 5 years ago—was that the increased O_2 delivery to tissues resulting from transfusion would permit greater O_2 consumption at the cellular level, and that this would translate into better outcome. Although simplistic, such concepts have long provided the impetus for "topping up" hemoglobin levels in acutely ill patients [19, 20].

In fact, this specific intervention—red cell transfusion—has been subjected to several important clinical studies, with unexpected results [21, 22]. To test the acute effects of red cell transfusion on tissue oxygenation, Marik and Sibbald [21] transfused patients suffering from systemic sepsis who were mildly anemic. Several important lessons were learned. First, global O_2 consumption was not increased when directly measured, despite indirect estimation suggesting the contrary. Second, at a local tissue level the majority of the transfusions resulted in adverse, not beneficial, changes in the oxygenation status. This was detected using gastric tonometry, a technique that assesses the O_2 supply-demand status of the vulnerable mucosal cells that line the stomach. In addition, the age of the transfused red cells was predictive of the degree of mucosal dysoxia, raising the possibility that storage duration, well within ranges common in North America, resulted in dysfunctional red cells.

While the pathophysiological responses to stored red cells are of mechanistic interest, a subsequent clinical study has provided important outcome data that may mandate changes in practice [22]. This study demonstrated that transfusion, even to a modest hemoglobin concentration, does not improve the status of anemic patients who are acutely ill in the intensive care unit; in fact subgroup analysis suggests that it may increase mortality [22], perhaps due to leukocyte-mediated actions [23] or altered volume status. Other examples exist where treatment aimed at normalizing variables can result in adverse outcome. For example, rapid correction of serum sodium concentration in cases of hyponatremia can result in brainstem destruction from central pontine myelinolysis [24]; conversely, rapid normalization of hyperosmolar states, such a hyperosmolar coma and diabetic ketoacidosis, can result in accelerated cerebral edema, with devastating consequences. In preterm infants the targeting of normal, not high, levels of oxygenation with low amounts of supplemental O_2 was hypothesized to improve neurodevelopment [25]. The hypothesis, although apparently soundly constructed, turned out to be false [25], and the approach instead of helping caused harm, resulting in an increased incidence of chronic lung disease. Finally, it is now apparent that the high tidal volumes associated with frankly lowered $PaCO_2$ towards or below normal levels in patients with acute respiratory distress syndrome (ARDS) are associated with increased mortality [26, 27, 28]; indeed alternative approaches to management of ARDS have been proposed [29, 30].

Ablation of physiological benefit

Whereas abnormal physiological variables always suggest an abnormal milieu or disease state, this does not mean that all abnormal variables are directly causing harm. Indeed, in some situations abnormal variables (e.g., mild hypotension) may benefit the patient.

Resuscitation of trauma victims who have developed hypotension due to blood loss has traditionally followed the "A, B, C" (i.e., airway, breathing, circulation) approach [31, 32]. In this scenario the patient's airway is controlled, breathing assured, and the depleted circulating volume is restored, all in rapid succession. However, the idea that circulating volume should be rapidly restored has undergone reevaluation during the past decade. Indeed, a randomized controlled trial in hypotensive trauma patients suggested that delayed correction of depleted circulating volume, as compared with the traditional immediate correction, leads to superior outcome in terms of survival and duration of hospital stay [33].

How could such an approach be beneficial? The results of that study suggest that hypotension in such a population [33], although reflecting severe depletion of circulating volume, is in fact protective because it reduces the

propensity for ongoing bleeding. The idea is supported by direct experimental evidence [34, 35]. Thus although it is not suggested that prolonged or severe hypotension is beneficial per se, or is even sustainable, the data do indicate that rapid volume correction without first attending to the sources of bleeding may be associated with elevated systemic blood pressure, reinitiating or increasing blood loss, and escalating the risk of death from hemorrhage [33]. Thus in this specific context and perhaps in others, for example, ruptured aortic aneurysm, temporary hypotension is protective.

