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# A model of asynchronous left ventricular relaxation predicting the bi-exponential pressure decay

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SUMMARY A new model for the pressure relaxation of the left ventricle is proposed. The model presumes that the myocardium relaxes asynchronously, but that when regions begin to relax, after a delay, the local wall stress decays as a mono-exponential process. This formulation results in an apparently bi-exponential process (two time constants) which has been previously reported. It is shown that the ratio of the two time constants ($T_2/T_1$) can be interpreted as the fraction of the myocardium which relaxes synchronously. Data are presented illustrating the model during transient coronary occlusion in patients undergoing percutaneous transluminal coronary angioplasty.

Most models of the time course of left ventricular pressure decay focus on an exponential process. There is evidence that the relaxation of isolated papillary muscles can be approximated by this model,[5] and as a first approximation it appears to apply to the myocardium as a whole.[2] The exponential function is an Eigen function of the differential operator, and would be expected to occur when the rate of decay is proportional to the dependent variable.

Recent studies, however, have focussed on those cases where the simple mono-exponential model does not appear to be followed. *Ad hoc* modifications have been proposed to provide a better fit to the data. For example, Thompson[8] found that the pressure, especially in the latter phase of relaxation, is described by $P = A + B \exp(-t/T)$, ie mono-exponential with offset. Rousseau,[7] using a similar rationale, developed the model $P = A \exp(-t/T_1) + B \exp(-t/T_2)$, ie bi-exponential, primarily on the basis that the pressure curve when plotted on semi-log paper was noted to follow two straight lines rather than the one predicted by the mono-exponential.

Further studies have clearly shown that the measured pressure departs from the mono-exponential model under a variety of stimuli and circumstances, and that asynchronous relaxation may be involved.[1 3 4] For example, fig 1a shows the log P vs time curve, from peak –dP/dt to 5 mmHg above the previous end-diastolic pressure, for a patient with coronary artery disease. Fig 1b shows the same patient 15 s after the onset of percutaneous transluminal coronary occlusion during angioplasty, when asynchronous relaxation was confirmed by echocardiography. The pressure deviates substantially from the simple mono-exponential model. In this report we develop this idea further and propose a plausible model of pressure relaxation of the left ventricle explicitly incorporating asynchronous relaxation.

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*Key words:* relaxation; angioplasty; coronary artery disease; asynchrony; left ventricle; bi-exponential.

## Methods

### THEORETICAL MODEL

The model of LV pressure relaxation developed here assumes that the onset of relaxation is governed by the distribution function g(t). That is, in an infinitesimal time interval dt, g(t)·dt fraction of the myocardium initiates relaxation. The integral $\int_0^t g(x)\,dx$ gives the total fraction of the myocardium initiating relaxation from time 0 to t. Once the onset of relaxation has begun, regions of the myocardium relax as a simple mono-exponential with the same time constant $T_2$. The observed time constant $T_1$ results from the combined action of that fraction of the myocardium in the process of relaxing and the remainder yet to initiate relaxation. The LV pressure during the relaxation phase is thus given by:

$$P(t)=P_0\left[1 - \int_0^t g(x)\,dx + \int_0^t g(x)\exp(-(t-x)T_2)\,dx\right] \quad (1)$$

where $P_0$ is the pressure at time $t = 0$. The term $1 - \int_0^t g(x)\,dx$ in equation (1) represents the fraction of the myocardium not having initiated relaxation up to time t. The other term in equation (1) represents the total contribution to pressure at time t of that fraction of the myocardium having initiated relaxation at a time governed by the distribution function $g(x)$.

