

Estimation of time constant of left ventricular relaxation

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SUMMARY When the fall in left ventricular pressure during isovolumic relaxation is treated as a monoexponential the rate of relaxation can be measured by a time constant. Though an empirical measurement, the time constant has been used extensively to study relaxation. It can be accepted, however, as a valid measurement only if isovolumic pressure fall approximates very closely to a monoexponential in a wide range of circumstances.

We analysed 60 beats recorded at different heart rates in 20 patients with a variety of left ventricular disease. In the first part of the study a powerful non-linear regression program was used off-line to test three exponential models: (1) a monoexponential, the asymptote of which is zero, (2) a monoexponential with a variable asymptote, and (3) a biexponential. The pressures predicted by models 2 and 3 were in very close agreement with measured pressure, whereas the predictions of model 1 were consistently less accurate. Model 3 had no advantage over model 2. Thus, in all the beats tested isovolumic pressure fall approximated very closely to a monoexponential of which both the time constant and asymptote are variable. A second exponential term does not increase precision, and is an unnecessary complication.

In the second part of the study the same 60 beats were analysed by a small program on the catheter laboratory computer. The time constant was estimated by two methods, corresponding to models 1 and 2 described above: (1) from the slope of \ln (pressure) against time, and (2) by a method of exponential analysis. The first method underestimated the time constant of model 1, particularly in beats where pressure fell to low levels. The second method accurately estimated the time constant of model 2.

It is concluded that isovolumic pressure fall approximates closely to a monoexponential in a wide variety of circumstances, and it is legitimate, therefore, to describe the rate of relaxation by a time constant. But the time constant must be estimated by a method based upon an exponential model of which both the time constant and asymptote are variable. We have shown that such a time constant can be estimated reliably by a small program suitable for use on-line. The usual method of estimating the time constant, from the slope of \ln (pressure) against time, provides an unreliable estimate of the time constant of an unsatisfactory model.

During isovolumic relaxation the fall in left ventricular pressure from the point of its maximum rate of change until it reaches the level of end-diastolic pressure of the preceding beat approximates to a monoexponential and can be characterised by a time constant.¹⁻⁴ Though it has been used widely to study relaxation of the intact ventricle¹⁻⁷ the time constant is a purely empirical measurement, as cardiac muscle has no intrinsic property which dictates that pressure

must decay exponentially during relaxation. Its use can be justified only if isovolumic pressure fall approximates closely to a monoexponential in a wide range of circumstances. In addition, the estimate of the time constant is highly dependent upon its method of calculation.^{8,9} The purpose of this study was to test critically three exponential models of isovolumic pressure fall.

The first model is a monoexponential, the asymptote of which is zero. The usual method of estimating the time constant, from the slope of \ln (pressure) against time,¹⁻⁶ assumes that pressure fall conforms

to this model. Previously its validity has been tested by the correlation coefficient of the \ln (pressure) — time plot¹⁻³; but if this method is applied when the asymptote is not zero the estimate of the time constant is unreliable, and the correlation coefficient does not test its validity.^{8,9} The second model is a monoexponential with a variable asymptote. This is a more complex model, but avoids the problems that result from assuming the asymptote to be zero.^{8,9} The third model is a biexponential. This was chosen because it has been suggested that isovolumic pressure fall is best described by two time constants applicable to early and late relaxation¹⁰ and that late in relaxation pressure may deviate from a monoexponential.¹¹

Three beats recorded at different heart rates in each of 20 patients with a range of left ventricular disease were studied. In the first part of the study the 60 beats were analysed off-line using a powerful commercially available non-linear regression program. For each beat the variables of the three models were estimated, and the pressures predicted by the models were compared with measured pressure.

Such complex analysis cannot be used routinely, so in the second part of the study the same 60 beats were analysed by a much smaller program on the catheter laboratory computer. Two estimates of the time constant were made: from the slope of \ln (pressure) against time¹⁻⁴ and by a method of exponential analysis.^{8,9} These estimates were compared with those derived from models 1 and 2 in the first part of the study.

Patients and methods

Three heart beats from each of 20 patients were analysed. To ensure that the study encompassed a wide range of left ventricular disease four patients were selected from each of the following diagnostic groups.

- Group 1:* Patients investigated for chest pain in whom no cardiac abnormality was found.
- Group 2:* Patients with coronary artery disease who did not develop angina during pacing.
- Group 3:* Patients with coronary artery disease in whom pacing provoked angina.
- Group 4:* Dilated cardiomyopathy.
- Group 5:* Hypertrophic cardiomyopathy.

