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Afterload induced changes in myocardial relaxation: A mechanism for diastolic dysfunction

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Abstract

Background: Diastolic left ventricular (LV) dysfunction manifests as an upward shift of the diastolic pressure–volume relation. One of the possible causes of diastolic LV dysfunction is incomplete myocardial relaxation. It is well known that high afterload slows myocardial relaxation. This contribution investigated to what extent afterload elevation could also affect LV filling pressures including end-diastolic LV pressure (LVP). **Methods:** Selective, beat-to-beat elevations of afterload were induced in anaesthetised open-chest rabbits ($n=9$) by abrupt narrowing of the ascending aorta during the diastole of the preceding heartbeat. This was performed with physiological heart rate and blood pressure. **Results:** These interventions increased systolic LVP from 90±3 mm Hg at baseline to 103±4, 123±5, 139±5 and 154±6 mm Hg. The last intervention was a total aortic occlusion inducing a first beat isovolumetric contraction. Smaller afterload elevations decreased τ (accelerated LVP fall) and did not elevate diastolic pressure-internal diameter relation (P-ID). Larger afterload elevations increased τ (decelerated LVP fall), induced an upward shift of the diastolic P-ID and increased end-diastolic LVP. Effects of afterload on end-diastolic LVP were correlated with effects on τ ($r=0.89$; $P<0.01$). Incomplete relaxation or load-dependent residual active state appeared to be the mechanism for this diastolic dysfunction. Similar findings were made retrospectively in dogs instrumented with circumferential segment length gauges ($n=16$). **Conclusions:** Diastolic LV dysfunction was induced by elevated afterload in healthy hearts of rabbits and dogs. If this mechanism could be shown to be operative in the failing heart, reversal of diastolic dysfunction should contribute to the beneficial effects of vasodilating and inotropic therapy on pulmonary congestion. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Experimental; Heart; Pathophysiology; Afterload; Diastole; Heart failure; Hemodynamics; Ventricular function

1. Introduction

When systolic dysfunction of the heart occurs, elevated filling pressures are due to a shift along an unchanged end-diastolic pressure–volume relation [1]. This can be observed in the supply type of ischemia, such as in the acute myocardial infarction [2]. Diastolic dysfunction corresponds to an upward displacement of the end-diastolic pressure–volume relation, with a higher pressure at any volume [3]. Diastolic dysfunction is typically present in angina pectoris [2], in LV hypertrophy [4] and in the demand type of ischemia, for example in stress induced angina pectoris [2].

Diastolic LV properties are determined by: (i) structural and geometric changes of the ventricular wall; (ii) extraventricular causes, including pericardial constraint, right–left ventricular cross-talk and pulmonary diseases; (iii) extent of relaxation and residual cross-bridge activation [5,6]. When myocardial relaxation is not completed at end-diastole, diastolic dysfunction will result. Myocardial relaxation is a dynamic process which follows contraction and which takes place during the major part of ejection,

Abbreviations: ID, Anterior–posterior left ventricular internal diameter; LV, Left ventricle or left ventricular; LVP, Left ventricular pressure; Relative load, 'systolic LVP/isovolumetric LVP (%)'; ED(pre), End-diastole at the beginning of the cardiac cycle; ED(post); End-diastole at the end of the cardiac cycle.

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LVP fall and early filling [6]. In normal circumstances relaxation is completed during rapid filling near minimum LVP [7].

Several investigators have shown that elevating afterload slows LVP fall [8–15]. The amount of slowing appears to be related to systolic cardiac function [13,16]. If cardiac function is fair, limited slowing is observed and if cardiac function is severely impaired, rate of LVP fall becomes increasingly dependent on systolic LVP [13,15,16]. More recently, it was demonstrated that in healthy hearts, small afterload elevations actually accelerated LVP fall, while slowing of LVP fall was observed only in the presence of larger elevations of afterload [13]. Therefore, slowing of LVP fall in response to an elevation of systolic LVP may be observed in healthy hearts with markedly increased afterload and in failing hearts even with slightly increased afterload. These findings can be explained by the concept of *relative load*, which represents the ratio of systolic LVP to isovolumetric LVP [17]. A similar systolic LVP represents a higher relative load in the failing than in the normal heart. When relative load is low, afterload reserve still is available allowing the heart to face increased afterload without slowing of LVP fall. When relative load is high, afterload mismatch [18] occurs and a pronounced slowing of LVP fall is observed [17].

Diastolic dysfunction had been associated with decreased extent of myocardial relaxation but not with decreased rate. Glantz [5,19] for instance recently wrote: ''Several factors affect the relaxation rate but do not shift the entire diastolic pressure–volume relationship because none of the changes in relaxation rate is large enough to affect the ventricular pressure at end-diastole. Changes in relaxation rate do, however, affect the atrioventricular pressure gradient and thus affect the left ventricular filling rate during early diastole'' [19].

In the present study we challenged this view and tested the hypothesis that an afterload elevation which increases relative load and markedly slows rate of LVP fall would result in incomplete myocardial relaxation and in an upward shift of the entire diastolic pressure–dimension relation.

