

◆ EDITORIAL VIEWS

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Halogenated Anesthetics and Human Myocardium

THE effects of halogenated anesthetics on the myocardium have been studied extensively *in vivo* and *in vitro* in various animal species. In the past, investigators have focused their efforts on heart function, myocardial mechanics, and electrophysiology.¹ During recent years, considerable knowledge has been obtained by new investigative methodologies, including molecular and cellular biology²⁻⁴ and animal models of disease.^{5,6} Important interaction of halogenated anesthetics with pharmacologic agents on the myocardium have also been recently emphasized,^{7,8} leading to a better knowledge of their effects on signal transduction, particularly through G-proteins.⁷ In the current issue of ANESTHESIOLOGY, Hanouz *et al.*⁹ make an important contribution to our knowledge on the myocardial effects of halogenated anesthetics, although they have used a simple methodology (isolated atrial trabeculae in isometric conditions). Why is this work important to us? This is the first study to compare the inotropic effects of the four main halogenated anesthetics (halothane, isoflurane, sevoflurane, and desflurane) in human myocardium. This work must be considered as important as that from Gelissen *et al.*,¹⁰ who first compared the inotropic effects of the main intravenous anesthetic agents in human myocardium.

The clinical relevance of experimental research is an important issue. Indeed, species differences have been emphasized as long as animals have been used in research. Although molecular and cellular biology have shown the high degree of conservation of myocardial protein structure and function across numerous mammalian species, and although animal models of cardiac human disease have also shown their close relationship to human pathophysiology,¹¹ species differences remain a critical issue in cardiac physiology. For example, con-

siderable differences exist between rat and human myocardium: heart rate (250–300 beats/min in the rat), force–frequency relationship (an increased frequency decreases force in the rat in contrast humans), action potential, participation of the sarcoplasmic reticulum *versus* calcium exchange to the calcium influx to the myofilaments (higher in the rat), isomyosin isoform predominance (fast V1 in the rat *vs.* slow V3 type in humans), response to inotropic agents (*e.g.*, the positive inotropic effect of α -adrenoceptor stimulation is increased in the rat).⁸ These species differences in cardiac physiology explain why ketamine induces a positive inotropic effect in the rat but a negative inotropic effect in the guinea pig.¹² Thus, the study by Hanouz *et al.*⁹ provides important information on the negative inotropic effect of halogenated anesthetics (halothane > sevoflurane, isoflurane > desflurane), confirming the previous results obtained in various animal species. These results also suggest that species differences in the myocardial effects is less important for halogenated anesthetics than for intravenous anesthetics.

Hanouz *et al.*⁹ suggest that desflurane releases intramyocardial catecholamine stores in human myocardium as it was observed in rat myocardium.¹³ This effect explains why desflurane induces a less pronounced negative inotropic effect compared with other halogenated anesthetics and probably participates to the preserved hemodynamic conditions or the sympathetic activation that occurs with desflurane administration. However, this effect deserves further study to elucidate the origin of these catecholamines (nerve endings of extracardiac neurons, intrinsic cardiac neurons, non-neuronal adrenergic cardiac cells) and, overall, the beneficial or deleterious consequences of this release in healthy and diseased myocardium. Indeed, intramyocardial catecholamines play a role in the maintenance of cardiac function and may interfere with ischemic preconditioning.

By following the lead of Hanouz *et al.*,⁹ we can develop the use of human myocardial tissue to understand better the effects of anesthetic agents and their interactions with endogenous and exogenous pharmacologic agents encountered during anesthesia. Several recommendations should be followed for future research. First, no single experimental approach is uniquely suited for this evaluation.¹¹ Integration of data derived from complementary methodologies, using subcellular, cellular,

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and organ studies, with clinical studies will provide the best approach. Second, human myocardial tissues are usually obtained in nonhealthy humans, and thus the possible interference with cardiac disease may occur, requiring careful selection of patients.⁹ Even if cardiac tissues are obtained from brain-dead patients without known cardiac disease, we cannot rule out the possibility of brain death-related cardiac damage.¹⁴ Conversely, it could be a unique opportunity to understand better the effects of anesthetics on diseased myocardium. Third, ethical issues must be kept in mind. Conducting research in human tissue required ethical guidelines (ethical committee approval and informed consent, particularly when genetic analysis is performed). There are some ethical difficulties in obtaining tissue in brain-dead patients because they are not capable of giving approval with regard to the scientific use of their tissues, and because there is no clear and direct benefit for another patient compared with transplantation.¹⁵ Scientists should be prepared to deal with these obstacles to be able to conduct fruitful research in human tissues.