CATHETERISATION PROCEDURE

The catheterisation procedure has been described in detail elsewhere.^{12,13} After diagnostic pressure measurements and coronary arteriography, the left heart catheter was replaced by a catheter-tip micromanometer (Telco MM52, No. 5 Millar, or No. 8 Gaeltec) which was positioned in the left ventricle via a long sheath.¹⁴ Left ventricular pressure was measured at basal heart rate, and during incremental coronary

sinus or atrial pacing. Measurements were not made for at least 20 minutes after arteriography. Left ventricular cineangiography was performed at the end of the study.

MEASUREMENT OF PRESSURE

Left ventricular pressure was measured simultaneously by the catheter-tip micromanometer and via the fluid-filled lumen of the Telco or Gaeltec, or coaxially via the long sheath when a 5 Millar was used. Each recording was accompanied by a zero and calibration signal for the fluid-filled pressure system. The sternal angle was used as the zero reference.

The catheter laboratory computer (Varian 620/L-100) analysed the signals in periods of nine seconds. The nine second record was split into individual beats by computer recognition of the R wave of the electrocardiogram. The micromanometer signal was digitised at 5 ms intervals, and the fluid-filled signal every 10 ms. After a suitable correction for time delay, the two signals were matched, and by least squares regression the correct zero and calibration for the micromanometer were calculated, and used in the analysis of that record.

In each beat the computer identified the part of isovolumic relaxation to be analysed as starting at the time of $\min dp/dt$ and ending when pressure fell to the level of end-diastolic pressure of the preceding beat.^{1,3} The digital values of micromanometer pressure were retrieved from the computer.

Three beats were selected from each patient: one at basal heart rate, and one at each of two different pacing rates. One beat in each patient in group 3 was recorded during angina. The beats were displayed during analysis, so that extrasystolic, post extrasystolic, or technically unsatisfactory beats were not selected.

EXPONENTIAL MODELS

Three models of exponential pressure fall were tested. (1) A monoexponential of which the asymptote is zero:

$$\text{Thus } P(t) = ae^{bt}$$

where t = time after the point of $\min dp/dt$

$$P(t) = \text{pressure at time } t.$$

$$\text{The time constant } (T_{\text{model 1}}) = -\frac{1}{b}$$

(2) A monoexponential, the asymptote of which is variable:

$$\text{Thus } P(t) = ae^{bt} + c$$

where c = asymptote

$$\text{The time constant } (T_{\text{model 2}}) = -\frac{1}{b}$$

(3) A biexponential:

$$P(t) = a_1e^{b_1t} + a_2e^{b_2t}$$

The three models were applied to the 60 beats. The digitised pressure records were analysed using a powerful non-linear regression program (P3R,BMDP).¹⁵ By iteration the values of the model variables were found which minimised the difference between predicted and observed pressures. No constraints were applied to the range of possible values of the variables.

ESTIMATION OF TIME CONSTANT BY CATHETER LABORATORY COMPUTER

The same 60 beats were analysed by a much simpler program on the catheter laboratory computer. The time constant was estimated by two methods, corresponding to models 1 and 2.

(1) *Semilogarithmic method.*¹⁻⁴

This assumes the asymptote to be zero

$$\text{thus } P(t) = ae^{bt}$$

$$\text{so that } \ln(Pt) = A + bt$$

b was estimated by linear regression from the plot of $\ln(\text{pressure})$ against time. The time constant

$$(T_{\ln}) = -\frac{1}{b}$$

(2) *Exponential method*

A modification of a program previously described was used.^{8,9}

This does not assume the asymptote to be zero.

$$\text{Thus } P(t) = ae^{bt} + c$$

The variables a, b, and c can be estimated by considering three points equispaced in time on the pressure-time curve. For three values of pressure at times o, m, and 2m it can be shown that

$$b = \frac{-1}{m} \ln \left[\frac{P_{(2m)} - P_{(m)}}{P_{(m)} - P_{(o)}} \right] \quad (1)$$

$$c = P_{(o)} - a \quad (2)$$

$$\text{where } a = \frac{P_{(2m)} - P_{(o)}}{e^{b2m} - 1} \quad (3)$$

These equations were applied to the digitised pressure signals as follows: b was calculated by equation (1) for $P_{(0)}$, $P_{(20)}$, and $P_{(40)}$ (where 0,20,40 refer to time after min dp/dt in ms), then for $P_{(5)}$, $P_{(25)}$, and $P_{(45)}$ until all the points were used. The mean value of b was found for that beat.