2. Methods

The investigation conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Anaesthetised open-chest rabbits (n=9)

Male New Zealand White rabbits (*Oryctolagus-cuniculus*, 2.7±0.1 kg) were premedicated with ketamine hydrochloride (50 mg/kg, im) and xylazine hydrochloride (5 mg/kg, im). An auricular vein was cannulated and a prewarmed solution containing 20 mEq KCl and 40 mEq $NaHCO_3$ in 500 ml 0.9% NaCl was administered to compensate for perioperative fluid losses. A tracheostomy was performed and mechanical ventilation initiated, delivering oxygen-enriched air. Respiratory rate and tidal volume were adjusted to keep arterial blood gases and pH within physiological limits. Anaesthesia was maintained with ketamine hydrochloride (33 mg/kg/h, im), pentobarbital sodium (12.5 mg/kg, iv before opening the chest, then 2.5 mg/kg iv as needed) and vecuronium bromide (0.5 mg/h, iv) [20]. A 20-gauge catheter was inserted in the right femoral artery and connected to a pressure transducer to monitor heart rate and arterial pressure and to obtain samples for blood gas analysis. The heart was exposed by a median sternotomy and the pericardium was widely opened. A silk suture was placed around the ascending aorta and passed through a plastic tube for performing aortic occlusions. A 3F high-fidelity micromanometer (MTC P3FC, Dräger Medical Electronics) was inserted through an apical puncture wound into the left ventricular cavity, positioned at the midventricular level, and secured in place with a purse-string suture to measure LVP. The manometer was calibrated against a mercury column and zeroed after stabilisation for 30 min in a water bath at body temperature. The zero was set at the level of the right atrium. LV dimensions were measured with miniaturised ultrasonic dimension gauges using a sonomicrometer amplifier (Triton Electronics, San Diego, CA); one pair of crystals (3 mm diameter) was sutured in place onto LV anterior and posterior epicardial surface to measure anterior–posterior LV external diameter. A third crystal (1 mm diameter) was tunnelled at a 30–45° angle into the subendocardium facing the LV anterior epicardial crystal. The anterior epicardial crystal and the subendocardial crystal were combined to measure wall thickness. A limb ECG (DII) was recorded throughout. At the end of the experiment, the animal was sacrificed with an overdose of anaesthetics and the position of crystals and manometer verified at necropsy.

2.2. Experimental protocol

Multiple graded aortic occlusions were performed by abruptly narrowing or occluding the ascending aorta during the diastole separating two heartbeats. The preceding beat is control and the following beat is test heartbeat. The analysed intervention therefore was a selective alteration of afterload without changes of preload or long-term load history. Systolic LVP of the first heartbeat following the intervention varied as a function of the strength of the tension on the silk suture and the extent of ascending aorta narrowing. The aortic clamp was quickly released in order to avoid neurohumoral reflex changes in cardiac function [21]. The animal was stabilised for several beats before another intervention was performed. The animals were not

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paced, but heart rate did not vary during the experimental protocol (221±8 bpm).

2.3. Data acquisition and analysis

Recordings were made with respiration suspended at end expiration. Parameters were converted on line to digital data (Codas, Dataq). An analog signal of the first derivative of LVP (dP/dt) was recorded with a cut-off filter set at 50 Hz. Peak rates of LVP rise (dP/dt_{max}) and fall (dP/dt_{min}) were measured. The ID was calculated as external diameter minus two times wall thickness. End-diastole was set at the lower right corner of the LVP–ID loop. To distinguish between end-diastole at the start and at the completion of the analysed cardiac cycle, the end-diastole at the start was referred to as ED(pre), while end-diastole at the completion was referred to as ED(post). LVP was measured at the start of the cardiac cycle ($LVP_{ED(pre)}$), at peak-systole (LVP_{max}), at its protodiastolic nadir (LVP_{min}), and at end-diastole ($LVP_{ED(post)}$). The ID was measured at the start of the cardiac cycle ($ID_{ED(pre)}$), at its minimum value (ID_{min}), at LVP_{min} and at end-diastole ($ID_{ED(post)}$). Fractional shortening was calculated as '$(ID_{ED(pre)}-ID_{min})/ID_{ED(pre)}$ (%)'. Afterload levels were presented as *relative load*, previously defined as ''LVP_{max}/peak isovolumetric LVP (%)'' [17]. Time intervals were measured from end-diastole (ED(pre)) to dP/dt_{min} and from dP/dt_{min} to the next end-diastole (ED(post)). Pressure fall was evaluated with dP/dt_{min}, and with the time constant tau (τ). For calculating τ, the portion of the LVP tracing between dP/dt_{min} and a pressure equal to $LVP_{ED(post)}$ was selected. The curve was fitted to a monoexponential model (τ_{exp}) [7,9,22] with non zero asymptote, given by the following equation:

$$P(t) = P_0\, e^{-t/\tau_{exp}} + P_\infty$$

where P_∞ is a nonzero asymptote (mm Hg), P_0 is an amplitude constant (mm Hg), t is time (ms), and τ_{exp} is the time constant of the exponent (ms). The r^2 yielded values >0.99. According to this formula relaxation will be 97% complete after a time interval of $3.5*\tau_{exp}$ (ms) starting from dP/dt_{min} [7]. The curve was also fitted to the logistic model ($\tau_{logistic}$). The logistic time constant was shown to better describe LVP fall in heavily afterloaded conditions where the course deviates from monoexponential [23]. This time constant was calculated from the equation:

$$P(t) = P_A/(1 + e^{t/\tau_{logistic}}) + P_B$$

where P_B is a nonzero asymptote, P_A is an amplitude constant, t is time, and $\tau_{logistic}$ is the time constant of the exponent. The r^2 yielded values >0.995.

