Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function


Summary
We have determined the effects of alterations in preload on ischaemia-induced diastolic dysfunction in anaesthetized beagles instrumented to measure left ventricular pressure and regional dimensions. Low-flow regional ischaemia decreased peak lengthening rates in ischaemic (mean $-26$ (SEM 6) mm s$^{-1}$, $P < 0.01$) and non-ischaemic ($-8.6$ (3.4) mm s$^{-1}$, $P < 0.05$) myocardium. Peak lengthening rates and the time constant of isovolumic relaxation ($\tau$) were not affected by alterations in preload. Absolute values of $\tau$ failed to distinguish between ischaemia and control. The ischaemia-induced decrease in peak negative dP/dt was preload dependent and caused mainly by a concomitant decrease in peak left ventricular pressure. We conclude that indices derived from segmental lengthening are sensitive to ischaemia and insensitive to preload, in contrast with indices derived from left ventricular pressure. It remains to be determined if monitoring of early segmental lengthening will improve detection and assessment of perioperative myocardial ischaemia. (Br. J. Anaesth. 1996; 76: 419–427)

Key words

Myocardial ischaemia has profound effects on both systolic and diastolic cardiac performance. There is, however, clinical and experimental evidence that diastolic function is particularly sensitive to myocardial ischaemia. Dodek, Kassebaum and Bristow reported repeated episodes of pulmonary oedema in patients with a normal heart size [1]. Moreover, despite the absence of systolic dysfunction, diastolic dysfunction may occur in a high proportion of patients with coronary artery disease, both at rest and during pacing-induced ischaemia [2, 3]. In experimental models of myocardial ischaemia, diastolic dysfunction precedes contractile dysfunction [4] or may even be the predominant, if not only, sequel of ischaemia [5].

Given the impact of myocardial ischaemia on cardiac morbidity and mortality [6], early detection and rigorous treatment of ischaemic episodes might lead to improvement in perioperative outcome. Recent advances in technology allow non-invasive assessment of diastolic function using echocardiography (segmental re-extension), pulsed wave Doppler echocardiography (filling pattern), or both. However, even mild alterations in preload (change in end-diastolic pressure $\pm 4–5$ mm Hg) were reported to mimic or mask diastolic dysfunction as derived from the mitral inflow velocity profile [7, 8]. As rapid and substantial changes in preload cannot be excluded in the perioperative period, preload-induced modifications have to be taken into account in order to interpret indices of diastolic function. It is currently not known if and how alterations in preload affect regional segmental lengthening or interact with ischaemia-induced alterations in the pattern of left ventricular relaxation and lengthening.

The aim of the present investigation was to determine the effects and interactions of alterations in circulating blood volume on global and regional indices of left ventricular diastolic function in the absence and presence of myocardial ischaemia.

Materials and methods
EXPERIMENTAL PREPARATION

The study conformed to the United Kingdom Animals Act (Scientific Procedures, 1986, Home Office licence No. PPL 30/00887). Nine beagles of both sexes (mean weight 14.4 (SEM 1.2) kg) were premedicated with morphine 1.0 mg kg$^{-1}$ i.m. Anaesthesia was induced with sodium thiopentone 1.0–1.5 % and maintained with 1.0–1.5 % halothane and nitrous oxide in oxygen ($F_{O_2} = 0.4$).
Inspiratory and end-tidal gas concentrations were measured continuously (gas analyser M1025A, Hewlett-Packard, Bracknell, UK) and mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide concentration at 4.5–5.5 %. Mid-oesophageal temperature was maintained at 36–37 °C using a Servo-controlled heating element incorporated into the operating table. Ringer’s lactate 5 ml kg⁻¹ h⁻¹ was infused continuously through an i.v. cannula inserted in the left hind leg. A left thoracotomy was performed, the fifth and sixth ribs excised, and the heart isolated and suspended in a pericardial cradle.

