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Contribution of asynchrony and nonuniformity to mechanical interaction in normal and stunned myocardium

DONGSHENG FAN, LOE KIE SOEI, RENE STUBENITSKY, ERIC BOERSMA, DIRK J. DUNCKER, PIETER D. VERDOUW, AND ROB KRAMS

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Fan, Dongsheng, Loe Kie Soei, Rene Stubenitsky, Eric Boersma, Dirk J. Duncker, Pieter D. Verdouw, and Rob Krams. Contribution of asynchrony and nonuniformity to mechanical interaction in normal and stunned myocardium. *Am. J. Physiol.* 273 (Heart Circ. Physiol. 42): H2146–H2154, 1997.—In anesthetized pigs, we investigated whether asynchrony (ΔT) and nonuniformity (regional differences) in contractility (ΔE) could describe the interaction between normal and stunned myocardium. Mechanical interaction was evaluated by regional postsystolic work (PSW) before and after production of stunning by a 5-min occlusion of the left circumflex coronary artery [LCX (LCX stunning)] and a subsequent 10-min occlusion of the left anterior descending coronary artery [LAD (LAD stunning)]. ΔT and ΔE were intensified by intracoronary (LAD) infusions of dobutamine. From regional end-systolic pressure-segment length relationships, systolic segment shortening (SS), end-systolic elastance (E), external work (EW), and PSW were determined. LCX stunning decreased SS_{LCX} from 14 ± 2 (mean \pm SE, $n = 9$) to $10 \pm 2\%$ and E_{LCX} from 103 ± 25 to 52 ± 7 mmHg/mm, whereas the LAD region was unaffected. EW_{LCX} decreased from 165 ± 16 to 138 ± 20 mmHg·mm, whereas PSW_{LCX} increased from -4 ± 6 to 8 ± 3 mmHg·mm. Additional LAD stunning reduced SS_{LAD} from 16 ± 2 to $9 \pm 3\%$ and E_{LAD} from 79 ± 10 to 31 ± 6 mmHg/mm, without affecting SS_{LCX} and E_{LCX} . In the normal myocardium, PSW_{LAD} increased and PSW_{LCX} decreased, but, during local LAD dobutamine infusions after stunning, both PSW_{LCX} and PSW_{LAD} increased. In normal myocardium, the changes in PSW_{LCX} could be described by ΔT ($65 \pm 11\%$) and ΔE ($37 \pm 15\%$). After stunning of the LAD area, the contribution of ΔE increased to $55 \pm 14\%$ at the expense of ΔT ($37 \pm 15\%$). Similar contributions of ΔE ($54 \pm 13\%$) and ΔT ($57 \pm 13\%$) were found when both the LCX and LAD distribution areas were stunned. In normal myocardium, both ΔT and ΔE modulate mechanical interaction, with the contribution of ΔT exceeding that of ΔE . In stunned myocardium, both factors contribute, but the contribution shifts in favor of ΔE .

myocardial interaction; inotropic intervention; end-systolic pressure-segment length relationship; pig

MECHANICAL INTERACTION between different myocardial regions has been studied extensively during regional ischemia, a condition in which regional myocardial function of the ischemic segment is decreased but that of the adjacent normal myocardium may be increased (2, 5, 7, 8, 12, 16–18, 20, 23). In these studies, regional myocardial function is usually assessed by load-dependent parameters such as systolic segment shortening or systolic wall thickening. However, several groups of authors have proposed that regional end-systolic elastance (E), a parameter derived from regional left ventricular (LV) pressure-segment length

relationships, is less load dependent and may be a more appropriate index for regional myocardial contractility (3, 14, 15). This approach also has the advantage that the area inside the LV pressure-segment length loop provides an estimate of the external work (EW) (6, 19, 24, 27, 29). Most of the EW is performed during LV ejection, but a fraction can occur during isovolumic relaxation after the ejection period [postsystolic work (PSW)]. Because total LV volume remains constant during isovolumic relaxation and thus global PSW is zero, positive PSW in one region implies that PSW must be negative in another region. Hence, PSW may be used as an index for mechanical interaction.

In regionally stunned myocardium, EW is not only decreased but also a larger fraction is performed as PSW (1, 4, 14, 15). This PSW is believed to result from a slower contraction of the stunned myocardial region (asynchrony). It has been shown repeatedly that contractility is decreased in stunned myocardium (3, 14, 15), but whether PSW is also affected by the decrements in contractile force of the stunned region has not yet been investigated. In addition, it is not yet known how contractility changes of the adjacent nonstunned region modulate PSW of the stunned region. To clarify the contribution of contractility and asynchrony on mechanical interaction during stunning and to investigate whether factors other than loss of contractility and asynchrony are needed in stunned myocardium, selective intracoronary infusions of dobutamine were used before and after stunning that region.

Furthermore, because stunned myocardium retains its contractile reserve, it is often treated with intravenous administration of inotropic agents (13a, 14). Knowledge about mechanical interaction is important in these conditions, because the effect of these agents on regional inotropy could be modulated by the concomitant increase in contractility of the adjacent nonstunned myocardium.

The aim of the present study was therefore to evaluate in anesthetized pigs the contribution of asynchrony of contraction (ΔT) and regional nonuniformity in contractile force (ΔE) to mechanical interaction in normal regions, in normal stunned regions, and in stunned-stunned regional myocardium.

MATERIALS AND METHODS

General

All experiments were performed in accordance with the "Guiding Principles in the Care and Use of Laboratory Animals" as approved by the Council of the American Physi-

ological Society and under the regulations of the Animal Care Committee of the Erasmus University Rotterdam.