$$\text{From equation (3) } a = \frac{P_{(j)} - P_{(o)}}{e^{bj} - 1}$$

where $P_{(j)}$ = pressure at the end of isovolumic relaxation

and j = time in ms after min dp/dt

c was calculated from equation (2)

$$\text{The time constant } (T_{\text{EXP}}) = -\frac{1}{b}$$

STATISTICAL METHODS

For each beat the non-linear regression program calculated the pressures predicted by the three models and the residual sum of squares (RSS), that is the sum of the squares of the differences between observed and predicted pressures. The ratio of the residual to total sum of squares (RSS/TSS) was used to estimate the proportion of the total variance in the pressure-time curve that could not be accounted for by the model. Thus, the smaller the ratio the better the agreement between predicted and observed pressures.

The residual mean square (RMS) was used to compare the "goodness of fit" of the three models. This takes into account the differing complexity of the models, as it is calculated as RSS divided by the residual degrees of freedom (that is the number of points analysed minus the number of variables in the model).

Elsewhere, linear regression has been used.

Results

THE THREE MODELS

The application of the three models to an individual beat is illustrated in Fig. 1. This beat was recorded at basal heart rate in a patient from group 1. For model 1 $P(t) = 91.2 \times e^{-0.0312t}$; thus $T_{\text{model 1}} = 32$ ms. For model 2 $P(t) = 113.4 \times e^{-0.01882t} - 30.1$; thus $T_{\text{model 2}} = 53$ ms. For model 3 $P(t) = 369.7 \times e^{-0.01321t} - 281.5 \times e^{-0.00956t}$; the two time constants are 75 ms and 105 ms. It can be seen that the pressures predicted by models 2 and 3 are similar (Fig. 1).

Each of the three exponentials predicted by the different models agree quite well with measured pressure (Fig. 1), but it is obvious that model 1 is less successful than either model 2 or model 3. For model 1 RSS/TSS = 1.7%, whereas for models 2 and 3 RSS/TSS is 0.12% and 0.1%, respectively, and the three values of RMS are 6.44, 0.48, and 0.44. Thus, for this beat there is little to choose between models 2 and 3, both of which are superior to model 1.

Fig. 2 shows RSS/TSS for the three models in each of the 60 beats. In each of the five groups RSS/TSS was greater for model 1 than for either model 2 or 3. In every beat RSS/TSS for models 2 and 3 was less than 1%. Neither heart rate nor angina (group 3) had any consistent effect upon RSS/TSS.

The RMS for models 1 and 2 in each of the 60 beats are plotted in Fig. 3. In most cases RMS was considerably greater for model 1 than for model 2; no example was found where RMS was lower for model 1. In every case $T_{\text{model 1}}$ was shorter than $T_{\text{model 2}}$ and the ratio of the two could be related to the estimate of the asymptote made by model 2 (Fig. 4).

The RMS for models 2 and 3 are shown in Fig. 5. No consistent advantage of one model over the other

