The Role of Inotropic Variation in Ventricular Function during Atrial Fibrillation

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ABSTRACT A series of experiments were performed upon intact anesthetized dogs to determine the relevance of a variety of hemodynamic variables to the irregular ventricular performance associated with atrial fibrillation. During experimentally induced atrial fibrillation central aortic pulse pressure was measured in relation to the duration of the preceding diastolic interval, the relative degree of cycle-length change, the magnitude of the preceding aortic end-diastolic pressure, the rate of ventricular tension development (at a fixed diastolic tension), and to ventricular end-diastolic pressure. While all of the latter variables bore a significant relation to the chosen parameters of ventricular function, the most linear correlation lay with the rate of ventricular tension development. It has been suggested, as a consequence, that the irregular ventricular performance observed during atrial fibrillation under these experimental conditions, may be more directly related to variation in the inotropic state of the ventricular myocardium than to an expression of the Frank-Starling concept, resulting from variable ventricular filling. The lability of the inotropic or contractile state has in turn been attributed to abrupt cycle-length change effecting inotropic alteration analogous to postextrasystolic potentiation of contractility and, at rapid rates, effecting an alternation of the contractile state.

INTRODUCTION

The strength of ventricular contractions varies markedly in the presence of atrial fibrillation with normal atrioventricular (A-V) conduction (1–7). This variation is manifested by wide fluctuations in systolic pressure, pulse pressure, and, often, by an apical/radial "pulse deficit." And the basis for the phenomenon has been a subject of considerable interest since the description of the arrhythmia by Lewis (8) in 1912. In general, it has been suggested that the variation in ventricular function is the consequence of the variable diastolic filling interval (1–7); the more forceful ventricular contractions terminate the longer diastolic periods. Einthoven and Korteweg (1), in 1915, concluded that the lower aortic diastolic pressure after the longer diastolic filling period permitted a more forceful ventricular contraction. Other investigators (4–7) have suggested that the association of long diastolic periods with more forceful contraction is attributable to the Frank-Starling phenomenon; a longer diastolic interval permits greater filling and a larger end-diastolic volume, from which a more forceful ventricular contraction ensues. Also invoked (5) has been a direct correlation between end-systolic "volume" and the height of the succeeding pressure pulse. In this manner, a more forceful contraction yields a smaller end-systolic volume from which ventricular filling is initiated during the subsequent diastole. Conversely, a weak contraction leaves a greater end-systolic volume. Thus, the subsequent end-diastolic volume may vary independently of the duration of the diastolic filling period per se. This latter hypothesis is also in accord with the Frank-Starling mechanism, suggesting that the variation in ventricular function during atrial fibrillation is a function of both end-systolic residual volume and diastolic filling volume and, hence, of variable left ventricular end-diastolic volumes.

The possible role of variation in the contractile or inotropic state of the myocardium has not been considered in these postulations, however. If inotropy is defined in terms of the velocity of shortening of the contractile elements (9) (enhanced by digitalis, catecholamines, calcium, etc.), there is reason to anticipate that alteration in the intensity of the inotropic state, from beat to beat, may be of significance in relation to the

Received for publication 10 June 1969 and in revised form 27 October 1969.

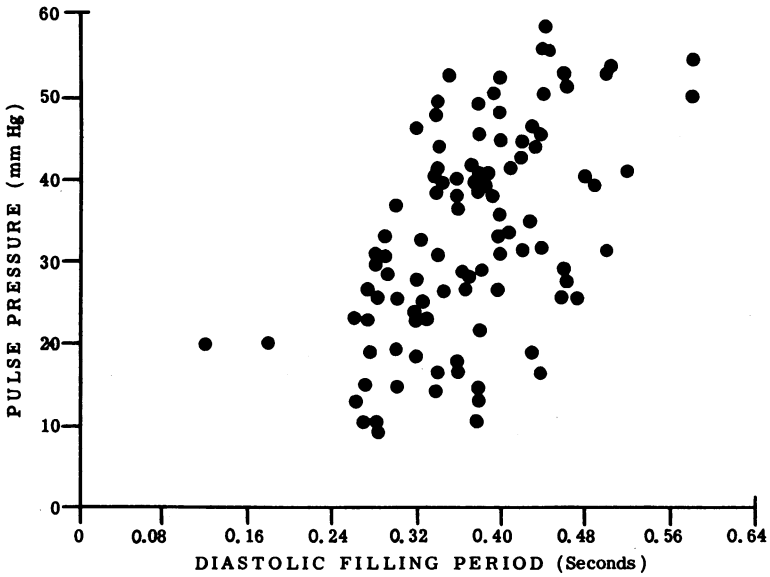

FIGURE 1 This graph relates the duration of the diastolic filling period (in seconds), to the magnitude of the subsequent pulse pressure, during the course of artial fibrillation with an irregularly irregular ventricular response. A direct relation is apparent among 100 consecutive observations. Correlation coefficient, $r = 0.532$, $P < 0.001$.

