

EDITORIAL VIEWS

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Anesthetic Action in Heart Muscle: Further Insights Through the Study of Myocardial Mechanics

WHILE IT IS WELL appreciated that the potent inhalational anesthetics are capable of directly modifying myocardial mechanical activity, our understanding of the mechanism(s) by which this is accomplished is, as yet, incomplete. Information regarding mechanism is important, as it may suggest effective ways of counteracting the myocardial actions of these agents, and also may provide clues for the development of potent anesthetics with less prominent myocardial effects.

Anesthetics may act at a number of subcellular sites in heart muscle.¹ These include the contractile proteins,²⁻⁴ the sarcolemma,⁵⁻⁷ and the sarcoplasmic reticulum.⁸⁻¹⁰ While the relative importance of anesthetic actions at these sites is not well understood, it is now generally believed that such actions serve to decrease the level of intracellular ionized calcium during systole and/or possibly to modify the responsiveness of the contractile proteins to activation by Ca^{2+} . Much of the experimental evidence underlying this belief has been derived from the study of organelles removed from their normal cellular environment or from the study of cellular preparations which have been modified abnormally. Some of this evidence may be misleading, since the act of modifying the environment of these organelles may modify their function.¹¹ The two technically excellent studies of Housmans and Murat^{12,13} in this issue of ANESTHESIOLOGY are welcomed, as they represent studies performed in *intact* myocardial tissue, which provide evidence for actions of halothane, enflur-

ane, and isoflurane on subcellular organelles that are intact and functioning in their normal environment. In addition, they have examined equipotent concentrations (using species specific MAC) of these three anesthetics during identical conditions. Their finding of a *lesser direct* negative inotropic effect of isoflurane, compared with both halothane and enflurane, strongly supports previous evidence derived from different mammalian species.^{8,14}

Each study of Housmans and Murat employs a complex analysis of the mechanical behavior of isolated ferret papillary muscles, an understanding of which demands the full attention of the reader. The variables examined fall into two broad categories: those related to force development and derived from isometric twitch contractions, *i.e.*, peak developed force (DF), time to peak force (TPF), maximal rate of rise of force (+dF/dt), half time for isometric relaxation ($RT_{1/2}$), and maximal rate of fall of force (-dF/dt); and those related to shortening, derived from isotonic contractions, *i.e.*, maximal velocity of shortening or velocity of lengthening at preload (+V, -V), maximal amount of shortening at preload (DL), maximal unloaded (0 load) velocity of shortening (MUVS), and time to MUVS (TMUVS). Certain of these variables are thought to reflect fundamental processes related to contraction. For example, MUVS correlates with the maximum rate of turnover of myosin crossbridges (myosin ATPase activity), while TMUVS coincides closely with the time to the peak of the intracellular Ca^{2+} transient. Likewise, a shortening of $RT_{1/2}$ (corresponding to an increased rate of relaxation) is caused by an increase in the rate of unbinding of Ca^{2+} from the contractile protein troponin, although it may, in some instances, reflect an increase in the rate of Ca^{2+} uptake by the sarcoplasmic reticulum. A decrease in DF reflects a decrease in the number of force-generating cross bridges resulting from a decreased level

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of activating intracellular Ca^{2+} and/or from a decrease in the myofibrillar responsiveness to Ca^{2+} .

In study 1, marked "Contractility,"¹² the effects of 0.25 MAC incremental steps in the concentration of halothane and enflurane (to 1.5 MAC) and isoflurane (to 2.0 MAC) were examined. As stated above, isoflurane was significantly less depressant than halothane and enflurane for both the isometric and the isotonic variables. All agents decreased DF. As noted, this could indicate a decrease in the amplitude of the intracellular Ca^{2+} transient. Supportive evidence for such a decrease in the Ca^{2+} transient has been provided by Bosnjak and Kampine¹⁵ who report a dose-related decrease in intracellular Ca^{2+} -dependent aequorin fluorescence caused by halothane. Housmans and Murat suggest that the decrease in DF may also be due to a decreased " Ca^{2+} responsiveness of the contractile apparatus" as indicated by their observation of an anesthetic-induced acceleration of isometric relaxation (a shortened $\text{RT}_{1/2}$, see above). All agents decreased MUVS. Housmans and Murat state that this most likely reflects a reduction in actomyosin ATPase activity, *i.e.*, in the cycling rate of the myosin crossbridges. All agents increased TMUVS, which is consistent with the observed effect¹⁵ of halothane to increase the time to peak of the intracellular Ca^{2+} transient.