Cross-bred Landrace \times Yorkshire pigs (HVC, Hedel, The Netherlands) of either sex (23–30 kg) were sedated with 20 mg/kg ketamine im (AUV, Cuijk, The Netherlands) and anesthetized with 20 mg/kg pentobarbital sodium (Apharmo, Arnhem, The Netherlands) before intubation and connection to a ventilator for intermittent positive pressure ventilation with an O_2 - N_2 (1:2, vol/vol) mixture. Respiratory rate and tidal volume were controlled to keep arterial blood gases within the normal range. An 8-Fr fluid-filled catheter was placed in the superior caval vein for continuous infusion of 5–10 mg \cdot kg $^{-1}$ \cdot h $^{-1}$ of pentobarbital sodium, and another 8-Fr catheter was placed in the descending aorta for withdrawal of arterial blood samples and measurement of central aortic blood pressure. A 7-Fr Sensodyn micromanometer-tipped catheter (B. Braun Medical, Uden, The Netherlands) was inserted into the left carotid artery and advanced into the LV cavity for measurement of LV pressure and its first derivative (LV dp/dt). A 7-Fr Fogarty balloon catheter was inserted into the right carotid artery and advanced into the ascending aorta to vary afterload for the determination of the LV end-systolic pressure-segment length relationships (ESPSLR; see below).

After administration of 4 mg of pancuronium (Organon Teknika, Boxtel, The Netherlands), the thorax was opened via a midline sternotomy. The left mammary vessels were ligated, the second left rib was removed, and the heart was suspended in a pericardial cradle. An electromagnetic flow probe (Skalar, Delft, The Netherlands) was placed around the ascending aorta for measurement of blood flow cardiac output. Proximal parts of the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCX) were dissected free for later positioning of an atraumatic clamp, while the proximal LAD was cannulated for intracoronary infusion of dobutamine. Rectal temperature was maintained between 37 and 38°C using external heating pads and appropriate coverings for the animals.

Regional myocardial segment length changes were monitored by sonomicrometry (Triton Technology, San Diego, CA) by placing one pair of ultrasonic crystals (Sonotek, Del Mar, CA) in the distribution territory of the LAD and a second pair in the distribution area of the LCX. The crystals were placed in the midmyocardium in the direction of circumferential muscle fibers (25) at a distance of ~ 10 mm. Proper positioning of the crystals in the allocated distribution areas was verified by brief coronary artery occlusions.

Experimental Protocols

After a stabilization period of 30–45 min, baseline recordings were made of systemic hemodynamic variables and regional myocardial function. With the respirator switched off, ascending aortic blood pressure was increased over a 5- to 10-s period by gradual inflation of the balloon of the Fogarty catheter to determine the regional LV ESPSLR. LV pressure and regional segment-length signals were digitized (sample rate 400 Hz) with an eight-bit analog-to-digital converter and stored on disk for off-line analysis (14, 15).

After baseline recordings were made, three sequential experimental protocols were performed. In the first protocol ($n = 9$), mechanical interaction in the normal LV was studied by intracoronary LAD infusion of three doses (0.01, 0.02, and 0.04 μ g \cdot kg $^{-1}$ \cdot min $^{-1}$) of dobutamine (Dobutrex, Eli Lilly Nederland, Nieuwegein, The Netherlands). The doses of intracoronary dobutamine were based on previous studies from our laboratory using intravenous dobutamine (14, 15). Data were collected before infusion of dobutamine and after 3

min of each infusion rate. In the second protocol ($n = 8$), the distribution territory of the LAD was stunned by a 5-min occlusion and 10 min of reperfusion, and the contribution of these parameters to the mechanical interaction between regionally stunned and the adjacent nonstunned myocardium was studied by repeating the intracoronary dobutamine (LAD) infusions. In the third protocol ($n = 6$), mechanical interaction between two stunned regions was studied. Hitherto, the distribution area of the LAD was also stunned by a 10-min occlusion and 30 min of reperfusion before the local dobutamine infusions were repeated. The shorter occlusion duration for the LCX region was employed to avoid gross impairment of global LV pump function. Each protocol was performed after a 30-min washout period, which was sufficiently long to allow functional parameters to return to predobutamine values.

Data Analysis and Statistics

Systolic segment shortening (SS) was calculated as the difference between the segment length at end diastole, defined as the instant that LV dp/dt increased to >250 mmHg/s, and that at end systole (determined at peak $-LV dp/dt$), expressed as a percentage of end-diastolic length.

The ESPSLR was determined by fitting the LV end-systolic pressure-segment length data points to a second-order polynomial, using an interactive algorithm (14, 15). Each ESPSLR was characterized by the slope (E ; an expression of elastance) at 120 mmHg and the intercept of the regression equation, or the length at zero LV pressure (L_0) (14, 15). The area inside the LV pressure-segment length loop was taken as a measure of regional EW, of which the fraction that occurred after closure of the aortic valve is PSW (22). PSW was considered positive when minimal length (L_{min}) was less than end-systolic length and negative when L_{min} was greater than end-systolic length (Fig. 1). The duration of contraction in the LAD and LCX regions was defined as the time intervals between LV end diastole and regional L_{min} (T_{LAD} and T_{LCX} , respectively). Asynchrony of contraction between the LAD and LCX regions was defined as $\Delta T = T_{LAD} - T_{LCX}$.

A univariate regression analysis was performed with PSW_{LCX} as the dependent variable and T_{LAD} , T_{LCX} , ΔT , E_{LAD} , E_{LCX} , and ΔE as independent variables. Significantly correlated independent variables were entered into a multivariate regression analysis, which was performed for each of the three protocols. Multicollinearity between the independent variables was evaluated by the variance inflation factor (VIF) and the condition index (CI), applying a standard statistical software package (SPSS, Chicago, IL) (9). The relative contribution of each parameter in the multivariate linear regres-

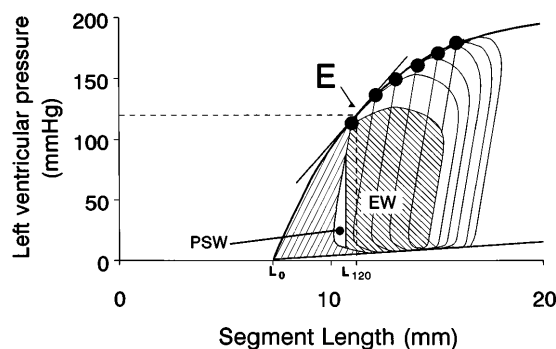


Fig. 1. Schematic representation describing parameters derived from time-varying elastance concept, including postsystolic work (PSW). E , end-systolic elastance (mmHg/mm); EW , external work (mmHg \cdot mm); L_0 , length at zero LV pressure.

sion model was evaluated by standardizing the parameter. Standardization involved subtracting its mean and dividing by its SD (9). The multiregression analysis was repeated with these standardized parameters. Statistical analyses of hemodynamic and functional data were performed by repeated-measures analysis of variance. When significance was reached ($P < 0.05$), paired t -tests were applied with a Bonferroni correction for multiple measurements. All data have been presented as means \pm SE.

