

Interregional Differences in the Systolic and Diastolic Response of Nonischemic Myocardium to Remote Coronary Occlusion

Stephan C. U. Marsch, M.D., D.Phil.,* Hernan R. Muñoz, M.D., M.Sc.,† Serge Dalmas, M.D.,‡
Pierre Foëx, M.D., D.Phil.§

Background: Previous work showed a twofold increase in stiffness of nonischemic myocardium at the base during ischemia of the left anterior wall. Whether the diastolic response of nonischemic myocardium to remote ischemia depends on the localization of the ischemic or the nonischemic area is unknown.

Methods: In dogs with open chests, regional function in ischemic and nonischemic myocardium was assessed (sonomicrometry) before and 5 min after occlusion of the left anterior descending coronary artery (LAD; $n = 7$) or the left circumflex coronary artery (LCX; $n = 7$).

Results: In nonischemic myocardium at the base, left anterior descending and left circumflex coronary artery occlusion both resulted in a twofold increase in chamber stiffness, whereas contractility and peak lengthening rate remained unchanged. In nonischemic myocardium of the posterior wall, left anterior descending coronary artery occlusion resulted in a significant ($P < 0.05$ vs. control, $P < 0.05$ vs. base) increase (mean \pm SD) in chamber stiffness ($25 \pm 6\%$), contractility ($17 \pm 5\%$), and peak lengthening rate ($28 \pm 6\%$). In nonischemic myocardium at the apex, left circumflex coronary artery occlusion resulted in a significant ($P < 0.05$ vs. control, $P < 0.05$ vs. base) increase in chamber stiffness ($15 \pm 5\%$), contractility ($16 \pm 4\%$), and peak lengthening rate ($19 \pm 6\%$).

Conclusions: Stiffening of remote nonischemic myocardium occurs regardless of the localization of the ischemic and nonischemic area. The systolic and diastolic responses of nonisch-

emic myocardium are not necessarily homogenous but may vary among different regions. (Key words: Coronary circulation; heart function and disease; myocardial ischemia.)

ALTHOUGH it has long been recognized that myocardial ischemia is associated with an increase in end-diastolic pressure, the underlying mechanisms are not clear. Stiffness, defined as change in pressure relative to a change in volume, is a quantitative measure of the left ventricular pressure-volume relation. We reported that low-flow myocardial ischemia is associated with an increase in stiffness in remote nonischemic myocardium.¹ Several studies have shown that the increased stiffness in nonischemic myocardium occurs regardless of the conscious or anesthetized state, the anesthetic agent used, or the experimental model used (open-chest or closed-chest).²⁻⁴ In the presence of an unaltered stiffness of nonischemic myocardium, an increase in end-diastolic pressure would be difficult to explain, solely by the increase in stiffness of the ischemic area.⁵ Stiffening of remote nonischemic myocardium may therefore be a prerequisite of the ischemia-induced increase in end-diastolic pressure. Therefore, further investigation of this phenomenon could have important physiologic and clinical implications. However, some important limitations of experimental data currently available¹⁻⁴ have to be recognized: First, the ischemic area was exclusively located in the apical region of the anterior wall (left anterior descending [LAD] coronary artery supply). Second, the remote nonischemic area was exclusively located in myocardium supplied by the left circumflex (LCX) coronary artery. Particularly, investigations indicating the precise location of the nonischemic region assessed the response to ischemia exclusively at the base. Third, the increase in stiffness in nonischemic myocardium was observed using uniaxial length measurements in the short-axis plane. However, uniaxial measurements may be insufficient to reflect three-dimensional alterations in nonischemic myocardium.⁶ More-

* Staff Anesthetist, University of Basel, Basel, Switzerland.

† Staff Anesthetist, Catholic University of Chile, Santiago, Chile.

‡ Staff Anesthetist, University of Lille, Lille, France.

§ Professor of Anesthesia, University of Oxford, Oxford, United Kingdom.

Received from The Nuffield Department of Anaesthetics, University of Oxford, Oxford, United Kingdom. Submitted for publication September 30, 1998. Accepted for publication April 29, 1999. Supported by grant G9102838SA from the Medical Research Council of Great Britain, London, United Kingdom; the Ciba-Geigy Jubilaeumsstiftung, Basel, Switzerland (Dr. Marsch); the Roche Research Foundation, Basel, Switzerland (Dr. Marsch); and the Imperial Chemical Industries Fellowship of the European Academy of Anaesthesiology (Dr. Dalmas).

Address reprint requests to Dr. Marsch: Departement Anaesthesie, Kantonsspital, 4031 Basel, Switzerland. Address electronic mail to: marsch@ubaclu.unibas.ch

over, different regions of the heart may differ in sarcomere length and geometric arrangement of muscle fibers. In the absence of myocardial ischemia, apical and basal myocardium differ in stiffness, contractility, and response to positive or negative inotropic interventions.⁷⁻¹⁰ In addition, there is evidence that the contractile response of nonischemic myocardium is influenced by the localization of the ischemic area.^{11,12} Whether regional diastolic function in remote nonischemic myocardium depends on the localization of the ischemic area or on the localization of the remote nonischemic area, or both, is not known.

The current study was designed to test the hypothesis that stiffening of remote nonischemic myocardium is not restricted to the basal region but is a physiologic response to ischemia that occurs regardless of the localization of the ischemic and nonischemic area.

Materials and Methods

The study conforms to the United Kingdom Animals Act (Scientific Procedures, 1986).

Experimental Preparation

The experimental preparation is described in detail elsewhere.^{3,4} Briefly, a thoracotomy was performed during halothane anesthesia in 14 beagles of either sex, and the heart was exposed in a pericardial cradle. Instrumentation included a tube mounted on an umbilical tape around the inferior cava vein proximal to the right atrium for caval occlusions; micromanometer-tipped 8-French catheters in the aortic arch and in the left ventricle for measurement of systemic and ventricular pressures; and a Doppler flow probe placed around the proximal ascending aorta. For the measurement of segmental dimensions, pairs of piezoelectric crystals (5 MHz, 2-mm outer diameter) were implanted in the sub-endocardium approximately 10 mm apart *via* small stab wounds. Crystals were implanted in myocardium supplied by the LAD and LCX coronary arteries.