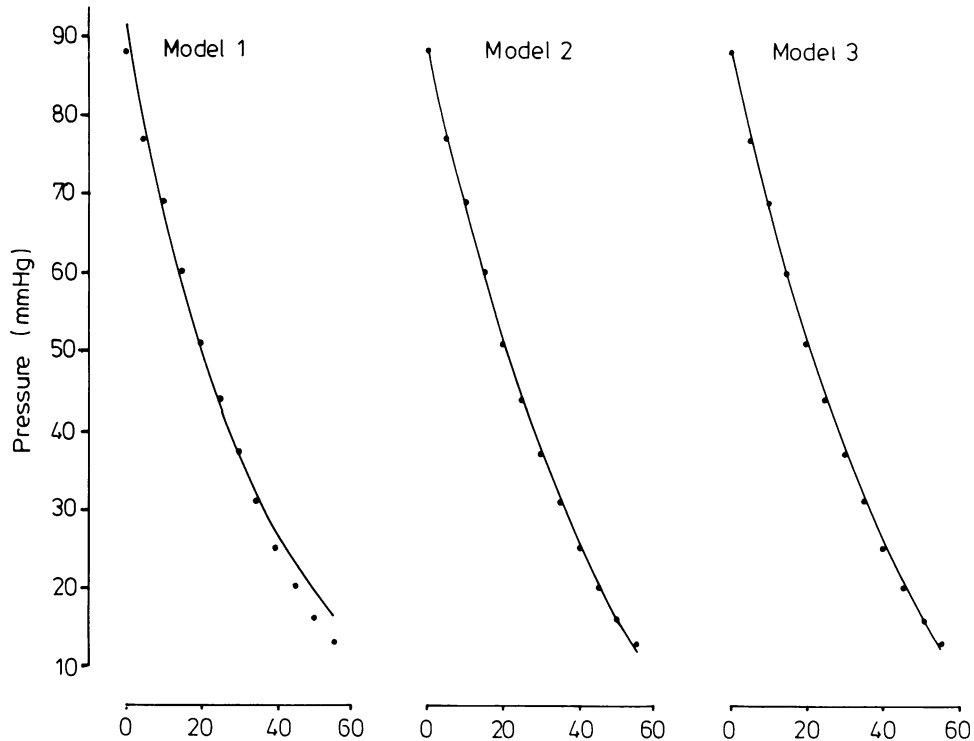


Fig. 1 The analysis of a single beat. Measured pressure (dots) plotted against time (ms) compared with the predictions of the three models (solid lines).

Model 1: $P(t) = 91.2 \times e^{-0.0312t}$. $RSS/RSS = 1.7\%$, $RMS = 6.44$

Model 2: $P(t) = 118.4 \times e^{-0.01882t} - 30.1$. $RSS/TSS = 0.12\%$, $RMS = 0.48$

Model 3: $P(t) = 369.7 \times e^{-0.01321t} - 281.5 \times e^{-0.00956t}$. $RSS/TSS = 0.1\%$, $RMS = 0.44$.

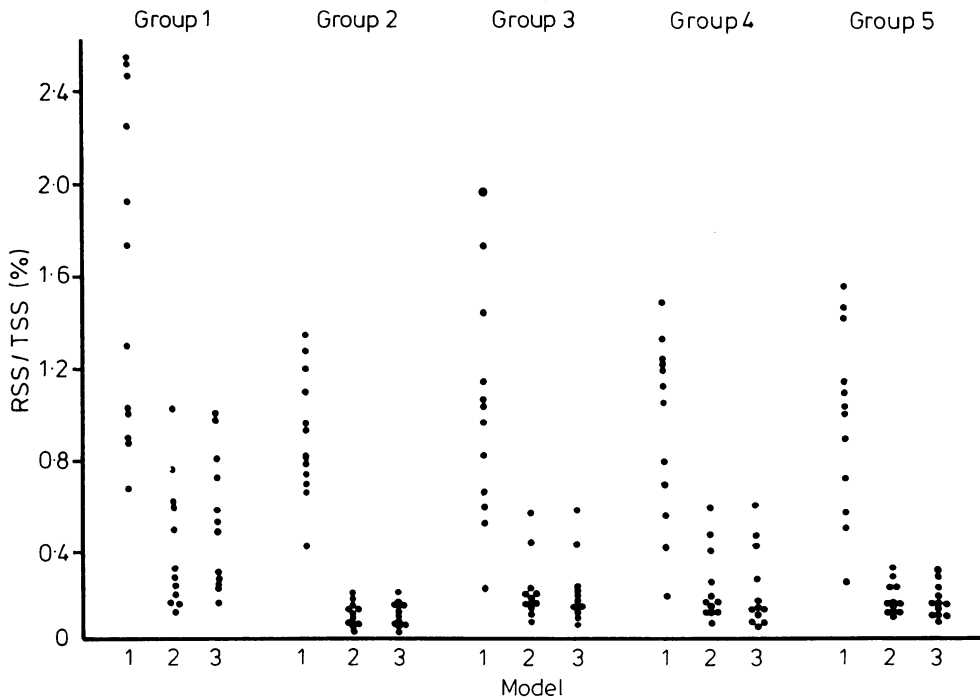


Fig. 2 The ratio of RSS to TSS for the three models in the 12 beats in each of the five groups. The predictions of each of the models agree well with measured pressure, but the predictions of models 2 and 3 are superior to those of model 1.

