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Bupivacaine-induced Cardiac Arrest

Fat Is Good—Is Epinephrine Really Bad?

LIPID emulsion as therapy for local anesthetic–induced cardiotoxicity has come a long way since its chance discovery a decade ago. Transit from laboratory bench top to the antidote cupboards of operating theaters and, increasingly, emergency and critical care units worldwide has been swift. Guidelines endorsing lipid* now hang prominently anywhere regional anesthesia is practiced; reminders that the poisoned patient "cannot be considered dead, until they're lipemic and dead." This revolution has been largely driven by some elegant animal work from the laboratory of Guy Weinberg, M.D., accumulating case report data, and not in the least absence of efficacious alternate antidotes for what remains a feared complication of regional anesthesia. In this issue of ANESTHESIOLOGY, however, the same investigators that brought us lipid question the coadministration of epinephrine in lipid-based resuscitation from bupivacaine-induced cardiac arrest.[1] At a juncture when the uptake of lipid is almost universal, it seems timely to consider just how many questions surrounding this novel therapy remain unanswered.

Despite much basic science work we are still unclear how IV injection of lipid emulsion results in amelioration of local anesthetic–induced cardiotoxicity. The "lipid sink" has been forwarded as one potential explanation; induction of an expanded plasma lipid phase serving to sequester toxins of high lipophilicity.[2,3] Alternative postulates favor a metabolic mechanism with bolus free fatty acid provision overcoming pharmacologic inhibition to mitochondrial oxidative phosphorylation,[4] or *via* elevation of intramyocyte calcium concentration.[5] It is not inconceivable that all hypotheses may eventually be implicated as being in part causative. This fundamental absence of defined mechanistic action of lipid poses significant unknowns when assessing the potential benefit (or otherwise) of adjuvant drugs in resuscitation.

That bolus injection of lipid emulsion may result in seemingly miraculous recovery from inadvertent local anesthetic overdose seems beyond doubt. A wealth of animal data[2–4] and accumulating cases purporting successful resuscitation outcome[6–12] provide a compelling argument. However, despite the best intentions of clinicians and journal editors, initial success with any therapy is subject to significant reporter and publication bias, favoring dissemination of cases wherein outcome has proven favorable. This is undoubtedly true in the case of lipid therapy where numerous reports of positive outcome, and none of failure, have crowded the literature. Yet sporadic anecdotes such as these, no matter how impressive, fail to become *data* until the true denominator of frequency of use is considered. Case compilation in a formal registry of use is now urgently required.

There is much pertaining to the administration of lipid that remains unknown. What formulation of free fatty acids and phospholipids is best? What infusion protocol delivers optimum balance between efficacy and safety? Perhaps most significant, and formative in the latest work from Hiller *et al.*, is how to incorporate lipid emulsion into standard resuscitation algorithms. Inherent in this question is the role of additional agents used during cardiac arrest; and that of the ubiquitous epinephrine in particular.

In their experimental model, Hiller *et al.* examine resuscitation outcome after incremental single-dose epinephrine, coadministered with lipid emulsion, in a rodent model of bupivacaine-induced asystole. By all measures (including an ingeniously constructed recovery index), animals treated with 25 mcg/kg epinephrine had a deleterious outcome. High-dose epinephrine is, however, known to result in poorer outcome when injected in a variety of cardiac arrest scenarios.[13,14] Therefore, while the causative mechanism (*i.e.*, bupivacaine) in the present study is new, the finding that (while not strictly "high") elevated dose epinephrine is associated with lactic acidemia, pulmonary edema, and lesser return of spontaneous circulation might superficially be deemed unsurprising.

The finding of significantly reduced hemodynamic and metabolic metrics in the 10 mcg/kg epinephrine group requires greater notice. At clinically endorsed levels epinephrine resulted in lesser postrecovery cardiovascular parameters and increased serum lactate; this despite initial augmentation of spontaneous circulation. Perhaps most informative, however, is the comparison of recovery in the lipid-only, 1, and 2.5 mcg/kg epinephrine–treated animals. Circulatory return developed, on average, some 2.5 min sooner in animals receiving epinephrine—intuitively beneficial for the hearts of both patient and treating clinician. Regardless, survival, rate pressure product, and metabolic metrics were identical at 15 min, suggesting that any potential benefit arising from sooner return of spontaneous circulation is in part offset by detrimental metabolic consequences of adrenergic stimulation. Conversely stated, the

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* Resuscitation Council of the United Kingdom. Cardiac Arrest or cardiovascular collapse caused by local anesthetic. Available at: http://www.resus.org.uk/pages/caLocalA.htm. Posted 1 July 2008.

omission of epinephrine conferred no disadvantage to resuscitation outcome in the authors' model.

Few studies have compared lipid alone with vasopressors in local anesthetic–induced cardiac arrest. Weinberg *et al.* have demonstrated both epinephrine[15] and vasopressin[16] to result in lesser hemodynamic and metabolic recovery, as compared with lipid alone, in rodent models of bupivacaine-induced asystole. Epinephrine was reported as being no better than a saline bolus in the former experiment, with both vasopressors implicated in development of pulmonary edema and worsening lactic acidosis. Conversely, in their swine model of bupivacaine-induced cardiac arrest complicated by significant asphyxia, Mayr *et al.*[17] demonstrated combination epinephrine/vasopressin to effect superior recovery as compared with lipid alone. Lipid-treated pigs were, however, not only more acidotic, but subjected to prolonged asphyxia and basic life support resuscitation before lipid administration—both potent stimulants to endogenous epinephrine release. Lipid emulsion has furthermore been shown to be detrimental in animal models of sole asphyxia-induced cardiac arrest.[18] The stoichiometric differences in phosphate-to-oxygen ratios, and inherently greater oxygen debt incurred with myocardial fatty acid oxidation, may in part underpin these findings.

