EUROPEAN JOURNAL OF CARDIOLOGY, 1978, 7/Suppl., 133—145

Postextrasystolic relaxation in the dog heart

Paulus J.P. Kuijer, Robert M. Heethaar, Johan N. Herbschleb, Ariaen N.E. Zimmerman and Frits L. Meijler

Department of Cardiology, University Hospital Utrecht, The Netherlands

KUIJER, P.J.P., HEETHAAR, R.M., HERBSCHLEB, J.N., ZIMMERMAN, A.N.E. and MEIJLER, F.L. (1978): Post-extrasystolic relaxation in the dog heart. *Europ. J. Cardiol., 7/Suppl., 133—145.*

Left ventricular relaxation was studied in 8 dogs using parameters derived from the left ventricular pressure: the fastest pressure fall and the time constant of pressure decline.

Effects of extrasystolic rhythm interventions were examined on the relaxation parameters of the post- relative to the preextrasystolic beat.

Postextrasystolic potentiation of these parameters could not be demonstrated. Possible influences of physiologic variables as peak left ventricular pressure, endiastolic aortic and enddiastolic left ventricular pressure on relaxation mechanisms were evaluated. The nonselective description of myocardial relaxation by pressure derived parameters is discussed.

relaxation; postextrasystolic potentiation; pressure derived parameters

Introduction

During an attack of angina pectoris, an elevated left ventricular enddiastolic pressure (PLVED) can be observed. This increment of PLVED can be explained by a failure of relaxation [1]. It is interesting and of clinical importance, that this disturbance in the relaxation process seems to manifest itself at an earlier stage in the disease than failure of contraction [2]. This is in agreement with previously reported experimental evidence that relaxation and contraction can be influenced separately [3].

Relaxation is an active energy-consuming process, which is dependent on oxydative phosphorylation. The energy needed is delivered by the aerobic mitochondrial system which supplies the contractile proteins (filaments) with the required high energy phosphates for their proper physiologic functioning [4]. Some authors suggest consequently that the basic physiologic processes underlying relaxation mechanisms are more sensitive to lack of

oxygen than the contraction process [5,6]. Since relaxation seems to be not a purely passive phenomenon, an inotropic intervention such as postextrasystolic potentiation might have an influence on relaxation as well [7,8].

In this study the effect of the postextrasystolic rhythm intervention on relaxation of the left ventricle of the dog heart has been investigated.

Methods

A. Animal preparations

All experiments were performed on 8 healthy 1 yr old beagles of either sex, Anesthesia was induced with penthotal (25 mg/kg body weight, i.v.) and maintained with 0.75% halothane. The dogs were intubated with a cuffed endotracheal tube and ventilated with a respiratory gas mixture, consisting of equal parts of O_2 and N_2O. During the experimental period, halothane percentage was adjusted to the depth of the anesthesia. Cathetertip manometers were introduced into the aorta ascendens through a femoral artery and into the left ventricle through a carotid artery. The maximum rate of pressure rise was used as contraction parameter and the maximum rate of pressure fall and the time constant (see Methods C) as relaxation parameters. Right atrial stimulation was effected with a bipolar electrode catheter introduced via a femoral vein and positioned near the sinus node.

B. Stimulation procedure and experimental set-up

To study postextrasystolic relaxation in a reproducible and controlled manner artificial atrial stimulation was applied resulting in normal ventricular excitation patterns and normal atrial contributions to ventricular filling [9]. To meet the prerequisite that the duration of the postextrasystolic RR interval is equal to the basic RR interval, the atrial stimulation pattern has been generated in such a way that changes in AV nodal conduction times due to the extrasystolic PP interval changes were compensated for. This has been achieved by using the experimental set-up, shown in Figure 1.