There are other examples whereby an abnormal parameter is protective. It has been suggested that acidemia, the presence of a pH in the extracellular fluid that is lower than normal, may protect against the ongoing production of endogenous organic acids such as lactic and keto acids [36] as well as augmenting release of oxygen from hemoglobin [37, 38]. In diabetic ketoacidosis the standard approach is to provide insulin and careful rehydration, with assiduous attention to osmolality and electrolyte abnormalities. Administration of insulin addresses the generation of ketoacids, the fundamental biochemical disorder in this syndrome, and that as the ketoacids are cleared a major component of the acidemia resolves. In some circumstances clinicians have opted for treating the pH per se by buffering with intravenous bicarbonate. Significant concerns have arisen with this approach, however, with the evolving awareness that bicarbonate therapy may worsen, not improve, cerebral oxygenation in this condition [39]. Indeed, a clinical trial has demonstrated that such therapy does not help in treating the underlying condition; on the contrary, buffering the pH reverses resolution of the underlying ketoacidosis [40]. The same approach to normalizing pH has also been in another acute illness, septic shock [41]. Here the important findings were that buffering the pH did not improve either the cardiovascular performance, or the effectiveness of the vasoactive drugs being used [41].

Although not translated into the clinical setting, several laboratory studies suggest that abnormal physiology may have protective effects (e.g., hyperpyrexia in sepsis [42], and hyperosmolarity [43] and hypercapnia [44] in reperfusion injury). It has recently been suggested that multiple organ dysfunction in the context of critical illness represents a protective adaptive response rather than a set of circumstances to be aggressively prevented or reversed [45]. It was further argued that such organ dysfunction represents an effort on the part of the body to cope with on-going critical illness, and that attempts to correct this pathophysiological state could therefore result in harm [45].

Generation of associated errors

Medical error has been the focus of intense recent interest. In hospitalized patients error is an important source of morbidity and mortality, with 75% of errors being associated with "diagnostic mishaps" and 70% occurring in acute care settings [46]. An important type of error is misinterpretation of data, and when monitoring the acutely ill errors in the acquisition or interpretation of data can certainly mislead. Many examples of errors in monitoring have been described, and in many cases these result in a cascade of events that lead to significant patient harm [47].

We present an example in which experienced clinicians were misled by an incorrectly placed central vascular catheter; in this example, the response to subsequent therapy compounded the misimpression that catheter placement was correct, and that the therapy was effective [48]. The patient was assessed in the emergency room and was noted to be cyanosed, febrile, and hypotensive. The clinicians diagnosed septic shock in a patient with cyanotic cardiac disease, performed a procedure to insert a catheter into the femoral artery for monitoring purposes, and commenced infusion of a vasoconstrictor agent. The initial response, elevation in intravascular pressure in response to the therapy, appeared gratifying. However, the patient deteriorated, and upon placement of an additional central vascular catheter, which was placed in a central artery, it became obvious that the initial catheter had been placed in a vein instead of an artery. The error was detected because the waveforms of the two intravascular pressures were different. However, the error was possible because of the conditions presented. The patient had severe tricuspid valve regurgitation, and in the setting of systemic hypotension and cyanosis this resulted in severely elevated venous pressures being mistaken for arterial pressures. The error was compounded, however, because the response to therapy being sought, elevation in systemic arterial pressure, appeared to be obtained, but in fact the elevation was that of venous pressure. Thus instead of providing cardiovascular support with increased arterial pressure the therapy was compromising the heart, reducing forward flow, and increasing backward regurgitant flow. This is an example in which experienced clinicians were deceived by assumption of correct monitoring placement, a false assumption that was compounded by an apparent beneficial response to administered medication [48].

