EFFECT OF LOCAL CARDIAC SYMPATHECTOMY ON REGIONAL MYOCARDIAL CONTRACTION

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To investigate the response of locally sympathectomized myocardium to sympathetic stimulation, 90% phenol solution was painted on the left ventricular anterior wall surface in 13 open chest anesthetized dogs. Two pairs of ultrasonic crystals were implanted into the mid-myocardium and the left ansa subclavia was stimulated (LSS) at a frequency of 4 Hz. Heart rate, left ventricular systolic pressure and peak dP/dt increased following LSS before and after phenol application. After phenol application, the increase in peak dP/dt was significantly lower than before phenol application ($p < 0.01$) despite similar increases in both heart rate and left ventricular systolic pressure. Before phenol application, norepinephrine (NE) overflow was observed following LSS (1.60 ng/ml) but after phenol application NE overflow decreased to 0.45 ng/ml, indicating that phenol interrupted sympathetic nerve conduction. During LSS, in both anterior and posterior walls, %shortening (%dL) increased from 13 ± 1 (mean $\pm$ SE) to $22 \pm 3\%$ and 12 ± 1 to $20 \pm 2\%$, respectively. After phenol application, LSS caused an increase of %dL in the posterior wall from 10 ± 1 to $17 \pm 2\%$, while in the anterior wall it decreased from 15 ± 2 to $8 \pm 3\%$. At the end of the experiment, when NE was infused to maintain the left ventricular systolic pressure similar to that obtained during LSS, %dL increased from 15 ± 2 to $21 \pm 3\%$ in the anterior wall. Pressure-length loop during LSS showed an early systolic expansion in the phenol treated anterior wall which disappeared during NE infusion. These observations indicated that the abnormal pressure-length loop was derived from the delayed contraction in the phenol treated region.

SYMPATHETIC stimulation to the heart results in a beta-receptor mediated positive inotropic and chronotropic effect on the myocardium.¹⁻⁶ Barber et al⁷ reported that transmural infarction produced sympathetic denervation in noninfarcted myocardium distal to the necrotic area. However, there have been few reports as to the effects of local sympathectomy on regional myocardial function. Geis et al³

reported that phenol applied regions resulted in ablation of contractile response to sympathetic stimulation, but they did not study wall motion characteristics in detail.

The present study was undertaken to evaluate the effect of local cardiac sympathectomy on regional contraction patterns and to clarify the relationship between regional myocardial and overall left ventricular functions.

Key words:

Phenol application
Asynchronous wall motion
Impaired nerve conduction
Contraction disparity

METHODS

Experiments were performed on 13 mongrel dogs weighing 13–30 kg. After premedication

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Fig.1. Schematic representation of the experiment. Ninety % phenol solution was applied along the left anterior descending artery (LAD) and the second diagonal branch. Sympathetic denervation is shown by stippled area. Ultrasonic dimension gauges were implanted in the denervated area (anterior wall) and the normally innervated area (posterior wall). LV, left ventricle.

with morphine hydrochloride (1 mg/kg), the dogs were anesthetized with alpha-chloralose (70 mg/kg iv), and the drug (20 mg/kg/hour) was continuously infused to maintain a steady anesthetic state. Respiration was controlled by a Harvard pump delivering room air via an endotracheal tube. Bilateral thoracotomy was performed at the 4th intercostal space, and both vagi were cut at the level of neck. The heart was exposed and suspended in a pericardial cradle. The great cardiac vein (GCV) was cannulated and connected with a polyethylene tube to the right jugular vein. A 6-French catheter was inserted into the right atrium for infusion of norepinephrine (NE). Sodium heparin (100 U/kg) was administered intravenously before the extracorporeal bypass was opened. The anterior and posterior ansa subclavia from the left stellate ganglion were separated from the surrounding tissue and stimulated with bipolar platinum

electrodes at supramaximal intensity (10V) for a period of 2 min (2 msec duration) at a frequency of 4 Hz using an electric pulse generator. Rectal temperature was held at 37°C with a heating pad. A 14-French teflon catheter was inserted into the left atrium and connected to a pressure transducer (Toyo Baldwin, MPU-0.5-290-0-III). Zero pressure was set at the midchest level. A catheter-tip manometer (Millar Instruments, Houston, TX) was inserted into the left ventricle through the left atrial appendage. The first derivative of the left ventricular pressure (dP/dt) was calculated by an analog differentiator. As shown in Fig. 1, 2 pairs of ultrasonic dimension gauges were inserted into the left ventricular midmyocardium through small stab wounds to measure the segment length. One pair was placed in a phenol treated portion of the anterior wall, while the other was positioned in the posterior wall to represent the control region. End-diastolic length (EDL) was defined as the onset of the systolic upstroke of dP/dt , and end-systolic length (ESL) was determined as peak negative dP/dt or at the time the control wall reached its maximum thickness. Segment length was normalized by dividing the observed length by the control end-diastolic length and multiplying by ten. The percent change in segment length (%dL) was calculated by the formula: $\%dL = ((EDL - ESL)/EDL) \times 100$.

Assay for plasma norepinephrine

Blood samples from GCV and aorta were obtained simultaneously at the control period and at the end of sympathetic stimulation. Samples were collected in a chilled glass tube containing EDTA-Na, centrifuged at 4°C, and stored at -80°C until the analysis. Samples were added to acid-washed almina in 1M Tris-HCl buffer (pH 8.6), after addition of 3, 4-dihydroxybenzylamine (3000 pg) as internal standard and shaken mechanically for 15 min. Then almina was washed 5 times with distilled deionized water. After centrifugation, the washings were eluted with 200 μ l of 0.01M $HClO_4$. Plasma NE levels were determined by high pressure liquid chromatography with an electrochemical detector (Yanagimoto Co. Ltd., Model L2000L-101). NE uptake and overflow from the heart were calculated by the formula: (GCV NE concentration) - (arterial NE concentration).