A test series of atrial stimulation pulses is generated and RR intervals are measured on line by a computer. In an iterative procedure AV nodal conduction changes are measured and finally atrial stimulation intervals corrected in such a fashion that the postextrasystolic RR interval is equal to the preextrasystolic cardiac cycle (Fig. 2). Stimulation series were composed of 20 basic stimuli, followed by an extrasystolic and postextrasystolic stimulus. Basic stimulation intervals were chosen in the range from 325 to 505 msec. Per stimulation series, 3 different extrasystolic intervals were generated: the shortest extrasystolic interval was selected by the operator, whereas the other extrasystolic beats were generated by computer by subdividing the time difference between basic and shortest extrasystolic interval in 3 equal parts. Shortest extrasystolic intervals varied from 265—365 msec.

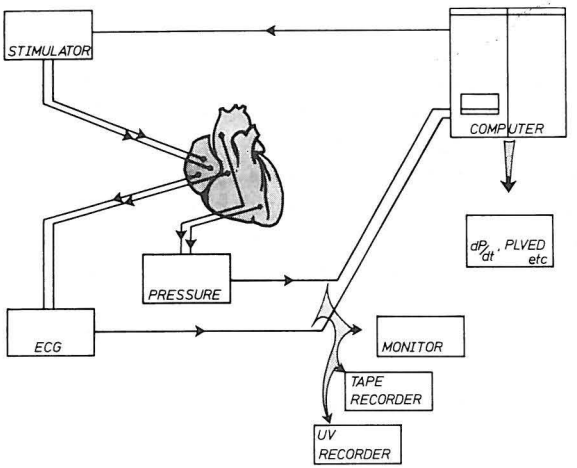

Fig. 1. Block diagram of the experimental set-up.

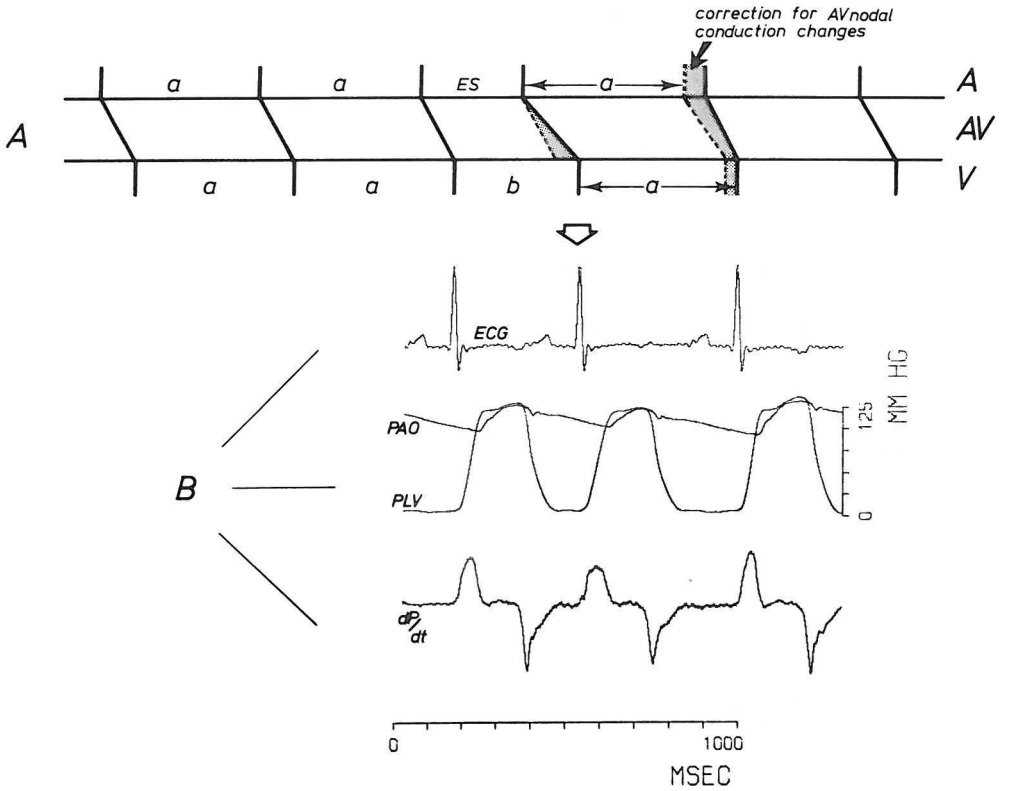

Fig. 2. Atrial stimulation sequence and RR intervals (A). Computer plots of left ventricular and aortic pressures and first derivative of left ventricular pressure (B).

