

## Determination of Decay Constants from Time-varying Pressure Data

To the Editor:—Swanson and Muir<sup>1</sup> present an interesting and timely paper evaluating left ventricular pressure-volume relationships and diastolic decay constants during anesthesia in dogs.

Unfortunately, whereas the experiment appears elegantly conducted, the authors have committed a fundamental error in the data analysis so seductive that it has been repeated several times in the medical and physiology literature.<sup>2,3</sup> The problem arises from the form of the monoexponential decay model which they have chosen:

$$P = e^{At+B}, \quad (1)$$

where  $P$  = time varying pressure;  $A$  = reciprocal of the time constant  $T$  ( $T = -1/A$ ); and  $B$  = logarithm of the pressure at  $t = 0$  (equation 2 from their paper has  $T$  substituted for the independent variable  $t$ ). This equation has the desirable property of being easily linearizable by taking logarithms or by semilog plotting of  $P$  versus  $t$ . The time constant for relaxation,  $T$ , is determinable by a least square regression. However, the model implicitly assumes that the data goes through  $P = 0$  at  $t \rightarrow \infty$ , an assumption which is unnecessary and probably incorrect.

Any segment of a monoexponential pressure-time decay relationship is appropriately and generally represented as:

$$P(t) = [P_0 - P_{\text{asym}}]e^{At} + P_{\text{asym}}, \quad (2)$$

where  $P_0$  = starting pressure (when  $t = 0$ ); and  $P_{\text{asym}}$  = asymptotic pressure (as  $t \rightarrow \infty$ ). Equation 2 is not treatable in the same fashion as equation 1, since it is  $\ln(P(t) - P_{\text{asym}})$  which is linear with  $t$  rather than  $\ln P(t)$ , and  $P_{\text{asym}}$  is, in general, unknown. This difficulty may be

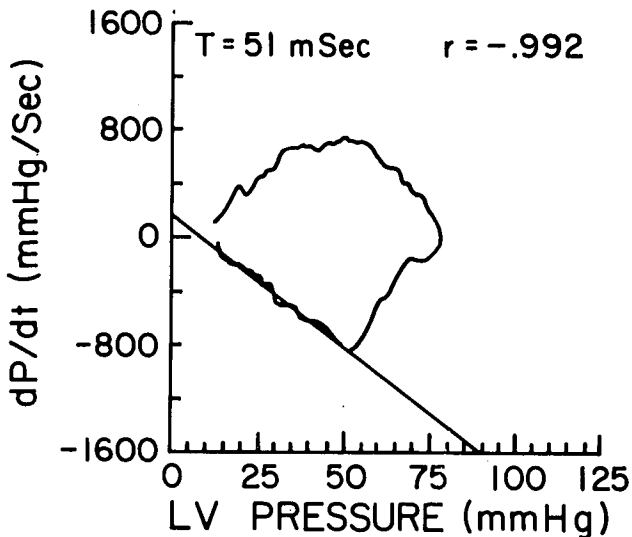


FIG. 1. Left ventricular pressure (LVP) versus time. Isovolumic pressure decay between maximum negative  $dP/dt$  (Max  $-dP/dt$ ) and mitral valve opening (estimated as LVEDP of the previous beat) is demonstrated. Curve A was obtained from a patient with coronary artery disease. Curve B was generated by vertical translation of the raw data to approximate a zero asymptote of the analyzed beat. The value of  $T$ , as calculated from equation 1 (see text), is shown before and after the translation. Clearly,  $T$  is affected by this shift even though the decay constants should be identical.