RESULTS

Systemic Hemodynamics

In each of the three protocols, the intracoronary dobutamine infusions produced dose-dependent increases in maximum LV dP/dt , without affecting any of the other system hemodynamic parameters (Table 1).

Regional Segment Length and ESPSLRs

Normal LAD and LCX myocardium. SS_{LCX} and E_{LCX} did not change during the selective LAD infusions of dobutamine. In contrast, E_{LAD} increased dose dependently from 65 ± 8 to 155 ± 24 mmHg/mm ($P < 0.05$), but SS_{LAD} remained unchanged. EW_{LAD} and EW_{LCX} were also not affected by the dobutamine infusions, but PSW_{LAD} and PSW_{LCX} , which were not different from zero at baseline, became negative and positive, respectively (Table 2).

Normal LAD and stunned LCX myocardium. After stunning of the distribution area of the LAD, SS_{LCX} decreased from 14 ± 2 to $10 \pm 2\%$ ($P < 0.05$) and E_{LCX}

decreased from 103 ± 25 to 52 ± 7 mmHg/mm ($P < 0.05$), whereas SS_{LAD} and E_{LAD} remained unchanged. During the dobutamine infusions, neither SS_{LAD} nor SS_{LCX} was affected, whereas E_{LAD} increased from 61 ± 7 to 229 ± 54 mmHg/min ($P < 0.05$). E_{LCX} , which had remained unchanged during the LAD dobutamine infusions before stunning, now increased from 52 ± 7 to 113 ± 32 mmHg/min. Both E_{LAD} and E_{LCX} returned to predobutamine values during the washout period. Stunning the LAD region had no effect on EW_{LAD} but produced a decrease in EW_{LAD} from 165 ± 16 to 138 ± 20 mmHg \cdot mm ($P < 0.05$). The subsequent dobutamine infusions did not affect EW_{LAD} or EW_{LCX} compared with stunning levels. PSW_{LCX} , which had increased from -4 ± 6 mmHg \cdot mm at baseline to 8 ± 3 mmHg \cdot mm following stunning ($P < 0.05$), decreased dose dependently to -10 ± 4 mmHg \cdot mm ($P < 0.05$) during the dobutamine infusions. PSW_{LAD} , which had decreased after stunning of the LCX region, decreased further during the dobutamine infusion (Fig. 2).

Stunned LAD and LCX myocardium. After additional stunning of the distribution area of the LAD, SS_{LAD} decreased from 16 ± 2 to $9 \pm 3\%$ and E_{LAD} from 79 ± 10 to 31 ± 6 mmHg/mm (both $P < 0.05$), whereas in the LCX region these variables remained unchanged. During the dobutamine infusions, SS_{LAD} increased to $12 \pm 2\%$, while E_{LAD} increased almost fourfold (both $P < 0.05$). The responses of SS_{LCX} and E_{LCX} to dobutamine were similar to the responses when only the distribution area of the LCX was stunned.

Table 1. Systemic hemodynamics after intracoronary (LAD) infusions of dobutamine in anesthetized pigs

	Baseline	Stunning	Dobutamine, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			Recovery
			0.01	0.02	0.04	
Heart rate, beats/min						
Control	104 ± 6		102 ± 6	98 ± 6	96 ± 9	99 ± 6
Stunning _{LCX}	104 ± 8	101 ± 8	101 ± 10	103 ± 10	101 ± 10	104 ± 10
Stunning _{LCX+LAD}	97 ± 9	104 ± 11	102 ± 11	101 ± 12	111 ± 14	108 ± 12
Systolic arterial pressure, mmHg						
Control	106 ± 4		103 ± 4	108 ± 5	111 ± 6	102 ± 7
Stunning _{LCX}	103 ± 4	111 ± 4	105 ± 5	104 ± 4	104 ± 6	102 ± 3
Stunning _{LCX+LAD}	102 ± 4	106 ± 3	107 ± 4	107 ± 6	116 ± 4	104 ± 3
Mean arterial pressure, mmHg						
Control	81 ± 2		80 ± 2	81 ± 3	83 ± 4	80 ± 2
Stunning _{LCX}	89 ± 4	80 ± 4	85 ± 5	84 ± 6	81 ± 5	83 ± 4
Stunning _{LCX+LAD}	84 ± 2	81 ± 4	81 ± 5	84 ± 4	83 ± 4	82 ± 5
LV end-diastolic pressure, mmHg						
Control	7.5 ± 0.9		7.4 ± 0.9	6.7 ± 0.9	6.8 ± 1.0	8.0 ± 0.8
Stunning _{LCX}	8.0 ± 0.7	7.4 ± 0.8	7.7 ± 0.8	7.6 ± 0.7	7.0 ± 0.8	7.4 ± 0.7
Stunning _{LCX+LAD}	6.3 ± 1.1	6.8 ± 1.0	6.3 ± 0.8	6.7 ± 0.8	6.5 ± 0.5	6.7 ± 1.2
LV dP/dt_{max} , mmHg/s						
Control	$2,390 \pm 180$		$2,420 \pm 230$	$2,750 \pm 230^*$	$2,870 \pm 270^*$	$2,200 \pm 240$
Stunning _{LCX}	$2,260 \pm 220$	$1,990 \pm 200$	$2,150 \pm 250$	$2,150 \pm 280$	$2,600 \pm 280^\dagger$	$1,930 \pm 240$
Stunning _{LCX+LAD}	$2,080 \pm 290$	$1,940 \pm 340$	$2,090 \pm 350$	$2,250 \pm 330^\dagger$	$2,810 \pm 440^\dagger$	$2,030 \pm 370$
Stroke work, mmHg \cdot ml						
Control	$2,040 \pm 180$		$1,990 \pm 200$	$2,130 \pm 230$	$1,880 \pm 290$	$1,900 \pm 180$
Stunning _{LCX}	$1,880 \pm 130$	$1,740 \pm 170$	$1,680 \pm 170$	$1,680 \pm 180$	$1,430 \pm 160^*^\dagger$	$1,680 \pm 190$
Stunning _{LCX+LAD}	$1,720 \pm 310$	$1,730 \pm 420$	$1,740 \pm 440$	$1,870 \pm 440$	$1,390 \pm 350^\dagger$	$1,460 \pm 240$

Values are means \pm SE. Control, normal myocardium ($n = 9$); stunning_{LCX}, myocardium in distribution area of left circumflex coronary artery (LCX) is stunned ($n = 8$); stunning_{LCX+LAD}, myocardium in distribution areas of LCX and left anterior descending coronary artery (LAD) is stunned ($n = 6$); LV, left ventricle; LV dP/dt_{max} , peak positive LV pressure. * $P < 0.05$ vs. baseline; $^\dagger P < 0.05$ vs. stunning.