C. Hemodynamic parameter analysis

During computer controlled atrial stimulation, electrocardiogram, stimulus artifact and left ventricular and aortic pressures were passed through analog filters of 25 Hz and digitized on line with a sample frequency of 400 Hz using a PDP-15/XVM computer. Calculations and derivations were made from the stored samples on magtape [10]. The statistical analysis of the differences between sets of parameters were tested with the Wilcoxon matched-pairs signed rank method. The first derivative of the signals has been determined by fitting a 4th degree polynomial through 5 consecutive sample points and calculating the first derivative in the midpoint; this procedure has been repeated for all samples.

The following hemodynamic parameters of pre- and postextrasystolic beats were studied (Fig. 3).

PLVED : left ventricular enddiastolic pressure (mm Hg) defined as the LV pressure at the moment the first derivative of the up-

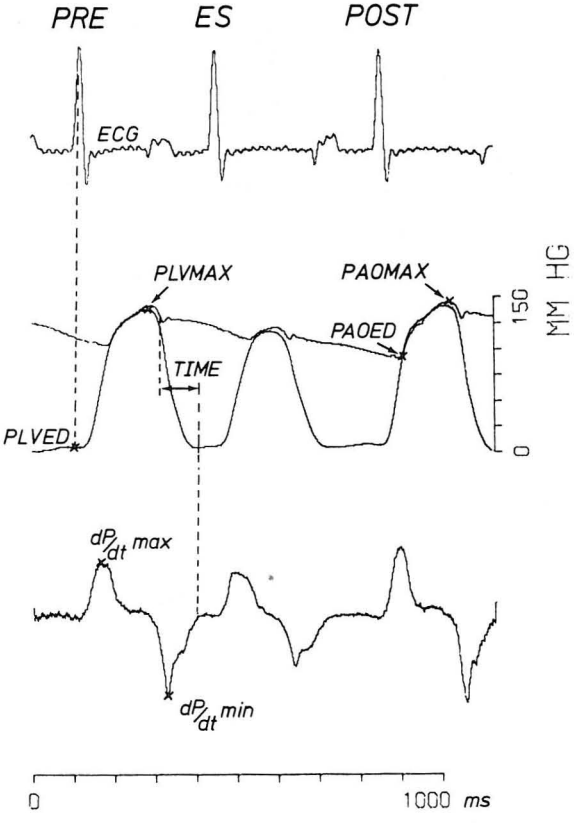

Fig. 3. Representation of the parameters used. For abbreviations see text.

stroke of the R wave reaches its maximum in lead II.

PLVMAX : peak value of left ventricular pressure (mm Hg).

PAOED : enddiastolic aortic pressure (mm Hg), defined as the pressure prior to the opening of the aortic valves.

dP/dt max : maximum value of the first derivative of the left ventricular pressure (mm Hg/sec).

dP/dt min : minimum value of the first derivative of the left ventricular pressure (mm Hg/sec).

Time constant: the left ventricular pressure decline can be fitted by the method of least squares to the function: $P(t) = Ae^{-t/\tau}$ in the period which begins 10 msec prior to the minimum of the first derivative of the ventricular pressure until the pressure has fallen below 25 mm Hg. The time constant is indicated by τ(msec).

TIME : the duration of the period which begins when aortic pressure and left ventricular pressure differ 10 mm Hg after the closure of the aortic valves until the first derivative of the left ventricular pressure reaches the 0 value (msec).