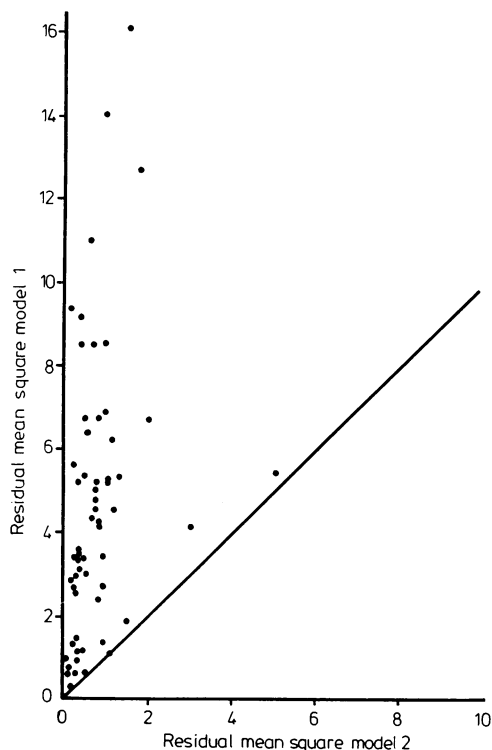


Fig. 3 Comparison of the RMS of models 1 and 2. In each of the 60 beats RMS was greater for model 1 than for model 2. Solid line: line of identity.

could be shown. For model 3 in each of the 60 beats either a_1 or a_2 was negative. Thus, in a biexponential model the minimum value of RMS could be obtained only by considering $P(t)$ to be the sum of a negative and positive pressure. The values of b_1 and b_2 for each beat are plotted in Fig. 5; in most beats b_1 and b_2 were similar.

ANALYSIS BY CATHETER LABORATORY COMPUTER

The estimate T_{1n} , made by the catheter laboratory computer, was consistently lower than $T_{\text{model } 1}$ (Fig. 6). The ratio of the two estimates could be related to end-diastolic pressure (that is the last value of pressure analysed); the lower the pressure the greater the discrepancy between the two estimates (Fig. 6). The analysis of an individual beat is shown in Fig. 7. For this beat $T_{1n} = 25$ ms and $T_{\text{model } 1} = 32$ ms. It can be seen that $\ln(\text{pressure})$ does not fall linearly with time, the slope becoming steeper at low values of pressure. Despite this, $r = -0.98$. Measured pressure and the pressures predicted by T_{1n} do not agree very well, demonstrating the unreliability of the correlation coefficient as a test of the validity of T_{1n} .

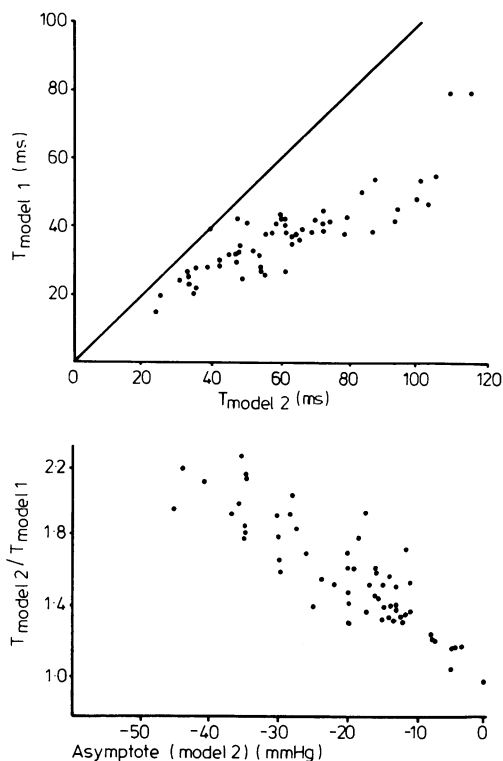


Fig. 4 Upper panel: the time constant estimated by model 1 has been plotted against the time constant estimated by model 2. Solid line: line of identity.

Lower panel: the ratio of the two estimates of the time constant plotted against the estimate of the asymptote of pressure fall derived from model 2.

The estimate T_{EXP} , made by the catheter laboratory computer, was in close agreement with $T_{\text{model } 2}$ over a wide range of values (Fig. 8). The regression line lies close to the line of identity. Similarly, the estimates of a and c made by the catheter laboratory computer agreed well with the corresponding variables of model 2 (Fig. 9).