Table 2. Segment length changes after intracoronary (LAD) infusions of dobutamine in anesthetized pigs

	Baseline	Stunning	Dobutamine, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			Recovery
			0.01	0.02	0.04	
<i>End-diastolic length, mm</i>						
LAD distribution area						
Control	13.0 \pm 0.8		13.2 \pm 0.9	12.7 \pm 0.8	11.7 \pm 1.0	13.0 \pm 0.9
Stunning _{LCX}	11.2 \pm 1.1	11.7 \pm 1.1	10.7 \pm 1.0	11.1 \pm 1.0	10.6 \pm 1.1	10.6 \pm 1.1
Stunning _{LCX+LAD}	11.2 \pm 0.8	12.0 \pm 1.2	11.5 \pm 1.1	12.1 \pm 1.2	10.6 \pm 1.1	10.9 \pm 1.1
LCX distribution area						
Control	12.1 \pm 0.7		12.3 \pm 0.9	11.8 \pm 0.6	10.6 \pm 0.7	12.2 \pm 0.9
Stunning _{LCX}	10.5 \pm 0.8	10.4 \pm 0.6	9.9 \pm 0.6	10.1 \pm 0.6	9.6 \pm 1.0	9.8 \pm 0.6
Stunning _{LCX+LAD}	10.0 \pm 0.6	9.9 \pm 0.5	9.7 \pm 0.6	10.0 \pm 0.6	9.8 \pm 0.7	10.1 \pm 0.5
<i>End-systolic elastance, mmHg/mm</i>						
LAD distribution area						
Control	65 \pm 8		79 \pm 9*	102 \pm 7*	155 \pm 24*	70 \pm 8
Stunning _{LCX}	71 \pm 10	61 \pm 7	89 \pm 17	158 \pm 39*†	229 \pm 54*†	78 \pm 13
Stunning _{LCX+LAD}	79 \pm 10	31 \pm 6*	40 \pm 7*	74 \pm 23	125 \pm 59	33 \pm 7*
LCX distribution area						
Control	121 \pm 18		123 \pm 18	108 \pm 23	120 \pm 32	120 \pm 23
Stunning _{LCX}	103 \pm 25	52 \pm 7*	63 \pm 10	93 \pm 26	113 \pm 32†	57 \pm 13*
Stunning _{LCX+LAD}	71 \pm 15	63 \pm 12	91 \pm 15	79 \pm 21	116 \pm 18	72 \pm 20
<i>External work, mmHg·mm</i>						
LAD distribution area						
Control	207 \pm 13		238 \pm 14	216 \pm 17	229 \pm 21	201 \pm 12
Stunning _{LCX}	194 \pm 16	184 \pm 13	180 \pm 14	188 \pm 13	175 \pm 26	178 \pm 12
Stunning _{LCX+LAD}	187 \pm 12	126 \pm 24*	133 \pm 18*	137 \pm 17	139 \pm 26	122 \pm 14*
LCX distribution area						
Control	162 \pm 16		174 \pm 22	177 \pm 18	165 \pm 31	151 \pm 21
Stunning _{LCX}	165 \pm 16	138 \pm 20*	131 \pm 19	131 \pm 22	100 \pm 21*	119 \pm 16*
Stunning _{LCX+LAD}	121 \pm 23	122 \pm 19	121 \pm 13	122 \pm 18	139 \pm 29	120 \pm 10
<i>Postsystolic work, mmHg·mm</i>						
LAD distribution area						
Control	3 \pm 3		-2 \pm 4	-10 \pm 7	-17 \pm 6*	6 \pm 6
Stunning _{LCX}	3 \pm 5	-2 \pm 5	-2 \pm 5	-9 \pm 6	-24 \pm 14*†	-2 \pm 2
Stunning _{LCX+LAD}	3 \pm 3	31 \pm 7*	17 \pm 9	3 \pm 10	-9 \pm 9†	24 \pm 7
LCX distribution area						
Control	-7 \pm 5		-3 \pm 6	3 \pm 5*	8 \pm 9*	-12 \pm 7
Stunning _{LCX}	-4 \pm 6	8 \pm 3*	6 \pm 4	2 \pm 4	-10 \pm 4	10 \pm 2
Stunning _{LCX+LAD}	10 \pm 2	10 \pm 8	9 \pm 7	-3 \pm 9	-8 \pm 7	13 \pm 8

Values are means \pm SE. Control, $n = 9$; stunning_{LCX}, $n = 8$; stunning_{LCX+LAD}, $n = 6$; * $P < 0.05$ vs. baseline; † $P < 0.05$ vs. stunning.

After the LAD distribution area was stunned, EW_{LAD} decreased from 187 ± 12 to 126 ± 24 mmHg·mm ($P < 0.05$), whereas EW_{LCX} remained unaffected. The dobutamine infusions did not affect EW_{LAD} or EW_{LCX} . PSW_{LAD} increased from 3 ± 3 to 31 ± 7 mmHg·mm ($P < 0.05$) after LAD stunning but decreased to -9 ± 9 mmHg·mm during the highest dose of dobutamine. The response of PSW_{LCX} was not different from the response when only the distribution area of the LCX was stunned (Fig. 3).

Duration of Contraction

In the normal heart, T_{LAD} decreased up to 26% ($P < 0.05$) during the dobutamine infusion, whereas T_{LCX} remained unaffected (Table 3).

