Correspondence

Cyclopropane and Contractility

To the Editor.—In a recent study (Anesthesiology 33:497-502, 1970), Shimosato and his colleagues deduced that cyclopropane exerted no significant depressant effects on the intrinsic contractile state of the myocardium of the intact dog. They further concluded that the cyclopropane-mediated depression found in isolated heart preparations was not incompatible with their findings because sympathetic drive brought on by the anesthetic in their intact preparation would tend to offset any direct depressive influence. There are several reasons why we feel less confident about these observations and conclusions than do the authors.

We are struck by their observation that the absence of any depression of $V_{max}$ by cyclopropane does not carry over to any of the other contractile indices measured. Mean arterial pressure, cardiac output, stroke volume, stroke work, peak force and peak $dP/dt$ are depressed despite the absence of depression of $V_{max}$. In some cases depression of these indices was dramatic and highly significant. Moreover, if figure 1 of their paper is representative, the force-velocity curve (and hence CE power) is depressed as well, although no statistics are presented to establish significant levels in these cases. In light of the depression of all of these hemodynamic variables, one wonders about the significance of the absence of depression of $V_{max}$.

In order to estimate $V_{max}$, one must first calculate the ratio of $dP/dt$ to $P$ where $P$ is the left ventricular pressure. The value of $dP/dt$ is obtained by differentiating $P$. Shimosato and his associates effected this differentiation with a differentiator that had a flat frequency response to 40 Hz. However, it is clear from the principles of Fourier analysis and the shape of the ventricular pressure wave that a differentiator with a frequency response of at least 100 Hz is necessary for faithful representation of $dP/dt$; on the other hand, frequency responses as low as 15 Hz have been employed by some with claims that some information is still retrievable. Recently, Marlon et al. (Fed. Proc. 30:612, 1971) demonstrated clearly that only if the frequency response of the differentiator was above 100 Hz could reliable values of $dP/dt$ be obtained. The lower the frequency response, the further the apparent value of $dP/dt$ deviated from its actual value.

Without accurate values for $dP/dt$, it is difficult to muster any confidence in the significance of the ratio of $dP/dt$ to $P$, and hence in computed $V_{max}$. The conclusions of Shimosato et al.—that the contractility is not reduced because $V_{max}$ is not reduced—needs re-evaluation with a better method of differentiation, particularly in light of the depression of all the other hemodynamic indices.

The frequency response limitation might also explain why the depression of peak $dP/dt$ with cyclopropane (about 50 per cent) was out of proportion to the depressions found for all the other indices. The authors attributed this dramatic depression to the influence of the slightly reduced arterial pressure on peak $dP/dt$. Mason (Amer. J. Cardiol. 23:516, 1969) had previously noted a trend in such a direction. But the recent studies of Marlon et al. shed new light on this influence. Within limits, they found no reduction of peak $dP/dt$ with reduced aortic pressure when the frequency response of the differentiator was adequate. When $dP/dt$ was measured with apparatus of compromised frequency response, large depressions of peak $dP/dt$ did accompany reduced aortic diastolic pressures, precisely as found in this cyclopropane study.

The second conclusion drawn in this paper is that any possible depressive effects of cyclopropane directly on the contractile mechanism are offset by sympathetic stimulatory effects of this drug. While we do not dispute that this could be the case, we do question whether the evidence for its role in this study is as simple and clear-cut as implied by the authors. Stimulation of the sympathetic nerves is normally associated with an increase in
heart rate (e.g., Cranata et al., Circ. Res. 16: 114, 1965). In the experiments of Shimosato and co-investigators, however, the heart rate dropped significantly (186 to 150; \( P < 0.05 \)) after administration of cyclopropane. An increase in sympathetic drive associated with a decrease in heart rate can be the result of a relatively pronounced release of norepinephrine, but under these circumstances an increase in arterial blood pressure would be expected instead of a decrease. We wonder whether the sympathetic compensatory mechanism, if any, is not more complex than the authors imply?

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To the Editor—Dr. Reneman’s and Pollack’s criticism of our use of a differentiator with a frequency response less than the 100 Hz considered necessary for faithful representation of \( \Delta p/\Delta t \) is not valid. The natural and undamped frequency response of our differentiating circuit itself is 3,333 Hz. However, its amplitude is a linear function of frequency to 40 Hz (±5 per cent) with a low pass filter to obtain an optimal damping. It is generally considered that instruments with a uniform dynamic sensitivity to the tenth harmonic of the fundamental frequency of a complex waveform are suitable for high-fidelity recordings (Wood, E. H.: Science 112:707–715, 1950; Noble, F. W.: Electrical Methods of Blood-Pressure Recording, Charles C Thomas, 1950). Therefore, for cardiac signals with a maximum repetition rate of 4/sec (240 beats/min), the most rapid components do not usually exceed 40 or 50 Hz. Indeed, most catheter–transducer recording systems have a self-limiting factor for frequency response up to 40 or 50 Hz. The fundamental requirements for any recording system must include the following three criteria: 1) static accuracy (stability and uniqueness); 2) dynamic accuracy (frequency–amplitude as well as frequency–phase curves and linearity); 3) operational simplicity. Any instrument is useful only over the range of frequency for which the amplitude range is constant to overcome overshoot and noise. Therefore, a differentiator equipped merely with high frequency–amplitude response characteristics does not guarantee obtaining a more reliable value of \( \Delta p/\Delta t \). Data provided by Marlon et al. (Fed. Proc. 30:612, 1971) are difficult to evaluate, since they did not provide information related to both static and dynamic accuracy of the differentiators they used. A recent study showed that the values of \( V_{\text{max}} \) calculated from ventricular pressure tracings using a more sophisticated differentiator with a frequency cut-off at 40 Hz did not differ significantly from those obtained with the same differentiator with a frequency cut-off at 400 Hz (Urschel, C. W.: The Cardiovascular Unit, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Massachusetts: Personal communication, 1971). Thus, the use of differentiators with a flat frequency response to 40 Hz does not significantly distort the determination of \( V_{\text{max}} \).

Drs. Reneman’s and Pollack’s comments concerning the influence of cyclopropane anesthesia upon the extrinsic cardiac control mechanisms seem naive. During cyclopropane anesthesia changes in hemodynamics, particularly arterial pressure due to increased release of catecholamines, are not necessarily related to the isotropic influence of the neurohormones. Cyclopropane may exert a dual effect on the autonomic nervous system: sympathomimetic and parasympathomimetic (Esten and Li, Brit. J. Anaesth. 34:884–889, 1962). Thus, directional changes in hemodynamics during anesthesia may be related to a predominating influence of the agent upon the autonomic nervous system, eliciting changes in heart rate via the cholinergic system and changes in blood pressure via the adrenergic system.

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