Troponin: Important in Severe Trauma and a First Step in the Biological Marker Revolution

THIS issue of the Journal contains an important clinical study that describes the significance of a cardiac troponin I release in severe trauma patients.[1] The incidence of troponin release was 12% and the authors identified three different patterns of troponin release: 1) a very transient (≤12 h) and limited (<2 μg/l) release that is likely related to the hyperadrenergic state observed in hemorrhagic shock[2] or severe head trauma,[3] 2) a transient (≤36 h) and significant (≥2 μg/l) release, and 3) a sustained (>36 h) and significant (≥2 μg/l) release that was associated with coronary artery injury in 41% of the cases. Diagnosis of the lesions of the heart related to blunt trauma is difficult, mainly because of confusion about the term used and the absence of recognized standards.[4] Several conclusions can be drawn from the study from Edouard *et al.*[1] First, as previously noted,[5] troponin is probably not the key diagnostic method for myocardial contusion because a troponin release can be attributable to several other causes in severe trauma patients and because no detectable troponin release may occur in small myocardial contusion. Myocardial contusion is an elusive diagnosis that should be replaced by the term "blunt cardiac trauma" only in the presence of pump failure or malignant cardiac arrhythmias.[6] Numerous clinical evidences suggest that repeated electrocardiogram remain appropriate to detect blunt cardiac trauma with malignant cardiac arrhythmias and that echocardiography is appropriate to detect blunt cardiac trauma with pump failure or pericardial lesions.[4] The study from Edouard *et al.*[1] demonstrates that serial troponin dosages are appropriate to identify blunt cardiac trauma with coronary traumatic lesions. Two important issues remain a matter of debate. First, because coronary angiography was not performed in patients with significant but transient release, one cannot make a conclusion regarding the need for further invasive examination in this subpopulation. It should be pointed that the incidence was low (2%), meaning that this concerns few patients, and that occult coronary traumatic lesions may explain some late death attributed to blunt cardiac trauma.[7] Therefore, I suggest that coronary angiography be discussed in these cases until further studies have been conducted. Second, the absence of any prognosis value of troponin release in the study from Edouard *et al.*[1] should be cautiously analyzed. Indeed, the power of their study was relatively low because of the small number of patients with a sustained and significant release. Moreover, mixing patients with significant and nonsignificant release of troponin, which reflects different pathophysiological processes, may not be appropriate. The study from Edouard *et al.*[1] has markedly clarified the role of troponin dosage in severe trauma patients and even provides some insights on the different pathophysiological mechanisms involved in troponin release.

For more than a decade, troponin has been known as a highly sensitive and specific marker of myocardial damage mainly resulting from myocardial ischemia. There are few biologic markers that could be considered as sensitive and as specific as troponin. Therefore, it is amazing that such an efficient marker took such a long time to be incorporated into guidelines for the diagnosis of myocardial infarction.[8] Moreover, it is interesting to note that several very recent studies have markedly improved our knowledge concerning troponin release in the postoperative period, cardiac surgery,[9] and now severe trauma.[1] Troponin is now also recognized as an important prognosis marker in cardiac surgery,[9] in critically ill patients, and in acute pulmonary embolism.[10] The troponin story illustrates the long way necessary to precisely assess the diagnostic and prognostic values and the clinical significance of a new biologic marker in different clinical situations.

We must think well about the troponin story because many new biologic markers, such as natriuretic peptides and procalcitonin, are now available.[11] A wave of new biologic markers exploring central nervous system ischemia, sepsis, and the cardiovascular system is under the scrutiny of bioengineering companies. It is likely that we will see a biologic revolution as we have seen an imaging technique revolution during recent years. Assessing these markers is complex and difficult and will need considerable efforts, but it is worth it in perioperative and critical care, and emergency medicine. Do not underestimate the task and remember the troponin story, a highly sensitive and specific marker that means so different things in so many different clinical situations such as chest pain and severe trauma. An improvement in the methodology used to assess the interest of these biologic markers is also mandatory. Although considerable progress has been made in the methodology and report