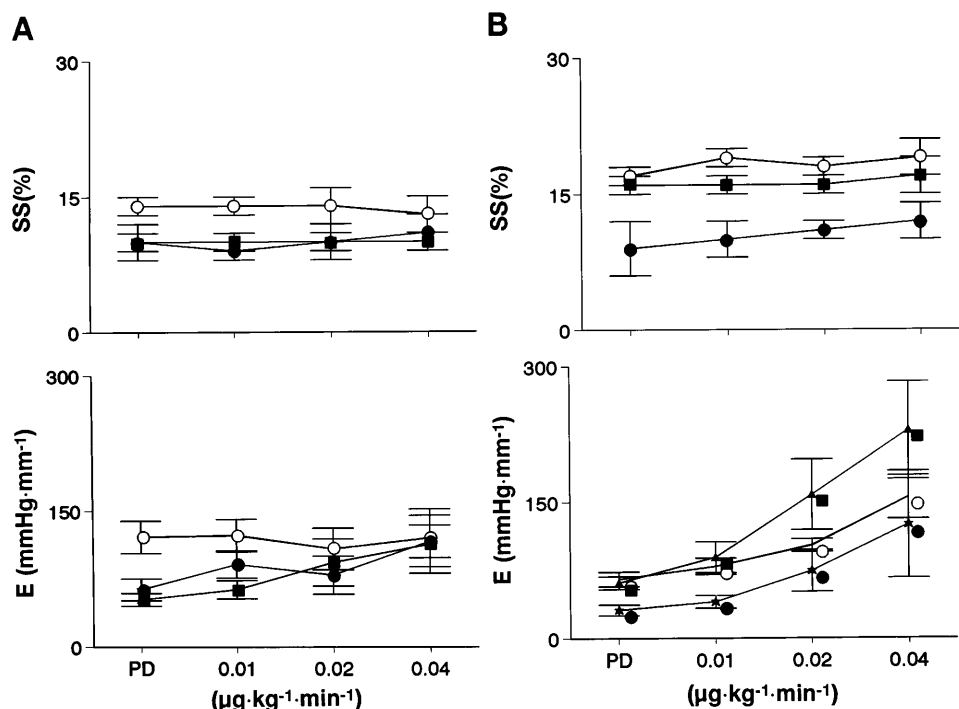
After stunning of the LCX region, T_{LCX} increased up to 23% ($P < 0.05$), indicating that contraction of the LCX region had become slower. During the subsequent dobutamine infusions, T_{LAD} decreased dose dependently. Unlike the LCX region before stunning, T_{LCX} now decreased during the dobutamine infusion ($P < 0.05$).

Stunning of the LAD region slowed the contraction in that region, as reflected by a significant decrease in T_{LAD} ($P < 0.05$), which was restored by the infusion of dobutamine. A decrease of T_{LCX} was again observed during the dobutamine infusion.

Contribution of ΔT and ΔE to Mechanical Interaction

Univariate analyses revealed that E_{LAD} , E_{LCX} , T_{LCX} , and T_{LAD} were not significantly related to PSW_{LCX} in any of the three study protocols but that both ΔE and ΔT were statistically significant predictors of PSW_{LCX} in all three protocols (Table 4, Fig. 4). Consequently, as the second step, the multiregression model, $PSW_{LCX} = \alpha\Delta E + \beta\Delta T + \gamma$ was applied to each of the three experimental protocols; γ was introduced to evaluate whether an unknown factor might still contribute significantly. Table 4 shows that the contribution of ΔE (α) increased after LCX stunning, whereas the contribution of ΔT (β) decreased; γ was not significantly different from zero in the first and second protocol but achieved statistical significance in the third protocol.

Fig. 2. Systolic shortening (SS, top) and left ventricular E (bottom) during selective left anterior descending coronary artery (LAD) infusion of dobutamine (0.01, 0.02, and 0.04 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) during baseline conditions (\circ), after stunning the distribution territory of left circumflex coronary artery (LCX; \blacksquare), and after stunning the distribution territories of both LCX and LAD (\bullet). Data are presented as means \pm SE. Notice that, in distribution territory of LAD, effect of dobutamine on SS was negligible but that E_{LAD} consistently increased. Responses in distribution territory of LCX were different before and after stunning. PD, pre-dobutamine.



Additional analysis focused on the detection of multicollinearity between ΔE and ΔT . The VIF (1.2, 1.1, and 1.0 for protocols 1, 2, and 3, respectively) and CI (maximum values of 2.2, 2.4, and 2.8 for protocols 1, 2, and 3, respectively) were small compared with the values (8–10) considered significant for collinearity (9).

Standardization of the parameters revealed that ΔT explained $65 \pm 11\%$ and ΔE explained $37 \pm 15\%$ of the variation in PSW_{LCX} in the normal myocardium (Fig. 4). After LCX stunning, ΔT and ΔE explained 37 ± 15 and

$55 \pm 14\%$ (both $P < 0.05$), respectively, of the variability in PSW_{LCX} . The contribution of ΔE remained at $54 \pm 13\%$ ($P < 0.05$) after additional LAD stunning, whereas the contribution of ΔT increased to $57 \pm 13\%$, which was similar to that during baseline conditions.

Model Simulations

To evaluate the independent effect of ΔT and ΔE on the shape of the pressure-segment length loops, a

Fig. 3. EW (top) and PSW (bottom) in LCX (A) and LAD (B) distribution territories during selective LAD infusions (0.01, 0.02, and 0.04 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) of dobutamine during baseline conditions (\circ), after stunning distribution territory of LCX (\blacksquare), and after stunning distribution territories of both LCX and LAD (\bullet). Notice that EW of both regions was only minimally affected but that there was an inverse relationship between PSW and dobutamine infusion ratio before stunning and a positive relationship after stunning.