A further condition is that

$$\int_0^L g(x)\,dx = 1$$

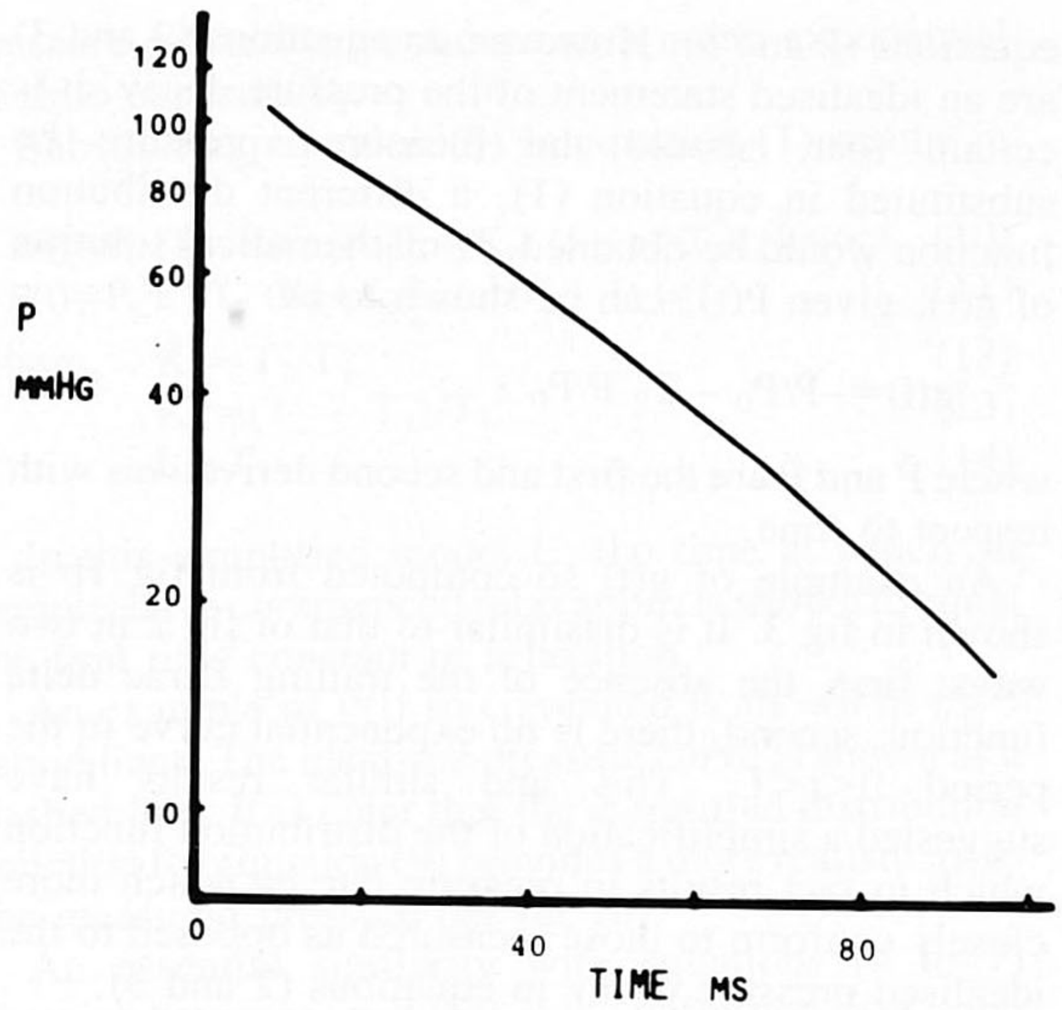


FIG 1A *Logarithm of left ventricular pressure vs time in a patient with coronary artery disease. Pressure is measured from the moment of peak – dP/dt to 5 mmHg above the previously measured EDP. The pressure curve is shifted 8 ms to the right for purposes of illustration.*

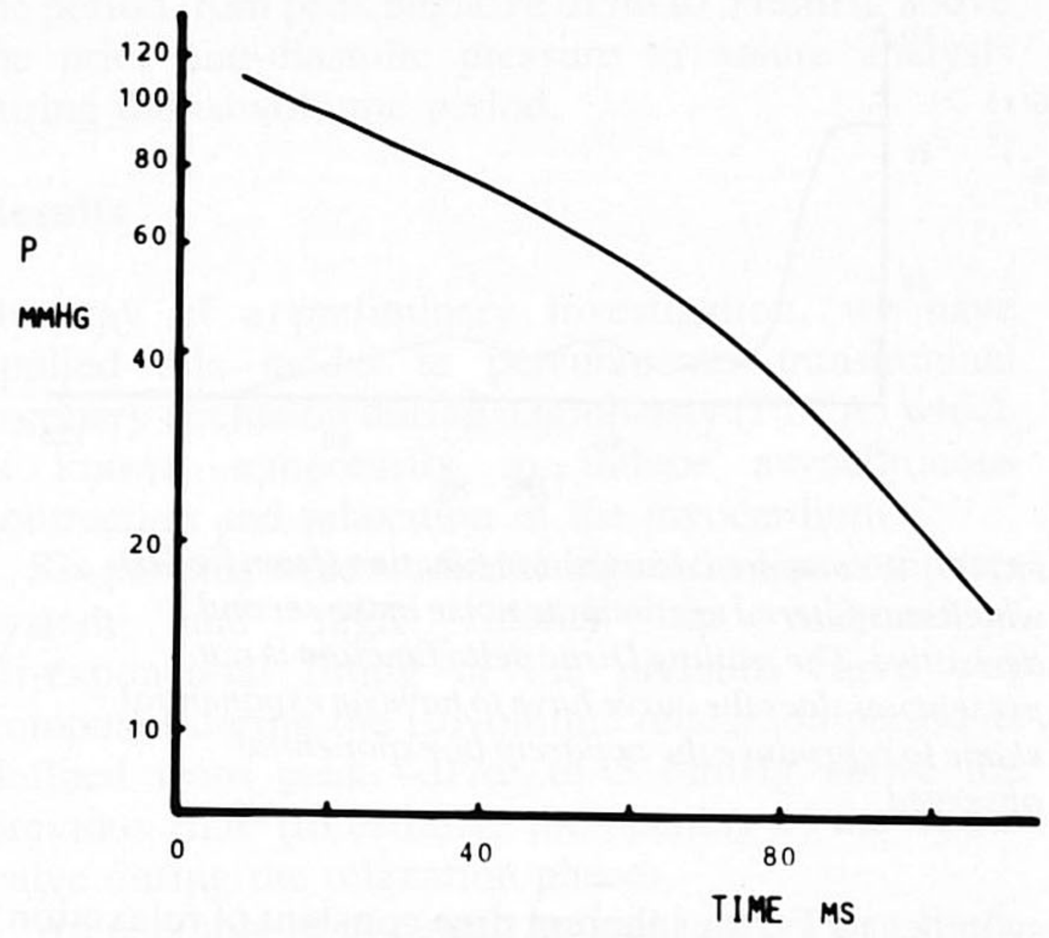


FIG 1B *Pressure in the same patient 15 s after the onset of percutaneous transluminal coronary occlusion during angioplasty. A bi-exponential pressure decay is now apparent. Asynchronous relaxation was confirmed with echocardiography.*

and that g($x$) is zero for $x<0$ and $x>$L, where L represents the time at which all regions have commenced relaxation. the pressure, P(t), is a directly measureable quantity, but for sake of argument suppose that it can be idealised from that shown in fig 1a and 1b. P(t) over the entire time interval is idealised as

$$P(t) = P_0 \exp(-t/T_1) \qquad 0 \leqslant t < L \qquad (2)$$
$$= P_0 \exp(-L/T_1) \exp -(t-L)/T_2 \qquad t \geqslant L \qquad (3)$$
$$T_1 \geqslant T_2$$

EXACT SOLUTION

It can be shown that a solution for g($x$) in equation (1) is

$$g(x) = K_0\,\delta(x) + K_1 \exp(-x/T_1) + K_2\,\delta(x-L) \qquad (4)$$
$$g(x) = 0 \text{ for } x<0 \text{ and } x>L$$

where $\delta$ is the Dirac delta function (see Appendix for explanation).