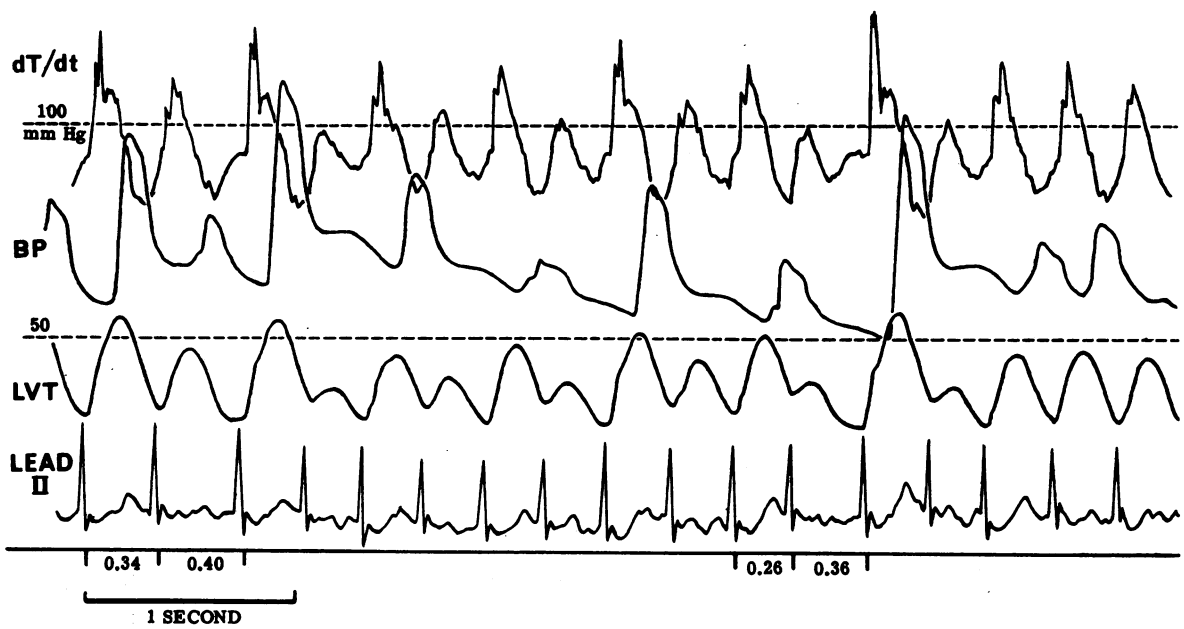

FIGURE 2 This recording illustrates the nature of the relation depicted in Fig. 1. The two more forceful contractions (the 3rd and 13th in the tracing) terminate the two longest diastolic periods, but the stronger of the two (reflected by the pulse pressure, tension recording, and dT/dt of ventricular tension) succeeds the shorter of the two diastolic periods (0.36 sec, as opposed to 0.40 sec). However, the shorter of the two intervals is more prolonged in relation to the preceding diastole (i.e., $0.36/0.26 = 1.39$; while $0.40/0.34 = 1.18$). Lead II indicates a conventional lead II electrocardiogram, and LVT indicates left ventricular tension development.

An alternation of left ventricular tension developed after the first of the two strong contractions on the recording. After the diastolic period labeled 0.40 sec, the next five contractions alternate in intensity in spite of virtually unchanging diastolic intervals. The rate of contractile shortening (dT/dt) also alternates during this interval. See text for discussion.