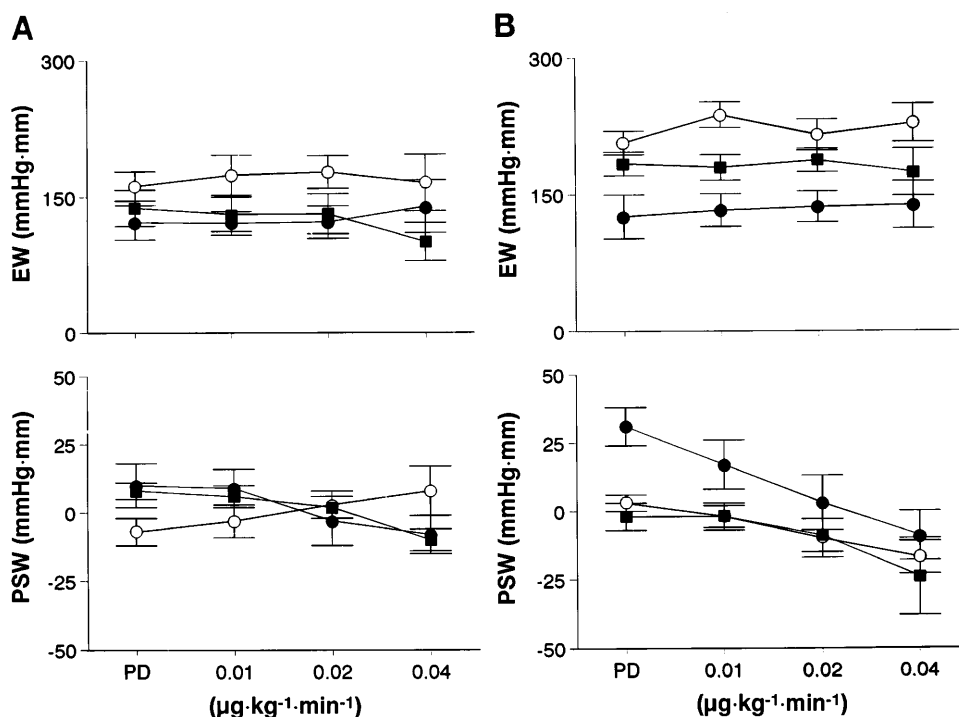


Table 3. *Contractile sequences of regional myocardium after intracoronary (LAD) infusions of dobutamine in anesthetized pigs*

	Baseline	Stunning	Dobutamine, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			Recovery
			0.01	0.02	0.04	
T_{LAD}						
Control	390 \pm 30		340 \pm 20	340 \pm 20	270 \pm 30*	370 \pm 30
Stunning _{LCX}	370 \pm 30	360 \pm 30	340 \pm 30†	290 \pm 30*†	250 \pm 20*†	340 \pm 40
Stunning _{LCX+LAD}	360 \pm 30	460 \pm 50*	360 \pm 40	330 \pm 50†	280 \pm 40†	470 \pm 50
T_{LCX}						
Control	370 \pm 20		370 \pm 30	370 \pm 20	350 \pm 30	360 \pm 20
Stunning _{LCX}	370 \pm 20	450 \pm 20*	410 \pm 20†	360 \pm 20†	340 \pm 20†	450 \pm 40*
Stunning _{LCX+LAD}	440 \pm 50	440 \pm 70	370 \pm 50	370 \pm 40	340 \pm 20	440 \pm 70

Values are means \pm SE. Control, $n = 9$; stunning_{LCX}, $n = 8$; stunning_{LCX+LAD}, $n = 6$; T , time interval between LV end diastole and the instant at which the myocardial segment reaches its minimum length. * $P < 0.05$ vs. baseline; † $P < 0.05$ vs. stunning.

mathematical model was developed based on a two-spring model in series (see APPENDIX). A ΔE of 50%, without ΔT , induced a backward leaning of the simulated LV pressure-segment length loop (Fig. 5A). ΔT of 10% of the cardiac cycle, without a change in contractility, induced asymmetric loops with a backward leaning of the simulated pressure-length loop during isovolumic relaxation (Fig. 5B). A combination of a 50% ΔE and 10% ΔT is compatible with the present experimental findings. When differences in both contractility and asynchrony were applied, the backward leaning of the loop was increased above each individual effect (Fig. 5C). However, the backward leaning of the simulated pressure-length loop was not found when the low contractile muscle contracted earlier than the strong muscle (Fig. 5D). It is to be noted that backward leaning implies a positive PSW and thereby signifies the changes found during LAD and LCX stunning.

DISCUSSION

The present study describes the mechanical interaction between normal and stunned myocardial segments

Table 4. *ΔT and ΔE as predictors of mechanical interaction*

	α , mm^{-2}	β , $\text{mmHg} \cdot \text{mm} \cdot \text{s}^{-1}$	γ , $\text{mmHg} \cdot \text{mm}$	r
Univariate analysis				
Control		$-0.13 \pm 0.02^*$	$-5.6 \pm 1.8^*$	0.76
Stunning _{LCX}		$-0.06 \pm 0.03^*$	3.7 ± 3.2	0.35
Stunning _{LCX+LAD}		$-0.04 \pm 0.02^*$	$10.5 \pm 3.0^*$	0.50
Control	$0.13 \pm 0.04^*$		2.2 ± 2.7	0.48
Stunning _{LCX}	$0.12 \pm 0.03^*$		$4.4 \pm 2.2^*$	0.62
Stunning _{LCX+LAD}	$0.16 \pm 0.05^*$		$16.9 \pm 3.5^*$	0.48
Multivariate analysis				
Control	$0.07 \pm 0.03^*$	$-0.12 \pm 0.02^*$	2.2 ± 2.2	0.80
Stunning _{LCX}	$0.11 \pm 0.03^*$	-0.04 ± 0.03	2.6 ± 3.0	0.66
Stunning _{LCX+LAD}	$0.20 \pm 0.04^*$	$-0.05 \pm 0.01^*$	$22.0 \pm 3.0^*$	0.77

Values are means \pm SE. ΔT , asynchrony in contraction; ΔE , nonuniformity of contractile force. Control, $n = 36$ pigs; stunning_{LCX}, $n = 32$; stunning_{LCX+LAD}, $n = 34$. For univariate analysis, the model was either postsystolic work (PSW)_{LCX} = $\alpha\Delta E + \gamma$ or PSW_{LCX} = $\beta\Delta T + \gamma$. For the multivariate analysis, the model PSW_{LAD} = $\alpha\Delta E + \beta\Delta T + \gamma$ was used. * $P < 0.05$ parameter significantly different from zero.

in the porcine LV and determined the relative contributions of ΔE and ΔT to mechanical interaction.