**INSTRUMENTATION**

Instrumentation included limb lead II of the electrocardiogram (subcutaneous electrodes); an 8-French gauge fluid-filled cannula in the left common carotid artery for withdrawal of blood; a 7-French gauge pulmonary artery catheter (Swan–Ganz, American Edwards Laboratories, Anasao, Puerto Rico) inserted into the pulmonary artery via the left jugular vein; a micromanometer-tipped 8-French gauge catheter (Millar, Houston, TX, USA) inserted into the aortic arch via the right femoral artery for measurement of systemic pressures; a second micromanometer-tipped 8-French gauge catheter in the left ventricle (inserted via a stab wound in the apical dimple) for measurement of ventricular pressures; Doppler flow probes (Triton, San Diego, CA, USA) placed around the proximal ascending aorta and the left anterior descending coronary artery (LAD) distal to its first diagonal branch; a snare positioned distal to the flow probe on the LAD and attached to a micrometer controlled occluder; and two pairs of piezoelectric crystals (5 MHz, 2 mm in diameter, Triton Technologies, San Diego, CA, USA) implanted approximately 1 cm apart in a circumferential plane via small epicardial stab wounds in the subendocardium of a near apical (ischaemic area, supplied by the LAD) and a basal area (non-ischaemic area, supplied by the left circumflex coronary artery) for ultrasonic measurement of segmental length.

After completion of surgery and instrumentation, arterial blood-gas analysis was performed, and ventilation adjusted if necessary. Halothane was discontinued, a bolus dose of fentanyl 100 μg kg⁻¹ administered, and a continuous infusion of fentanyl 2 μg kg⁻¹ min⁻¹ commenced and maintained throughout the study. After a stabilization period of 1 h, 200 ml of arterial blood (four aliquots with 50 ml each) was obtained and kept at body temperature in a heated water bath while 200 ml of Dextran (5 %, average molecular weight 70 000) was infused into the femoral vein. A period of 30 min was then allowed for the haemodynamic state to stabilize before the circulating blood volume was increased stepwise: after recording baseline haemodynamic variables, 50 ml of blood was infused in the femoral vein over 30 s and further haemodynamic variables were recorded 1 min after completion of the infusion. Infusion of the following aliquot was started 3 min after completion of the previous infusion. This was repeated three times (total volume infused 200 ml). The 200 ml of blood was then withdrawn over a period of 15 min. After a stabilization period of 10 min, the snare around the LAD was tightened until the onset of obvious systolic lengthening, as assessed by the apical circumferential length–ventricular pressure loop (tilt of the loop to the right) which was displayed continuously on an oscilloscope. After completion of baseline recordings 10 min after the onset of ischaemia, the circulating blood volume was increased in a manner identical to that described for the control stage.

**DATA COLLECTION AND ANALYSIS**

ECG, pressure (aortic, left ventricular, airway), flow (aortic, coronary) and myocardial segment lengths signals were converted using an analogue-digital converter (AT-MIO-16, National Instruments Corporation, Austin, TX, USA) and displayed continuously on the screen of an IBM AT personal computer using the real-time mode software designed in this department. After every volume modification, data were recorded at a sampling frequency of 500 Hz during a period of three respiratory cycles and stored on the hard disk. Cardiac output was measured in triplicate by thermodilution (COM-2 Baxter, Santa Ana, USA) before the start of volume modification at each stage.

At the end of the experiment, the animals were killed with an overdose of halothane. A fine catheter was inserted into the LAD and 5 ml of Evans blue dye injected. In all animals necropsy confirmed the subendocardial placement of the crystals within or outside the blue stained region.

Data analysis was performed on an IBM AT personal computer using the play-back mode of the above-mentioned software. To minimize the respiratory effects on haemodynamic variables, end-expiratory data were used for analysis. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. End-diastole was defined as the first upward (positive) deflection of the left ventricular dP/dt signal. End-systole was defined as the first return to zero of the aortic flow signal.