In study 2, marked "Relaxation,"¹³ Housmans and Murat introduce the concept of load-sensitivity of relaxation¹⁶ in a detailed analysis of the effects of halothane, enflurane, and isoflurane on this rather (from an anesthetic standpoint) neglected phase of myocardial activity. The authors define load-dependency of relaxation as a phenomenon in which the duration of isotonic contractions against progressively decreasing loads becomes progressively shortened as compared to the control isometric contraction. They propose that the underlying mechanism for this phenomenon is a lessened affinity of troponin for Ca^{2+} during isotonic shortening at low loads¹⁷ and that, in consequence, less Ca^{2+} remains bound to the myofilaments than during an isometric contraction. The authors further hypothesize that, with rapid off-binding of Ca^{2+} from the myofilaments, the time course of isotonic relaxation will reflect the time course of dissipation of the intracellular Ca^{2+} transient, which is, in turn, dependent upon the pumping ability of the sarcoplasmic reticulum. Load sensitivity of relaxation is not seen in myocardial preparations in which the sarcoplasmic reticulum is sparse, *e.g.*, frog ventricle, or in preparations in which sarcoplasmic reticular function has been suppressed, *e.g.*, by caffeine or hypoxia¹⁸ where the Ca^{2+} transient is prolonged.

Halothane, enflurane, and, to a lesser extent, isoflurane caused a dose-dependent decrease in the load sensitivity of relaxation. This was brought about by a concomitant slowing of isotonic lengthening and an abbreviation of

isometric relaxation. Using reasoning developed above, Housmans and Murat suggest that these anesthetics cause both a relative depression of sarcoplasmic reticular function (slowing of isotonic lengthening secondary to a prolonged time course of the Ca^{2+} transient) and a decreased myofibrillar responsiveness to Ca^{2+} (abbreviation of isometric relaxation, shortened $\text{RT}_{1/2}$).

Load dependence of relaxation has been demonstrated in the intact mammalian heart¹⁹ and it has been suggested that it may be of benefit during the early rapid filling phase, allowing the heart to be filled more quickly.¹⁶ Housmans and Murat propose that anesthetic-induced loss of load dependence of relaxation may be of clinical importance in that ventricular filling would be slowed during anesthesia. A single preliminary study²⁰ indicates that isoflurane depresses diastolic function and filling in healthy, chronically instrumented dogs. Additional studies of *in situ* ventricular diastolic function, where anesthetic-induced alterations of load dependence of relaxation are specifically related to filling dynamics, will be helpful in establishing the clinical importance of this phenomenon.

The work of Housmans and Murat is important since, as already mentioned, it provides some needed insight concerning subcellular actions of the volatile anesthetics in the intact cell. These studies are especially important with regard to the elucidation of possible direct myofibrillar actions of anesthetics. At present, despite the existence of numerous studies, the relative importance of such actions is unclear. While there are several reasons for this,¹ a major one is the fact that, for the most part, previous work has been carried out in isolated myofibrillar preparations or in disrupted cell preparations where certain forms of regulation of the myofibril have been suppressed or lost.¹¹ Presumably, such regulation has been preserved in the intact muscles employed by Housmans and Murat, and their results indicate that, under these conditions, there are possibly important direct actions of the anesthetics at the level of the myofibril. As they indicate, their work does not differentiate anesthetic effects on Ca^{2+} binding to troponin from myofibrillar effects which are further "downstream," *i.e.*, effects of anesthetics on what they describe as the myofibrillar responsiveness to Ca^{2+} .

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