Discussion

The observation that isovolumic pressure fall approximates to a monoexponential allows the rate of relaxation of the left ventricle to be characterised by a time constant.¹ The rationale of this analysis is purely empirical, as isovolumic pressure fall might be described equally well by a variety of mathematical models of varying complexity. The advantage of a time constant is its simplicity, which has led to its extensive use in the study of relaxation.²⁻⁷

In the first part of this study we tested critically three models of exponential pressure fall by analysing

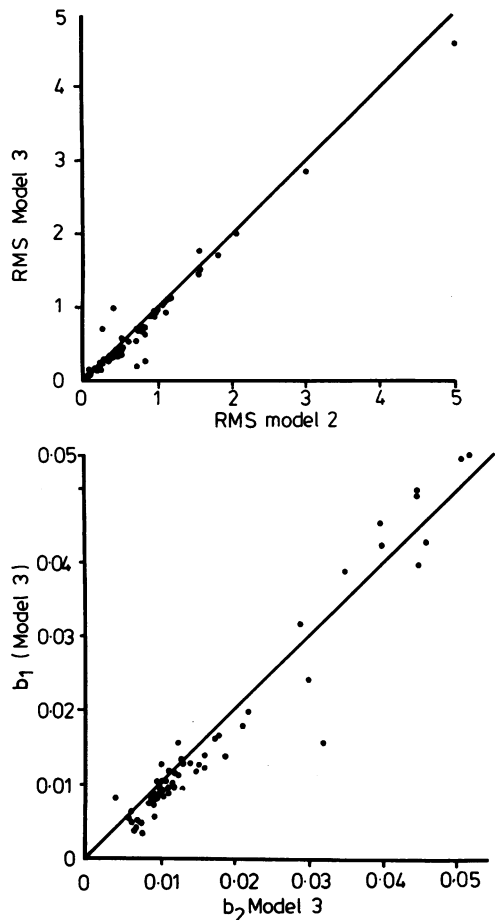


Fig. 5 Upper panel: RMS for model 3 plotted against RMS for model 2. Lower panel: model 3; the variables b_1 and b_2 are plotted against each other. Solid lines: lines of identity.

60 beats recorded at different heart rates in patients with a variety of left ventricular disease. The pressures predicted by the two monoexponential models agreed quite well with measured pressure, but in every beat the predictions of model 2 were superior to those of model 1. Indeed the predictions of model 2 were extremely close to measured pressure; RSS/TSS was always less than 1%, and usually less than 0.5%. Though model 2 is more complicated than model 1 this is compensated for by the consistent gain in precision illustrated by the substantial differences in RMS between the two models.

Model 1 assumes the asymptote to be zero, whereas the asymptote estimated by model 2 was always negative with respect to zero reference pressure. The time constant derived from model 2 was invariably longer than the estimate made by model 1, and, as would be

expected, the difference between the two was related inversely to the asymptote.⁹ Thus, because it assumes the asymptote to be zero, model 1 consistently underestimated the time constant, and when the asymptote was very low the error of the estimate was considerable.

The third model tested was a biexponential. This was chosen because it has been suggested that pressure fall is best described by two time constants applicable to early and late relaxation.¹⁰ We found that model 3 had no statistical advantage over model 2, and that in each beat the pressures predicted by the two models were very similar. The program estimated the model variables by iteration, and no constraints were applied to their numerical values, so that each could either be negative or positive.¹⁵ For model 3 in each beat either a_1 or a_2 was negative; thus the best fit between predicted and observed pressure was obtained when $P(t)$ was considered to be the sum of a negative and positive pressure. In the majority of beats the variables b_1 and b_2 of model 3 were similar, which, in conjunction with the lack of statistical

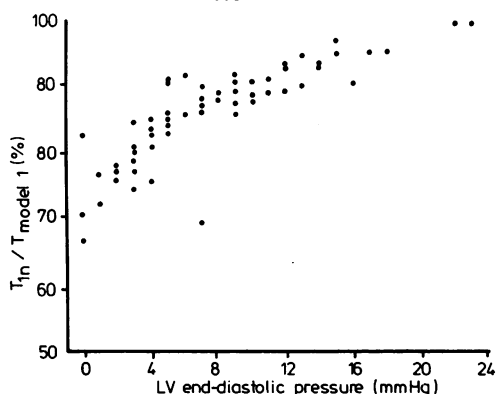
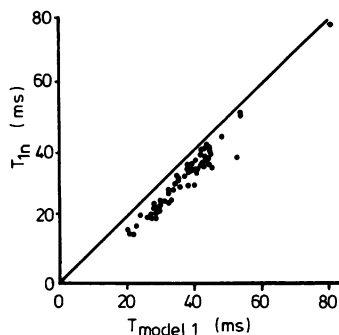


Fig. 6 Upper panel: T_{1n} (the semi-log estimate of T made by the catheter laboratory computer) plotted against $T_{model 1}$. Solid line: line of identity. Lower panel: the ratio $T_{1n} / T_{model 1}$ plotted against left ventricular end-diastolic pressure (that is the last value of pressure analysed).