2.4. Statistical analysis

Group data are presented as mean values±SEM. Several data sets, combining the four afterload levels and the corresponding control values, failed in the Kolmogorov-Smirnov test for normality. The nonparametric Friedman repeated-measures analysis of variance on ranks was therefore selected (SigmaStat™, Jandell Scientific, Erkrath, Germany). When treatments were significantly different, the Student-Newman-Keuls test was selected to perform pairwise multiple comparison. Statistical significance was set at $P<0.05$ unless specified.

2.5. Anaesthetised open-chest dogs ($n=16$)

In order to exclude species-dependent observations, pressure-segment length loops were constructed from retrospective analysis of published experiments on dogs [13], instrumented with a high-fidelity micromanometer in the LV and circumferential segment length gauges. Atrially paced heart rate was 130±2 bpm. Beat-to-beat afterload elevations were obtained with a balloon positioned in the lumen of the ascending aorta and inflated during the diastole separating control and test beat.

3. Results

3.1. Open-chest anaesthetised rabbits

At baseline the LV operated at a systolic LVP of 90±3 mm Hg, which corresponded to a relative load of 59±2%. The first beat after aortic narrowing or occlusion was analysed. Four levels of afterload were selected from the multiple available interventions (Table 1). The relative load of these interventions corresponded to 67±1%,

Table 1
Effects of afterload elevations on systolic LV function[a]

	Control	70%	80%	90%	100%
$LVP_{ED(pre)}$ (mm Hg)	6.1±0.4	6.0±0.4	6.2±0.4	6.3±0.4	6.1±0.6
dp/dt_{max} (mm Hg/s)	3499±195	3493±204	3490±209	3498±201	3520±241
LVP_{max} (mm Hg)	90±3	103±4[b]	123±5[b,c]	139±5[b,c,d]	154±6[b,c,d,e]
$ID_{ED(pre)}$ (mm)	12.0±1.1	12.0±1.1	12.0±1.1	12.0±1.1	12.0±1.1
Fractional shortening (%)	23.3±1.9	21.7±1.7[b]	18.1±2.0[b,c]	12.5±2.9[b,c,d]	5.9±2.3[b,c,d,e]

[a] Data are presented as means±SEM; $n=9$. $LVP_{ED(pre)}$, $ID_{ED(pre)}$, end-diastolic LVP and ID at the beginning of the cardiac cycle; LVP_{max}, peak systolic LVP; dP/dt_{max}, peak rate of LVP rise. $P<0.05$ indicated significance: [b] vs. control. [c] vs. 70%. [d] vs. 80%. [e] vs. 90%.

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Table 2
Effects of afterload elevations on LVP fall[a]

	Control	70%	80%	90%	100%
dP/dt_{min} (mm Hg)	−3145±170	−3258±162	−2888±128[b,c]	−2261±136[b,c,d]	−1985±155[b,c,d,e]
Time to dP/dt_{min} (ms)	157±5	168±6[b]	180±7[b,c]	186±7[b,c,d]	186±8[b,c]
τ_{exp} (ms)	18.3±0.9	17.4±1.0[b]	21.4±1.0[b,c]	33.3±2.2[b,c,d]	48.5±6.1[b,c,d,e]
$\tau_{logistic}$ (ms)	9.8±0.6	9.2±0.6[b]	10.8±0.5[b,c]	14.8±0.9[b,c,d]	20.8±1.8[b,c,d,e]

[a] Data are presented as means±SEM; $n=9$. dP/dt_{min}, peak rate of LVP fall; τ_{exp}, $\tau_{logistic}$, monoexponential and logistic time constants of LVP fall, respectively. $P<0.05$ indicated significance: [b] vs. control. [c] vs. 70%. [d] vs. 80%. [e] vs. 90%.

80±1%, 91±1% and 100%, and was referred to as 70%, 80%, 90% and 100%. The 100% intervention was a total aortic occlusion (isovolumetric heartbeat). The intervention did not manifest itself before aortic valve opening of the analysed heartbeat so that $LVP_{ED(pre)}$ and dP/dt_{max} remained unaffected. The peak systolic pressure elevation induced on a first beat basis by an isovolumetric contraction was 64±4 mm Hg. Fractional shortening progressively decreased as afterload increased.

Effects of afterload on LVP fall were reported in Table 2 and illustrated in Fig. 1. The left panel shows a representative example of superposed heartbeats: control (beat 1), 70% (beat 2), 80% (beat 3), 90% (beat 4) and 100% (beat 5). LVP fall was progressively delayed due to the combined effects on timing and course of LVP fall. The right panel shows the group values of $\tau_{logistic}$ as a function of relative load. At 70%, $\tau_{logistic}$ decreased indicating acceleration of LVP fall. From 80% on, $\tau_{logistic}$ progressively increased indicating deceleration of LVP fall. For isovolumetric heartbeats (100%) this deceleration corresponded to a 212% increase of the control value of $\tau_{logistic}$. Similar findings were derived from τ_{exp}.