The function g($x$) is illustrated in fig 2. The parameters $K_0$, $K_1$, $K_2$ are simply related to the idealised pressure vs time curve by the following conditions.

$$K_0 = T_2/T_1 \qquad (5)$$
$$K_1 = (T_1 - T_2)/T_1^{\,2} \qquad (6)$$
$$K_2 = (T_1 - T_2)/T_1 \exp(-L/T_1) \qquad (7)$$

The presence of the Dirac delta function, $\delta$(t) in the distribution function, g(t), is interpreted as a process which occurs quickly in relation to other events.

The physiological significance of the parameter $K_0$ is that it is the fraction of the myocardium which begins to relax synchronously. In the interval $0<t<L$, an additional fraction of myocardium relaxes, governed by $K_1 \exp(-t/T_1)$. At $t=L$ all the remaining unrelaxed fractions of the myocardium (fraction $K_2$) begin to relax. After this point the pressure ceases to have a relaxation time constant $T_1$ and abruptly

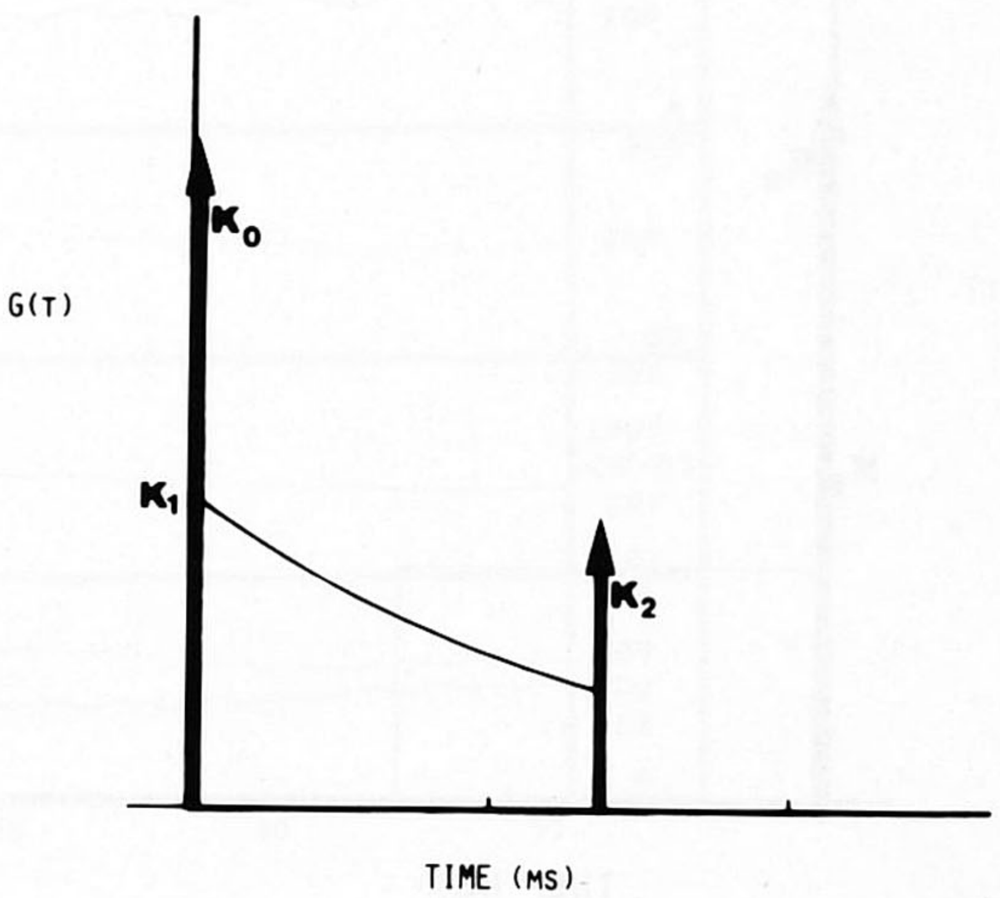


FIG 2 *The distribution function, g(t) giving a precise solution to equations 1 to 3, showing that some asynchrony in the relaxation process can give rise to a bi-exponential pressure decay.*

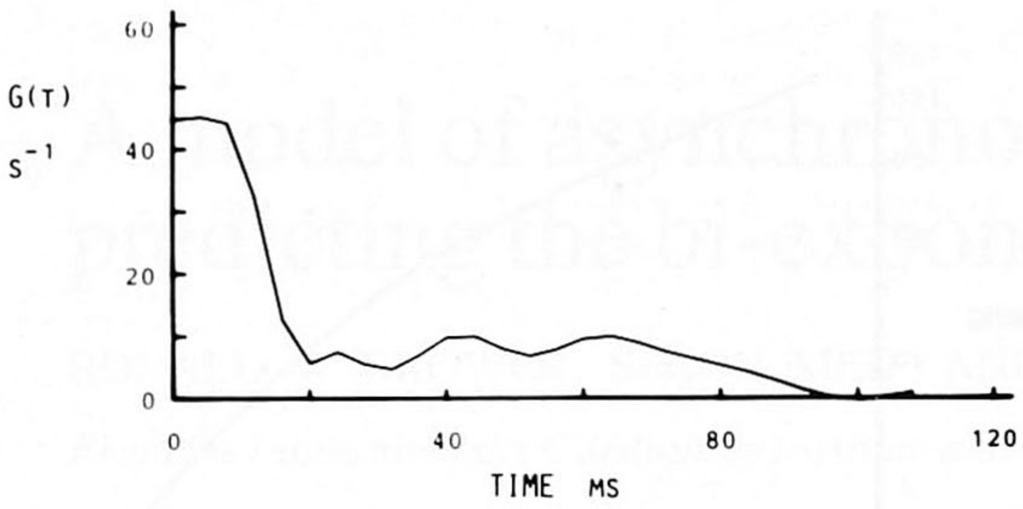


FIG 3 *A computed distribution function (from fig 1B) which was filtered to eliminate noise in the second derivative. The trailing Dirac delta function is not present nor does the curve have to have an exponential shape to reproduce the apparent bi-exponential observed.*

switches to $T_2$, the inherent time constant of relaxation of the myocardial tissue. The time constant $T_1$ is not directly related to a relaxation process *per se*.