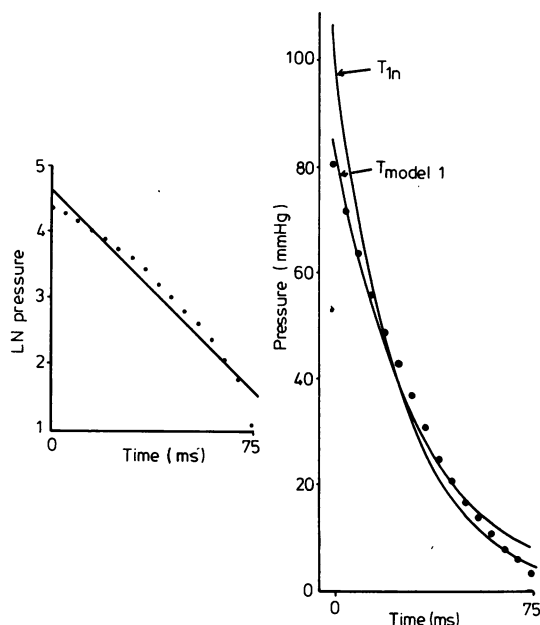


Fig. 7 analysis of a single beat from a patient in group 2 at basal heart rate. Left hand panel: semilogarithmic plot of pressure against time from which T_{1n} was estimated. Note that the slope becomes steeper at low values of pressure, but $r = -0.98$.

Right hand panel: the same beat. Measured pressure (dots) compared with the pressures predicted by T_{1n} and model 1.

advantage of model 3 over model 2, suggests that a second exponential term is an unnecessary complication, and that a monoexponential model is perfectly adequate. That pressure fall is biexponential was suggested initially because the slope of $\ln(\text{pressure})$ against time differs for the early and late parts of relaxation.¹⁰ There are, however, powerful objections to this conclusion,⁹ as when the asymptote is negative $\ln(\text{pressure})$ and time are related by a curve (Fig. 7), so that regression analysis of its early and late parts will yield inevitably two different time constants.

From the first part of this study it is concluded that in a wide variety of circumstances the fall in pressure during isovolumic relaxation approximates very closely to a monoexponential of which both the time constant and asymptote are variable. The time constant of relaxation should be estimated by a method derived from this model. The usual method of its estimation¹⁻⁷ assumes the asymptote to be zero, and therefore is much less reliable.

The complex off-line computing used in the first part of the study is unsuitable for routine use. In the second part of the study the same 60 beats were analysed by a smaller program on the catheter laboratory computer. The time constant was estimated by two

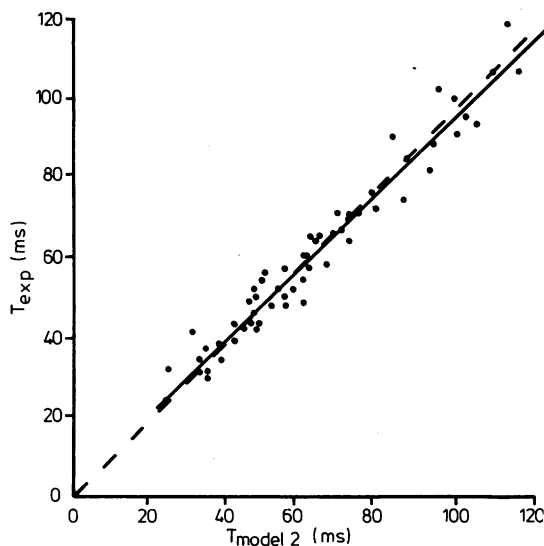


Fig. 8 For each of the 60 beats T_{EXP} (the exponentially derived estimate of T made by the catheter laboratory computer) has been plotted against $T_{model 2}$. Broken line: line of identity. Solid line: regression line. $r = 0.98$, $p < 0.001$. $T_{EXP} = 1.7 + [T_{model} \times 0.934]$ SE of the estimate = 4.6 ms.

methods: from the slope of $\ln(\text{pressure})$ against time¹⁻⁷ (analogous to model 1), and by a method of exponential analysis comparable to model 2.

