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Are Experiments Performed Using Nonphysiologic Experimental Conditions Appropriate for Pharmacologic Studies?

To the Editor:—In a recent paper, Cook and Housmans, using an isolated ferret papillary muscle preparation, showed that propofol may have direct negative inotropic effect.[1] In contrast, using intact rabbit hearts, we recently showed that, when compared to thiopental, a reference drug known to decrease contractility, propofol did not depress myocardial performance of blood-perfused rabbit hearts.[2] A negative inotropic effect was observed, however, in Krebs-perfused rabbit hearts.

There are several major differences between to the two models to explain the discrepancy between the two studies. First, the bath of the solution in the ferret's papillary muscle was physiologic salt solution oxygenated with 95% O_2, whereas we used a blood perfusate oxygenated with 25% O_2. Second, Cook and Housmans' study was performed at 30°C, whereas ours was performed at 37°C. The lower temperature may alter ionic active transport through the sarcolemmal membrane. Third, the rate of stimulation is less than physiologic in Cook and Housmans' experiments (15 beats/min) and close to normal in our experiments (100–130 beats/min).

Taking into account these major differences and considering that we observed a negative inotropic effect in Krebs-perfused hearts,[2] the results of Cook and Housmans were not unexpected. Therefore, one wonders whether the papillary muscle model and the experimental conditions described should be considered as an acceptable model for pharmacologic studies.

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References

1. Cook DJ, Housmans PR: Mechanism of the negative inotropic effect of propofol in isolated ferret ventricular myocardium. ANESTHESIOLOGY 80:859–871, 1994

2. Mouren S, Baron JF, Albo C, Szekely B, Arthaud M, Viars P: Effects of propofol and thiopental on coronary blood flow and myocardial performance in an isolated rabbit heart. ANESTHESIOLOGY 80: 634–641, 1994

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In Reply:—The papillary muscle preparation is an established model for pharmacologic investigations. Our laboratory as well as others have published many studies using this preparation because of its physiologic elegance. Whereas a tissue preparation in an organ bath may differ with respect to temperature, stimulation rate, or bath solution, this model has distinct advantages. Unlike a perfused-heart preparation, we are able to rigorously control loading conditions; assessment of the intrinsic inotropic effect of a drug is critically dependent on controlling this variable. Under the experimental conditions we use, the papillary muscle preparation is stable for many hours and allows for a rigorous assessment of inotropy, lusitropy, and load dependence over a range of pharmacologic conditions. This model also enables us to examine the dynamic effects of a drug on intracellular Ca^{2+} handling.

We are aware that a preparation such as ours is physiologically more remote from the intact circulation than is a perfused-heart preparation, just as a skinned-fiber or biochemical preparation is further removed than is a papillary muscle model. Each model is specifically designed to answer questions at a particular level of organization, and ultimately these models complement one another. It is naive to suggest that any model is unacceptable as long as the conclusions drawn from it do not exceed the limitations of its methodology.

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