Effects of afterload on diastole were reported in Table 3 and illustrated in Fig. 2. The left panel shows five superposed LVP–ID loops corresponding to the five LVP tracings of the left panel of Fig. 1. Beat 2 (70%) did not alter diastolic LVPs. Beat 3 (80%) slightly elevated diastolic LVPs. Beats 4 (90%) and 5 (100%) elevated

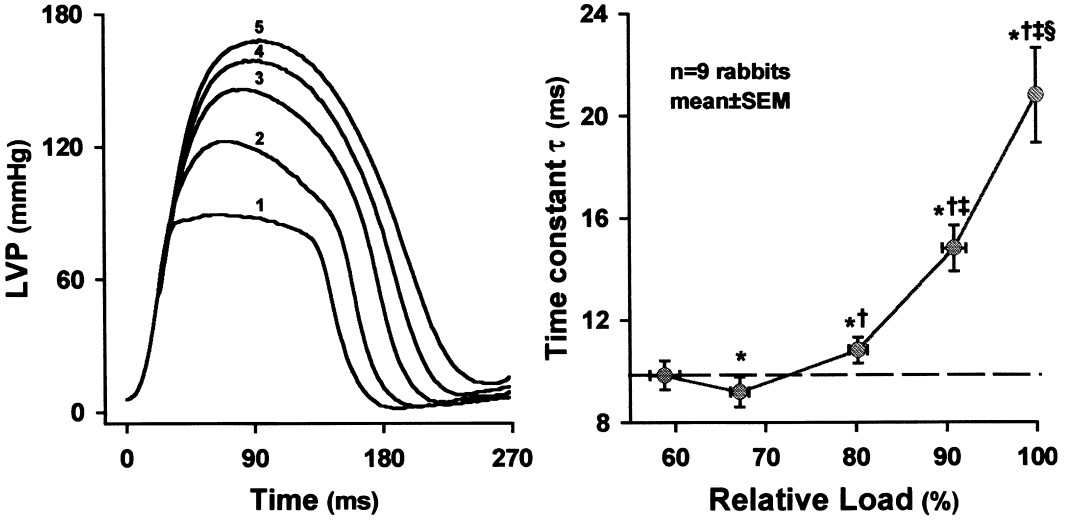

Fig. 1. Left: Five superposed heartbeats: control (beat 1), 70% (beat 2), 80% (beat 3), 90% (beat 4), and 100% (beat 5, isovolumetric). LVP fall was progressively delayed due to the combined effects on timing and course of LVP fall. LVP fall was accelerated in beat 2 and decelerated in beats 3, 4 and 5. Right: Group values of $\tau_{logistic}$ as a function of relative load. At 70%, $\tau_{logistic}$ slightly but significantly decreased indicating acceleration of LVP fall. From 80% on $\tau_{logistic}$ progressively increased indicating deceleration of LVP fall. $P<0.05$ indicated significance. * vs. control; † vs. 70%; ‡ vs. 80%; § vs. 90%.

Table 3
Effects of afterload elevations on LV filling[a]

	Control	70%	80%	90%	100%
LVP_{min} (mm Hg)	2.1±0.6	2.4±0.6	3.4±0.7[b,c]	7.1±0.9[b,c,d]	9.3±1.2[b,c,d]
ID at LVP_{min} (mm)	10.1±1.1	10.2±1.1	11.0±1.1[b,c]	11.5±1.1[b,c,d]	11.8±1.1[b,c,d]
$LVP_{ED(post)}$ (mm Hg)	6.2±0.4	6.2±0.5	7.6±0.5[b,c]	10.4±0.8[b,c,d]	14.0±1.2[b,c,d,e]
$ID_{ED(post)}$ (mm)	12.0±1.0	12.0±1.1	12.1±1.1	12.2±1.1	12.1±1.0

[a] Data are presented as means±SEM; $n=9$. LVP_{min}, minimal LVP; $LVP_{ED(post)}$, $ID_{ED(post)}$, end-diastolic LVP and ID at the end of the cardiac cycle, respectively. $P<0.05$ indicated significance: [b] vs. control. [c] vs. 70%. [d] vs. 80%. [e] vs. 90%.

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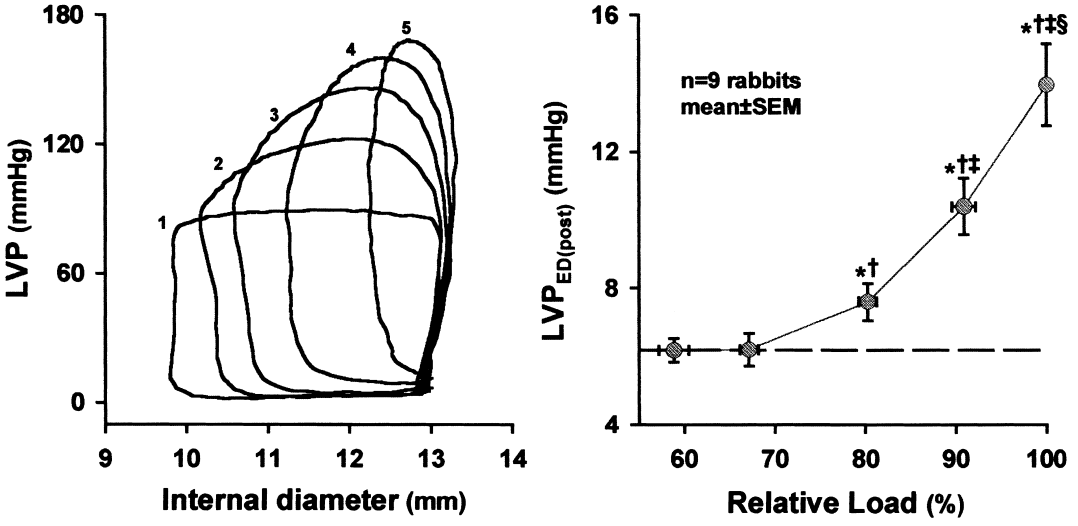