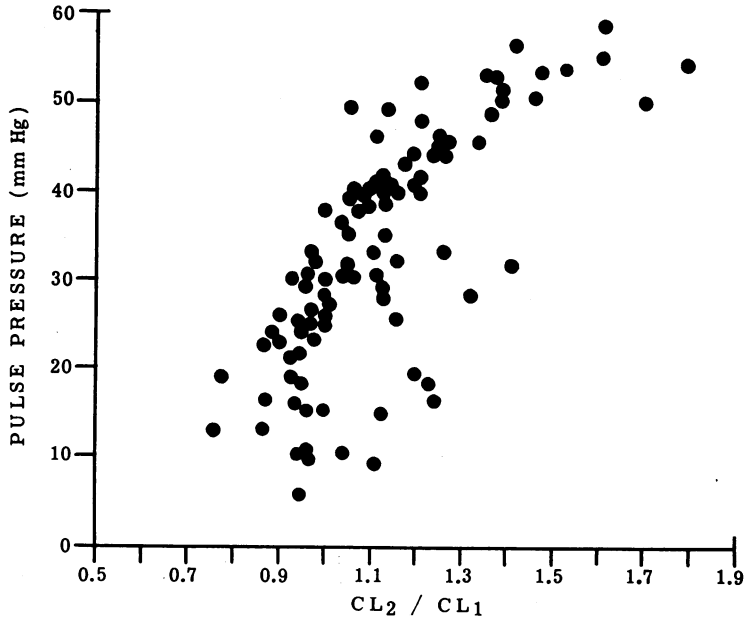

FIGURE 3 The relationship between abrupt cycle-length change and the subsequent pulse pressure development is shown here. These data were obtained from the same events described in Fig. 1. CL_2 refers to the cycle-length immediately preceding the systolic contraction to be assessed (here, in terms of pulse pressure development); CL_1 denotes the duration of the *previous* cycle-length. Thus, CL_2/CL_1 signifies the *relative* length of the diastolic interval or cycle-length preceding the systole in question. A direct relation exists between the relative degree of cycle-length prolongation and the amplitude of the succeeding pulse pressure. Correlation coefficient, $r = 0.730$, $P < 0.001$.

irregular stroke volume and pulse pressure encountered in the presence of atrial fibrillation. Alteration in the intensity of contractile performance, associated with cycle-length alteration and occurring independently of resting fiber length or tension, has been described by many observers (10–12). Accordingly, a study was initiated to assess the possible role of variation in the inotropic state as a source of the irregular ventricular performance in the presence of atrial fibrillation.

METHODS

10 adult mongrel dogs (5 of either sex) were anesthetized with sodium pentobarbital (4 mg/kg intravenously) and subjected to thoracotomy. A Walton-Brodie strain gauge arch was sewn upon the free wall of the left ventricle in a base-axis orientation, and stretched to 50% beyond the resting length of the underlying muscle in order to preclude the contribution of a variable venous return to tension development (13). Subsequent changes in the rate of tension development are thus considered to reflect primary alterations in the velocity of contractile shortening or inotropic state, since variation in the resting fiber length is no longer a factor (diastolic tension remains constant even in highly magnified recordings). The corresponding intraventricular pressure was recorded from a catheter inserted into the appropriate ventricle via direct puncture of the isolateral atrium. In five studies, left ventricular wall tension was recorded with aortic blood pressure (from a retrograde femoral arterial catheter). In five other experiments, left ventricular wall tension, aortic blood pressure, and left ventricular pressure were recorded. A conventional lead II electrocardiogram was recorded in each experiment. Atrial fibrillation was produced in one of two ways: electrical stimulation of the distal, cut end of the isolated right vagal nerve, followed by mechanical stimulation of one or the other atrium; or by the focal application of acetylcholine to one or the other atrium. Atrial fibrillation characteristically ensued with an irregularly irregular ventricular response, for periods varying from 30 sec to 15 min, before spontaneous reversion to sinus rhythm.

RESULTS

The relation of aortic pulse pressure (an index of ventricular performance found to correlate closely with stroke volume [7]) to the duration of the preceding diastolic interval, in atrial fibrillation with an irregular ventricular response, is exhibited in Fig. 1. While there

