For want of a few good shams

MARK L. ENTMAN, TARECK O. NOSSULLI, VENKATESH LAKSHMINARAYANAN, AND LLOYD H. MICHAEL
Section of Cardiovascular Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas 77030

THE WORK of Nossuli and co-workers (4) describes some of the pitfalls involved in animal modeling of human disease. They demonstrate that, in examining the inflammatory cytokine response following reperfusion of the infarcted myocardium, the surgical trauma associated with acute occlusion and reperfusion seriously complicates the interpretation of the data. Their data suggest that surgical trauma not only elevates the baseline cytokine induction but also appears to exaggerate the cytokine response in comparison to the cytokine response after surgical trauma has been allowed to dissipate. This suggests the possibility that the inflammatory response to surgical trauma may actually prime the inflammatory response to the experimental intervention being studied. This postulate is further suggested by the much greater variance in the experimental signal in the acute experiments, which may result from the variance of more than one factor.

Modern biology has demonstrated that “inflammatory mediators” are functionally important in a variety of cardiac disease models. Thus, when examining animal models of disease, regardless of the species used, it is important to be aware of the inflammation emanating from the trauma of the acute surgical manipulation during animal preparation. In a closed-chest dog model of myocardial ischemia-reperfusion, Michael et al. (3) demonstrated that creatine kinase and phosphorylase were significantly increased in cardiac lymph for 3-5 days after the initial surgery, suggesting that significant myocardial cell damage occurs with surgical manipulation. They further demonstrated that the consequence of this damage may last for several days (3).

Similarly, Weihrauch et al. (5) developed a chronically instrumented dog model to assess mitogenic activity in cardiac lymph and its relationship to subsequent coronary collateralization during repeated 2-min left anterior descending coronary artery (LAD) occlusions and reperfusion over a 21-day period. These investigators demonstrated that mitogenic activity of the myocardial interstitial fluid was prominent until 6 days after the initial surgical instrumentation of the animals. Therefore, Weihrauch et al. (5) did not begin their repetitive coronary occlusion protocol until 7 days after the initial surgery.

In addition to the data presented in dogs (3, 5) and mice (4), Grosjean et al. (1) presented similar findings of surgery-induced inflammation in rats. These investigators attempted to study the regulation of inducible nitric oxide synthase (iNOS) in a rat model of heart failure. Utilizing surgical ligation of the LAD to induce heart failure, these investigators found a robust expression of iNOS mRNA in the sham-operated animals that was indistinguishable from animals undergoing the ischemia protocol. This finding significantly confounded the interpretation of their results and forced them to abandon this method of heart failure induction in favor of chronic subcutaneous isoproterenol injections. The effect of surgery in iNOS upregulation was also found by Losonczy et al. (2), who showed an increased urinary excretion of nitrates in sham-operated rats that underwent a renal surgical procedure.

These experiences from several laboratories expose the problem of the use of shams in modeling cardiovascular disease. Each investigator may find that the conditions and requirements may be different depending on the variables measured and the hypothesis tested. However, it is likely that this experience is not merely a function of inflammation emanating from surgical injury; exaggerated autonomic response might be expected to exert similar effects. The work of Nossuli et al. (4) suggests that each experimental paradigm will have to be individually evaluated.

The data suggest that the technical difficulty may also extend to an arithmetic dilemma as well. Subtraction of a sham value to quantify an experimental response assumes an arithmetic relationship in the quantities measured of a given variable. Nossuli et al. (4) suggests that this is not always appropriate; a particular response such as genetic induction of a mediator or, alternatively, the response to a cytokine or growth factor may demonstrate features of potentiation that would exaggerate the “experimental” response and complicate interpretation of the data. This latter factor may account for greater variance of the response, which could also complicate statistical analysis using parametric methods.

Careful choice of variables measured and development of the disease models may avoid some of these complications and evolve an experimental paradigm.
that reduces complexity and allows more straightforward interpretation. It seems obvious that acute surgical trauma may confound interpretation by many mechanisms; the degree and time course of the difficulty may vary with the experiment.

Address for reprint requests and other correspondence: M. L. Entman, Section of Cardiovascular Sciences, Dept. of Medicine, Baylor College of Medicine, One Baylor Plaza, MS F-602, Houston, TX 77030 (E-mail: mentman@bcm.tmc.edu).

REFERENCES