Fig. 2. Left: Superposed LVP–ID loops corresponding to the five LVP tracings of the left panel of Fig. 1. Beat 2 (70%) did not alter diastolic LVPs. Beat 3 (80%) slightly while beats 4 (90%) and 5 (100%) markedly increased diastolic LVPs. The diameter of the LV at the end of the heartbeat was similar for all load levels. Right: Group data displaying end-diastolic LVP ($LVP_{ED(post)}$) as a function of relative load. $P<0.05$ indicated significance. * vs. control; † vs. 70%; ‡ vs. 80%; § vs. 90%.

diastolic LVPs to an important extent including $LVP_{ED(post)}$. The right panel summarised the group data by displaying $LVP_{ED(post)}$ as a function of relative load. Changes in $LVP_{ED(post)}$ appeared to parallel the changes in $\tau_{logistic}$ and the right panel of the graph of Fig. 2 looks similar to the right panel of the graph of Fig. 1. Of note, the LV end-diastolic diameter of the test heartbeat ($ID_{ED(post)}$) was similar for all load levels, indicating that in the first diastole following an elevation of afterload there was no significant filling beyond the previous diastolic diameter ($ID_{ED(pre)}$). The difference between end-diastolic LVP at the end and at the beginning of the cardiac cycle ($LVP_{ED(post)} - LVP_{ED(pre)}$) therefore reflected the magnitude of the upward shift of the end-diastolic LVP–ID relation and the occurrence of diastolic dysfunction. LVP_{min} was altered to a similar extent as $LVP_{ED(post)}$. These changes of LVP_{min} may also be appreciated from the LVP tracings of Fig. 1.

The difference $LVP_{ED(post)} - LVP_{ED(pre)}$ induced by afterload elevations was plotted in Fig. 3 as a function of fractional changes of $\tau_{logistic}$ for the four afterload levels of all animals (36 interventions). The effects of afterload on $LVP_{ED(post)}$ were closely correlated to the effects on $\tau_{logistic}$ ($r=0.89$, $P<0.01$). A similar relation was obtained for τ_{exp} (not shown). Slowing of LVP fall therefore appeared to be predictive for the magnitude of diastolic failure induced by a selective elevation of afterload.

It remained to be evaluated to what extent diastolic dysfunction and the elevation of $LVP_{ED(post)}$ could be attributed to slowed and incomplete myocardial relaxation. Mathematically, relaxation is 97% complete after a time interval corresponding to 3.5 times τ_{exp} after dP/dt_{min} [7]. Table 4 compared the observed time intervals from dP/dt_{min} till the next end-diastole to the expected 97% completion of relaxation. For control and 70% the expected values were smaller than the observed time interval. For the 80% load clamps the two values were similar. The expected values exceeded observed values for the 90% and 100% interventions. Incomplete relaxation was likely to be present in the 90 and 100% interventions. If we look at the 80% interventions, mean observed time for relaxation slightly exceeded 3.5 times τ_{exp} (ns). Nevertheless $LVP_{ED(post)}$ increased from 6.2 to 7.6 mmHg. This increase corresponded to 2.6% of end-systolic LVP (LVP at dP/dt_{min}).

To exclude the possible contribution of increased myocardial turgor induced by elevated systolic pressures, wall thickness was measured at ED(pre) and ED(post) for all interventions. Wall thickness did not increase. For the 100% isovolumetric interventions end-diastolic wall thickness went from 3.6±0.3 at the beginning to 3.5±0.3 mm at the end of the cardiac cycle. As is apparent from the tracings in Fig. 4 there was even a non-significant trend toward a decrease.

3.2. Open-chest anaesthetised dogs

Heavily afterloaded and isovolumetric heartbeats induced an upward shift of the end-diastolic LVP-segment length loops. This issue was illustrated in Fig. 5 in which a control beat, two afterloaded beats and an isovolumetric beat were represented. The shift was present for both the heavily afterloaded and the isovolumetric heartbeats. For the isovolumetric heartbeats ($n=16$), $LVP_{ED(pre)}$ was 5.2±0.3 mm Hg, systolic LVP went from 125±4 to 167±7 mm Hg, τ_{exp} went from 41±2 to 118±17 ms, LVP_{min} went from 3.0±0.5 to 5.8±0.8 mm Hg and $LVP_{ED(post)}$ was elevated to 8.0±0.9 mm Hg.

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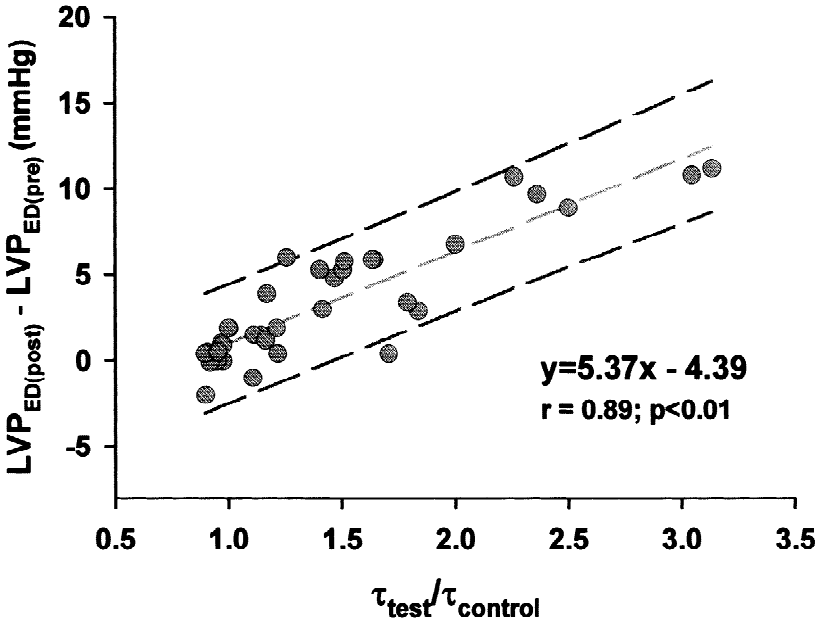