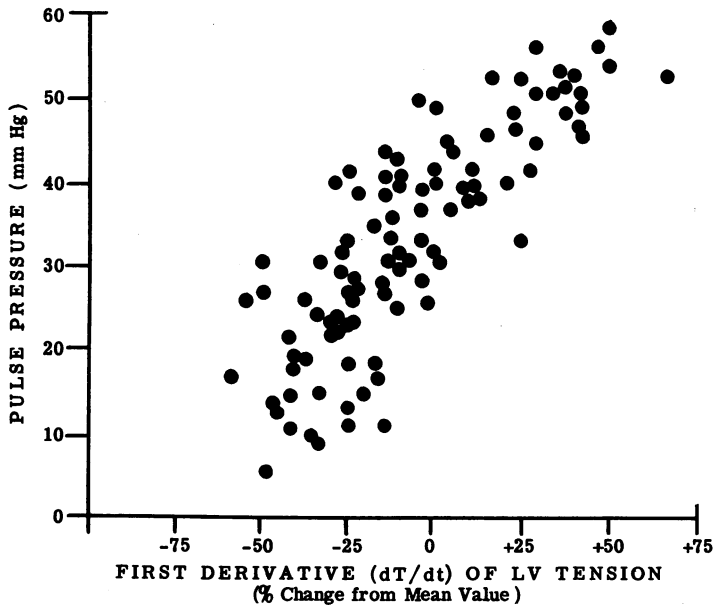

FIGURE 4 Utilizing data from the identical sequence depicted in Figs. 1 and 3, a correlation is revealed between the rate (dT/dt) of left ventricular tension development and the amplitude of the associated pulse pressure. Correlation coefficient, $r = 0.818$, $P < 0.001$. The rate (dT/dt) is expressed as a per cent change from a mean value for purposes of clarity; the actual figures (mm Hg/second) reflect tension development in a segment of left ventricle stretched 50% beyond its resting length, and are of little relevance per se.

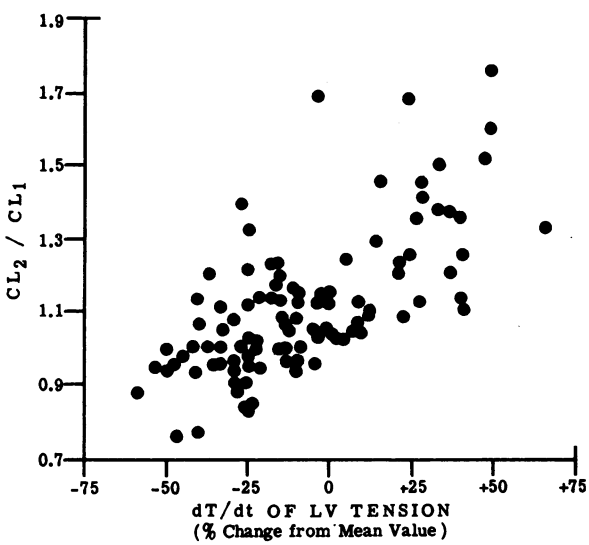

FIGURE 5 The rate (dT/dt) of left ventricular tension development is related to the relative length of the preceding cycle-length (i.e, CL_2/CL_1). Again, using the same data as in Figs. 1, 3, and 4, a significant correlation is present ($r = 0.688$, $P < 0.001$).

is a tendency for the pulse pressure to increase after the longer diastolic interval, there is a wide scatter of observed values (correlation coefficient, $r = 0.532$, $P < 0.001$). Fig. 2 presents a representative recording, illustrating the inconsistent relation of systemic pulse pressure to the duration of the preceding diastole. It is to be noted that the long diastolic filling interval is terminated by a more forceful contraction particularly when the long interval succeeds a short one (and in direct proportion to the ratio of the long interval/short interval).

The effect of abrupt cycle-length alteration upon ventricular performance is summarized in Fig. 3. A distinct correlation is noted here between the relative degree of cycle-length change and the magnitude of the pulse pressure produced by the succeeding systole. That is, the relatively prolonged cycle-length is terminated by a ventricular contraction yielding a widened pulse pressure; the relatively premature contraction, on the other hand, gives rise to a more narrow pulse pressure. As mentioned, a correlation is observed here ($r = 0.730$, $P < 0.001$) which is somewhat more linear (the significance of the differences, $P = 0.02$) than that ob-