Experimental Protocol

In the animals of group A (LAD ischemia, $n = 7$) we investigated the effects of myocardial ischemia in an apical area of the anterior wall on remote nonischemic myocardium located in the posterior wall and the basal region of the anterior wall. Moreover, in the basal region, we assessed the response to ischemia in both the short-axis plane and the long-axis plane. A snare was

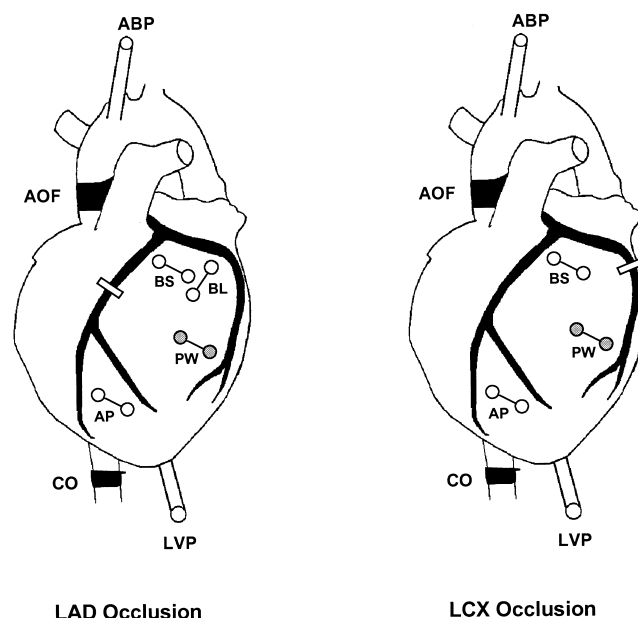


Fig. 1. Diagram illustrating the experimental instrumentation for left anterior descending coronary artery (LAD) occlusion (*left*) and left circumflex coronary artery (LCX) occlusion (*right*), respectively. Sonomicrometers were pairwise implanted in the short-axis plane in the near apical region (AP) of the anterior wall, in the posterior wall (PW) midway between the apex and the base, and near the base of the anterior wall (BS). In experiments involving LAD occlusion, an additional pair of sonomicrometers were implanted in the long-axis plane of the base (BL). ABP = aortic blood pressure; AOF = aortic flow; CO = tape around the inferior caval vein for caval occlusion; LVP = left ventricular pressure.

placed around the LAD coronary artery distal to the first diagonal branch, and piezoelectric crystals were implanted in the short-axis plane in the near-apical region of the anterior wall (ischemic area); in the short-axis plane of the posterior wall, midway between the apex and the base; in the short-axis plane of basal myocardium of the anterior wall; and in the long-axis plane of basal myocardium of the anterior wall (fig. 1, left).

In the animals of group B (LCX ischemia, $n = 7$) we investigated the effects of myocardial ischemia of the posterior wall on remote nonischemic myocardium located in the apicoanterior region of the anterior wall and the basal region of the anterior wall. A snare was placed around the LCX coronary artery distal to the first marginal branch, and piezoelectric crystals were implanted in the short-axis plane of the posterior wall, midway between the apex and the base (ischemic area); in the short-axis plane in the near-apical region of the anterior wall; and in the short-axis plane of basal myocardium of the anterior wall (fig. 1, right).

NONISCHEMIC MYOCARDIAL FUNCTION

Table 1. Effects of 5-min LAD Occlusion on Global Hemodynamics (n = 7)

	Baseline	Occlusion
Heart rate (beats/min)	112 ± 11	110 ± 13
Systolic arterial pressure (mmHg)	119 ± 13	95 ± 16*
Diastolic arterial pressure (mmHg)	79 ± 11	66 ± 5*
LV end-diastolic pressure (mmHg)	6.7 ± 1.3	9.9 ± 1.6*
Peak positive dP/dt (mmHg/s)	2,103 ± 429	1,470 ± 342*
Peak negative dP/dt (mmHg/s)	2,225 ± 490	1,511 ± 318*
τ (ms)	27 ± 5	31 ± 5*

Values are mean ± SD.

LV = left ventricular; τ = time constant of isovolumic relaxation.

* $P < 0.05$ versus baseline.

After instrumentation, halothane was discontinued and fentanyl ($100 \mu\text{g/kg}$ then $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was administered intravenously. Mechanical ventilation (40% oxygen in nitrogen) was adjusted to maintain the end-tidal carbon dioxide concentration at 34–41 mmHg. The preparation was allowed to stabilize for 1 h before the experiment was started. Mid esophageal temperature was continuously measured and maintained at 36–37°C using a servocontrolled heating element incorporated in the operating table.

After completion of baseline recordings, a caval occlusion was performed by sliding down the tube on the tape around the cava vein. A period of 5 min was allowed for hemodynamics to recover after the caval occlusion. The snare around the coronary artery (LAD in group A, LCX in group B) was then abruptly tightened to achieve complete coronary occlusion, and hemodynamic recordings, including caval occlusion, were repeated after 5 min of occlusion.

Data Collection and Analysis

Hemodynamic signals were recorded during apnea at a sampling frequency of 500 Hz and stored on hard disk. The left ventricular dP/dt was obtained by electronic differentiation and the time constant of isovolumic relaxation (τ) was obtained as previously described.¹³ Length measures were normalized to an initial end-diastolic length of 10 mm. The following definitions were used to quantify regional wall movement: end-diastolic length (EDL), defined as length at the first upward (positive) deflection of the left ventricular dP/dt signal; length at the end of the isovolumic contraction (IVL), defined as length at the first upslope of the aortic flow signal; end-systolic length (ESL), defined as length at the first return to zero of the aortic flow signal; minimum

diastolic length after ESL (L_{\min}); maximum length during systole (L_{\max}).

