

Commentary

Measurements in the intensive care unit: what do they mean?

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Abstract

Intensivists depend upon a large number of measurements to make daily decisions in the ICU. However, the reliability of these measures may be jeopardized by the effects of therapy. Moreover, in critical illness, what is normal is not necessarily optimal. Procalcitonin, a putative marker of occult infection, is emerging as a valuable diagnostic marker in the ICU. Although questions remain regarding its specificity, an increasing body of work suggests that it is reliably elevated in the setting of infection. As demonstrated by Level and colleagues in this issue of *Critical Care*, its utility as a diagnostic marker is not affected by concomitant hemodialysis.

Keywords continuous venovenous hemodialysis, critical illness, intensive care unit, measure, procalcitonin

Measurement is the currency of critical care. Illness in the intensive care unit is defined not by pathologic changes in a particular tissue or by structural changes in a specific organ, but by a constellation of quantifiable changes in physiological and biochemical measures. To round in an intensive care unit is to be exposed to a cacophony of numbers – the pH, the Glasgow Coma Scale, the fibrinogen level. To be an intensivist means to take this chaotic melange of digits and to transform them into a clinical profile that will support a therapeutic decision. An uninitiated visitor to a contemporary intensive care unit could be forgiven for concluding that the intensity of intensive care referred to the zeal with which its practitioners measure things: the continuous recording of the pulse, the blood pressure and the transcutaneous oxygen saturation, and the frequent assay of circulating factors whose function is familiar (e.g. potassium or hemoglobin) as well as those factors whose biologic significance is less so. High on the list of those less significant factors is procalcitonin.

In the present issue of *Critical Care*, Level and colleagues report the results of a carefully conducted cohort study of 15 patients undergoing continuous venovenous hemodialysis [1]. They show that procalcitonin (PCT) is cleared by continuous venovenous hemodialysis at conventional filtration rates and that the protein adsorbs to the filter, so as much as

20% of PCT is removed through the membrane. The consequences of this removal are modest, however, and are probably not clinically significant. Also, the residual plasma levels remain essentially constant.

What message should the beleaguered intensivist, struggling to maintain a focus in the face of an onslaught of new measures and new sources of uncertainty, take from this report? I believe there are two: one message regarding the utility of PCT as a diagnostic marker, and the second message addressing the more fundamental question of how to interpret the masses of numeric information generated within the intensive care unit.

PCT is the pro form of the calcium-regulating hormone calcitonin. A report by Assicot and colleagues a decade ago, evaluating 79 children suspected of being infected, suggested that elevated levels of PCT could reliably discriminate patients who were truly infected from those patients in whom clinical signs of acute inflammation were initiated by noninfectious stimuli [2]. Since that report, and driven in no small part by the development of a reliable assay for PCT, a Medline search using the keyword 'procalcitonin' currently identifies 483 publications. The majority of these publications addresses the utility of PCT as a diagnostic

PCT = procalcitonin.

marker. These studies suggest that, although PCT levels can be elevated in noninfectious conditions such as the treatment of transplant rejection with antibodies to CD3 [3], elevated levels of PCT are a reliable and specific marker of invasive infection [4–6], and that adequate treatment of such infection results in a reduction in the levels of circulating PCT [7]. The utility of PCT as a diagnostic marker appears to be less in its sensitivity to detect infection than in its specificity to rule it out [8]. In particular, a low level of PCT permits the clinician to be confident that infection is not present with greater than 90% certainty.

But if PCT is a promising marker that permits us to conclude that a critically ill patient is not infected (and so to avoid noninformative diagnostic investigations or exposure to unnecessary antibiotics), how confident can we be that the information it provides can be applied in all critically ill patients? Clinicians must make categorical, yes/no decisions based on data that are continuous in character. Arbitrary cutpoints are therefore established to aid that categorical decision. A culture of a venous catheter tip is considered positive if more than 15 colonies of bacteria are present following a standardized method of culture [9], or transfusion is administered if the hemoglobin level is less than 70 g/l [10].

The validity of each of these thresholds has been established empirically, but their successful application depends on the reliability of the measure that is used. Can that reliability be significantly jeopardized by an artifact resulting from the confounding effects of the underlying disease or its treatment? This is the question that Level and colleagues sought to address, and a question of practical importance to the interpretation of diagnostic tests in the intensive care unit.

The circulating level of a given molecule depends on three factors: the rate of production and release of the molecule, the rate of its removal, and the volume within which it is diluted. When rates of production and removal are equal, a steady-state constant level results. However, the actual measured level of that steady state will depend on the volume of distribution. Although the kinetics of the synthesis and release of PCT are not well understood, its synthesis and release appear to be triggered by invasive infection, with the result that levels in the circulation increase. The magnitude of this increase is clearly large enough to offset the reduction in concentration that might result from the presence of a larger volume of redistribution in the resuscitated, septic patient. Is it, therefore, either artefactually increased in renal failure or reduced by hemodialysis?

Herget-Rosenthal and colleagues studied PCT levels in 68 patients with acute or chronic renal failure treated by intermittent hemodialysis. They found that elevated PCT levels had an 84% positive predictive value and an 87% negative predictive value for the diagnosis of infection. Low flux membranes did not alter these figures after the start of

dialysis, while high flux membranes did result in a significant reduction in the negative predictive value to 54% [11]. In contrast, in a study of 26 patients undergoing continuous venovenous hemofiltration, Meisner showed that although PCT was adsorbed to the membrane, and removed in the ultrafiltrate, plasma levels remained constant [12]. This is a finding replicated by the present report. It thus appears that continuous venovenous hemodialysis at conventional flow rates does not jeopardize the diagnostic utility of PCT; whether high-volume hemofiltration has an effect remains to be determined.

From a broader perspective, the evolving literature on PCT underlines the conceptual quandaries that confront the contemporary intensivist. Why is the pro form of a calcium-regulating hormone released during bacterial infection? Is its release a marker of an appropriate host response to that infection, or is it a marker of a maladaptive response that might contribute to the morbidity of sepsis? Is PCT simply a convenient diagnostic marker, or is it an appropriate target for therapy [13]? Are the diagnostic criteria of infection used to evaluate PCT performance indicative of a disease process (infection) whose timely and appropriate treatment might improve outcome? Or, rather, are the criteria surrogate markers of an alternate disease (hyperprocalcitonemia) that merits therapy in its own right?

The emergence of the intensive care unit as a locus for providing supportive care for critically ill patients has confronted us with challenges that are unprecedented in medical history. Intensive care units care for a population of patients who, if nature were permitted to take her course, would die a rapid death. In the absence of fluid replacement and circulatory support with exogenous catecholamines and vasoactive agents, the end result of shock is a quiet death from circulatory insufficiency; without the mechanical ventilator, hypoxemia similarly leads inevitably to a rapid demise. But if survival under these circumstances is unprecedented, how should we interpret the biochemical and physiologic events that occur in patients who remain alive only because of the intervention of the intensivist? There is no compelling evolutionary argument to support the advantages of one physiologic state over another: those who in an earlier era would have died do not contribute to the gene pool, and even in our own brave new age reproduction while on the ventilator is distinctly uncommon. Under these circumstances, what is normal may not be what is optimal, and what is abnormal may not be reliable.

Competing interests

None declared.

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