Fig. 3. The difference between end-diastolic LVP at the end and at the beginning of the cardiac cycle ($LVP_{ED(post)} - LVP_{ED(pre)}$), which reflects the magnitude of the upward shift of the end-diastolic LVP–ID relationship, was plotted as a function of fractional changes of $\tau_{logistic}$ ($\tau_{test}/\tau_{control}$) for the 4 afterload levels in each animal (36 interventions). Linear regression and 95% prediction limits are shown as dashed lines. The effects of afterload on end-diastolic LVP ($LVP_{ED(post)}$) were fairly well related to effects on the time constant $\tau_{logistic}$ ($r=0.89$, $P<0.01$).

Table 4
Evaluation of the completion of myocardial relaxation[a]

	Control	70%	80%	90%	100%
Observed time from dP/dt_{min} to ED(post) (ms)	104±4	93±4	82±4	74±2	76±3
Predicted completion of relaxation (ms)	64±3[b]	61±3[b]	75±4	116±8[b]	170±21[b]

[a] Data are presented as means±SEM; $n=9$. ED(post), end-diastole at the end of the cardiac cycle.
[b] $P<0.05$. The predicted completion of relaxation was computed as $3.5*\tau_{exp}$.

4. Discussion

The present study investigated the effects of selective afterload interventions on the diastolic LVP–ID relation and related these effects to the time course of isovolumetric myocardial relaxation. Elevated afterloads prolonged τ and resulted in an upward shift of the diastolic LVP–ID relation. These results challenge the prevailing view [5,19] that none of the factors that affect relaxation rate would shift the entire diastolic pressure–volume relationship.

4.1. Afterload and systolic function

When afterload and systolic LVPs were experimentally increased, fractional shortening decreased. End-diastolic pressures, end-diastolic dimensions and dP/dt_{max} were similar in control and test beats. This experimental situation corresponded to afterload mismatch [18] and represented abnormal systolic performance in the presence of normal contractility. In the failing heart, systolic performance may be impaired to the same extent as in the normal heart with excessive afterload, even in the presence of normal aortic input impedance. One aspect of this impaired systolic performance is altered LV geometry resulting in increased wall stress. Another aspect is decreased contractility with a limited ability to develop pressure during systole. Both aspects lead to a condition where the failing heart operates at a high relative load even with normal systolic LVPs. Afterload mismatch and low ejection fraction therefore may be induced in the normal heart by elevating systolic pressures, but may be present at baseline in the failing heart.

4.2. Afterload and LV relaxation

Increasing afterload accelerated LVP fall up to a certain afterload level. Above that level relaxation was slowed and this corresponded to afterload mismatch. The biphasic effect of afterload on LVP fall, previously described in dogs [13], was also present in the intact ejecting heart of the rabbit. Quantitative differences were, however, observed. The transition from acceleration to deceleration occurred at a lower relative load in rabbits (73–76%) than in dogs (81–84%). This species difference could be

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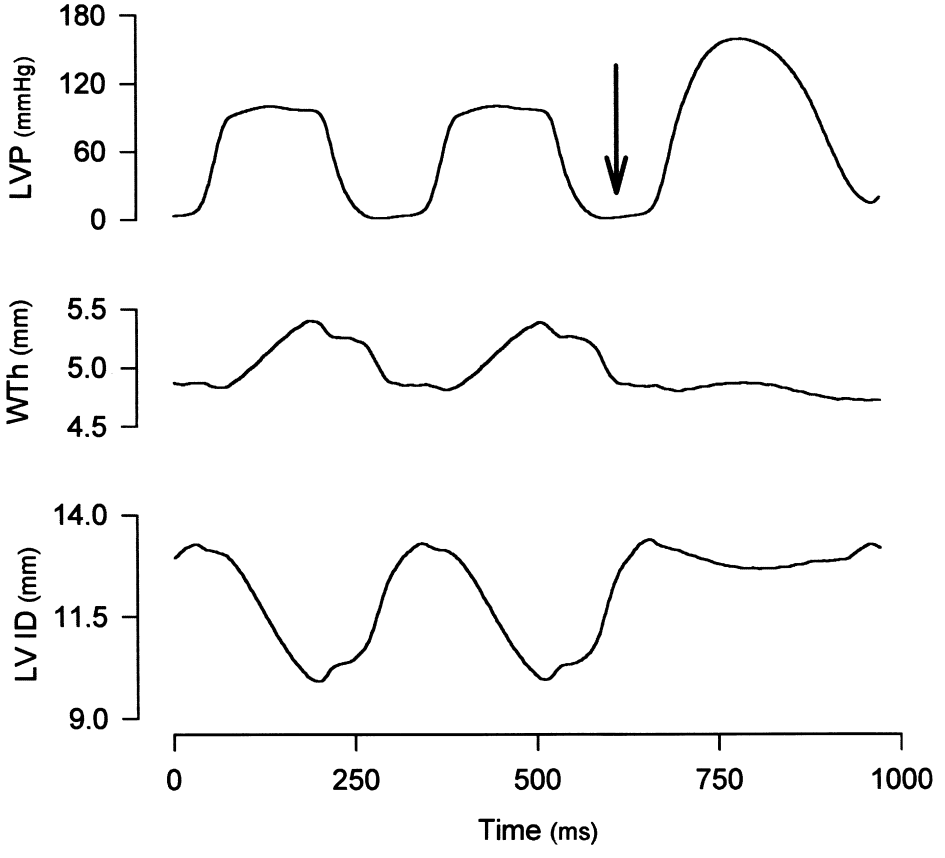