**REGIONAL WALL MOTION**

Length measures were normalized to an initial end-diastolic length of 10 mm. The following variables were used to quantify regional wall motion: end-diastolic length (EDL); end-systolic length (ESL); minimum diastolic length (L min); and maximum length during systole (L max). Total shortening was defined as EDL - L min (mm). Systolic shortening was defined as ESL - L min and expressed as a percentage of total shortening. Post-systolic shortening was defined as ESL - L min and expressed as a percentage of total shortening. Thus systolic and post-systolic shortening together = 100 %. Systolic lengthening was defined as L max - EDL and expressed as a percentage of EDL.
TIME CONSTANT OF ISOVOLUMIC RELAXATION

The time constant of isovolumic relaxation (τ) was obtained by the method described originally by Weiss, Frederiksen and Weisfeldt [9]: the slope of the natural logarithm of left ventricular pressure (P) vs time (t) relation (from peak – dP/dt to the ventricular pressure that exceeds end-diastolic pressure by 10 mm Hg) was obtained by a least squares linear regression and τ was defined as the negative inverse of that slope:

\[ lnP = At + c \]
\[ τ = -1/A \]

where A = slope and c = intercept of the lnP vs t relation.

The rationale for the use of a method which assumes an asymptotical pressure–stress decay to zero rather than an asymptotical decay to an unknown baseline pressure–stress was that values yielded by the former approach are much closer to the “true” time constant of isovolumic relaxation obtained by preventing filling and thus allowing the ventricle to relax completely [10].

LENGTHENING

The base value of lengthening was defined as L_min and the interval between the preceding R wave of the ECG and L_min was defined as the R–L_min interval. The peak lengthening rate (PLR) was obtained by electronic differentiation and the interval between the preceding R wave of the ECG and PLR was defined as the R–PLR interval. Relaxation time (RT) was defined as the interval between peak negative dP/dt and the time when lengthening rate had decreased to 50% of PLR [11]. The end of the rapid lengthening phase was defined as the time when the lengthening rate had decreased to less than 2 mm s⁻¹ (normalized units and hence equal to a lengthening rate of 0.2 (end-diastolic length) per second). The segmental length at this time was termed L_ms (length at minimum speed). Thus L_ms divides segmental re-extension into a rapid and slow portion [12]. The fraction of lengthening occurring during the rapid lengthening period (RL%) was expressed as a percentage of total lengthening:

\[ RL\% = [(L_{ms} - L_{min})/(EDL - L_{min})] \times 100 \]

STATISTICS

All values are expressed as mean (SEM). Data were analysed on an IBM AT personal computer using SPSS, a commercially available statistical analysis program (SPSS for Windows, Release 5, SPSS Inc, Chicago, IL, USA). P < 0.05 was considered to represent statistical significance. Means of the two different stages were compared by a paired Student’s t test. Combined effects of volume loading and the experimental interventions (control, ischaemia) on global and regional haemodynamics were assessed using GLIM (generalized linear interactive modelling, version 3.77 update 2, The Royal Statistical Society, London, UK). Interactive modelling was performed by forward stepwise multiple linear regression (P < 0.05 for inclusion or exclusion of a variable as obtained by F-test) for the following equation:

\[ \text{Variable} = \text{constant} + V \times (\text{infused volume in ml}) + \]
\[ S_i (\text{ischaemia}) + I_i (\text{interaction volume/ischaemia}) \]

where V, S_i, and I_i = maximum likelihood variable estimates. The constant and the term S are expressed in the units of the variable concerned, while the terms V and I are expressed in units of the variable concerned per millilitre volume infused. A significant term for V indicates a correlation between volume loading and dependent variable; a significant term for S indicates a parallel shift of the regression line compared with baseline; a significant term for I indicates a difference in slope. For all variables tested, models assuming a linear relationship between dependent variable and volume yielded a better fit (as indicated by residual sum of squares) than models assuming a log-linear relationship.

RESULTS

GLOBAL FUNCTION

Infusion of 200 ml of blood increased left ventricular end-diastolic pressure from 6.7 (0.6) to 11.3 (0.9) mm Hg during control experiments and from 7.7 (0.8) to 13.2 (1.6) mm Hg during ischaemia. The combined effects of myocardial ischaemia and volume loading on global cardiac function are shown in table 1.