Training effect

The "science" of medicine involves understanding the processes and mechanisms of sickness. Such insight should enable clinicians to adapt to altered circumstances within the context of an illness and in addition to translate knowledge and techniques from one illness state to another. While we often consider why research findings are "lost in translation" between scientific research and patient benefit [49, 50], we may not consider how appropriate it is

to translate findings from one illness context to another. Examples of translation include application of positive airways pressure to sleep apnea instead of its original use in acute respiratory failure [51], the use of a therapy that was originally thought to act on the coagulation pathway (e.g., activated protein C) to treatment of sepsis [52], and high frequency oscillatory ventilation, developed originally for treatment of neonatal respiratory failure, and now being studied in adults with ARDS [53, 54]. Such translation of treatment modalities from one disease state or population to another presupposes that the clinician understands the mechanisms of action in the original disease as well as the mechanisms of action and risk-benefit profile in the subsequent disease. In fact, although physiological insight is continuously evolving and would be necessary to predict successful "knowledge transfer" from one situation to another, there is often a major gap between physiological expectation, as predicted by the clinician, and the results of careful context-specific physiological evaluation. Thus certain interventions that may seem to make sense from past experience may ultimately be detrimental when used in an alternative context.

We present an example of a traditional therapy, hyperventilation, almost certainly highly effective in incipient brainstem herniation but harmful when translated to other patients with brain trauma in the absence of cerebral hyperemia. It has been known for decades that hyperventilation reduces intracranial pressure [55], and in subsequent years it became apparent that this could be used to clinical advantage. In incipient brainstem herniation the intracranial pressure is critically elevated, and the compliance characteristic of the solid cranium and the flexible brain are such that whereas a slight increase in pressure results in herniation and brain death, a slight reduction prevents herniation at that time. Many such patients are the victims of head trauma; indeed, almost all patients with significant head injury serious enough to require intensive care or neurosurgical intervention have at least some degree of elevated intracranial pressure. However, because acute hyperventilation is accepted practice in conditions in which intracranial pressure is most dangerous, it became commonplace to institute the same therapy in the presence of intracranial hypertension, of lesser severity. Unfortunately, this assumed the "benefits" of hyperventilation (i.e., reduction in elevated intracranial pressure, prevention of brainstem herniation) in patients in whom such factors were not important. Conversely, whereas the disadvantages of hyperventilation (i.e., focal ischemia due to vasoconstriction, diminished release of O_2 from circulating hemoglobin, and potentially increased local O_2 demand) appear minimal when weighed against impending death or irreversible brain damage, they may not be minimal when weighed against no benefit. Indeed a randomized controlled trial demonstrated that prophylactic hyperventilation in patients with severe head trauma increased the incidence of long-term CNS disability [56].

Targeting variables: balancing theory, physiology, and outcome

The above account, with examples selected to support the particular points in question, requires balance; while balance is needed, in practice it is difficult. The clinician faces many problems in balancing among the issues he thinks he understands, those he does understand, and those for which he can provide evidence of benefit. Indeed the situation is even more complex because over time the response of some illness states changes. For example, goal-directed therapy in early septic shock may decrease mortality [1], but extending the notion of normalization to pharmacological supranormalization applied in later phases of the same illness can cause harm [15]. In another important condition common in the critically ill, acute respiratory distress syndrome, attempts to recruit lung volume, while successful in early stages of the disease, appear to be far less successful in more established disease [57]. Finally, hyperventilation, while harmful if applied globally to patients with severe head injury [56], may help a small number of patients with intracranial hypertension due to cerebral hyperemia.

The above clinical trials [1, 4, 22, 26, 33] are presented in a simplistic manner. While simplicity has the advantage of clarity, it ignores both the complex nature of the trials and the disease entities involved. Indeed it is important to note that several detailed critiques have generated significant debate about the interpretation and incorporation of clinical studies into practice [2, 30, 58, 59, 60].

Conclusion

Multiple examples of therapies exist in the acute care setting that are based on physiological principles, and that involve monitoring and titrating against physiological endpoints. Many such approaches either have been directly responsible for saving lives in acutely ill patients or have reflected such management strategies. Nonetheless, clinicians recognize that following physiological principles is not the same as normalizing all physiological variables. To illustrate this distinction, and the dangers associated with the latter, we have identified five patterns, with examples of each, whereby such an approach can lead to harm. As knowledge advances, clinicians will integrate evidence-based information, mechanistic knowledge, and evolving error prevention strategies to incorporate advances in monitoring technology for provision of optimal patient care.

Acknowledgements The authors acknowledge Drs. Deborah Cook and Arthur Slutsky for their insightful comments.

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