It is interesting to note that in an intervention or disease which affects the synchrony of relaxation, the parameter $K_0=T_2/T_1$ would most directly quantify the fraction of the heart unaffected.

The distribution function, g($x$) during the remainder of asynchronous relaxation is not critical to the reproduction of the shape of the pressure curve, and as discussed below, can take on other forms.

MEASUREMENT OF THE DISTRIBUTION FUNCTION

The distribution function, g(t), in equation (4) is an exact solution given the pressure decay described in equations (2 and 3). However, as equations (2 and 3) are an idealised statement of the pressure decay, it is certain that, should the measured pressure be substituted in equation (1), a different distribution function would be obtained. A mathematical solution of g(t), given P(t), can be shown to be

$$g(t)=-\dot{P}/P_0 - T_2\,\ddot{P}/P_0 \qquad (8)$$

where $\dot{P}$ and $\ddot{P}$ are the first and second derivatives with respect to time.

An example of g(t) so computed from fig 1b is shown in fig 3. It is dissimilar to that of fig 2 in two ways: first, the absence of the trailing Dirac delta function; second, there is no exponential curve in the period $0<t<L$. This and similar results have suggested a simplification of the distribution function which in fact results in pressure curves which more closely conform to those measured as opposed to the idealised pressure decay in equations (2 and 3).

SIMPLIFIED DISTRIBUTION FUNCTION

The distribution function, g(t), may be simplified to

$$\begin{aligned} g(t) &= K_0\delta(t)+K_1\,h(t) && 0\leqslant\ t<L \\ &= 0 && t\geqslant L \end{aligned} \qquad (9)$$

on condition that $K_0+(K_1\cdot L) = 1$. This distribution function is illustrated in fig 4. The physiological significance is similar to that of fig 2: the first term, $K_0$ $\delta(t)$, represents that fraction of the myocardium relaxing synchronously; the second term, $K_1$ h(t) represents a uniform rate of recruitment of the remaining myocardium in the relaxation process. When all the myocardium is recruited, at t=L,

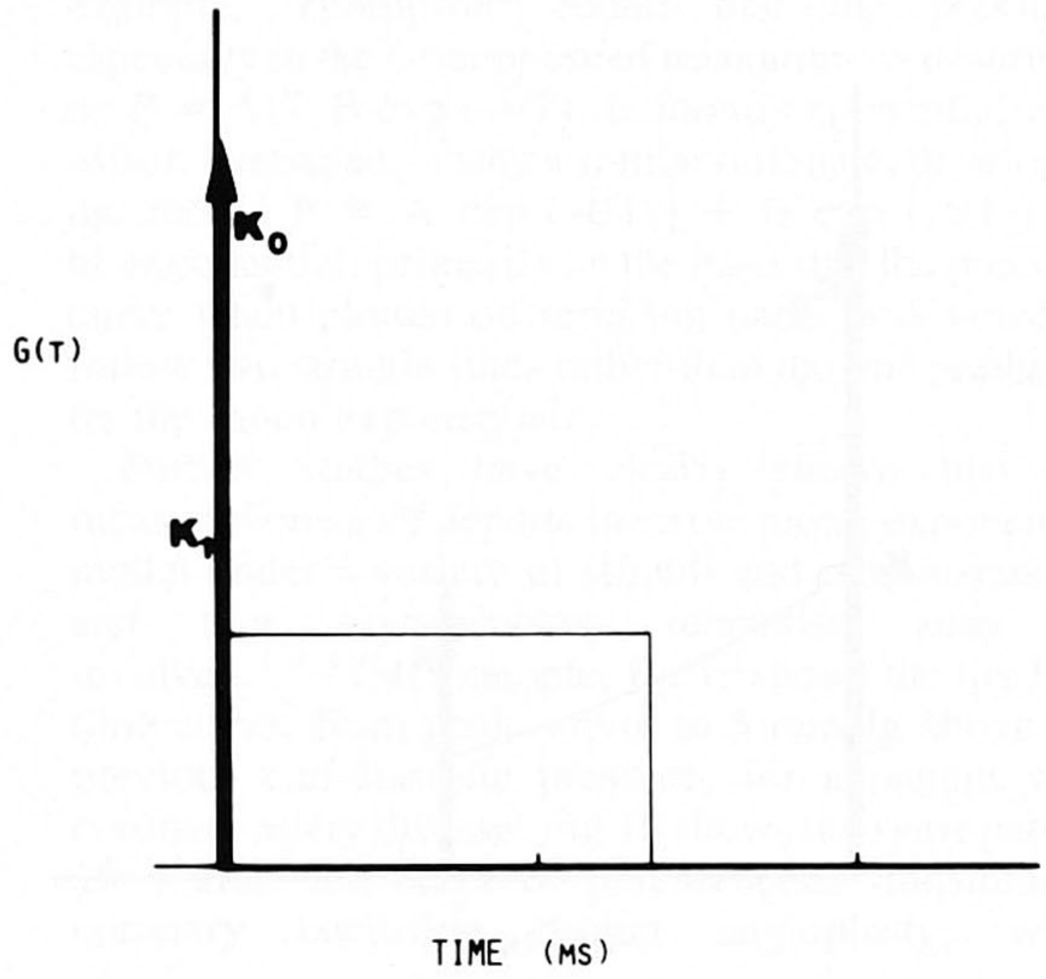


FIG 4 *An idealised and simplified distribution function which more closely predicts the measured pressure decay than the exact solution.*