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Use and Abuse of Neonatal Neurobehavioral Testing

ONE of the primary concerns of obstetric anesthesia is its safety for both mother and neonate. Much has been written about this issue, in particular consequences for the neonate. Clinical and laboratory measurement scales, including Apgar scores,¹ umbilical blood venous and arterial acid-base balance analysis,² and neonatal neurobehavioral testing scales,³ have been developed to assess neonatal well-being. In 1982, a report by Amiel-Tison *et al.*⁴ was published in *ANESTHESIOLOGY* that described an assessment scale called the Neonatal Neurologic and Adaptive Capacity Score (NACS). The NACS was proposed as a simple, noninvasive, quick neurobehavioral examination to assess subtle effects of drugs on neonates and to distinguish such drug effects from birth trauma, perinatal asphyxia, or neurologic disease. This publication was accompanied by a critical editorial that claimed the test to be deficient as a valid research instrument.⁵ It has now been almost 20 yr since the NACS was described, and initial criticism notwithstanding, it has been widely embraced by the obstetric anesthesia community and used worldwide by investigators examining neonatal effects of peripartum medications. In this issue of *ANESTHESIOLOGY*, Brockhurst *et al.*⁶ conduct a systematic review of the NACS in obstetric anesthesia research and conclude that the reliability and validity of this test has still not been established. Here we examine this issue in greater depth.

Why has the NACS become so popular? The answer: Simplicity. The test is easy and quick (< 5 min per examination), it can be performed with minimal training, it is non-noxious (thus easily performed in the presence of parents), and lends itself to simple statistical

analysis. More traditional measures for neonatal performance, such as the Brazelton Neurobehavioral Assessment Score,³ require approximately 20 min for a trained examiner to perform; include a large number of items (or clusters), each scored on a nine-point scale; and include statistical analysis that can be complex. Many studies using the Brazelton Neurobehavioral Assessment Score also include testing at age 14 and 30 days, allowing for integration into a variety of infant developmental paradigms.⁷ This is virtually never performed with the NACS. In contrast, the NACS has 20 items, each scored as 0, 1, or 2, for a total possible score of 40. Individual items are summed, and a single score is assigned to the neonate. No special training or certification is required to perform the NACS. This enticing simplicity was part of the editorialist's original concern in 1982: "For such an instrument, speed of administration is hardly the primary concern (should it be clinically?), but rather its ability to find or not to find effects of the variables of concern on the functioning neonate."⁵ As noted by Brockhurst *et al.*, virtually all of the studies using the NACS show no differences between groups of infants. In the few studies in which differences are noted, the circumstances are such that they would be expected to occur and expected to be obvious, *e.g.*, general *versus* regional anesthesia for cesarean delivery. Studies using the NACS to assess neonatal effects of maternally administered local anesthetics or opioids for either vaginal or cesarean delivery have yielded inconsistent results, frequently showing no differences between groups or differences that may be questioned on statistical grounds.

Why was the test so controversial? It is noteworthy that the original publication of the NACS was accompanied by not one, but two editorials. One editorial by a researcher prominent in infant developmental psychology criticized the NACS as being statistically flawed, improperly conceived, overly simplistic, and inappropriate as a research tool.⁵ The other editorial, by the then Editor-in-Chief of *ANESTHESIOLOGY*, John Michenfelder, lamented the difficult position of an editor considering a manuscript for which there are widely varying recommendations by the editorial review board.⁸ Michenfelder noted that outright rejection might result in premature condemnation, whereas publication requires that the

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readers be informed of the limitations of the work. He concluded that “determination of the validity, sensitivity, and merits of the examination will follow.”⁷ In other words, punt—let the chips fall where they may, and challenge the scientific community to determine if the initial criticisms were valid. Brockhurst *et al.* conclude that such validation is still lacking despite widespread use of the NACS examination, and we concur. Widespread use of a test is not evidence of validity, and investigators should use caution and discretion in interpreting its results. Moreover, in some instances, this test has been used (or misused) on the assumption that validation has been established. In our opinion, this misuse has resulted in some interesting conclusions, examples of which follow.