Results

Hemodynamic parameters PLVMAX, PAOED and PLVED

Parameters which reflect the contractile behavior of the heart: enddiastolic left ventricular and aortic pressure (PLVED, resp. PAOED) and maximum left ventricular pressure (PLVMAX) which might influence also cardiac relaxation, are listed in Figure 4 for a single experiment. No significant dif-

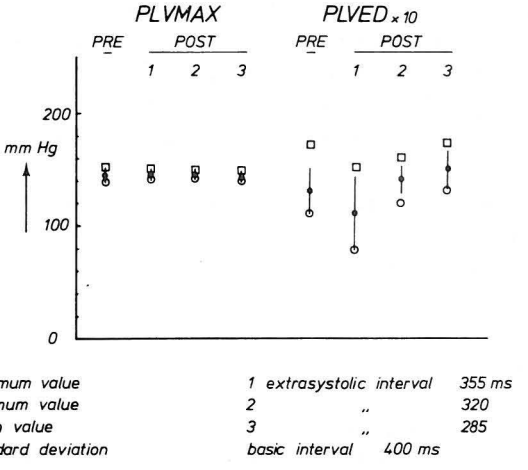

Fig. 4. Minima, maxima, means and SD of PLVED and PLVMAX of pre- and postextrasystolic beats.

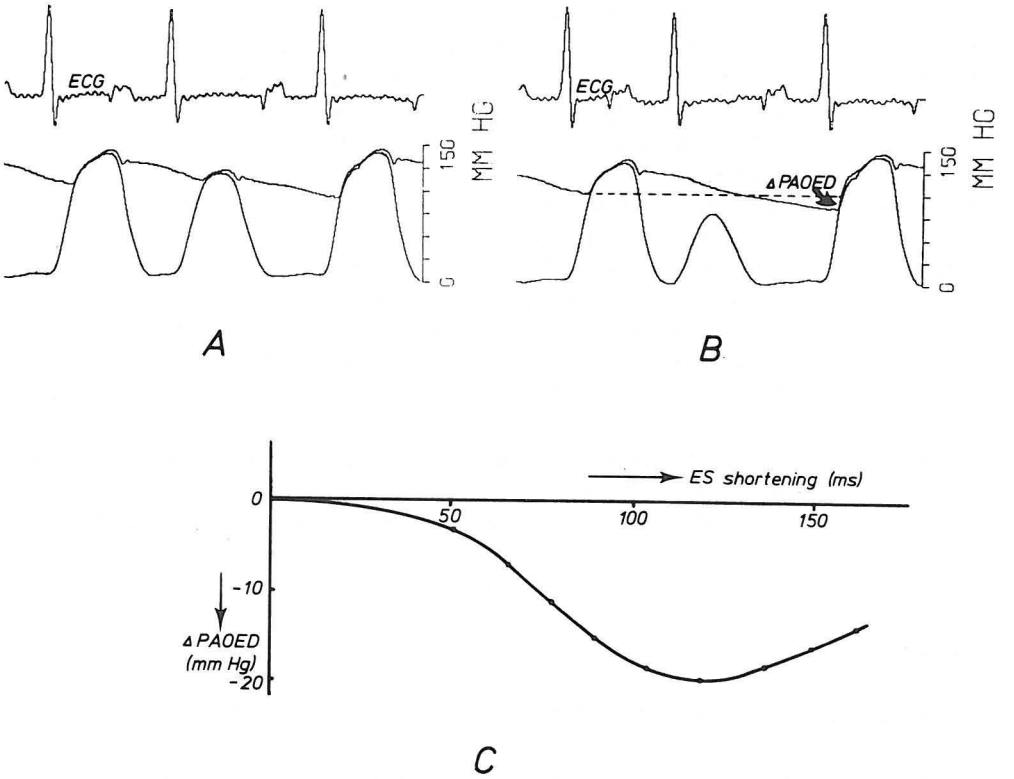

Fig. 5. Computer plots of left ventricular and aortic pressure when the aortic valves open (A) and (B) if not. Difference in post- and preextrasystolic PAOED versus extrasystolic shortening (C).

ferences could be found at a confidence level of 5% between PLVED and also for PLVMAX of pre- and postextrasystolic beats. A typical example of a computer plotted recording is demonstrated in Figure 5. Figure 5C shows that the course of the postextrasystolic PAOED as referred to the preextrasystolic PAOED depends largely upon the degree of shortening of the extrasystolic interval.

In Figure 6 it can be seen that measurements with artifical ventilation temporarily switched off, showed no difference with repect to PLVED of pre- and postextrasystolic beats for 2 experiments.