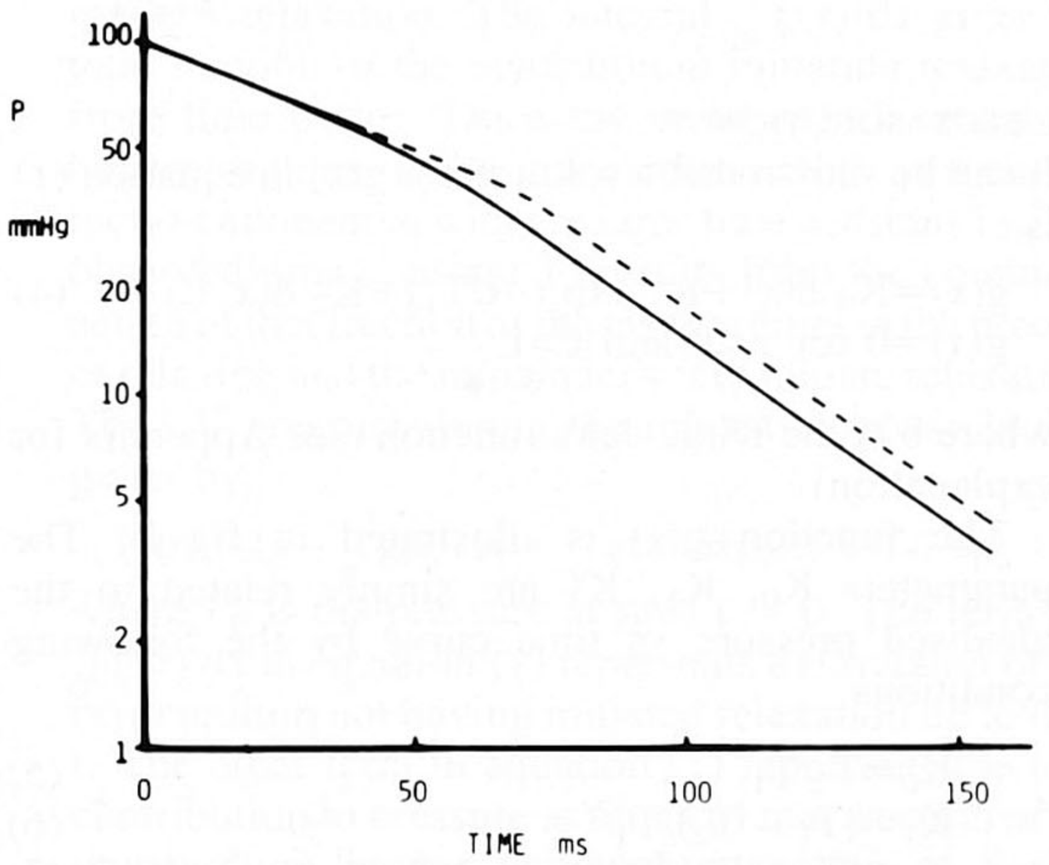


FIG 5 *The dashed curve shows the calculated log P vs time curve using the exact solution, while the solid curve shows that predicted from the simplified model.*

pressure relaxation continues as a mono-exponential of time constant $T_2$.

Substituting equation (9) in equation (1) results in

$$P(t)=P_0\,[1 - K_1 t+(K_1 T_2 - K_0)\,(1 - e^{-t}/T_2)],\ 0\leqslant t<L \quad (10)$$

$$P(t)=P_0\,e^{-t}/T_2\,(K_0+K_1 T_2\,(e^{L}/T_2 - 1)\ t\geqslant L \quad (11)$$

where $K_0=T_2/T_1$ (12)

$K_1=(T_1 - T_2)/{T_1}^2$ (13)

$L=T_1$ (14)

In this simplified model L, the time at which all regions have commenced relaxation, is shown to equal the first time constant of relaxation.

An example of P(t) so computed is shown in fig 5 (solid line). The idealised pressure curve is shown as a dashed line. It is clear that the simplified distribution function for equation (9) provides a more realistic fit to the measured pressure (eg fig 1b).

An essential similarity with equations (4 to 7) remains however, and that is the definition of $K_0$ and $K_1$. This also applies to their physiological interpretation.

## MEASUREMENT METHODOLOGY

Left ventricular pressure was measured with a Millar micromanometer catheter and digitised at 250 samples per s. Combined analogue and digital filtering resulted in an effective time constant of less than 10 ms. This employed an updated version of the beat to beat analysis program described previously.[10 11]

The two time constants of relaxation were computed using a least squares fit to the log P vs time curve over the period from peak negative dP/dt to 5 mmHg above the prior end-diastolic pressure to assure analysis during the isovolumic period.

## Results

By way of a preliminary investigation, we have applied this model to percutaneous transluminal coronary occlusion during angioplasty (PTCA) which is known temporarily to induce asynchronous contraction and relaxation of the myocardium.

Six patients were studied using an on-line computer system and high fidelity tip manometry. Bi-exponential fitting of the pressure curve was computed during the isovolumic relaxation period as defined from peak –dP/dt to 5 mmHg above the previous EDP (to estimate the opening of the mitral valve during the relaxation phase).

An example of one such patient is shown in fig 6. This shows, from top to bottom, LV end-diastolic pressure, end-systolic pressure, peak –dP/dt, and the time constants of relaxation. The gap at beats 8 to 10 represent the inflation of the catheter tip balloon at the onset of PTCA. For the time constant (tau) panel, three lines are shown: the topmost dashed line represents $T_1$, the bottom-most dotted line represents $T_2$, and the middle solid line represents the time constant obtained from a mono-exponential fit.