Total segmental shortening (TS) was defined as $\text{EDL} - L_{\min}$ (in millimeters). Shortening during the isovolumic period was defined as $\text{EDL} - \text{IVL}$ and expressed as a percentage of total segmental shortening. Ejection shortening was defined as $\text{IVL} - \text{ESL}$ and expressed as a percentage of total segmental shortening. Postsystolic shortening was defined as $\text{ESL} - L_{\min}$ and expressed as a percentage of total segmental shortening. Thus, isovolumic shortening, ejection shortening, and postsystolic shortening add up to 100%. Paradoxical systolic bulging was defined as $L_{\max} - \text{EDL}$ and expressed as a percentage of EDL. Peak lengthening rates (PLRs; dL/dt_{\max}) were obtained by electronic differentiation. Regional contraction time was defined as the interval between the preceding R wave of the electrocardiogram and L_{\min} .

The regional preload recruitable stroke work (SW) relation was calculated as previously described.¹⁴ Briefly, segmental SW was obtained by electronic integration of the area of the segmental pressure-length loop. SW of consecutive beats during a caval occlusion was plotted against the corresponding EDL. Linear least-squares regression analysis was performed to calculate the slope (M_w) and length intercept (L_w) of the SW *versus* EDL relation:

$$\text{SW} = M_w \cdot \text{EDL} + L_w \quad (1)$$

For each caval occlusion the regional chamber stiffness constant (k) was obtained by fitting the end-diastolic

Table 2. Effects of 5-min LAD Occlusion on the Ischemic Area (n = 7)

	Baseline	Occlusion
Total shortening (mm)	3.0 ± 1.0	1.3 ± 0.5*
Isovolumic shortening (% of total shortening)	3 ± 8	0 ± 0
Ejection shortening (% of total shortening)	93 ± 3	2 ± 5*
Ejection shortening (mm)	2.8 ± 1.0	0.1 ± 0.3*
PSS (% of total shortening)	4 ± 5	98 ± 5*
Systolic bulging (%)	1 ± 3	12 ± 5*
End-diastolic length (mm)	10	11.9 ± 1.3*
Chamber stiffness (mm^{-1})	0.41 ± 0.16	0.67 ± 0.22*
R- L_{\min} interval (ms)	252 ± 56	321 ± 80*
Peak lengthening rate (mm s^{-1})	75 ± 32	44 ± 16*

Values are means ± SD. All length measures are normalized to an initial end-diastolic length of 10 mm.

PSS = postsystolic shortening; R- L_{\min} = interval from preceding R wave of the electrocardiogram to the minimum segment length.

* $P < 0.05$ versus baseline.

Table 3. Effects of 5-min LAD Occlusion on Remote Nonischemic Myocardium (n = 7)

	Basal Area (short axis)		Basal Area (long axis)		Posterior Wall	
	Baseline	Occlusion	Baseline	Occlusion	Baseline	Occlusion
Total shortening (mm)	1.8 ± 0.5	1.9 ± 0.5	1.7 ± 0.5	1.9 ± 0.8	1.9 ± 0.8	2.3 ± 0.8*
ISO shortening (% of total shortening)	2 ± 3	14 ± 5*	4 ± 3	22 ± 13*	3 ± 3	13 ± 5*
Ejection shortening (% of total shortening)	96 ± 3	85 ± 5*	91 ± 5	74 ± 13*	95 ± 3	86 ± 5*
Ejection shortening (mm)	1.8 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	1.4 ± 0.5	1.8 ± 0.8	2.0 ± 0.8
PSS (% of total shortening)	2 ± 3	1 ± 3	5 ± 5	4 ± 5	2 ± 3	1 ± 3
Systolic bulging (%)	1 ± 3	0 ± 0	0.6 ± 0.8	0 ± 0	0.8 ± 1.3	0 ± 0
Slope PRSW (mmHg)	64 ± 16†	63 ± 16†	46 ± 21	52 ± 24	69 ± 24†	82 ± 27*†
Length intercept PRSW (mm)	7.5 ± 2.0	8.1 ± 1.6*	7.9 ± 1.3	8.3 ± 1.9*	7.1 ± 2.1	7.6 ± 1.9*
End-diastolic length (mm)	10	10.4 ± 0.3*	10	10.5 ± 1.3*	10	10.6 ± 0.5*
Chamber stiffness (mm ⁻¹)	0.62 ± 0.19†	1.01 ± 0.31*†	0.98 ± 0.24	1.33 ± 0.24*	0.56 ± 0.16†	0.72 ± 0.23*†
R-L _{min} interval (ms)	245 ± 58	217 ± 64*	234 ± 80	209 ± 66*	238 ± 77	213 ± 56*
Peak lengthening rate (mm s ⁻¹)	30 ± 8	35 ± 16	28 ± 16	32 ± 13	32 ± 19	41 ± 24*

Values are means ± SD. All length measures are normalized to an initial end-diastolic length of 10 mm.

ISO shortening = shortening during isovolumic contraction; PSS = postsystolic shortening; PRSW = preload recruitable stroke work; R-L_{min} = interval from preceding R wave of the electrocardiogram to the minimum segment length.

* $P < 0.05$ versus corresponding baseline.

† $P < 0.05$ versus corresponding value in the long axis of the basal area.

pressure-length data to equation 2 (A is a curve-fitting constant). High correlation coefficients ($r > 0.95$) were found in all animals.

$$P = Ae^{k \cdot L} \quad (2)$$

To minimize the potentially confounding effects of noncontractile components (*e.g.*, connective tissue), the comparison of stiffness constants between baseline and occlusion was performed over the same range of end-diastolic pressures. Thus, during the ischemic state all data above the end-diastolic pressure of the baseline state were discarded.

Statistical Analysis

Values are the mean ± SD. Means were compared by paired Student *t* test. The response of the different non-ischemic regions to myocardial ischemia in group A was compared by two-way analysis of variance followed by paired Student *t* tests using Bonferroni correction. A *P* value less than 0.05 was considered to represent statistical significance.