Relaxation parameter (dP/dt min)

In Figure 7, values of the fastest pressure rise dP/dt max and the fastest pressure fall dP/dt min have been plotted for a representative experiment as a function of the extrasystolic shortening relative to the basic interval. No potentiation of the postextrasystolic dP/dt min, the relaxation parameter,

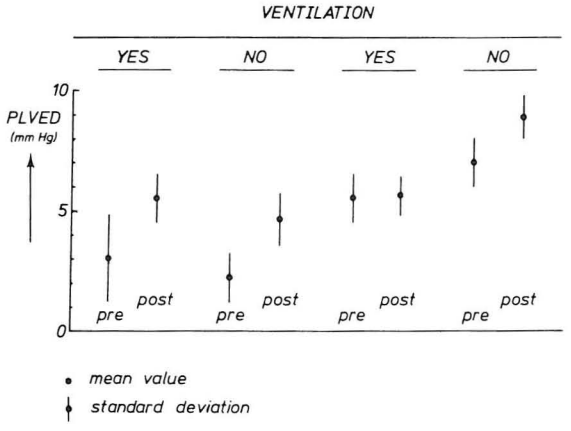

Fig. 6. PLVED measurements with and without artificial respiration.

could be demonstrated. Other experiments gave the same results: strongly potentiated dP/dt max and no potentiation of dP/dt min.

In Figure 8, an overall impression of all 12 series is given by the regression lines of the data of contraction and relaxation. For the relaxation parameter no significant difference with slope zero could be demonstrated for all lines. Scattering of the measured points per experiment were in the same order of magnitude as for the experiment shown in Figure 7.

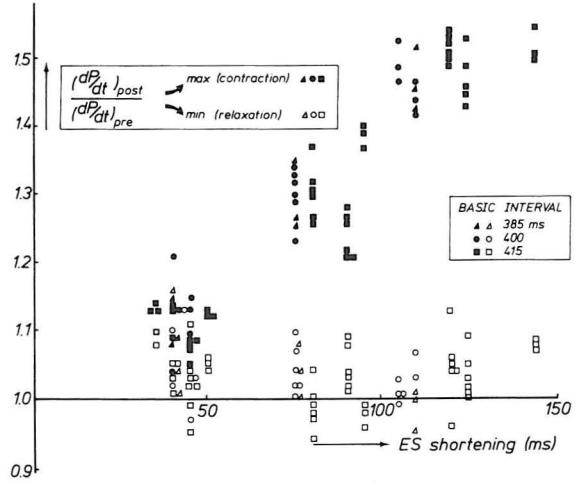

Fig. 7. (dP/dt max) and (dP/dt min) of the postextrasystolic beat related to the preextrasystolic beat versus extrasystolic interval shortening.

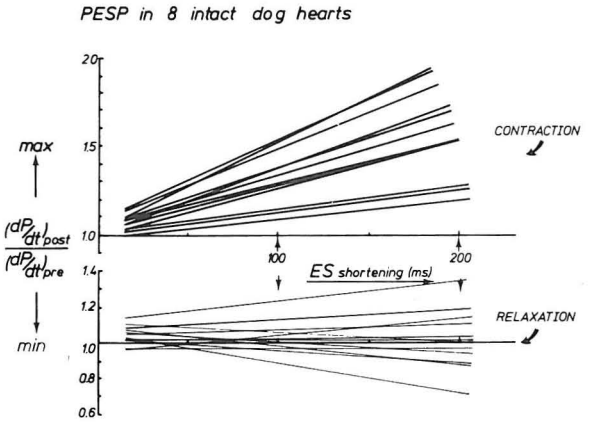

Fig. 8. Regression lines of 12 stimulation series of 8 dogs of (dP/dt max) and (dP/dt min) of the postextrasystolic beat related to the preextrasystolic beat at different ES shortenings.

Relaxation parameter (time constant)

In Figure 9, a typical phase plot is given of dP/dt/P versus PLV. The time interval starting at 10 msec prior to the moment when the first derivative of the left ventricular pressure reaches its minimum and ending when the left ventricular pressure falls below 25 mm Hg is indicated by the dashed segment.