Five beats after occlusion of the coronary artery, both –dP/dt and $T_1$ begin to change. It is clear that $T_1$ reaches a peak by beat 30 while –dP/dt continues to decline up to beat 45. Both ESP and EDP show a later

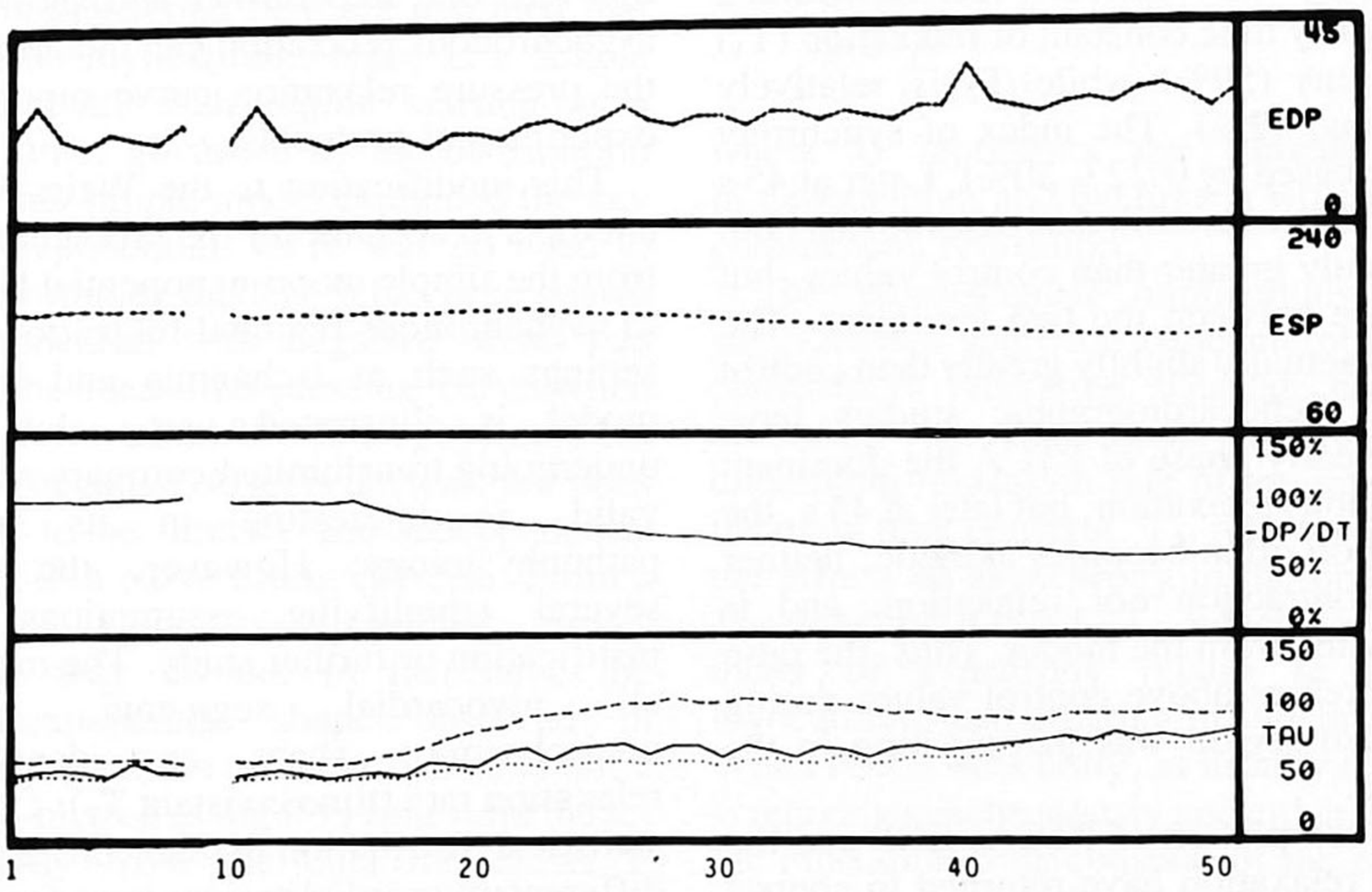


FIG 6 *Haemodynamic measurements in a patient during percutaneous transluminal coronary occlusion during angioplasty. EDP (scale 15 mmHg), end-systolic pressure (scale 60 mmHg, with 60 mmHg offset), peak –dP/dt expressed as a percentage of control values, the time constants of relaxation with $T_1$, dashed line, T solid line, $T_2$ dotted line (scale 50 ms).*

TABLE *Results of percutaneous transluminal coronary occlusion during angioplasty for 18 procedures in six patients.*

| *Measurement* | *M1* *mean±SD* | *M2* *mean±SD* | *P<* | *M3* *mean±SD* | *P<* | *M4* *mean±SD* | *P<* |
|---|---|---|---|---|---|---|---|
| GCVF (ml·min$^{-1}$) | 88±37 | — | — | 49±22 | 0.001 | 114±44 | 0.01 |
| LAV (mmol·litre$^{-1}$) | 0.17±0.13 | — | — | — | — | –0.77±0.76 | 0.001 |
| EDP (mmHg) | 14±5 | 16±6 | 0.01 | 23±5 | 0.001 | 13±5 | NS |
| $T_1$ (ms) | 56±7 | 89±11 | $10^{-6}$ | 68±13 | $10^{-4}$ | 57±7 | NS |
| $T_2$ (ms) | 41±7 | 46±7 | 0.01 | 56±10 | $10^{-5}$ | 41±6 | NS |
| IOS | 0.74±0.12 | 0.52±0.09 | $10^{-6}$ | 0.83±0.10 | $5\times10^{-4}$ | 0.72±0.11 | NS |

GCVF=great cardiac vein blood flow, LAV=arterio-venous lactate difference (mmol·litre$^{-1}$), EDP=end diastolic pressure, $T_1$=early time constant of relaxation, $T_2$=late time constant of relaxation, IOS=$T_2/T_1$ index of synchrony. Data were obtained at a control period (M1), at 15 s during PTCA (M2), at 45 s during PTCA (M3), and 2 min after completion of PTCA (M4). Data are reported as mean ± SD. Student's paired *t*-test with respect to measurements at M1. NS=no significant difference at the 0.01 level.

and less dramatic change. $T_2$ demonstrates very little change until beat 40. Compared with $T_1$ the mono-exponential fit is relatively unaffected during PTCA.