Results

Left Anterior Descending Ischemia

A 5-min complete LAD occlusion was associated with an increase in end-diastolic pressure and τ while decreases in peak positive dP/dt, peak negative dP/dt, and arterial blood pressure occurred (table 1). Note that

heart rate remained unaffected. In the ischemic area paradoxical systolic bulging occurred, and the hemodynamically effective shortening during the ejection period was replaced by ineffective postsystolic shortening (table 2). Consequently, no effective SW was performed and the preload recruitable SW (PRSW) relation (baseline: $M_w 94 \pm 24$, $L_w 6.7 \pm 1.6$) could not be calculated. This severe ischemia-induced systolic dysfunction was associated with an increased stiffness and a decreased PLR.

In the absence of ischemia, chamber stiffness was significantly greater in the long-axis plane of the base than in both the short-axis plane of the base and the posterior wall (table 3). In all three nonischemic areas, remote ischemia was associated with an increase in isovolumic shortening, end-diastolic length, length intercept of the PRSW, and regional chamber stiffness. Stiffening was significantly less pronounced in the posterior wall than at the base (figs. 2 and 3). Moreover, by contrast to the basal area, LAD ischemia was associated with an increase in PLR, an increase in total shortening, and steepening of the slope of the PRSW relation in the posterior wall (fig. 3). This increase in contractility however, resulted only in an increase in isovolumic shortening while ejection shortening decreased in relative terms and remained unchanged in absolute terms (table 3).

Left Circumflex Ischemia

The consequences of 5 min of LCX occlusion on global hemodynamics (table 4) and regional function in the

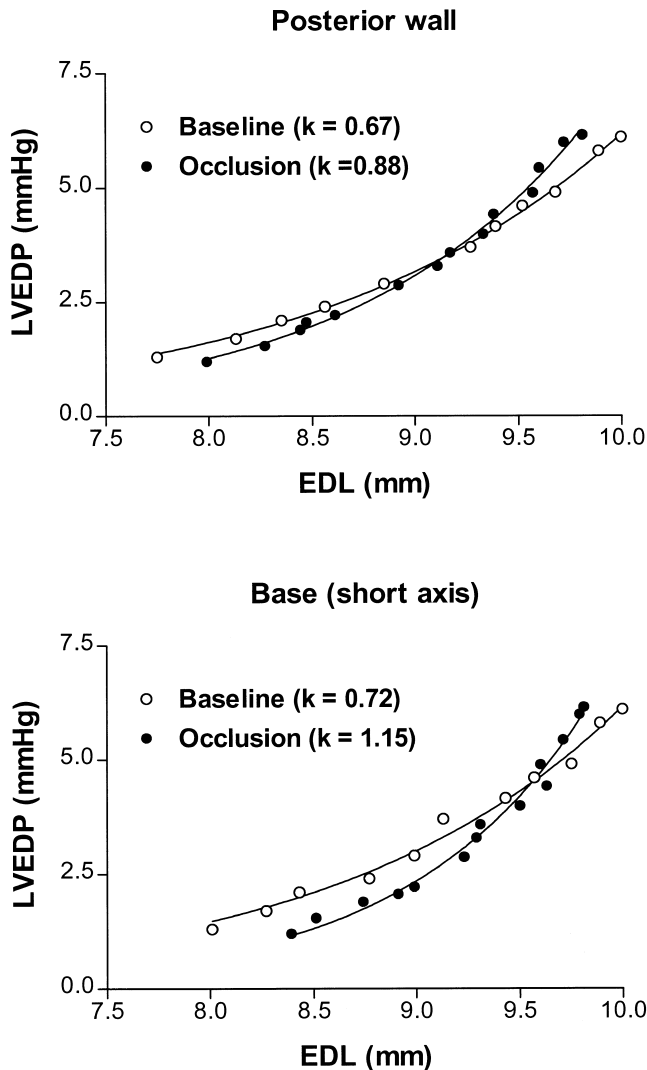


Fig. 2. End-diastolic pressure-length relations in nonischemic myocardium in the posterior wall (*top*) and at the base (*bottom*) before and during coronary occlusion of the left anterior descending coronary artery in a typical animal. Data were obtained from consecutive beats during occlusion of the cava vein. Note that during occlusion, all data above the end-diastolic pressure of the baseline state are discarded so the pressure-length relations cover the same pressure range. Curves were fitted through the data using the following equation: $LVEDP = Ae^{k \cdot EDL}$. Note that k increases (steepening of the slope) in both nonischemic regions during remote ischemia and that this increase in k is more pronounced at the base. EDL = end-diastolic length; k = chamber stiffness constant; LVEDP = left-ventricular end-diastolic pressure.

ischemic area (table 5) were very similar to that of LAD occlusion described previously.

During baseline, a greater PLR, a lower stiffness, and higher indices of contractility were found at the apex

compared to the base (table 6). In both the apical and basal areas of the remote nonischemic anterior wall, LCX coronary occlusion was associated with an increase in chamber stiffness (figs. 3 and 4). Note that this increase in stiffness was significantly more pronounced ($P = 0.005$) in the basal compared to the apical area (fig. 3).