EFFECTS OF MYOCARDIAL ISCHAEMIA ON REGIONAL WALL MOTION

During ischaemia, coronary blood flow velocity in the LAD was reduced to 16 (4) % of control. In the ischaemic area (LAD supply) this resulted in a marked reduction in total shortening; systolic shortening was replaced almost completely by haemodynamically ineffective post-systolic shortening (table 2). Myocardial ischaemia did not affect regional wall motion in the remote non-ischaemic area.

PEAK NEGATIVE dP/dt

Combined effects of ischaemia and alterations in circulating blood volume on peak negative dP/dt (− dP/dt) are shown in figure 1. Note the significant and independent effects of both volume loading and myocardial ischaemia. Figure 2 demonstrates that a highly significant correlation (r > 0.95, P < 0.001) between peak negative dP/dt and peak left ventricular pressure (LVP) was preserved during myocardial ischaemia. Assessing the combined effects of ischaemia, peak LVP and alterations in circulating blood volume on − dP/dt, general linear interactive modelling yielded the following variable estimates (SEM):

\[ -dP/dt (\text{mm Hg s}^{-1}) = -105(321) + [24(2) \times \text{LVP}] \]
\[ -[1.5(0.7) \times \text{volume}] - [267(102) \text{ if ischaemic}]. \]
Peak LVP was the single most important predictor ($F_{1,164} = 164$) and accounted for 66% of the overall variance (volume 4%, ischaemia 2%, residual variance 29%).

**TIME CONSTANT OF ISOVOLUMIC RELAXATION**

The time constant of isovolumic relaxation ($\tau$) increased consistently during ischaemia which resulted in a significant difference between control and ischaemia when assessed by paired comparison. However, when the combined effects of ischaemia and alterations in circulating blood volume on $\tau$ were assessed by general linear interactive modelling, the term “ischaemia” failed to reach statistical significance. Thus absolute values for $\tau$ could not distinguish between control and ischaemia. Only when values for $\tau$ were normalized to an initial value of 100% did a significant effect of myocardial ischaemia become apparent (variable estimate + 6.5 (1.5)%, $P \leq 0.01$). Alterations in circulating blood volume had no significant effect on $\tau$ (for both absolute values and percentage changes) during both baseline and ischaemia (fig. 3).

**REGIONAL LENGTHENING**

In the control stage, there was a significant inter-regional difference in peak lengthening rate (apex 68 (11) mm s$^{-1}$; base 45 (5) mm s$^{-1}$; $P < 0.05$), relaxation time (apex 123 (6) ms; base 88 (4) ms; $P < 0.05$) and R–PLR interval (apex 325 (14) ms; base 290 (11) ms; $P < 0.05$). The combined effects of ischaemia and volume loading on regional indices in ischaemic and non-ischaemic myocardium are shown in tables 3 and 4. Note that despite a significant increase in the R–L$_{\text{ens}}$ interval in the ischaemic area, the interval between R wave and peak lengthening rate (R–PLR) remained unchanged. Likewise, the decrease in R–L$_{\text{ens}}$ of the remote non-ischaemic area was accompanied by an unchanged R–PLR interval. Myocardial ischaemia was associated with a decrease in PLR in both ischaemic and remote non-ischaemic myocardium and in neither area did volume loading modify PLR during the control and ischaemic stages.

**Discussion**

Myocardial ischaemia affected the lengthening pattern in both ischaemic and remote non-ischaemic myocardium: in ischaemic myocardium the beginning of the lengthening period was delayed and PLR was reduced markedly while in remote non-ischaemic myocardium, lengthening started earlier and there was a moderate decrease in PLR. These changes were not modified by alterations in circulating blood volume. Moreover, alterations in circulating blood volume did not affect the time constant of isovolumic relaxation, both in the presence or absence of myocardial ischaemia. A highly significant correlation between peak negative $dP/dt$ and peak LVP was preserved during the ischaemic period and peak LVP was the most important predictor of peak negative $dP/dt$.