E was used to characterize the regional contractile state of the myocardium. Several studies have shown that E is a more appropriate parameter for regional contractility than SS or wall thickening (3, 14, 15). Consistent with earlier studies, we observed that, in both normal and stunned LAD myocardium, E was more sensitive than SS to local infusions of dobutamine and that T_{LAD} decreased. The distribution territory of the LCX responded differently before and after stunning. Before stunning of the LCX region, the LAD dobutamine infusion did not affect E_{LCX} and T_{LCX} , but after stunning of the LCX region, E_{LCX} increased while T_{LCX} decreased.

Changes in the area enclosed by the LV pressure-segment length relationship reflect changes in regional EW (19, 22, 29). During regional ischemia and stunning, a significant fraction of EW is performed during the isovolumic relaxation phase (1, 4, 5, 14, 15, 22) and therefore does not directly contribute to pump function. We used this PSW as an index of myocardial interaction because it occurs during a phase in which global LV volume is constant and might therefore be interpreted as the work of a myocardial region to stretch (if positive) or to be stretched by (if negative) another nonstunned region (1, 4, 16, 22). Indeed, we observed an inverse relationship between PSW_{LCX} and PSW_{LAD}

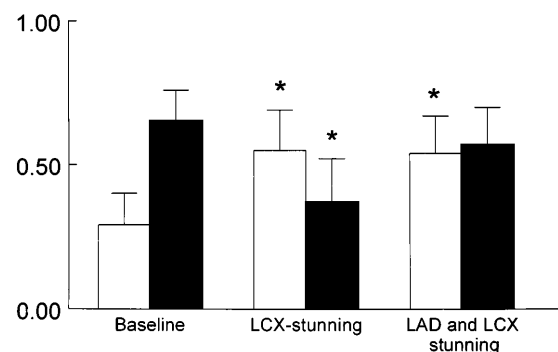


Fig. 4. Relative contribution of nonuniformity in contractile force (ΔE ; open bars) between LAD and LCX regions and asynchrony of contraction (ΔT ; filled bars) during baseline conditions, during normal conditions after LCX stunning, and after LAD plus LCX stunning.

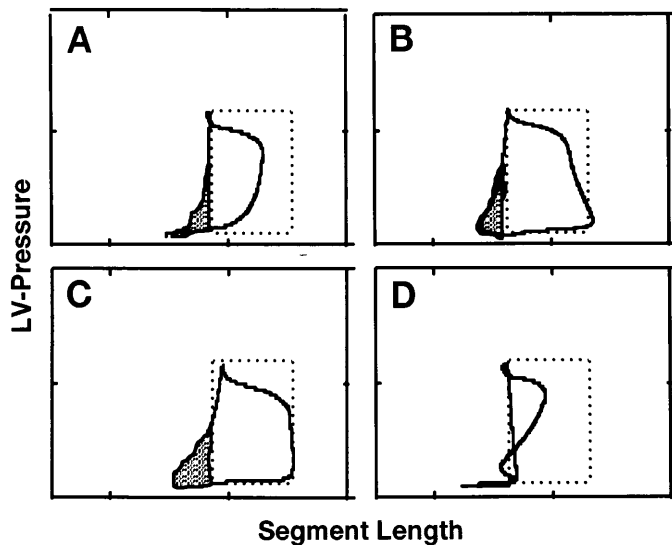


Fig. 5. Model simulations of pressure-segment length loops for 2 springs in series (for details see APPENDIX). Four conditions are simulated. *A*: distinct ΔE in which a change in contractility of 50% of control was simulated. *B*: a slower muscle (10% ΔT) at normal contractility levels is simulated. *C*: combined effect of a slower muscle and a decrease in contractility is simulated. *D*: combined effect of a faster muscle (10%) and a decrease in contractility (50%) is simulated. When 2 springs are equal, a pressure-segment length loop is simulated without forward or backward leaning (dotted lines). Changes in ΔE and ΔT used in present analysis were in the range found in our present experiment.

in normal myocardium during the dobutamine infusions, which is in agreement with previous studies (11, 23). However, after stunning of the LCX perfused region and also after additional stunning of the LAD region, dobutamine infusions induced parallel decreases of PSW_{LCX} and PSW_{LAD} . The mechanism underlying mechanical interaction has almost exclusively been studied during regional ischemia.

Underlying Mechanism

During ischemia, three independent factors have been identified to contribute to mechanical interaction: 1) changes in sympathetic tone, 2) the Frank-Starling mechanism, and 3) direct myocardial unloading (2, 7, 8, 10, 12, 16, 17, 20, 23, 28, 30). The proposed mechanism to explain mechanical interaction during ischemia is discussed for the present experimental conditions.

In the present experiments, changes in aortic pressure were very small in response to both stunning and intracoronary dobutamine infusions. As a consequence, the contribution of baroreceptor stimulation is (probably) negligible in the present experiments. Furthermore, because there were no significant changes in end-diastolic pressure and regional end-diastolic length in any of the experimental conditions, the involvement of a regional Frank-Starling mechanism appears also not to be a major factor for the explanation of the changes in PSW observed in the present study.

This implies that direct regional unloading of the muscle fibers is the most likely factor to explain the present findings. It has been postulated that, during regional ischemia, either a difference in contractility

(“weak and strong muscles in series”) or a difference in timing (“asynchrony”) between ischemic and nonischemic regions is responsible for the mechanical interaction (2, 16, 17, 20, 23, 28). In the present study, we confirmed a role for both mechanisms in regionally stunned myocardium. At the same time, we could exclude parameters that were related to absolute contractility or timing of the nonstunned and stunned regions. Moreover, we found evidence not only that both ΔT and ΔE contributed to mechanical interaction in stunned myocardium but also that, compared with normal myocardium, the relative contribution of ΔE to mechanical interaction increased at the expense of ΔT .