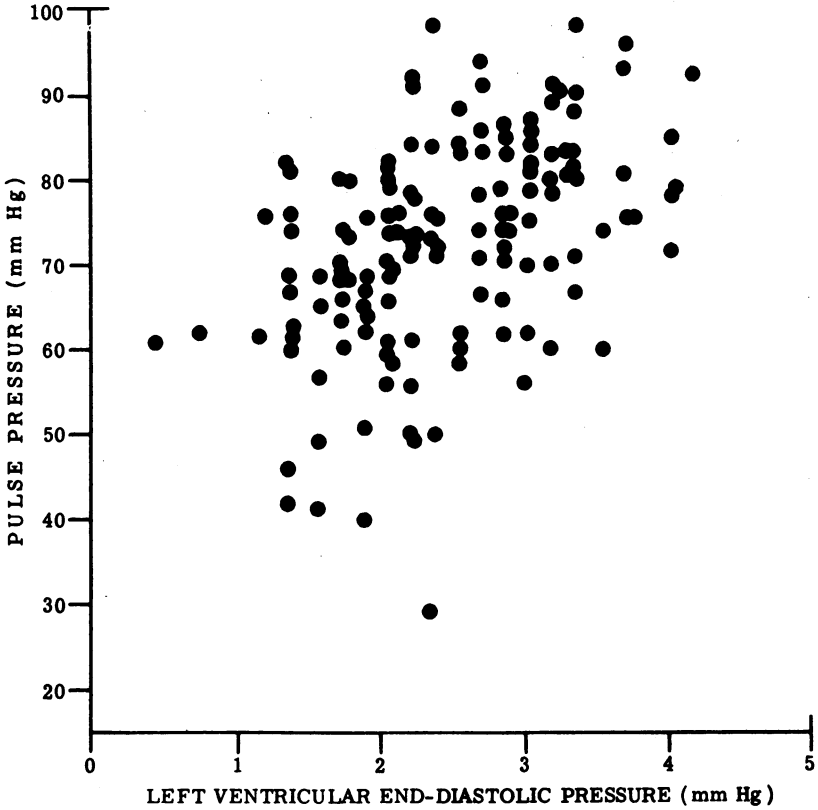

FIGURE 6 Data derived from a separate group of experiments, exhibiting 150 consecutive determinations (where end-diastolic pressure could be discerned with some degree of accuracy) reveal the relation between left ventricular end-diastolic pressure and the subsequent pulse pressure ($r = 0.450$, $P < 0.01$).

served in Fig. 1, although considerable scattering of the data occurs in this circumstance as well.

Using data derived from the same experiment from which Figs. 1–3 have been constructed, one finds a more precise correlation between the rate (dT/dt) of ventricular tension development (reflecting, here, variation in the intensity of the inotropic state) and the magnitude of the associated pulse pressure (Fig. 4, $r = 0.818$, $P < 0.001$). Thus, evidence has been provided which suggests that inotropic variation may in fact be of significance in determining the irregular ventricular performance associated with atrial fibrillation. This correlation is also significantly better ($P < 0.0002$) than that seen in Fig. 1, but does not differ significantly from that seen in Fig. 2 ($P = 0.12$). It is to be noted here that similar results were obtained in four additional experiments.

Assuming, furthermore, that this contractile variability may be interval-dependent in origin, we attempted to determine the relation, if any, of these parameters. A significant though not linear (correlation coefficient, $r = 0.688$, $P < 0.001$) relation of cycle-length alteration to the subsequent contractile response (as reflected by the first derivative of ventricular wall tension development) is shown in Fig. 5. That is, a cycle-length that is relatively prolonged (in relation to the prior cycle-length) is terminated by a contraction of enhanced vigor; in addition, the degree of contractile potentiation is directly related to the relative degree of cycle-length change. This phenomenon is analogous to the frequently recognized postextrasystolic, poststimulation, and rest potentiation of contractility. Conversely, a relatively abbreviated cycle-length (i.e. one which is shorter than the previous cycle-length) is terminated by a contraction which exhibits a depressed contractile state, and the more premature contraction is attended by an even greater depression of the contractile state. Another example of inotropic variation, also apparently interval-dependent, is illustrated in Fig. 2. Here, an alternation of contractile force occurs after the potentiated contraction terminating the diastolic interval labeled 0.40 sec. In spite of virtually unchanging diastolic intervals (the first interval is slightly longer but the rest remain unchanged), the next five contrac-