**GLOBAL DIASTOLIC FUNCTION**

A decrease in peak negative $dP/dt$ and an increase in both time constant of isovolumic relaxation ($\tau$) and end-diastolic pressure are well established features of myocardial ischaemia both in humans and in a variety of experimental models [3–5, 13, 14].

**PEAK NEGATIVE $dP/dt$ ($-dP/dt$)**

In the absence of myocardial ischaemia, $-dP/dt$ is influenced by left ventricular contractility, end-systolic volume and mean aortic pressure [15, 16]. Consistent with the present findings, Gaasch and colleagues observed an increase in $-dP/dt$ when an increase in preload, caused by volume expansion, was accompanied by an increase in afterload [17]. In contrast, an isolated increase in preload (increase in afterload prevented by aortic unloading) resulted in unchanged values for $-dP/dt$. Bahler and Martin observed a decrease in $-dP/dt$, associated with a decrease in peak systolic LVP, following a decrease
Preload and left ventricular diastolic function

in preload induced by caval occlusion [11]. In addition to confirming their finding of a highly significant correlation between $-dP/dt$ and peak LVP in normally perfused myocardium, our study has demonstrated that this correlation was well preserved during myocardial ischaemia. Using interactive statistical modelling we demonstrated that peak LVP was the most important predictor of $-dP/dt$. Thus the decrease in peak negative $dP/dt$, associated with myocardial ischaemia, appears to reflect mainly an ischaemia-induced decrease in developed pressure rather than direct impairment of early relaxation.

Table 2: Effect of volume loading on regional wall motion in ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Systolic shortening and post-systolic shortening are expressed as a percentage of total shortening (TS) and add up to 100 %. Variable estimates (V × I) indicate an effect of volume loading during the ischaemic state. *P < 0.05, **P < 0.01.

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Variable estimates (SEM) were obtained using general linear interactive modelling (see text). The interactive term (V × I) indicates an effect of volume loading during the ischaemic state. *P < 0.05, **P < 0.01.
TIME CONSTANT OF ISOVOLUMIC RELAXATION

Although a consistent increase in the time constant of isovolumic relaxation (\(\tau\)) (mean, SEM) occurred, absolute values did not distinguish between control (○) and ischaemia (●), as indicated by the overlapping error bars.

Table 3  Effect of volume loading on segmental lengthening in ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Variable estimates (SEM) were obtaining using general linear interactive modelling (see text). None of the interactive terms (not displayed) proved to be significant at the 0.05 level for any variable. R–PLR = Interval between preceding R wave of the ECG and the peak lengthening rate, R–L_{min} = PLR interval (ms) Control 290 (18) 297 (17) 301 (16) 245 (7) 0 0

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Table 4  Effect of volume loading on segmental lengthening in non-ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Variable estimates (SEM) were obtained using general linear interactive modelling (see text). None of the interactive terms (not displayed) proved to be significant at the 0.05 level for any variable. R–PLR = Interval between preceding R wave of the ECG and the peak lengthening rate, R–L_{min} = PLR interval (ms) Control 290 (18) 285 (13) 276 (17) 241 (4) 0 0

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- **P < 0.01
- *P < 0.05
- **P < 0.001
remained unchanged (increase in afterload prevented by aortic unloading), whereas an increase in $\tau$ was observed when volume loading increased both end-diastolic and peak systolic left ventricular pressure. However, despite an increase in peak systolic pressure in the present investigation, alterations in circulating blood volume did not affect $\tau$. The load-dependence, if any, of the time constant of isovolumic relaxation during myocardial ischaemia has not been investigated thoroughly. Our results demonstrated that modest alterations in preload had no significant effect on the ischaemia-induced increase in $\tau$.

REGIONAL DIFFERENCES IN DIASTOLIC FUNCTION

In agreement with a previous report [12], the present investigation demonstrated that baseline PLR was higher in the apex than in the base. In addition, we found a significantly shorter relaxation time at the base compared with the apex. Similarly, an isolated increase in left atrial pressure after mitral valve opening has been found to be associated with a significantly greater effect on the segmental PLR in apical compared with mid-wall or posterior myocardium [21]. Taken together, findings from the present and previous [12, 21] investigations indicate that inter-regional differences in segmental wall motion are not confined solely to the ejection period [22].

