The Frog Prince of calcium homeostasis*

The contribution by Egi and colleagues (1) in this issue of *Critical Care Medicine* provides an opportunity to briefly review how far we have traveled from studies on frogs to our current understanding of altered calcium homeostasis in our intensive care unit (ICU) patients. The physician-scientist Luigi Galvani first described “animal electric fluid” in 1791 as a unique property of living tissues that allowed a frog’s leg to contract in response to contact with metal (2). A physicist colleague, Alessandro Volta, believed that “metallic electricity” produced by an interaction between two different metals was responsible for the muscle contraction (2). Sidney Ringer (of Ringer’s lactate fame) later showed that Na, K, and Ca ions are essential for the contraction of the frog heart (3). Hodgkin et al (4) and Fatt and Katz (5) completed this circle of knowledge by revealing that the Na, K, and Ca ions carried the animal/metallic electricity through their respective ion channels by using the squid giant axon and crustacean skeletal muscle. Subsequent studies in a variety of animal species uncovered the central role played by Ca in intracellular signaling processes (6). A combination of exquisitely controlled spatial and temporal subcellular localizations of intracellular ionized free Ca (iCa) regulates such diverse but essential processes as muscle contraction, neurohormonal secretion, and apoptotic cell death. Minute changes in the subcellular concentrations of iCa can have profound physiologic and pathophysiologic consequences. Considerable metabolic effort is exerted to assure that iCa concentrations are optimally maintained in specified extracellular and intracellular compartments in accordance with the original description of “adaptive physiologic” homeostasis by Cannon (7). Therefore, small changes in iCa observed in the ICU setting could contribute to or be the con-

*See also p. 314.

Key Words: cell signaling; calcium; homeostasis; critical care

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e318205c34d
sequences of “maladaptive pathophysiologic” attempts to maintain homeostasis, as later described by Selley (8).

We now routinely use automated devices to very accurately measure concentrations of iCa and other electrolytes in our patients’ blood. It is interesting to note that homeostatic mechanisms maintain concentrations of these ions in an extremely narrow range when compared to macromolecules such as proteins and lipids. Circulating iCa are tightly maintained in equilibrium with calcium bound to plasma proteins (primarily albumin), phosphates, and citrates by a combination of dietary ingestion, renal excretion, and bone resorption—principally under the modulation of parathyroid hormone and vitamin D (9). Physiologic and pathophysiologic shifts in the distribution of iCa among and within these compartments can be detected clinically by the application of simple automated technologies.

Previous studies have provided evidence of such derangements in calcium homeostasis among critically ill patients (10, 11). Whittet al (11) recently proposed that elevated catecholamines during critical illness cause a shift of calcium from the circulating pool to intracellular compartments of various tissues. This “relative” hypocalcemia results in increased parathyroid hormone via a homeostatic negative feedback loop. Increased circulating catecholamines and parathyroid hormone further facilitate intracellular iCa overload. Mitochondrial iCa overload induces oxidative stress, opening of the permeability transition pore, and apoptotic cell death. Thus, a decrease in circulating iCa concentrations likely reflects a redistribution of iCa into cellular compartments and not an absolute decrease in total body iCa. Therefore, providing additional parenteral Ca would be analogous to adding sodium to treat dilutional hyponatremia as a result of inappropriate levels of antidiuretic hormone (syndrome of inappropriate antidiuretic hormone secretion). This hypothesis is supported by data in which calcium administration increased mortality in two different animal models of sepsis (12, 13).

These clinical and basic data provide a confusing picture as to the optimal management of hypocalcemia in the ICU setting. A key missing piece of this puzzle is the answer to the question of whether iCa levels independently predict poor outcome. An affirmative answer for hypocalcemia would suggest a potentially life-saving role for replacement therapy in the ICU. Such an easy implementation strategy would justify investment in a major multicentered clinical trial. On the other hand, failure to demonstrate an independent effect of hypocalcemia would suggest that simple replacement therapy will not improve outcome. Sufficient numbers of patients with adequate statistical analyses have been lacking to resolve this compelling issue. A recent authoritative Cochrane review of the literature on this subject, entitled “Parenteral calcium for intensive care unit patients,” concluded that “there is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients” (14). Thus, criteria for clinical equipoise appear to have been met to conduct a clinical trial to determine whether calcium supplementation would benefit hypocalcemic patients in the ICU.

Now enters the substantial contribution of Egi and colleagues (1) in this issue of Critical Care Medicine. They report the results of their very carefully designed and conducted retrospective multicentered study of a large heterogeneous critically ill population to assess the relationship between serum iCa levels and ICU and in-hospital mortality. Initial univariate analyses confirmed previous reports of an unfavorable outcome in patients with lower iCa levels. However, multivariate analyses, adjusting for other factors influencing mortality, showed that only extreme abnormalities of iCa are independent predictors of mortality. ICU and hospital mortality trends were driven by very low iCa values of less than 0.8 mmol/L and 0.9 mmol/L, respectively. Similarly, hospital and ICU mortalities were shown to be primarily dependent on patients with very high iCa levels (>1.4 mmol/L). The authors suggest that abnormalities of iCa concentrations represent physiologic derangements and are likely a marker of illness severity, rather than independently contribute to mortality.

The implications of the work of Egi and colleagues (1) are both obvious and profound. First of all, even relatively small changes in iCa levels are an important and consistent indication of poor prognosis in the ICU setting. Secondly, efforts to “fine tune” iCa levels to remain within the normal range are unlikely to yield improved outcomes for the vast majority of critically ill patients. And finally, efforts to understand the biological basis of altered Ca homeostasis in the ICU are more likely to yield useful clinically relevant insights than attempts to simply treat numbers. We need not look any further than studies into the basic mechanisms responsible for hyponatremia in congestive heart failure patients who led to the neurohumoral hypothesis underlying our current management of chronic heart failure (15). Disappointing “negative” results of recent clinical trials reminds us of the veracity of the old adage that you have to “kill a lot of frogs [basic experiments] before you find your prince [successful clinical trial]!”

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