The results for six patients during 18 attempts at PTCA are summarised in the table. This shows the great cardiac vein blood flow (GCVF) measured by thermodilution, arterio-venous lactate difference in the great cardiac vein (A-GCV), end-diastolic pressure (EDP), the two time constants of relaxation ($T_1$ and $T_2$), and the index of asynchrony (IOS=$T_2/T_1$) prior to PTCA, at 15 s and 45 s during PTCA, and at 2 min after PTCA. The fact that there is a significant fall in GCVF during the procedure with a negative A-V lactate difference after the end of PTCA demonstrates that PTCA did have a potent effect on the myocardium. The haemodynamic parameters show a response only during PTCA and fully recover within 2 min. At 15 s the early time constant of relaxation ($T_1$) increases by 33 ms (59%) while $T_2$ is relatively unchanged (+5 ms, 12%). The index of synchrony (IOS=$T_2/T_1$) decreased by 0.22 (–30%). Later at 45 s during PTCA, $T_2$ increases as $T_1$ decreases so that both are now significantly greater than control values, but with the difference between the two less clear. The ratio $T_2/T_1$ is now actually slightly greater than control values by 12%. Echocardiographic studies have shown that in the early phase of PTCA the dominant effect is asynchronous relaxation, but later at 45 s, the asynchronous region often becomes akinetic, neither contributing to contraction nor relaxation, and is effectively eliminated from the model. Thus, the ratio $T_2/T_1$ actually increases above control values during which the occluded region was participating in the relaxation process.

Two min after completion of PTCA, EDP and the time constants of relaxation have returned to control levels.

If the premise of the two time constant model developed here is correct, the early change in $T_1$ with constant $T_2$ represents an exaccerbation in the asynchrony of relaxation with the underlying time constant of relaxation, $T_2$, unaffected until much later in the procedure. $T_1$ thus represents one of the earliest and most sensitive indicators of regional perfusion deficit in as much as synchrony of relaxation is affected.

## Discussion

The connection between transient asynergy, myocardial ischaemia, and alterations in the time course of contraction and relaxation was pointed out as early as 1969 by Tyberg *et al.*[9] Indeed, the possibility that a non-exponential pressure decay may be directly connected to asynchronous relaxation has already been proposed.[1 3 4 7 8]

The contribution of the work reported here is to take this idea one step further and show that a model of asynchronous relaxation can quantitatively reproduce the pressure relaxation curve reported in numerous experimental protocols.

This modification to the Weiss-Weisfeldt model[2] attempts to account for the problems of: 1) deviations from the simple mono-exponential LV relaxation; and 2) asynchronous regional relaxation which occurs in settings such as ischaemia and hypertrophy. The model is illustrated using data from patients undergoing transluminal coronary angioplasty, and if valid, is interesting in its implications for pathophysiology. However, the model employs several simplifying assumptions which require justification or further study. The model assumes that all myocardial segments, ischaemic and nonischaemic, share an identical underlying relaxation rate (time constant $T_2$). Certainly there is a statistical distribution in time constant of relaxation of different myocardial regions even for the normal heart. Computations based on a rather broad Gaussian distribution in relaxation rate show that, when these regions relax synchronously, the resulting pressure is well described by a mono-exponential process with a

time constant equal to the mean relaxation rate. During regional ischaemia there is evidence that the relaxation rate does change, which on the face of it, would invalidate the model.

For a population of two constants, or a bi-modal distribution in time constants, the effect on the log pressure curve is to develop a positive curvature with the faster process occurring first, rather than the observed negative curvature with the apparently slower process ($T_1$) occurring first. The question therefore is whether during ischaemia the change in the distribution of time constants of relaxation or the occurrence of asynchrony of relaxation has the greater effect on the isovolumic pressure decay. Mathematical studies conducted in connection with the model suggested that asynchronous relaxation was the dominant mechanism in the generation of the bi-exponential pressure decay, but this is an important question which does require further clarification.

The fact that a group of asynchronously relaxing mono-exponentials can give rise to a bi-exponential is not entirely obvious. Thompson *et al*[8] even incorrectly state that it is not possible. It is true that given a set of several identical exponentials, having started at slightly different times, the measured pressure will yield a mono-exponential, but only *after* all the units have started to relax. It is precisely the period of recruitment of the identical exponentials that the other time constant in the bi-exponential process appears, and it relates directly to the extent of the myocardium not relaxing synchronously, ie, delay in onset of relaxation.

For the analysis developed here we assumed that small regions of the myocardium relax as a simple mono-exponential with each region starting at a slightly different time, governed by the distribution function g(t). As this simple model explained the key feature of the bi-exponential, there was no need to consider yet more complex models. It has been shown that a mono-exponential with negative offset can appear to mimic the measured pressure curve when plotted as log P vs time.[6 8] The physiological significance of the negative offset is unclear, nor does the off-set appear to be directly and independently measurable except as a curve fitting exercise. From a practical point of view, bi-exponential curves generated in this way do not in fact have the characteristic bi-exponential shape observed in reality. The latter part of the predicted curve is not a straight line (when plotted as log P vs time) and in fact departs significantly from the data the closer P approaches to the base line.

We avoided this particular error to some extent by limiting the least squares fit to 5 mmHg above the prior end-diastolic pressure.