Consider the definition of a “normal” NACS result. The authors of the original article on the NACS arbitrarily claim that a score of ≥ 35 (of a possible 40) is “normal.”⁴ They also acknowledge that validation of this figure requires additional data. Such data do not exist. No study to our knowledge has correlated specific NACS results, a score of 35 or otherwise, with any other measure of neonatal or early childhood performance. The consequences—either short-, medium-, or long-term—for neonates scoring, *e.g.*, 25, 30, 35, or otherwise on the NACS are not known. A recent study compared the effects of labor epidural analgesia using ropivacaine *versus* bupivacaine on neonatal outcome.⁹ The NACS was performed on all infants at 2 and 24 h after birth; the results were analyzed by a comparison of median scores and a comparison of number of infants with scores $>$ *versus* $<$ 35. No differences in median NACS were noted at 2 or 24 h, but there were more infants at 24 h (not at 2 h) with NACS $>$ 35 in the ropivacaine group. Based on this finding, advertisements for obstetric use of ropivacaine claim better neonatal performance *versus* bupivacaine. In light of no meaningful justification for a NACS of 35 as an appropriate measure of “normality” and no difference in median NACS at any time in that metaanalysis, this claim must be viewed with caution: *caveat emptor*.

Now consider the analysis of individual portions of the NACS. An overall score of 30 or 35 or 38 does not reveal which items resulted in lost points, just as an Apgar score of 6 or an American Society of Anesthesiologists Physical Status classification of III does not reveal the specifics of the underlying abnormalities. Very few studies using the NACS report individual subscores; usually only the total NACS is reported. In that the NACS has items related to habituation, active tone, passive tone,

and reflexes, it may be useful to know which items, if any, are consistently affected by any perinatal intervention. Such subgroup analysis might allow the NACS to differentiate drug effects from insults such as birth trauma or perinatal asphyxia. Nonetheless, the original report on the NACS⁴ does not tell how such distinctions are to be made, and Brockhurst *et al.* note that we still do not know how to use the NACS to make such distinctions. Consider a recent publication claiming that epidural analgesia reduces the efficacy of breast-feeding.¹⁰

This diatribe against epidural analgesia assumes (based on no data and no specific examples) that even infants scoring in the “normal” range (as if we know what normal is) on neurobehavioral tests may have specific subgroup deficiencies that could impair breast-feeding. A curious finding indeed, because so few studies actually report subgroup scores on the NACS. Moreover, the evidence that epidural analgesia actually has any effect on breast-feeding outcomes is nothing more than anecdotal at best. As the author of that article readily admits, no studies examined breast-feeding specifically as an outcome correlated with intrapartum analgesia. Rather, the admonition against epidural analgesia is based on a conjecture about what might occur if certain items are depressed—despite not knowing which items these are and if depression of any specific items (such as muscle tone), transiently or otherwise, actually has any effect on breast-feeding. Again, *caveat emptor*.

What can one conclude? Babies are complex and subject to a constellation of parental, socioeconomic, and environmental factors that have the potential to modify any intrauterine effects that may have occurred. To hope that any one assessment tool (*e.g.*, an Apgar score, acid-base balance, or, in this context, neurobehavioral testing) can predict developmental outcome (*e.g.*, breast-feeding success, early parental bonding, and growth, or later outcomes such as learning difficulties, behavioral problems, school performance, intelligence quotient, or even adult personality qualities) is overly optimistic. A statistical adage is relevant here: A statistically significant difference is only a difference if it makes a clinically important difference. One must first show, in a scientifically rigorous manner, that meaningful outcomes relevant to families and society are actually affected by intrapartum analgesia before the results of machinations like the NACS are to be taken seriously. The publication of the NACS in 1982 was accompanied by strong claims of lack of validity and applicability. The review by Brockhurst *et al.* in this issue of *ANESTHESIOLOGY* claims that additional work is still necessary to establish this validity.

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For now, the NACS will certainly continue to appear, like barnacle on a ship's masthead, in many studies of obstetric anesthetics. If the NACS does nothing else, at least it forces us to remember that neonatal concerns are an important part of obstetric anesthesia. That in itself is a worthwhile goal.

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