In the absence of myocardial ischaemia, alterations in circulating blood volume had no effect on PLR or on the percentage of lengthening during the rapid phase in both apical and basal myocardium. Similar findings were reported by Lew and LeWinter [12]. In contrast, Bahler and Martin demonstrated that acute reductions in preload (caval occlusion) were associated with proportional reductions in the peak rate of early diastolic re-extension and in the relaxation time measured in the internal short axis (midway between the apex and base) [11]. In addition, Ishida and colleagues found a 20% increase in peak transmitral flow rate after volume loading had increased end-diastolic pressure over a range similar to that of the present study (9.4–13.3 mm Hg) [23]. However, these apparently contradictory findings may simply result from assessment of regional function in a circumferential plane in the present study. Assuming that at the site of the crystals, the left ventricle may be regarded as a cylindrical annulus, changes in the area of the cavity and hence intra-cavitary volume ($V$), are proportional to the square of the measured subendocardial circumferential length ($V = kL^2$). Thus the change in volume ($dV$) which corresponds to any change in length ($dL$) depends on the instantaneous length ($dV/dt = 2kL \times dL/dt$). Accordingly, in the presence of an unchanged peak segmental lengthening rate the peak rate of volume change is proportional to $2L$. Thus the 10% increase in segmental length, brought about by volume modification under control conditions, is compatible with a 20% increase in $dV/dt$ found by Ishida and colleagues [23] in their study involving similar modification of left ventricular end-diastolic pressure.

DIASTOLIC FUNCTION OF ISCHAEMIC MYOCARDIUM

A decrease in the peak rate of regional wall thinning or PLR, or both, was demonstrated in an area subjected to exercise-induced ischaemia, pacing-induced ischaemia or flow deprivation as a result of coronary occlusion [24–27]. Whereas the effect of alterations in preload on re-extension in normally perfused myocardium has been investigated [11, 12], the present study is the first to demonstrate that moderate alterations in preload have no significant effect on ischaemia-induced changes in the pattern of segmental lengthening in ischaemic myocardium.

In the ischaemic area, myocardial ischaemia was associated with a reduction in the fraction of lengthening during the rapid phase. This finding, which was not influenced significantly by alterations in circulating blood volume, is compatible with a decrease in the early-to-late peak transmitral flow velocity (E-to-A ratio) which is found commonly in patients with coronary artery disease [28]. In contrast, the relaxation time [11] proved to be insensitive to both ischaemia and volume modification.

DIASTOLIC FUNCTION OF REMOTE NON-ISCHAEMIC MYOCARDIUM

Our results are in agreement with the findings of an earlier study from our laboratory that demonstrated an earlier onset and a decrease in maximal lengthening rate of non-ischaemic segments during coronary occlusions in anaesthetized dogs [29]. In contrast, Nonogi and colleagues demonstrated an increase in PLR of the non-ischaemic area during exercise-induced ischaemia in patients with coronary artery disease [30]. No such increase in PLR was found by Nakamura and colleagues during pacing-induced angina in patients with coronary artery disease [26]. In the anaesthetized pig, Takahashi, Levine and Grossman found a significant increase in PLR in non-ischaemic myocardium during pacing-induced ischaemia but not during coronary occlusions [27]. Their findings suggest that an increase in heart rate, caused by pacing or exercise, may have an independent effect on PLR in remote non-ischaemic myocardium. Whereas the effects of preload on systolic function in remote non-ischaemic myocardium have been investigated previously [31] the present study is the first to demonstrate the combined effects of myocardial ischaemia and alterations in preload on the regional lengthening pattern of remote non-ischaemic myocardium.