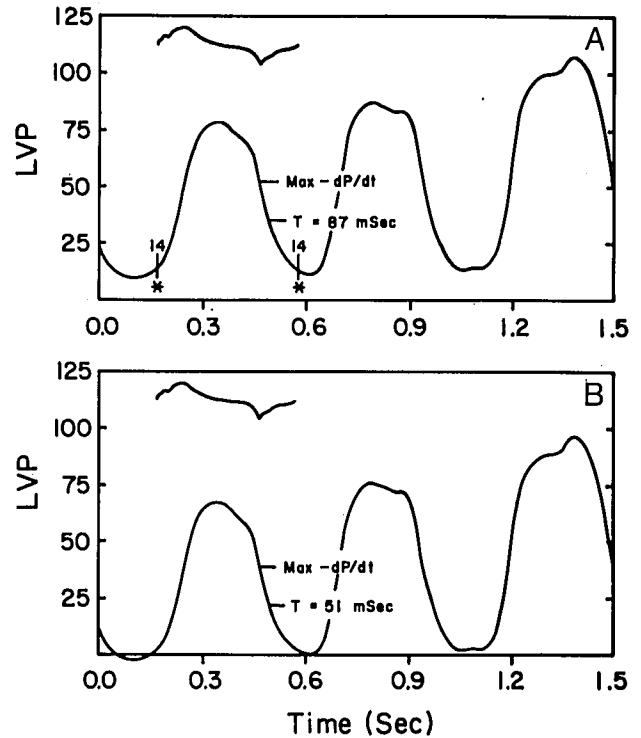


FIG. 2. Computer processed pressure-time data from the analyzed beat in figure 1A are plotted as  $dP/dt$  versus LVP. Least square regression of the points between maximum negative  $dP/dt$  and mitral valve opening is used for analysis of  $T$ , which is the negative inverse of the slope of this line (equation 4). This method eliminates the need to correct for  $P_{\text{asym}}$ .

eliminated by a simple mathematical technique.<sup>4</sup> Differentiating equation II with respect to time yields:

$$dP(t)/dt = [P_0 - P_{\text{asym}}]Ae^{At} \quad (3)$$

Substitution back into equation II yields:

$$dP(t)/dt = AP(t) - AP_{\text{asym}} \quad (4)$$

Equation 4 is the form of a straight line when  $dP/dt$  is plotted versus  $P$  and may be analyzed by linear least square regression, yielding a slope of  $-1/T$  msec<sup>-1</sup> and a  $P$  axis intercept of  $P_{\text{asym}}$ .

If data that have a non-zero asymptote are modeled by equation 1, values for  $T$  obtained by least square analysis of the semilog plot will not be correct. Figure 1 shows an experimental left ventricular pressure decay curve (A) obtained from an individual with coronary artery disease. Curve B was produced by displacing the raw data vertically downward to approximate the abscissa as the asymptote. Obviously the decay or relaxation constant should be the same for both curves. Using the linearized version of equation 1 yields  $T = 87$  msec for curve A and  $T = 51$  msec for curve B. Using equation 4 yields the correct value of 51 msec for both curves. Clearly, equation 1 yields the appropriate values of  $T$  only if  $P_{\text{asym}}$  is zero (or close to zero).

Figure 2 shows left ventricular  $dP/dt$  versus  $P$  data from the exper-

iment above for an entire cardiac cycle; note that the portion used for analysis of T is between maximum negative dP/dt and mitral valve opening (estimated as LVEDP of the preceding beat). The plot was generated using high fidelity pressure transducers, an analog-to-digital convertor, and special computer software to produce dP/dt from the digitized pressures and time. Since Swanson and Muir did not use an A/D convertor to capture their data, the differentiated pressures might be difficult for them to obtain.

We cannot predict whether the method of analysis herein proposed would change the conclusions of Swanson and Muir. Thompson *et al.*<sup>5</sup> have shown that techniques using equation 1 underestimate T. In fact, however, T may be either overestimated or underestimated, since the P axis intercept ( $P_{\text{asym}}$ ) from equation 4 may be positive or negative (cf figure 3 from reference 6). The error becomes greater as  $P_{\text{asym}}$  becomes increasingly different from zero. When values of T are compared between interventions that may change  $P_{\text{asym}}$  (such as halothane or ischemia), both the absolute values and the conclusions may suffer. Most investigators have abandoned the equation 1 model.<sup>4-6</sup>

Finally, it is well to note that the pressure-time asymptote (or the pressure axis intercept in the dP/dt *versus* P plot) is not necessarily identical to the actual physiologic pressure to which the system decays. The issue is really the "apparent" value of  $P_{\text{asym}}$  that applies over the range of P(t) that is analyzed for T. Over another pressure range, different values of both  $P_{\text{asym}}$  and T may be obtained. An outstanding feature of the dP/dt *versus* P display is that simple inspection will reveal the extent to which any portion of the relationship does or does not follow the presumed monoexponential fall-off.

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*In Reply:*—Drs Beattie *et al.* point out a fundamental analytical error in our data describing left ventricular relaxation. We agree with their assessment, and appreciate their critical reading of our manuscript.

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## Use Caution when Extrapolating from a Small Sample Size to the General Population

*To the Editor:*—Sears *et al.* recently reported "that the administration of a second dose of succinylcholine to healthy adult patients after induction with ketamine is safe with respect to cardiac rate and rhythm."<sup>1</sup> They based this conclusion on the results of a study performed on eight patients. We believe their conclusion is too strong. Because they encountered no dysrhythmias and did not have a statistically significant

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decrease in heart rate does not imply the true incidence of these undesirable side effects is insignificant.

Whenever the numerator is zero in the incidence of an effect, the true incidence in the population at large represented by the group is:

$$\sqrt[n]{p}$$