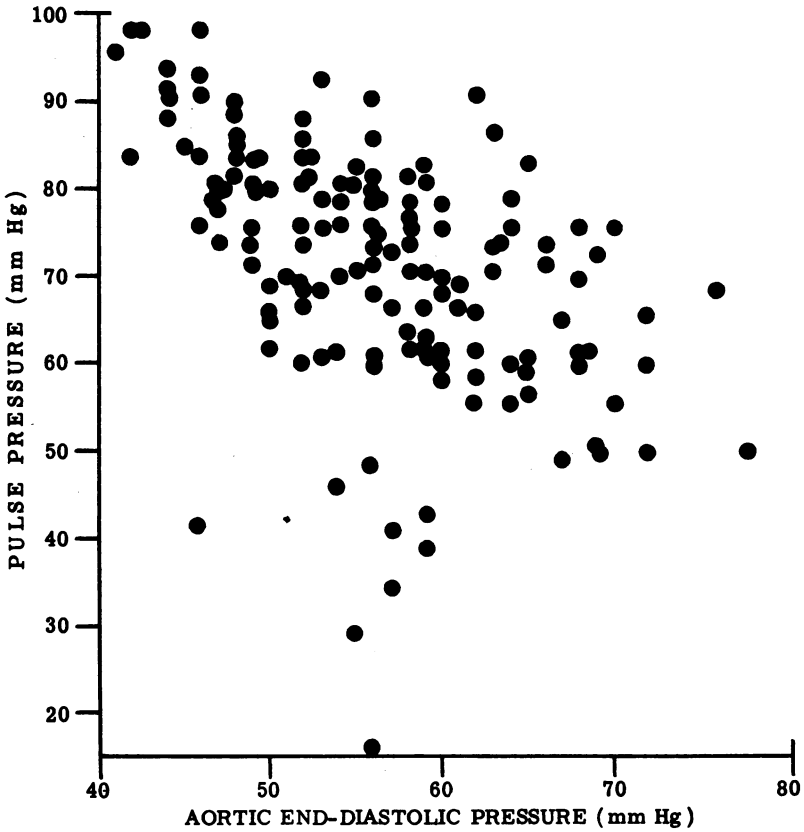

FIGURE 7 Here is demonstrated, from the same data recorded in Fig. 6, the relation between aortic diastolic pressure and the magnitude of the succeeding pulse pressure. An inverse correlation is present ($r = -0.521$, $P < 0.01$).

tions alternate in intensity. This sequence is analogous to mechanical alternans (12, 14), since it is precipitated by abrupt rate change and manifests an alternation of the inotropic state, reflected in the alternating rate of contractile shortening (dT/dt).

Another group of experiments was constructed to assess the relation of end-diastolic ventricular pressure (variation of which is presumed to reflect a variation in end-diastolic volume) to the pulse pressure of the subsequent ventricular contraction. These data are illustrated in Fig. 6. A direct correlation between these two parameters is present (correlation coefficient, $r = 0.450$, $P < 0.01$). In Fig. 7, the effect of after-load is considered. A negative correlation ($r = -0.521$, $P < 0.01$) is found between aortic diastolic pressure and the subsequent pulse pressure. Utilizing data from the same experiments, a more precise correlation (correlation coefficient, $r = 0.878$ ($P < 0.001$) is observed between the rate of ventricular tension development (as measured by the strain gauge) and the resultant pulse pressure. This association is demonstrated in Fig. 8. The relation of contractile state to pulse pressure variation is also significantly better ($P < 0.0002$) than either of the other two correlations (which do not differ significantly, one from the other). Fig. 9, in turn, exhibits a representative recording from the above experiment, in which disparities may be observed between end-diastolic ventricular pressure and the subsequent peak ventricular systolic pressure. Similar results were observed in four other experiments.

DISCUSSION

These data suggest that several factors must be considered to contribute to the variable pulse pressure encountered in the course of atrial fibrillation. And, while both the absolute duration of diastolic filling and the relative degree of cycle-length change correlate significantly with the subsequent pulse pressure, variation in the contractile state relates significantly better to this expression of variable ventricular function. Such a distinction, however, does not clearly assess the pertinence of the contractile state as opposed to ventricular filling volume; both diastolic filling intervals and cycle-length change bear some relation to interval-dependent