CRITIQUE OF METHODOLOGY

The present investigations were performed in acutely instrumented animals with an open chest and an open pericardium. Therefore, the effects of myocardial ischaemia occurred in the presence of, and may have been modified by, an acute surgical preparation. Our findings were obtained in a model of low-flow ischaemia and, therefore, cannot necessarily be extrapolated to demand-induced ischaemia. At present regional myocardial ischaemia can neither qualitatively nor quantitatively be defined using...
indices of diastolic (dys)function; we therefore defined ischaemia using a systolic wall motion abnormality (systolic shortening) and ensured the presence of severe myocardial ischaemia during the whole loading procedure. However, as the extent of systolic dysfunction (segmental shortening) was more marked than that of diastolic dysfunction (segmental shortening), further studies are necessary to determine if and how our findings may be modified in the settings of mild or moderate ischaemia. In agreement with a previous study from our laboratory [32], we found that systolic shortening was related inversely to preload. As it is unlikely that our loading procedure altered the passive properties of severely ischaemic myocardium, our observation may relate to the combined effects of preload and stretch caused by the shortening of non-ischaemic segments during the period of isovolumic contraction: in the presence of a low preload the ischaemic segment is situated on the flat part of its pressure–length relation and further shortening is easily accomplished during isovolumic contraction. In contrast, further shortening is difficult to achieve when a high preload has already placed the ischaemic segment on the steep part of its pressure–length relation.

The regional pattern of shortening was obtained from sonomicrometers implanted in a circumferential plane. Depending on the ventricular region, uniaxial measurements may underestimate the extent of both shortening and re-extension [33]. However, shortening and lengthening in the apical region of the anterior wall occurs predominantly in a circumferential plane [33]. To the best of our knowledge, the preferential plane(s) of regional deformations in basal areas of the anterior wall have not been described and, therefore, inter-regional comparisons have to be interpreted with caution.

General linear interactive modelling was used to assess the combined effects of myocardial ischaemia and alterations in circulating blood volume on dependent variables. In addition to identifying significant terms and interactions, this statistical method yields variable estimates which allow quantitative assessment of independent predictors. For example, the parameter estimates for the combined effects of ischaemia, peak ventricular pressure, and volume on $-\frac{dP}{dt}$ (see results) indicate that a similar decrease in $-\frac{dP}{dt}$ may be achieved by imposing myocardial ischaemia (−267 mm Hg s$^{-1}$) or by lowering the peak ventricular pressure by 11 mm Hg (−11 × 24 mm Hg s$^{-1}$).

**IMPLICATIONS**

As left ventricular diastolic function appears to be particularly sensitive to myocardial ischaemia, monitoring diastolic function may prove to be appropriate to detect and monitor perioperative myocardial ischaemia. However, in the perioperative period alterations in preload are common and, therefore, indices of diastolic function should be insensitive to alterations in circulating blood volume. Previous studies have demonstrated that moderate alterations in preload (changes in end-diastolic pressure ±4–5 mm Hg), caused by nitroglycerin or ventriculography, may mimic or mask diastolic dysfunction, as assessed by indices derived from the mitral inflow velocity profile [7, 8]. The present results suggest that indices derived from left ventricular pressure measurements are also of limited value: peak negative $\frac{dP}{dt}$ is preload-dependent and appears to reflect ischaemia-induced changes in contractility rather than relaxation. Absolute values for $\tau$, although preload-independent, failed to distinguish between ischaemia and control. However, our findings demonstrate that the pattern of segmental lengthening, while being sensitive to myocardial ischaemia, is not affected by alterations in preload. This suggests that the non-invasive monitoring of early segmental lengthening rather than flow profile or indices derived from left ventricular pressure may be useful for the detection and assessment of myocardial ischaemia. Further studies are necessary to determine if in the presence of other types of ischaemia (e.g. moderate low-flow ischaemia, demand-induced ischaemia) segmental lengthening is also sensitive to ischaemia and insensitive to alterations in preload. Moreover, clinical investigations (e.g. perioperative echocardiography) need to demonstrate if monitoring of the regional pattern of early lengthening is feasible and offers any advantage over the currently used monitoring of regional contractile function.

**Acknowledgements**

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