Fig. 4. Time courses of left ventricular pressure (LVP, upper panel), wall thickness (WTh, middle panel) and internal diameter (LV ID, lower panel) of three consecutive heartbeats (two control and one isovolumetric). Ascending aorta was totally occluded during the diastole separating control and isovolumetric heartbeats (arrow). Diastolic LVP increased even if LV ID remained matched with control. WTh did not increase, but rather showed a tendency to slightly decrease.

explained on the basis of different Ca^{2+} kinetics. That the rabbit is more dependent on activator Ca^{2+} from the extracellular space and less on sarcoplasmic Ca^{2+} release [24] is not likely to be related to this finding. What however could be related is a shorter Ca^{2+} transient and a faster Na^{+}–Ca^{2+} exchange during the decline of the Ca^{2+}

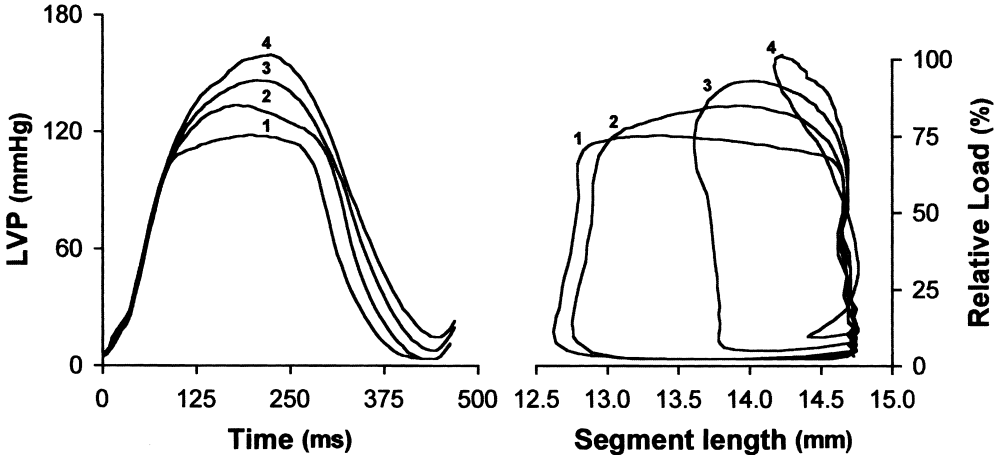

Fig. 5. LVP time courses (left panel) and LVP vs. segment length loops (right panel) of four superposed heartbeats: control (beat 1), afterloaded (beats 2 and 3), and isovolumetric (beat 4). Beats 3 and 4 slowed rate of LVP fall, increased diastolic LVPs, and induced an upward shift of the diastolic LVP-segment length relation.

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transient [24,25]. The relation between τ and intracellular Ca^{2+} kinetics was discussed previously [17]. We should keep in mind that the different results in dogs and rabbits could be affected as well by differences in the anaesthetic agents used in the two studies.

4.3. Afterload and diastolic function

In normal hearts different factors affect LVP during diastole, with different factors being important at different timings [5,19]. Active relaxation and elastic recoil are important during early diastole. Late in diastole, ventricular interaction, the pericardium, viscous forces and coronary vascular engorgement become predominant. With regard to myocardial relaxation it is generally accepted, as outlined above, that none of the factors that affect relaxation rate would shift the entire diastolic pressure–volume relationship, because none of the changes would be large enough to affect LVP at end-diastole [5,19]. To challenge this view we studied the effects of a selective beat-to-beat elevation of afterload on both relaxation rate and diastolic function. Only such a selective intervention would exclude confounding alterations of global hemodynamics due to decreased stroke volume, acute backward failure, increased LV filling pressures, neurohumoral responses and possibly afterload-induced myocardial ischemia [18]. The observations had to be performed in healthy hearts that were neither hypertrophic nor ischemic.

In the present study small afterload interventions (70%) did not alter the LVP–ID relation. For the 80% interventions a small elevation of end-diastolic pressure was observed corresponding to 2.6% residual active state. The computed time to complete relaxation was similar to the observed time from dP/dt_{min} till ED(post) and as a mean slightly longer (ns) (Table 4). This meant that at the end of the test cardiac cycle relaxation was somewhat more than 97% complete [7]. The observed elevation of end-diastolic pressure was consonant with a less than 3% residual active state. Such a theoretical extrapolation from isovolumetric indices should be applied with caution as the filling ventricle relaxes still slower than the non-filling ventricle [22]. Afterloads exceeding 80% of peak isovolumetric pressure increased diastolic pressures and resulted in an important upward shift of the diastolic LVP–ID relation. These levels of afterload induced frank diastolic dysfunction. This finding is clearly distinct from the observations performed several heartbeats after aortic occlusion with elevation of diastolic pressures due to decreased stroke volume, acute backward and forward failure, hence cardiovascular collapse [19,26–30]. In all these previous studies, elevated filling pressures had been explained as a rightward displacement along an unchanged end-diastolic pressure–volume relation [19,26–30]. From a mechanistic point of view this message is distinct from the upward shift of the end-diastolic pressure–volume relation observed in the present study both in rabbits and in dogs. Of note, the end-diastolic diameter of the first heartbeat following a total aortic occlusion was not significantly larger than the corresponding diameter of the preceding control beat. Dilatation of the heart and Frank-Starling compensation were observed only in the following heartbeats, which were not analysed in this study.