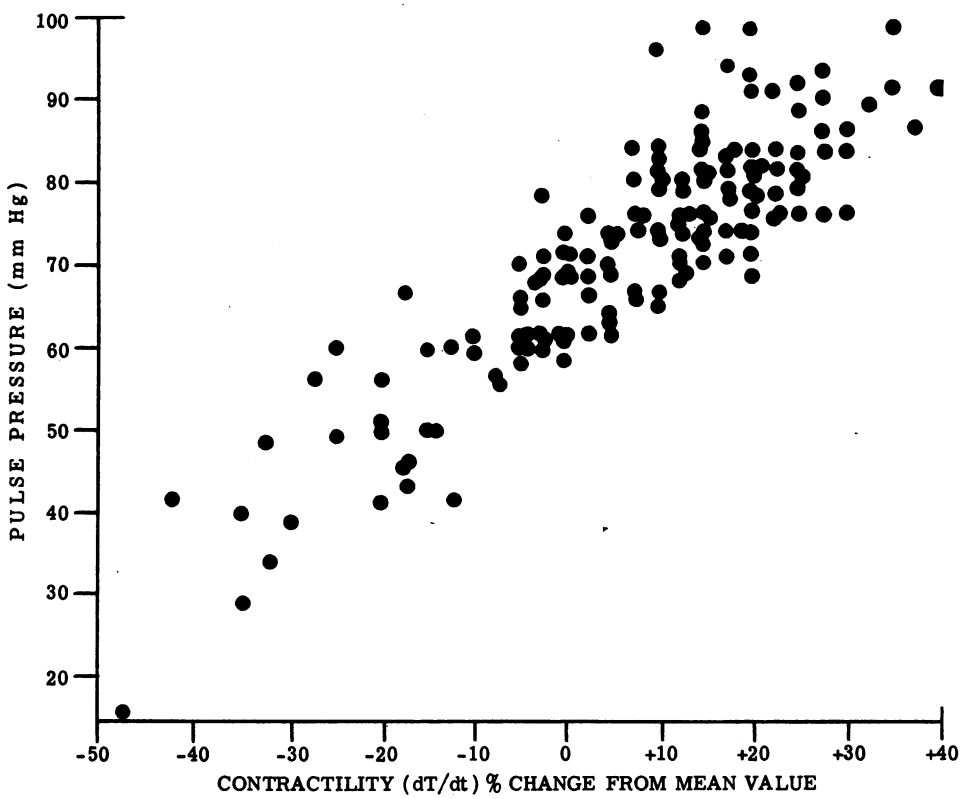

FIGURE 8 From the same events presented in Fig. 6, a closer correlation is found between pulse pressure and the concomitant rate (dT/dt) of left ventricular tension development ($r = 0.878$, $P < 0.001$).

contractile change as well. A more valid estimation of the relevance of contractile change as opposed to ventricular filling alteration lies in the study of ventricular end-diastolic pressure and the contractile state in relation to pulse pressure change. It appears from this latter study that variation in the contractile state may be a more significant determinant of ventricular function (as expressed by pulse pressure) than is end-diastolic pressure, in the course of atrial fibrillation. Variation in the after-load (aortic diastolic pressure), though associated with pulse pressure variation to some extent, is also a less significant determinant than is the contractile state. A fourth factor which one might also assume to be of pertinence here lies in variation of the duration of the active state. With highly irregular cycle-lengths, active state duration of succeeding contractions may vary to some extent (15), thereby limiting to a variable extent the expression of contractile force inherent to a given contractile state and diastolic volume. As the tension recordings were not actually isometric, however, it was felt that time-to-peak tension (TTP), with which active state duration correlates (16), could not be evaluated with sufficient precision to permit identification of subtle changes in TTP. In any case, the degree of linearity of the relation between contractile change and pulse pressure does not suggest that another qualifying factor greatly influenced this relation.

Thus, under these experimental conditions the variation in ventricular function (expressed by a variation in pulse pressure) appeared most closely related to variation in the contractile state. This scarcely permits one to conclude, however, that interval-dependent alterations in the contractile state constitute the principal or limiting factor under all circumstances. It may be anticipated for example, that the duration of ventricular filling may be far more critical in the presence of significant mitral stenosis, in which case a lesser proportion of diastolic filling may take place in early diastole. Such a consideration may explain the high correlation of pulse pressure with diastolic filling intervals in patients with mitral stenosis and atrial fibrillation, as reported by Braunwald, Frye, Aygen, and Gilbert (6). It has been reported (17–19), also, that digitalis tends to lessen the relative magnitude of interval-dependent contractile change; after augmentation of the basic contractile state, the muscle may be less capable of enhanc-