Support for the hypothesis that hyperadrenergic stimulation may be detrimental can be inferred from recent studies showing little or no benefit when lipid was combined with high dose epinephrine in local anesthetic-induced cardiac arrest. Evaluation of the Association of Anaesthetists of Great Britain and Ireland lipid infusion protocol in bupivacaine-induced asystole in whole rabbits conferred a mere 50% survival rate when epinephrine was repeatedly administered at 100 mcg/kg.[19] Furthermore, in the July issue of ANESTHESIOLOGY, Hicks *et al.*[20] demonstrate no benefit to resuscitation with lipid injection compared with saline, when coadministered with epinephrine at 100 mcg/kg and vasopressin at 1.5 U/kg, in bupivacine-intoxicated swine.

Successful human reports of local anesthetic–induced cardiotoxicity treated with lipid emulsion have variably included administration of epinephrine. Abolishment of ventricular arrhythmias[6] and reversal of local anesthetic–induced central nervous system and cardiac toxicity[7,8] have been reported with lipid infusion alone. Conversely, in numerous additional cases epinephrine was injected, and in many repeated, before lipid infusion and eventual favorable outcome.[9–12] Would successful return of spontaneous circulation in these cases have been achieved with cardiopulmonary resuscitation and lipid alone? Would physiologic parameters have proven to be more favorable post recovery? We will never know.

So what is happening here, and what part (metabolic villain or accumulating innocent) does lacticacidemia play? Certainly elevated lactate was associated with both increased epinephrine dose and poorer outcome in the work of Hiller *et al.* What basis then is there for causality? Cardiotoxicity of local anesthetics is known to increase in the presence of acidosis.[21] Lamentably, the affinity of lipid emulsion to bind local anesthetics conversely diminishes with reduction in pH.[22] By numerous mechanisms, epinephrine administration is known to result in acidemia, and in particular elevation of serum lactate concentration. Resultant exacerbation in cardiotoxicity and reduced efficacy of the sink function of lipid emulsion are likely contributors to the outcomes observed in this study. Intracellular lactate is furthermore known to inhibit glycolysis *via* increased NADH/NAD (dihydronicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide) ratios,[23] further compounding failing myocardial energetics in the presence of a metabolic poison. Additional direct causal effects of lactic acid on bupivacaine toxicity may yet be elucidated.

What, therefore, must we conclude? Clearly lipid emulsion is superior therapy to epinephrine and vasopressin alone, the issue of hypoxia notwithstanding. But is epinephrine really *bad* when coadministered with lipid emulsion in local anesthetic–induced cardiac arrest? Data to date certainly points to harm when administered in excess, but what about doses currently advocated? Or indeed lower still? In truth, we just don't know. Present evidence is insufficient to endorse omission of epinephrine from lipid-based resuscitative algorithms. But questions about our current practice have been raised, the significance of which may rival the discovery of lipid itself.

Note added in proof: A newly created registry of lipid use is accessible *via* the link http://www.lipidregistry.org.

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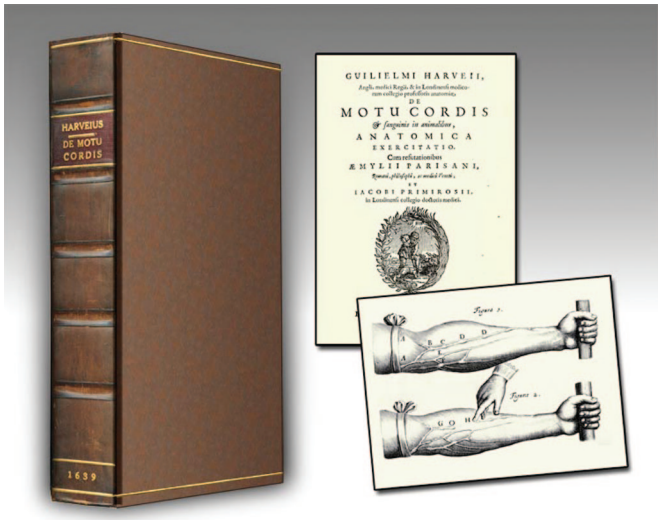
ANESTHESIOLOGY REFLECTIONS

Harvey's *De Motu Cordis*



Eleven years after releasing the first edition, English physician William Harvey (1578–1657) published this 1639 version, which, translated from Latin, he titled *Anatomical Exercises on the Motion of the Heart and Blood in Animals. With Refutations by Emilio Parisano and James Primrose*. Besides addressing the concerns of his critics Parisano and Primrose, Harvey hoped to reach an even broader range of academicians with his message that the "blood in the animal body is impelled in a circle, and is in a state of ceaseless motion. . . ." Courtesy of the Wood Library-Museum, the 1639 edition above depicts how valves permit venous return of blood solely toward the heart. From cardiovascular monitoring and physiology to vascular access and beyond, William Harvey's impact on today's clinical practice of medicine remains monumental. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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