For this period the pressure is fitted by an exponential curve $Ae^{-t/\tau}$ in which τ represents the time constant. These experiments show that no signi-

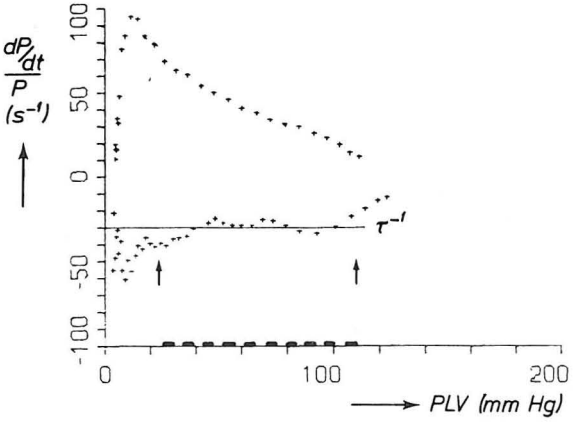

Fig. 9. Computed phase plot of dP/dt/P versus P. The dashed segment on the horizontal axis indicates the interval over which the time constant has been calculated. Time interval between plotted points is 2.5 msec.

TABLE I Cross-correlations

Experiment	1	2	3	4	5	6	7	8	9	10	11	12
$PLVMAX_{post}$	−0.16	−0.63	−0.84	−0.30	−0.27	−0.50	−0.72	−0.35	−0.61	−0.71	−0.92	−0.78
$dP/dt\ min_{post}$	NS	S	S	NS	NS	S	S	NS	S	S	S	S
$dP/dt\ max_{(post-pre)}$	−0.73	−0.88	−0.93	−0.89	−0.76	−0.97	−0.78	−0.87	−0.84	−0.88	−0.94	−0.69
$PAOED_{(post-pre)}$	S	S	S	S	S	S	S	S	S	S	S	S
$PLVMAX_{pre}$	0.71	0.82	0.52	0.72	0.75	0.29	0.93	0.20	0.85	0.95	0.96	0.99
$PAOED_{pre}$	S	S	S	S	S	S	S	NS	S	S	S	S

NS = not significant at 5% confidence level; S = significant.

ficant change in postextrasystolic time constant occurs due to extrasystolic shortening.

Interrelationships of parameters

In the experiments slight variations between the parameters of the preextrasystolic beats were found as was the case for the postextrasystolic beats (Fig. 4). In an attempt to find a relationship between relaxation and pressure parameters cross-correlations between $PLVMAX_{post}$ and $(dP/dt\ min)_{post}$, between $dP/dt\ max_{(post-pre)}$ and $PHOED_{(post-pre)}$ and finally between $PLVMAX_{pre}$ and $PAOED_{pre}$ have been calculated. In Table I, the different correlation coefficients are presented. It can be seen that dP/dt min is correlated with PLVMAX in most experiments.

Discussion

The description of the sequence of changes in mechanical events of the cardiac cycle are based upon Wiggers' classical diagram [11]. The onset and termination of the reduced ventricular ejection phase are less well defined than the beginning of ventricular systole. Prior to the isovolumic relaxation phase is the protodiastole during which the semilunar valves become approximated by a retrograde flow of blood, resulting in the beginning of the relaxation: closure of the aortic valves. The relaxation of the left ventricle in the intact circulation lasts until the opening of the mitral valves. During this period, relaxation takes place in such a fashion that besides the change in shape of the left ventricle also volume alters in spite of the generalized accepted description: isovolumic relaxation phase [12].

Relaxation indexed by the parameters dP/dt min and the time constant did not change by the positive inotropic extrasystolic rhythm intervention.