Increasing afterload resulted in a longer time from end-diastole to dP/dt_{min} (Table 2), due to combined effects on systolic duration and rate of pressure fall [13,31]. As a consequence, the duration of LV filling decreased, which presumably contributed as well to the observed diastolic dysfunction.

An important variable to be taken care of is heart rate. It is well known that an inappropriate increase in heart rate might induce an upward shift of the end-diastolic pressure–volume relation due to incomplete relaxation and impaired LV filling, even if relaxation rate is normal [7]. The issue of the present study however was distinct. The heart rates at which rabbits and dogs of the present study were studied were close to reported physiological heart rates of awake animals [32]. If we analyse Table 4 we observe that for high relative loads the necessary time for the LV to complete relaxation exceeded by far the available time. Heart rate would have to be reduced to very low and non-physiological values to entirely revert this afterload-dependent diastolic dysfunction.

Another variable to be taken in account is nonuniformity [33]. The effects of afterload on myocardial relaxation have been partially attributed to increased nonuniformity [12,14,15,33]. We showed previously that nonuniformity is not altered in our model of selective, beat-to-beat, afterload elevations [13].

Other factors affecting diastolic function were not likely to have contributed to our findings. The pericardium is an important modulator of the diastolic pressure–volume curve [19,29], but was widely opened in the present study and therefore could not constrain the heart. Ventricular cross-talk is modest when the pericardium is opened [34]. In the present study it might even be completely excluded because right ventricular volumes should not have changed during single beat interventions. Viscous forces increase with increasing length and/or increasing velocity of lengthening. None of these were increased in the afterloaded heartbeats. End-diastolic observations were performed at common dimensions, which excludes the effect of length. These results are consonant with previous studies that showed only small effects of afterload on viscous forces, which decreased with increasing afterload [19,35,36]. Coronary arterial engorgement may be altered by afterload, but its effect on diastolic pressures is modest [37–39]. If present, a significant increase of coronary engorgement would increase diastolic wall thickness [40], which was not observed. If anything the LV wall was squeezed rather than engorged (Fig. 4).

These observations add to our knowledge on the dynamic, all but passive, nature of diastole. Diastolic pres-

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sure–volume relations were previously shown to be dependent on preload [41] and on paracrine [42] regulation. The present contribution demonstrated that the diastolic pressure–volume relation was also affected by acute afterload mismatch and that afterload mismatch induced an incomplete myocardial relaxation or an increased residual active state. Such a dynamic nature of mechanical end-diastolic LV properties obscures the distinction [6] between relaxation and diastole [43].

4.4. Potential clinical implications

Ishizaka et al. [44] performed caval occlusion in dogs with pacing cardiomyopathy. Caval occlusion revealed an important load dependence of LVP fall in these diseased hearts, but not in normal hearts. Caval occlusion not only accelerated LVP fall but also reverted an upward shift of the diastolic segment of the pressure–volume loop. In view of the present findings we might interpret this observation by suggesting that afterload mismatch was present at baseline and was corrected by decreasing afterload during caval occlusion. We might, therefore, suggest that reversible relaxation disturbances, which are afterload dependent, should contribute to elevating diastolic pressures in patients with congestive heart failure, in whom afterload mismatch may be induced during moderate exercise or may be present even at rest. These data might have also important ramifications in terms of therapy for heart failure. Afterload mismatch is a causal mechanism, which may explain at least in part why vasodilators (that reduce afterload) and inotropic agents (that accelerate relaxation and decrease relative load) may lower filling pressures in the diseased heart.

4.5. Limitations of the present study

The data did not include direct evidence that the increase in end-diastolic LVP induced by afterload elevations was due to the concomitant increase in τ. The suggestion of a causal relationship was based on the close linear relation between τ and end-diastolic LVP, along with the fact that none of the other known determinants of diastolic function could provide a satisfactory explanation for our findings. In such circumstances it seemed reasonable to state that load-dependent residual active state was involved.

Another limitation concerns with the evaluation of relaxation rate by the time constant τ, given the fact that no model provides a perfect description of LVP fall. To obviate this limitation, two different models were used in the present study. The use of the 3.5 times τ rule to estimate the time to completeness of relaxation [7] might also raise some discussion, because relaxation rate is influenced by ventricular filling. The rule applies well to non-filling beats, but time to completeness of relaxation may be prolonged up to 5.4 times τ in filling beats [45]. If we had used a value bigger than 3.5, we would had end-up with an even more clear evidence of incompleteness of relaxation.

Finally, the analysed beat-to-beat changes in afterload are not identical to prolonged or chronic elevations in systolic LVP, in which the Frank-Starling compensation and neurohumoral readjustments add to the complexity of the regulation of myocardial relaxation and diastolic function. This fact should be taken in account when doing any sort of extrapolations.

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