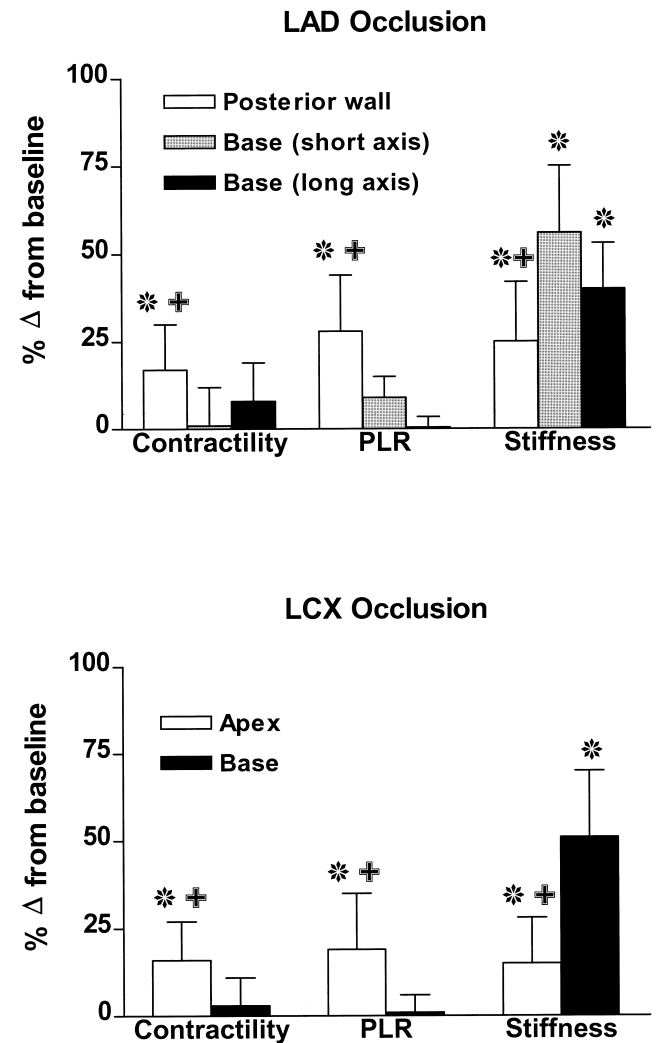


Fig. 3. Effect of 5 min of coronary occlusion on contractility (slope of the preload recruitable stroke work relation), peak lengthening rate (PLR), and regional chamber stiffness in remote nonischemic myocardium. Data are mean percentage changes from preocclusion values \pm SD. (*Top*) Effect of left anterior descending coronary artery (LAD) occlusion on nonischemic myocardium located in the posterior wall, the short-axis plane of the base, and the long-axis plane of the base. * $P < 0.05$ versus preocclusion value; † $P < 0.05$ versus base (both short axis and long axis). (*Bottom*) Effect of left circumflex coronary artery (LCX) occlusion on nonischemic myocardium located at the apex and the base of the anterior wall. * $P < 0.05$ versus preocclusion value; † $P < 0.05$ versus base.

Table 4. Effects of 5-min LCX Occlusion on Global Hemodynamics (n = 7)

	Baseline	Occlusion
Heart rate (beats/min)	108 ± 27	118 ± 24
Systolic arterial pressure (mmHg)	115 ± 19	92 ± 24*
Diastolic arterial pressure (mmHg)	80 ± 16	61 ± 13*
LV end-diastolic pressure (mmHg)	6.1 ± 2.4	8.6 ± 1.9*
Peak positive dP/dt (mmHg/s)	2,277 ± 604	1,682 ± 761*
Peak negative dP/dt (mmHg/s)	2,481 ± 596	1,757 ± 803*
τ (ms)	28 ± 5	33 ± 8*

Values are mean ± SD.

LV = left ventricular; τ = time constant of isovolumic relaxation.

* $P < 0.05$ versus baseline.

By contrast to the basal area, the apical area exhibited a compensatory increase in contractile function and PLR (table 6, figs. 3 and 5).

Remote Ischemia and Stiffness at the Base in the Thickness Plane

To assess the effect of remote ischemia on stiffness in the thickness plane, we reanalyzed data from a previous study from our laboratory.⁴ In that study, we implanted sonomicrometers at the base in both the short-axis and the thickness plane. Although stiffness constants were derived from the length measures, thickness measures were only used to calculate wall stress. We reanalyzed data from 11 animals that were subjected to a baseline stage and 45 min of severe myocardial ischemia of the anterior wall (LAD supply) during fentanyl anesthesia. In response to remote ischemia, chamber stiffness at the base in the short axis increased from $0.63 \pm 0.27 \text{ mm}^{-1}$ to $0.81 \pm 0.36 \text{ mm}^{-1}$ ($P < 0.05$), whereas, in the thickness plane, chamber stiffness increased from $1.04 \pm 0.31 \text{ mm}^{-1}$ to $1.43 \pm 0.48 \text{ mm}^{-1}$ ($P < 0.05$).

Discussion

Coronary occlusion results in almost immediate contractile dysfunction of the ischemic area that, in turn, no longer contributes to the mechanical function of the heart as a pump. In these circumstances, the nonischemic myocardium becomes critical for the maintenance of global cardiac function. Not surprisingly, a substantial number of laboratory and clinical studies focused on the contractile response of nonischemic myocardium to remote myocardial ischemia. By contrast, there are only limited data regarding diastolic function in remote nonischemic myocardium.

In a previous investigation, we were able to demonstrate that, during halothane anesthesia (0.8% v/v), myocardial ischemia of the anterior wall is associated with an increased stiffness of remote nonischemic myocardium at the base in dogs with open chests.¹ Subsequent work from our laboratory confirmed this finding during isoflurane (1.0% v/v) and fentanyl anesthesia.^{3,4} In conscious, long-term instrumented dogs, Pagel *et al.*² found an increase in stiffness of remote nonischemic myocardium located in an area supplied by the LCX coronary artery during brief (2 min) occlusions of the LAD coronary artery. It is noteworthy that, in all of the aforementioned investigations, the nonischemic area was located at the base, whereas the ischemic area was located in the apical area of the left anterior wall.