Model simulation helped to understand this finding as both ΔE and ΔT exerted an effect on the simulated pressure-segment length loop. A mathematical model incorporating a strong-weak muscle in series produced a backward leaning of the simulated pressure-segment length loop in the region of the weak muscle. An additional change in ΔT either increased or even prevented the leaning of the simulated pressure-segment length loop. With these two parameters, we could therefore qualitatively mimic some of the conditions studied during the experiments. However, the model did not offer an explanation for the increment in contractility of the stunned LCX region when the LAD region was stimulated by local infusion of dobutamine. Furthermore, the model could also not explain the large intercept of the regression model after both the LAD and LCX regions were stunned. These latter two observations imply that an additional factor, not included in the model, has to be taken into account. A possible explanation might be a third unobserved myocardial region contracting in asynchrony with either or both of the other two regions.

Consequence of Myocardial Interaction in Stunning

Myocardial stunning represents viable tissue with a low contractile state but with normal contractile reserve (14, 32). Inotropic interventions are used to reverse stunning, and increases in SS and E produced by inotropic agents are considered to be a direct effect of these agents on the stunned region. The present study shows that increases of the contractile state of normal myocardium, as is achieved by intravenous infusions, may also affect the indexes used to quantify the contractile state of stunned myocardium, such as SS and E .

Limitations of Method

Several confounding factors have to be excluded. First, overflow of dobutamine from the LAD into the LCX region could contribute to the explanation of the present findings. We believe this to be unlikely, because we could not detect Evans blue dye in the LCX region when this dye was injected into LAD at an infusion rate comparable to the highest dose of dobutamine.

Second, recirculation of dobutamine might have occurred, which implies that dobutamine could have exerted its effect on the LCX region directly. This possibility was evaluated by intravenous infusion of the highest dose of dobutamine at the end of the protocol. Because no changes in hemodynamic or regional me-

chanical parameters were detected, this possibility could also be excluded as playing a significant role.

The local infusion of dobutamine sometimes produced complex shapes of the pressure-segment length loops. As a consequence, especially during the highest dose, the end-systolic pressure-segment relationship points could not be determined in a number of cases (which is the reason for the smaller number of observations with the highest infusion rate of dobutamine). The reported data are reliable, because E responded to dobutamine and stunning as expected and the measurements were reproducible, which can be deduced from the washout measurements.

We have analyzed E only at 120 mmHg, which is in the measurement range. Analyses at different end-systolic pressures have been presented before (14, 15). In those studies, it was shown that stunning produced similar responses at different end-systolic pressures before and after dobutamine (3, 14, 15). In addition, several in vitro studies have provided evidence that changes in E reliably reflect changes in myocardial contractility. On the basis of these studies (3, 14, 15, 21, 26), it may be concluded that elastance is relatively insensitive to changes in loading conditions. However, it has never been investigated in vivo, which warrants some caution for the use of E as an index of contractility in vivo. As a consequence, identifying E as an index for contractility of the muscle fiber should be done with caution.

Two assumptions of the multivariate model need to be addressed: first, the assumption of absence of correlation between ΔE and ΔT , and, second, the absence of interdependence of ΔE and ΔT . The former assumption is important because synchrony and differences in contractility are usually coupled parameters. We have evaluated this assumption by the calculation of standard colinearity diagnostics (VIF, CI) (9). As those diagnostics were low, the model is not redundant. The latter assumption was also tested by introducing a cross term into the present model ($\Delta E \cdot \Delta T$). The coefficients of the cross term were not statistically different from zero in any of the three experimental protocols. Therefore, both assumptions seem justified.

To compare different conditions and tissue properties, it is customary in mechanics to use a normalized length value (strain). In the present experiment, L_0 could serve that purpose. Because we did not detect any systemic effects on L_0 , we have not adopted this approach and have presented the measurements without normalization.

The aim of the present study was to evaluate fiber contraction at the midmyocardium. It is known that different muscle layers exist with different fiber direction in the myocardium. Subendocardial muscle fibers are known to be more sensitive to ischemia than subepicardial fibers. We cannot exclude the possibility that part of the effects noticed in the present study are caused by changes in the different layers of muscle fibers, especially the subendocardial muscle fibers.

In conclusion, the present study provided evidence that mechanical interaction was affected by regionally

stunning the myocardium. The underlying mechanism could be explained by at least two independent factors: ΔE and ΔT between the region under study and the adjacent myocardium. During baseline conditions, ΔT was the main factor, whereas, after stunning of the LCX region, contractility increased its influence on mechanical interaction at the expense of ΔT . Stunning of both the LCX- and the LAD-perfused regions shifted the relative contribution of both parameters such that both factors contributed equally to mechanical interaction.

APPENDIX

A mathematical model was developed in SIMULINK (Math Works), describing the behavior of two active springs in series. The two springs signify the two regions under study (LCX and LAD regions) and were put in series to simulate the circumferentially oriented muscle fibers. We started with the description of a single muscle based on a time-varying stiffness according to Suga and co-workers (21, 26) for the whole ventricle. Second, two time-varying active springs were put in series. As a consequence, we have the following four equations

$$E(t) = E_1(t) \cdot E_2(t) / [E_1(t) + E_2(t)]$$

$$E(t)/E_2(t) = L_2(t) / [L_1(t) + L_2(t)]$$

$$E(t)/E_1(t) = L_1(t) / [L_1(t) + L_2(t)]$$

$$L(t) = L_1(t) + L_2(t)$$

where $E(t)$ represents the active spring elastance, $L(t)$ is the length of the total muscle, and E_1 and E_2 and L_1 and L_2 refer to the individual springs. The driving functions of the model are the two regional elastances [$E_1(t)$ and $E_2(t)$], which were simulated as sinusoids with the negative part forced to zero (rectified sinusoid), and the total length. Total length was simulated as an inverted sinusoid shifted 20°. In this way, simulated pressure-length loops during baseline conditions were close to the measured pressure-segment length loops. Note that the model calculates force while pressure is measured during the experiments. The input parameters of the model consisted of the systolic stiffness of each individual spring and their phase.

The assumption underlying the model is that the myocardium may be represented by a linear time-varying elastance, which may be subdivided into two regions with different properties (21, 26). Furthermore, coupling between these two regions is direct, without the assumption of a border zone. The time shift (ΔT) between two regions is constant over the cardiac cycle.

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