The 2 hemodynamic variables PLVED and PLVMAX demonstrate also no extrasystolic interval dependency in the postextrasystolic beat. The contraction parameter, dP/dt max, and the enddiastolic aortic pressure of the postextrasystolic beat did, on the contrary, depend on the extrasystolic interval. A similar relationship between extrasystolic interval shortening and contraction height of the postextrasystolic beat has been found in isolated rat hearts [7], as well as in isolated dog hearts. As outlined in Figure 7, the postextrasystolic dP/dt max increases in proportion to shortening of the extrasystolic interval; the inverse relationship exists for the postextrasystolic PAOED and the extrasystolic interval, providing the extrasystolic interval is not so short that the aortic valves remain closed (Fig. 5).

In an attempt to explain the nonreactivity of the relaxation process to the postextrasystolic rhythm intervention a few possible reasons will be discussed.

At first, starting from the principle that relaxation of the heart is determined by passive and active factors, we might assume that possible potentiation of the active components is masked by the absorptive power of the elastic recoil of structures as the connective tissue within the myocardium, the fibrous tissue of the cardiac valves, the elastic properties of intracellular substances, the membranes of the cells and the coupling between these elements. The active phenomenon is composed of the bonds formed between the contractile proteins, susceptible to a modulation on a beat-to-beat basis, achieved by an alteration in the calcium delivery to these proteins caused by the applied rhythm intervention. As McLaurin et al. hypothesized, it is likely that this part of the myocardial relaxation is responsive to a positive inotropic intervention rather than the mechanical elastic system [1]. The mechanical buffer capacity due to the elastic recoil of the tissue may conceal the possibly present potentiation of relaxation in the parameters we used.

A second reason that places the results in a clear view arises from the fact that the relaxation parameter dP/dt min is for the greater part determined by the magnitude of the PLVMAX [13]. Figure 4, derived from a representative experiment, shows that no potentiation of PLVMAX can be demonstrated. Since dP/dt min is closely related to the PLVMAX, dP/dt min does not show a relationship with extrasystolic shortening. To comment on PLVMAX of the postextrasystolic beat and its extrasystolic interval independency, using a postextrasystolic pause equal to the basic RR interval, it seems a reasonable assumption to state that the basic determinants for the PLVMAX are the dP/dt max and the PAOED. The more the extrasystolic interval shortens, the clearer the opposite effects of the two mentioned variables as seen in Figure 5.

The correlation studies shown in Table I, give evidence for these interrelationships in which dP/dt max and PAOED counteract their respective influences on PLVMAX. The possible role of the difference in PLVED of post- and preextrasystolic beats has been considered of minor importance, in spite of the fact that this difference in 7 of the 12 experiments was found significant, the biggest difference, however, amounting not more than 1.6 mm Hg. Variation in basic intervals makes no difference in the extrasystolic interval dependency of the 6 hemodynamic variables of the postextrasystolic beat studied. Weiss et al. [14] made clear, however in a different experimental set-up, that the time constant appears grossly dependent on the rate of systolic fiber shortening. In our studies we are not informed about this parameter. However, we know from as yet unpublished observations by Van der Werf [15], that in patients studied with this stimulation technique, no significant difference in left ventricular enddiastolic volumes between the pre- and postextrasystolic beats was found while, as could be expected, there was a striking difference between the left ventricular endsystolic volumes of the 2 beats, the postextrasystolic left ventricular endsystolic volume being approximately 30% smaller. This implies a considerably increased fiber shortening of the postextrasystolic beat. The fibers return to the same diastolic length in more or less the same time, but coming from a different

endsystolic fiber length. Thus the rate of fiber lengthening during postextrasystolic relaxation should, in those cases in which there is no change in the relaxation period (TIME, see Methods C) between pre- and postextrasystolic beats, be greater than during preextrasystolic relaxation. An experimental support for this reasoning can be found in the restoring forces as demonstrated by Brutsaert et al. [16]. As a final consideration it is therefore desirable to make some critical notes about the exact reflection of relaxation by the left ventricular pressure-derived parameters we used. Both relaxation parameters have the disadvantage of reflecting global relaxation of the entire left ventricle instead of presenting selectively muscle relaxation.

A more realistic view implicits that relaxation is an asynchronous process which probably takes place nonuniformly in the different parts of the myocardium. Filling and dynamic regional geometry of the heart chambers play an essential role in this opinion [17].