In the absence of myocardial ischemia, the base is stiffer than the apex. This may relate to structural differences in myocytes, geometric arrangement of muscle fibers, or tethering of the base to the mitral valve apparatus. All these factors may limit the ability of the base to stretch passively and may cause further stiffening in the settings of altered ventricular loading conditions brought about by myocardial ischemia. The current study shows that stiffening of the nonischemic myocardium occurred regardless of the localization of the ischemic and the nonischemic area. In addition, at the base, stiffening was not restricted to the short-axis plane but could be observed in the long-axis plane also. Moreover, reanalyzing data from our previous study revealed that stiffening at the base occurs also in the thickness plane. Therefore, stiffening of nonischemic myocardium in response to

Table 5. Effects of 5-min LCX Occlusion on the Ischemic Area (Posterior Wall)

	Baseline	Occlusion
Total shortening (mm)	1.5 ± 0.5	0.7 ± 0.3*
Isovolumic shortening (% of total shortening)	3 ± 8	0 ± 0
Ejection shortening (% of total shortening)	92 ± 11	13 ± 24*
Ejection shortening (mm)	1.4 ± 0.5	0.1 ± 0.3*
PSS (% of total shortening)	5 ± 5	87 ± 24*
Systolic bulging (%)	1 ± 3	7 ± 3*
End-diastolic length (mm)	10	10.6 ± 0.5*
Chamber stiffness (mm^{-1})	0.67 ± 0.19	1.08 ± 0.29*
R-L _{min} interval (ms)	235 ± 39	300 ± 39*
Peak lengthening rate (mm/s)	31 ± 11	14 ± 5*

Values are means ± SD (n = 7). All length measures are normalized to an initial end-diastolic length of 10 mm.

PSS = postsystolic shortening; R-L_{min} = interval from preceding R wave of the electrocardiogram to the minimum segment length.

* $P < 0.05$ versus baseline.

NONISCHEMIC MYOCARDIAL FUNCTION

Table 6. Effects of 5-min LCX Occlusion on Remote Nonischemic Myocardium of the Apical Wall

	Basal Area		Apical Area	
	Baseline	Occlusion	Baseline	Occlusion
Total shortening (mm)	2.2 ± 1.3	2.3 ± 1.3	2.5 ± 0.5†	3.1 ± 0.3*†
Isovolumic shortening (% of total shortening)	4 ± 5	9 ± 8*	5 ± 5	17 ± 11*†
Ejection shortening (% of total shortening)	93 ± 5	90 ± 8*	93 ± 5	81 ± 11*†
Ejection shortening (mm)	2.1 ± 1.3	2.1 ± 1.3	2.4 ± 0.5†	2.4 ± 0.3*†
PSS (% of total shortening)	3 ± 5	1 ± 3	2 ± 3	2 ± 3
Systolic bulging (%)	1.7 ± 2.9	0.6 ± 1.6	0.6 ± 1.3	0 ± 0
Slope PRSW (mmHg)	58 ± 19	60 ± 21	87 ± 19†	99 ± 27*†
Length intercept PRSW (mm)	7.4 ± 1.9	7.8 ± 1.6*	6.9 ± 1.3	7.6 ± 1.9*
End-diastolic length (mm)	10	10.3 ± 0.5	10	10.4 ± 0.3*
Chamber stiffness (mm ⁻¹)	0.71 ± 0.39	1.04 ± 0.51	0.44 ± 0.19†	0.52 ± 0.22*†
R-L _{min} interval (ms)	235 ± 56	213 ± 53*	238 ± 48	213 ± 16*
Peak lengthening rate (mm/s)	28 ± 19	29 ± 24	58 ± 21†	70 ± 19*†

Values are mean ± AD (n = 7). All length measures are normalized to an initial end-diastolic length of 10 mm.

PSS = postsystolic shortening; PRSW = preload recruitable stroke work; R-L_{min} = interval from preceding R wave of the electrocardiogram to the minimum segment length.

* $P < 0.05$ versus corresponding baseline value.

† $P < 0.05$ versus corresponding value in the basal area.

remote ischemia appears to occur independently of the localization of the ischemic area, the localization of the nonischemic area, and the plane used to assess regional function.

What are the potential implications of our findings? Pagel *et al.*² observed that 1.1 and 1.6 minimum alveolar concentration desflurane and 1.6 minimum alveolar concentration isoflurane attenuated the increase in stiffness of nonischemic myocardium, but also attenuated the ischemia-induced increase in left ventricular end-diastolic pressure. Because we observed that an increase in stiffness occurs in all parts of the nonischemic area, we suggest that stiffening of remote nonischemic myocardium is a prerequisite of the ischemia-induced increase in left ventricular end-diastolic pressure.

The majority of investigations that assessed the systolic response of nonischemic response found hyperkinesia (*i.e.*, an enhanced contractile function).^{2,11,12,15,16} However, without apparent reason, several studies, including studies from our laboratory, were unable to show hyperkinesia in remote nonischemic myocardium.^{1,3,4,17-21} Including the current investigation, we are aware of only three studies^{2,4} that assessed contractility of remote nonischemic myocardium using the PRSW, an index of contractility independent of loading conditions. In these studies, changes in the slope of the PRSW paralleled changes in shortening fraction. Thus, load dependence is an unlikely explanation for the absence of hyperkinesia in remote nonischemic myocardium in some studies, whereas it is present in most.

In nonischemic areas exhibiting an increase in contractility, we did not observe an increase in hemodynamically effective ejection shortening in nonischemic myocardium. Instead, isovolumic shortening increased, leading to the paradoxical outward movement (bulging) of the ischemic area. Noma *et al.*¹⁵ demonstrated that, at low levels of preload, hyperkinesia in nonischemic myocardium is predominantly caused by an increase in isovolumic shortening, whereas, at higher levels of preload, hyperkinesia reflects an increase in ejection shortening. A simple explanation for this observation may be that a high level of preload stretches the ischemic area already at end-diastole, so additional stretching forces, imposed by isovolumic contraction of nonischemic myocardium, can have only a limited effect. In keeping with this hypothesis is the observation that the extent of systolic bulge is inversely related to preload.^{22,23}

Divergent findings were reported concerning PLRs in remote nonischemic myocardium: although some investigators reported an increase in PLR,^{2,20} others observed an unchanged or even reduced PLR.^{3,4,20,24,25} In the current study, an increased PLR occurred in nonischemic segments that exhibited an increased contractility. By contrast, an unchanged PLR occurred in regions with unchanged contractility. This pattern is consistent with findings of *in vitro* and *in vivo* studies that have shown a close correlation of the extent of systolic shortening and the PLR.^{26,27}