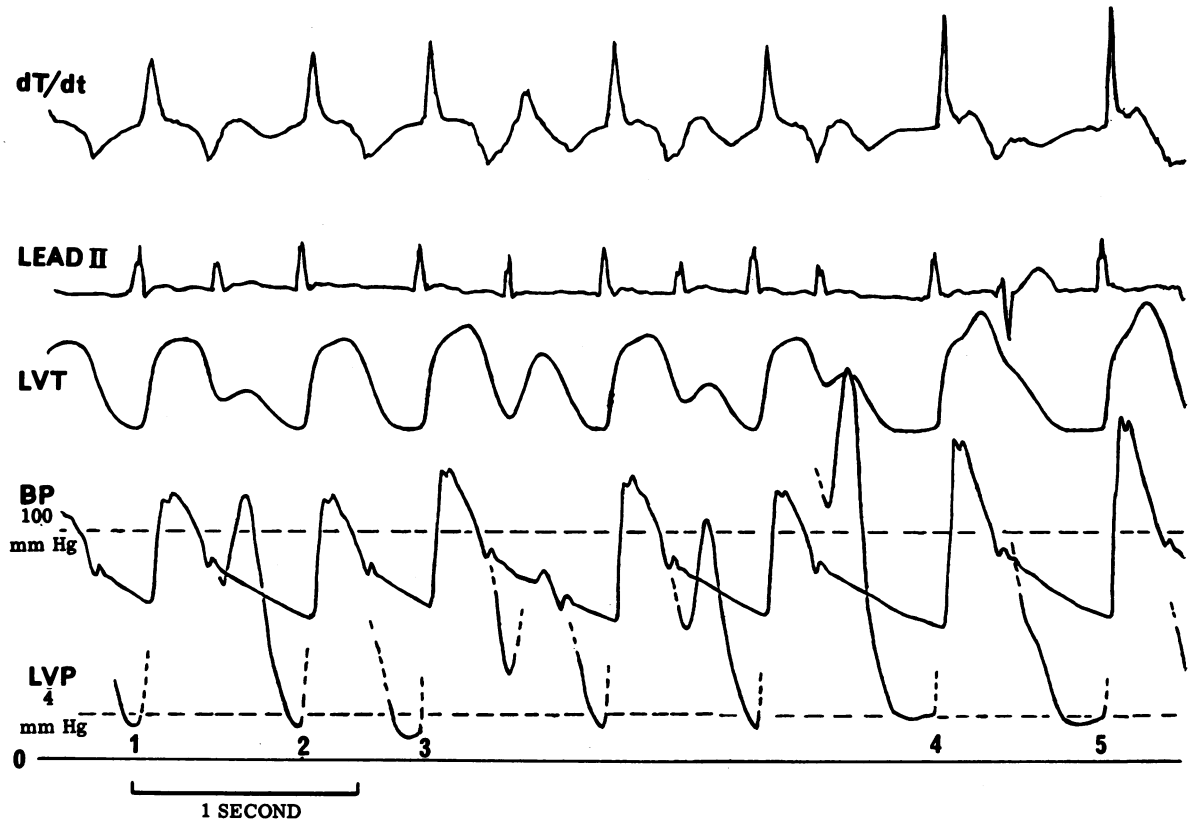

FIGURE 9 Disparities between end-diastolic pressure and the pulse pressure developed by the subsequent systolic contraction can be observed in this representative recording. In the recording of left ventricular pressure (LVP), five recordings of end-diastolic pressure are numbered at the bottom of the record (those circumstances where end-diastolic pressure is recorded accurately, not reflecting incomplete ventricular relaxation). The lowest end-diastolic pressure (No. *3*) precedes a pulse pressure exceeding that following Nos. *1* and *2*. End-diastolic pressure, No. *5*, preceding the largest pulse pressure, is less than that of No. *4*. Furthermore, the magnitude of dT/dt (the rate of ventricular tension development) correlates precisely with the associated pulse pressure. See text for discussion. LVP indicates left ventricular pressure. Calibration lines are drawn at 100 mm Hg blood pressure (BP) and 4 mm Hg LVP. The systolic portion of the LVP record has been deleted to clarify the figure. See Fig. 2 for the remainder of the legend.

ing its performance by interval-dependent means (assuming an ultimate "ceiling" to contractile performance). As a consequence, variation in ventricular function in atrial fibrillation may be less dependent upon interval-dependent contractile change when the myocardium is under the influence of the cardiac glycosides.

And, while abrupt cycle-length change is indeed attended by contractile alteration analogous to postextrasystolic potentiation and extrasystolic depression of contraction, a second temporal variable is to be considered in the description of the inotropic variation. Mechanical alternans, of variable duration and constituted by alternation of contractile state without relation to cycle-length change is commonly observed after abrupt rate change (12, 14). Other investigators (20) have, nevertheless, found mechanical alternans to be associated with alternating end-diastolic fiber lengths. And, while such an alternation in end-diastolic volume may well constitute a primary mechanism for pulsus alternans in some circumstances, an alternative explanation is offered here. It is suggested that an alternation of the contractile state, evoked by abrupt rate change, may well yield an alternation of end-diastolic volume. The more vigorous contraction would presumably leave a smaller end-systolic residuum while the weaker contraction would leave a larger end-systolic residuum. Thus, with unchanging diastolic filling intervals, one would anticipate that the smaller end-diastolic volume should precede the weaker contraction, while the larger end-diastolic volume should precede the stronger con-

traction of the alternans. As a consequence, it is suggested that mechanical alternans, in addition to the observed "postextrasystolic" contractile phenomenon, accounts in great part for the complex variation in inotropic state during the ventricular response to atrial fibrillation. Such interval-dependent contractile alterations appear to reflect an intrinsic property of myocardial tissue common to most mammalian species, for other studies (11) have shown that postextrasystolic potentiation is not dependent upon catecholamine stores or adrenergic innervation.

ACKNOWLEDGMENTS

This work was supported in part by the Herman C. Krannert Fund; U. S. Public Health Service Grants HE-6308, HTS-5363, and HE-5749; the Indiana Heart Association; and the American Medical Association Committee for Research on Tobacco and Health.

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