As noted by Raff and Glantz[6] for a mono-exponential

$$0 = d^2P/dt^2 + \frac{dP/dt}{T} \qquad (15)$$

where T is the time constant of relaxation.
We show that the distribution function, g(t), can be computed by a very similar expression (see equation 8):

$$g(t) = \frac{-dP/dt}{P_0} - T_2 \frac{d^2P/dt^2}{P_0}$$

where $T_2$ is the second time constant in the bi-exponential process and $P_0$ is the pressure at peak –dP/dt. For a mono-exponential equation (15) applies and g(t) = 0. The practical problems in calculating g(t) from measured data should not be minimised. The second derivative of LV pressure is exquisitely sensitive to noise, and furthermore, g(t) is determined as the difference between two large numbers, further contributing to its sensitivity to any form of noise. Filtering the signal is necessary and this results in some apparent degradation in g(t).

The precise form of g(t) is not critical to reproducing the bi-exponential log P vs time curve within the measurement accuracy of pressure. For example, we showed that a rectangular distribution of g(t) was as good as the theoretical prediction of g(t). Numerical computation of g(t) using measured pressure has not identified any particular characteristic shape of g(t). In order to reproduce the bi-exponential shape, three conditions appear essential:

1 $g(t) = T_2/T_1$ $\quad \delta(t)$ at $t=0$
2 $g(t) \geq 0$ $\quad 0 < t \leq L$
$g(t) = 0$ $\quad t > L$
3 $1 = \int_0^L g(t)\, dt$

where L represents the ''break point'' of the bi-exponential, and the time at which all regions have commenced relaxation.

The physiological implications of this model suggest a new approach to the interpretation of the time constants of relaxation. The late time constant, $T_2$, according to this model reflects the effective underlying relaxation rate of the myocardium, while the early time constant, $T_1$, reflects this in addition to the effects of asynchrony in the onset of relaxation. The quantity, $IOS = T_2/T_1$, which we define here as the index of synchrony relates to the fraction of myocardium participating in synchronous relaxation. When IOS is near unity, as usually reported, the heart is relaxing synchronously and either $T_1$ or $T_2$ specifies the relaxation time constant of the myocardium.

It is likely that $T_1$ and $T_2$ are to a large extent independently affected by medical interventions and loading changes. $T_1$ would be directly affected in studies where asynchrony of relaxation is induced, for example, in PTCA or regional administration of

cardioactive drugs. In patients with coronary artery disease, a certain amount of asynchrony may already be present. Whether IOS measured at rest or during stress testing proves to be a sensitive indicator of regional disease remains to be established in further studies.

## Appendix

The step function h(t) and Dirac delta function δ(t) can be simply described as follows:

$$h(t)=0 \quad \text{for } t<0$$
$$h(t)=1 \quad \text{for } t\geq 0$$

δ(t) can be defined as

$$\delta(t)=1/\epsilon \quad \text{for } 0<t<\epsilon,\ \epsilon \text{ arbitrarily small}$$
$$\delta(t)=0 \quad \text{otherwise.}$$

The essential properties are that

$$h(t)=\int_{-\infty}^{t} \delta(x)\,dx$$

and $$f(T_0)=\int_{-\infty}^{\infty} f(t)\,\delta(t-T_0)\,dt$$

The physiological relevance of the step function is that it is a useful formalism to describe a state which rapidly changes from one condition to another. By 'rapidly'' it is understood to occur faster than the ability to respond to the change. For example, the turning on of an alarm or the abrupt increase in pacemaker rate.

The Dirac delta function represents an impulse which occurs once and is over. It can be considered as the derivative of the step function. An example, would be a quick loud noise (book dropping in a library) or a single pulse from a pacemaker. The response is usually called the ''impulse response''.

In the context of this report, the Dirac delta function appears in a probability density function, g(t). It therefore represents a certain fraction of events which occur instantaneously, that is, much more quickly than the time constants involved in relaxation.

## References


1 Abe H, Tomotsune K. Asynchronous relaxation of the ischemic left ventricle. *Jpn Circ J* 1982;**46:**103–12.

2 Frederiksen JW, Weiss JL, Weisfeldt ML. Time constant of isovolumic pressure fall: determinants in the working left ventricle. *Am J Physiol* 1978;**235:**H701–6.

3 Kumada T, Karliner JS, Pouleur H, Gallagher KP, Shirato K, Ross J. Effects of coronary occlusion on early ventricular diastolic events in conscious dogs. *Am J Physiol* 1979;**237:**H542–9.

4 Kumada T, Katayama K, Matsuzaki M, Matsuda Y, Kusukawa R. Assessment of left ventricular relaxation in the disease heart in man. *Jpn Circ J* 1982;**46:**58–63.

5 Parmley WW, Sonnenblick EH. Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Am J Physiol* 1969;**216:**1084–91.

6 Raff GL, Glantz S. Volume loading slows left ventricular isovolumic relaxation rate. *Circ Res* 1981;**48:**813–24.

7 Rousseau M, Veriter C, Detry JMR, Brasseur L, Pouleur H. Impaired early left ventricular relaxation in coronary artery disease. *Circulation* 1980;**62:**764–72.

8 Thompson DS, Waldron CB, Juul SM, Naqvi N, Swanton RH, Coltart DJ, Jenkins BS, Weff-Peploe MM. Analysis of left ventricular pressure during isovolumic relaxation in coronary artery disease. *Circulation* 1982;**65:**690–7.

9 Tyberg JV, Parmley WW, Sonnenblick EH. *In-vitro* studies of myocardial asynchrony and regional hypoxia. *Circulation* 1969;**25:**569–79.

10 Meester GY, Bernard N, Zeelenberg C, Brower RW, Hugenholtz PG. A computer system for real time analysis of cardiac catheterization data. Catheterization and *Cardiovasc Diagnosis* 1975;**1:**112–23.

11 Meester GT, Zeelenberg C, Bernard N, Gorter S. Beat to beat analysis of cardiac catheterization data. Computers in Cardiology. Publ. IEEE Computer society, Los Angeles, 1974: 63–5.