In the absence of myocardial ischemia, apical and basal myocardium differ in contractility, PLR, and stiffness.⁷⁻¹⁰

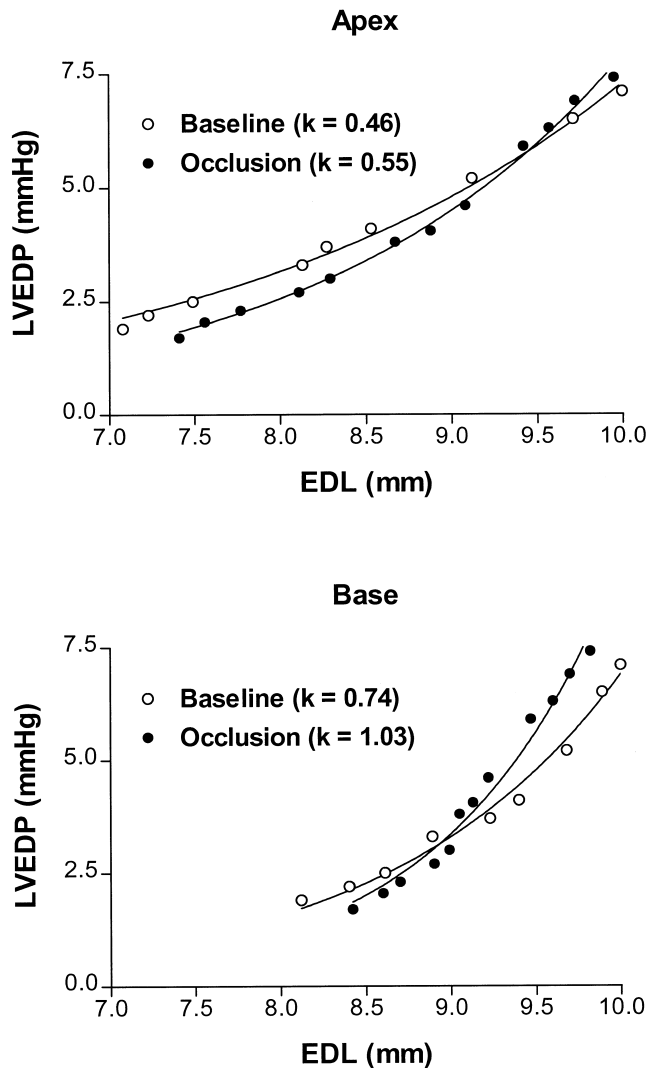


Fig. 4. End-diastolic pressure-length relations in nonischemic myocardium in the apex (*top*) and at the base (*bottom*) before and during coronary occlusion of the left circumflex coronary artery in a typical animal. Data were obtained from consecutive beats during occlusion of the cava vein. Note that during occlusion all data above the end-diastolic pressure of the baseline state are discarded so the pressure-length relations cover the same pressure range. Curves were fitted through the data using the following equation: $LVEDP = Ae^{k \cdot EDL}$. During baseline the base is much stiffer than the apex. Moreover, the increase in k during remote ischemia that occurs in both nonischemic areas is more pronounced in the base. EDL = end-diastolic length; k = chamber stiffness constant; LVEDP = end-diastolic pressure.

The current investigation shows that during conditions of remote ischemia, contractility increases predominantly in the already more-active apical myocardium, whereas stiffness increases predominantly in the less-compliant basal region. Thus, ischemia of the posterior

wall increases preexisting regional differences in mechanical function in the anterior wall. In the absence of ischemia, mechanical function did not differ between myocardium from the posterior wall and from the base. However, ischemia of the anterior wall led to interregional differences in contractility, peak lengthening, and regional chamber stiffness. Therefore, it appears that LAD and LCX coronary artery occlusion both induce mechanical heterogeneity, not only between ischemic and nonischemic segments, but also within nonischemic segments.

We studied anesthetized animals with open chests, but our findings concord with previous studies performed in conscious animals, particularly concerning the degree of stiffening of nonischemic myocardium.² Previous work showed the load dependency of the response of nonischemic myocardium to remote ischemia.^{15,22} In the current study, we did not systematically alter loading conditions during the ischemic state; therefore, we cannot exclude the possibility that regional differences in nonischemic mechanics may be modified by alterations in loading conditions.

In conclusion, the current study shows that coronary occlusion is associated with an increased stiffness in re-

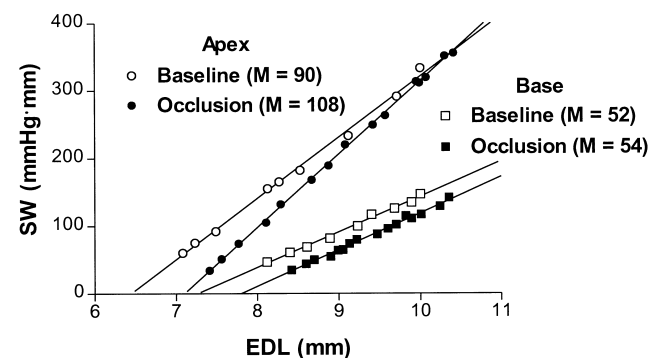


Fig. 5. Preload recruitable stroke work (PRSW) relation in nonischemic myocardium at the apex and the base before and during coronary occlusion of the left circumflex coronary artery. Data (from the same animal as in fig. 3) were obtained from consecutive beats during occlusion of the cava vein. Stroke work was obtained by integration of the area of segmental pressure-length loops and plotted against the corresponding end-diastolic lengths (EDL). Linear least-squares regression lines are fitted to the data. In the absence of ischemia, PRSW at the apex is considerably greater than at the base, indicating a greater contractility at the apex compared to the base. Remote occlusion results in an increase of the length intercept; *i.e.*, a rightward shift of the PRSW in both nonischemic regions. At the apex, remote occlusion results in a steepening of the PRSW relation, indicating an increase in contractility. By contrast, at the base PRSW relations during baseline and remote occlusion are parallel indicating an unchanged contractility during remote occlusion. M = slope of the PRSW relation.