When the asymptote of pressure fall is zero $\ln(\text{pressure})$ falls linearly with time and the time constant can be calculated as the negative reciprocal of the slope. If the asymptote is not zero this relation is a curve; the slope becomes progressively steeper when the asymptote is negative and shallower when it is positive. This is illustrated in Fig. 7. For this beat model 2 estimated the asymptote to be -18 mmHg, and the slope of $\ln(\text{pressure})$ against time becomes progressively steeper. Therefore, the time constant is estimated by applying linear regression to a curve, and the estimate will depend upon the part of the curve analysed, and hence the level to which pressure falls. It is not surprising, therefore, that the semilogarithmic estimate was lower than the time constant derived from model 1 in beats where the absolute value of pressure fell to low levels at the end of relaxation. This shows a serious deficiency in the usual method of estimating the time constant; not only is it based upon an inadequate model, but in addition its estimate of the time constant depends critically upon the absolute values of pressure. The correlation coefficient of the $\ln(\text{pressure})$ -time relation offers little guidance to the validity of the estimate of the time constant. For the beat in Fig. 7 $r = -0.98$, but the pressures predicted by the time constant deviate con-

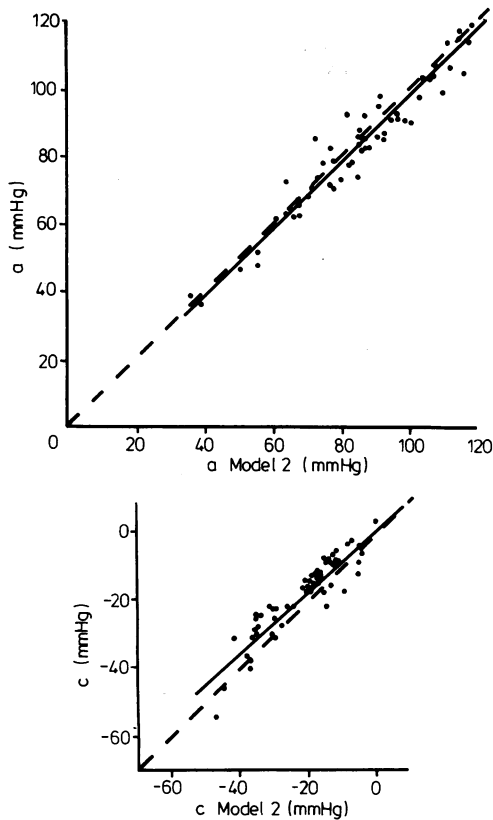


Fig. 9 Upper panel: *a*, derived from exponential analysis by the catheter laboratory computer, plotted against *a* derived from model 2.

$r = 0.97, p < 0.001. a = [a_{\text{model 2}} \times 0.988] - 1.1$
 SE of the estimate = 5.2 mmHg.

Lower panel: *c*, estimated by the catheter laboratory computer, plotted against *c* derived from model 2. $r = 0.91, p < 0.001$
 $c = [c_{\text{model 2}} \times 0.92] + 0.1. SE \text{ of the estimate} = 4.5 \text{ mmHg.}$
 Solid lines: regression lines. Broken lines: lines of identity.

spicuously from measured pressure. We conclude that this method of calculating the time constant is most unreliable, and its use in the study of the determinants^{2 3 11} and consequences^{5 6} of the rate of relaxation may be misleading because of its dependence upon absolute pressure.

The second method of analysis performed by the catheter laboratory computer was based upon model 2. The estimates of the time constant made by this method and by model 2 were in close agreement over a wide range. The regression line relating the two lay close to the line of identity, and no examples were found where the two estimates differed widely. Similarly, the estimates made by the two methods of the variables *a* and *c* agreed well. Despite its relative

crudeness this method is capable of estimating reliably the time constant of relaxation based upon the most successful of the three exponential models.

This study shows that in a wide range of circumstances the fall in left ventricular pressure during isovolumic relaxation approximates closely to a mono-exponential of which both the time constant and asymptote are variable. It is legitimate, therefore, to describe the rate of relaxation of the intact left ventricle by a time constant if it is estimated by a method based upon this model. We have shown that the time constant can be estimated reliably by a simple computer program suitable for use "on-line".

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