Summarizing, we may conclude that continuation of relaxation studies in the intact heart needs supply of local relaxation parameters including wall thickness and axial dimensions as well as more insight in fiber length behavior.

Acknowledgement

The authors wish to thank Dr. F.L. Lindemans for his critical remarks.

References

[1] Grossman, W. (1978): Evidence for impaired myocardial relaxation during acute ischemia in man. *Europ. J. Cardiol., 7/Suppl.*, 239.

[2] McLaurin, L.P., Rolett, E.L. and Grossman, W. (1973): Impaired left ventricular relaxation during pacing-induced ischemia. *Amer. J. Cardiol., 32*, 751.

[3] Parmley, W.W. and Sonnenblick, E.H. (1969): Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Amer. J. Cardiol., 216*, 1084.

[4] Katz, A.M. (1977): Physiology of the heart. Raven Press, New York.

[5] Amende, I., Coltart, D.J., Krayenbuehl, H.P. and Rutishauser, W. (1975): Left ventricular contraction and relaxation in patients with coronary heart disease. *Europ. J. Cardiol., 3/1*, 37.

[6] Amende, I., Coltart, D.J. and Rutishauser, W. (1975): Contraction and relaxation phase in coronary heart disease measured by pressure-derived parameters. In: *Coronary Angiography and Angina Pectoris*, p. 161. Symposium of the European Society of Cardiology, Hannover.

[7] Meijler, F.L., Van de Bogaard, F., Van der Tweel, H. and Durrer, D. (1962): Postextrasystolic potentiation in the isolated rat heart. *Amer. J. Cardiol., 202*, 631.

[8] Van der Werf, Tj., Van Poelgeest, R., Herbschleb, J.N. and Meijler, F.L. (1976): Postextrasystolic potentiation in man. *Europ. J. Cardiol., 4/Suppl.*, 131.

[9] Van Poelgeest, R., Herbschleb, J.N., Van Schaik, R., Van der Werf, Tj., Woudstra, B. and Meijler, F.L. (1976): A closed loop patients-computer-patient system for cardiac studies. *Digest 11th International Conference on Medical and Biological Engineering, Ottawa.*

[10] Herbschleb, J.N., Van der Werf, Tj. and Van Poelgeest, R. (1976): Off-line calculation and presentation of haemodynamic parameters. *Proceedings of Computers in Cardiology*, p. 353, Washington Univ., St. Louis, Mo.
[11] Wiggers, C.J. (1949): The sequence of cardiodynamic events. In: *Physiology in Health and Disease, 5th ed.*, p. 651. Lea and Febiger, Philadelphia, Pa.
[12] Ruttley, M.S., Adams, D.F., Cohn, P.F. and Abrams, H.L. (1974): Shape and volume changes during 'isovolumetric relaxation' in normal and asynergic ventricles. *Circulation, 50*, 306.
[13] Weisfeldt, M.L., Scully, H.E., Frederiksen, J., Rubenstein, J.J., Pohost, G.M., Beierholm, E., Bello, A.G. and Daggett, W.M. (1974): Haemodynamic determinants of maximum negative dP/dt and periods of diastole. *Amer. J. Physiol., 227*, 613.
[14] Weiss, J.L., Frederiksen, J.W. and Weisfeldt, M.L. (1976): Haemodynamic determinants of the time course of fall in canine left ventricular pressure. *J. clin. Invest., 58*, 751.
[15] Van der Werf, Tj. (1977): Unpublished data.
[16] Brutsaert, D.L., De Clerck, N.M., Goethals, M.A. and Housmans, P.R. (1978): Mechanisms of relaxation in isolated cardiac muscle. *Europ. J. Cardiol., 7/Suppl.*, 71.
[17] Cohn, P.F., Liedtke, A.J., Serur, J., Sonnenblick, E.H. and Urschel, C.W. (1972): Maximal rate of pressure fall (peak negative dP/dt during ventricular relaxation). *Cardiovasc. Res., 6*, 263.

Reprint requests to: Paulus J.P. Kuijer, Department of Cardiology, University Hospital, 101 Catharijnesingel, Utrecht, The Netherlands.