NONISCHEMIC MYOCARDIAL FUNCTION

remote nonischemic myocardium that occurs regardless of the localization of the ischemic and nonischemic areas. Moreover, regional differences may exist in both the diastolic and the systolic response to remote ischemia.

References

- Marsch SCU, Wanigasekera VA, Ryder WA, Wong LSS, Foëx P: Graded myocardial ischemia is associated with a decrease in diastolic distensibility of the remote non-ischemic myocardium in the anesthetized dog. *J Am Coll Cardiol* 1993; 22:899-906
- Pagel PS, Hettrick DA, Lowe D, Tessmer JP, Warltier DC: Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs. *ANESTHESIOLOGY* 1995; 83:1021-35
- Marsch SCU, Dalmas S, Philbin DM, Ryder WA, Foëx P: Myocardial ischemia and reperfusion are associated with an increased stiffness of remote nonischemic myocardium. *Anesth Analg* 1996; 82: 695-701.
- Marsch SCU, Dalmas S, Philbin DM, Ryder WA, Wong LSS, Foëx P: Effects and interactions of nitrous oxide, myocardial ischaemia, and reperfusion on left ventricular diastolic function. *Anesth Analg* 1997; 84:39-45
- Edwards CH, Rankin JS, McHale PA, Ling D, Anderson RW: Effects of ischemia on left ventricular regional function in the conscious dog. *Am J Physiol* 1981; 240:H413-20
- Villarreal FJ, Lew WYW: Finite strains in anterior and posterior wall of canine left ventricle. *Am J Physiol* 1990; 259:H1409-18
- Lew WYW, LeWinter MM: Regional circumferential lengthening patterns in canine left ventricle. *Am J Physiol* 1983; 245:H741-8
- Hoit BD, LeWinter M, Lew WYW: Independent influence of left atrial pressure on regional peak lengthening rates. *Am J Physiol* 1990; 259:H480-7
- Diedericks J, Leone BJ, Foëx P: Regional differences in left ventricular wall motion in the anesthetized dog. *ANESTHESIOLOGY* 1989; 72:82-90
- Sohma A, Foëx P, Ryder WA: Regional distensibility, chamber stiffness, and elastic stiffness constant in halothane and propofol anesthesia. *J Cardiothor Vasc Anesth* 1993; 7:188-94
- Hoit BD, Lew WYW: Functional consequences of acute anterior vs. posterior wall ischemia in canine left ventricles. *Am J Physiol* 1988; 254:H1065-73
- Marino PN, Kass DA, Becker LC, Lima JAC, Weiss JL: Influence of site of regional ischemia on nonischemic thickening in anesthetized dogs. *Am J Physiol* 1989; 256:H1417-25
- Weiss JL, Frederiksen JM, Weisfeldt ML: Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Invest* 1976; 58:751-76
- Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS: Linearity of the Frank-Starling relationship in the intact heart: The concept of preload recruitable stroke work. *Circulation* 1985; 71:994-1009
- Noma S, Askenase AD, Weintraub WS, Klein LW, Agarwal JB, Helfant RH: Augmentation of contraction in remote nonischemic zone during acute ischemia. *Am J Physiol* 1988; 255:H301-10
- Ning X-H, Zweng TN, Gallagher KP: Ejection- and isovolumic contraction-phase wall thickening in nonischemic myocardium during coronary occlusion. *Am J Physiol* 1990; 258:H490-9.
- Kumada T, Karliner JS, Pouleur H, Gallagher KP, Shirato K, Ross J Jr: Effects of coronary occlusion on early ventricular diastolic events in conscious dogs. *Am J Physiol* 1979; 237:H542-9
- Cox DA, Vatner SF: Myocardial function in areas of heterogeneous perfusion after coronary artery occlusion in conscious dogs. *Circulation* 1982; 66:1154-8
- Sakai K, Watanabe K, Millard RW: Defining the mechanical border zone: A study in the pig heart. *Am J Physiol* 1985; 249:H88-H94
- Takahashi T, Levine MJ, Grossman W: Regional diastolic mechanics of ischemic and non-ischemic myocardium in the pig heart. *J Am Coll Cardiol* 1991; 17:1203-12
- Homans DC, Asinger R, Elsperger J, Erlie D, Sublett E, Mikell F, Bache RJ: Regional function and perfusion at the lateral border of the ischemic myocardium. *Circulation* 1985; 71:1038-47
- Lew WYW, Ban-Hayashi E: Mechanisms of improving regional and global ventricular function by preload alterations during acute ischemia in canine left ventricle. *Circulation* 1985; 72: 1125-34
- Dalmas S, Wanigasekera VA, Marsch SCU, Ryder WA, Wong LSS, Foëx: The influence of preload on post-systolic shortening in ischaemic myocardium. *Eur J Anaesth* 1995; 12:127-33
- Meyer TE, Foëx P, Ryder WA: Regional interaction and its effect on patterns of myocardial segmental shortening and lengthening during different models of asynchronous contraction in the dog. *Cardiovasc Res* 1992; 26:476-86
- Nakamura Y, Sasayama S, Nonogi H, Miyazaki S, Fujita M, Kihara Y, Konishi T, Kawai C: Effects of pacing-induced ischemia on early left ventricular filling and regional myocardial dynamics and their modification by nifedipine. *Circulation* 1987; 76:1232-44
- Tamiya K, Sugawara M, Sakurai Y: Maximum lengthening velocity during isotonic relaxation at preload in canine papillary muscle. *Am J Physiol* 1979; 237:H83-9
- Caillet D, Crozatier B: Role of myocardial restoring forces in the determination of early diastolic peak velocity of fibre lengthening in the conscious dog. *Cardiovasc Res* 1982; 16:107-12