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of randomized trials in the past decade, we are behind the times concerning the assessment of diagnostic tests. It is important to handle the appropriate methodological tools to face this biologic marker revolution.[12]

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Picking Safe Combinations

IN his famous autobiography "Surely You're Joking, Mr. Feynman" the late Nobel laureate Richard Feynman describes with boyish enthusiasm how he picked the combinations of safes containing the blueprints for the atomic bomb at Los Alamos Laboratories.[1] Anesthesiologists are confronted with this same dilemma every day when selecting drugs for their patients: how to pick a safe combination. This is typically approached with some combination of experience, empiricism, and cookbook mentality. In this issue of ANESTHESIOLOGY, Sveticic *et al.*[2] refine an ingenious mathematical approach to picking safe combinations that would make Dr. Feynman proud.

The fundamental problem with finding combinations is dimensionality. Let us assume that you want to find the right dose from four possible doses (*e.g.*, "big dose," "high normal dose," "low normal dose," and "low dose"). Let us also assume that it takes six patients to reliably measure the effect. For two drugs in combination, there are 16 (4^2) possible "best" combinations, requiring a study with 96 subjects. For three drugs in

◆ This Editorial View accompanies the following article: Sveticic G, Gentilini A, Eichenberger U, Zanderigo E, Sartori V, Luginbühl M, Curatolo M: Combinations of bupivacaine, fentanyl, and clonidine for lumbar epidural postoperative analgesia: A novel optimization procedure. ANESTHESIOLOGY 2004; 101:1381–93

combination, there are 64 (4^3) combinations, requiring a study with 384 subjects. For four drugs, there are 256 (4^4) combinations, requiring a study with 1536 subjects. The dimensionality problem has generally limited us to studies only looking at two drugs in combination. An exception is the study by Minto *et al.*[3] for midazolam, propofol, and alfentanil. However, this is the exception that proves the rule: these authors needed 400 subjects to identify an optimum combination of three drugs for loss of consciousness. Scaling their model based approach to examine four drugs would, by extension, require 2900 patients:

$$(\sqrt[3]{400})^4.$$

The approach taken by Sveticic *et al.*[2] is an extension of a previously published search routine,[4,5] the importance of which has previously been highlighted in the editorial pages of ANESTHESIOLOGY.[6] In this approach, instead of trying to characterize the entire interaction surface in n-dimensional space (n = the number of drugs), the authors test approximately n^2 combinations (the exact number determined using simulations). For three drugs, this involves just eight combinations. Based on these tests, the authors identify a new region of the n-dimensional surface that may be interesting to explore. Like an n-dimensional amoeba crawling along the surface, this approach sends out sensing pseudopods and quickly converges on the optimum combination on the surface. The mathematical refinements in the present manuscript potentially accelerate an already efficient search algorithm.

Dixon brought about a revolution in characterizing drug potency with the introduction of the "up-down" method in 1965.[7] Dixon's methodology enables investi-

gators to efficiently zoom in on the effective dose of a single drug in clinical trials. The methodology of Sveticic *et al.* is exactly analogous to the Dixon approach for multiple drugs in combination. Of course, the methodological details are quite different from Dixon's, reflecting 40 yr of progress in modeling and regression since Dixon wrote his classic paper. And, like Dixon's methodology, the search efficiency comes at the price of not knowing the steepness of the dose *versus* relationship around the optimum combination.

Investigators in drug interactions should make every effort to become familiar with the methodology proposed by Sveticic *et al.* It is far more efficient than response surface approaches for characterizing optimum drug combinations.[8-11] Clinicians looking for evidenced-based guidance for drug combinations can expect to see studies using these methodologies, which will hopefully replace empiricism and cookbook approaches to giving drugs in combination. And although Richard Feynman is no longer with us, it is wonderful to see talented scientists pursuing his avocation of picking safe combinations.

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