Protocol

Segmental length, electrocardiogram, left ven-

TABLE I RESPONSES TO SYMPATHETIC STIMULATION BEFORE AND AFTER DENERVATION

	Before denervation		After denervation		
	Control	LSS	Control	LSS	NE infusion
<i>Hemodynamics</i>					
HR (bpm)	179 ± 8	196 ± 8	179 ± 8	194 ± 9	184 ± 9
LVSP (mmHg)	134 ± 6	174 ± 8	135 ± 5	163 ± 5	181 ± 7
LVEDP (mmHg)	3.8 ± 0.5	2.8 ± 0.5	4.8 ± 0.5*	3.3 ± 0.6	4.5 ± 0.6 §†
max dP/dt (mmHg/sec)	2179 ± 338	6668 ± 736	1913 ± 274	4562 ± 510*	3062 ± 386 §§††
<i>Regional wall motion</i>					
1) Anterior wall					
EDL (mm)	10.0	9.41 ± 0.16	10.0	9.15 ± 0.22	9.72 ± 0.17†
ESL (mm)	8.65 ± 0.14	7.38 ± 0.29	8.52 ± 0.19	8.38 ± 0.34*	7.72 ± 0.34†
%dL (%)	13.5 ± 1.4	21.7 ± 2.5	14.8 ± 1.9	8.4 ± 2.7**	20.8 ± 2.6††
2) Posterior wall					
EDL (mm)	10.0	9.51 ± 0.10	10.0	9.34 ± 0.14	9.90 ± 0.09††
ESL (mm)	8.82 ± 0.13	7.59 ± 0.21	8.99 ± 0.09*	7.76 ± 0.21	8.75 ± 0.17 §§††
%dL (%)	11.8 ± 1.3	20.2 ± 1.9	10.1 ± 0.9**	17.1 ± 1.6**	11.7 ± 1.3 §§††

All values are mean ± SE; LSS = left sympathetic stimulation; NE = norepinephrine; HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; max dP/dt = maximal dP/dt; EDL = end-diastolic length; ESL = end-systolic length; %dL = % shortening.

*p < 0.01; **p < 0.001 vs. before denervation; §p < 0.01; §§p < 0.001 vs. LSS before denervation; †p < 0.05; ††p < 0.01 vs. LSS after denervation

tricular pressure and dP/dt were recorded on a 6 channel pen recorder (NEC San-ei, Model 6173A) in the control period and during sympathetic stimulation. Respiration was suspended at end-expiration during all measurements. Then 90% phenol solution was applied with a writing brush over a narrow stripe (3–5 mm width) of epicardium along the left anterior descending artery as shown in Fig. 1. Similar measurements were performed 20 min after phenol application. Lastly, NE was infused from the right atrium so as to maintain the left ventricular systolic pressure similar to that produced by sympathetic stimulation, and recordings were again obtained. All data were continuously recorded on a magnetic tape recorder (SONY, Model FE-39A) throughout the experiment. The tapes were later replayed and digitized at a rate of 500 Hz by a computer assisted system (Texas Instrument, Model TI 980 b). To correct the small beat-to-beat variations of pressure and segment length, 8 heart cycles were averaged. Peak dP/dt served as a reference signal for the computer, and left ventricular pressure-length loops were depicted by an XY plotter. For statistical evaluation, the Student's t test was used. For two-group comparisons, differences were considered significant

when p < 0.05. Data were expressed as the mean ± SE.

RESULTS

Hemodynamic data (Table I)

Before phenol application (control period), sympathetic stimulation increased heart rate (179 ± 8 to 196 ± 8 beats/min; p < 0.01), left ventricular systolic pressure (134 ± 6 to 174 ± 8 mmHg; p < 0.01) and peak dP/dt (2179 ± 338 to 6668 ± 736 mmHg/sec; p < 0.01), while left ventricular end-diastolic pressure decreased (3.8 ± 0.5 to 2.8 ± 0.5 mmHg; p < 0.01). After phenol application, sympathetic stimulation and NE infusion caused similar increases in heart rate and systolic pressure, but peak dP/dt was much lower than that obtained in the control period.

Segment length data

In the control period, the changes in anterior and posterior wall motion following sympathetic stimulation were identical: both EDL and ESL were shortened and %dL increased markedly. Sympathetic stimulation following phenol application resulted in shortened EDL and unchanged ESL in the anterior wall, so that %dL decreased

Fig.2. Typical segmental changes following sympathetic stimulation (LSS) before and after denervation in dog No. 8. The control segment shows the same response to LSS before and after denervation. In the denervated segment, the response to LSS before denervation was similar to that of the control segment, but an early systolic expansion is shown after denervation. This expansion disappeared following external norepinephrine (NE) infusion. End-diastole was taken at the beginning of positive dP/dt (vertical lines) and end-systole was 20 msec prior to the nadir of negative dP/dt (vertical broke lines). SL, segment length; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure.

by 38% (Table I). In contrast, the posterior wall showed a similar response to that obtained in the control period. Typical tracings before and after phenol application are shown in Fig. 2. In the anterior wall, sympathetic stimulation after phenol application showed shortened EDL, early systolic expansion and prolonged shortening over end-systole, while in the posterior wall the response to sympathetic stimulation was similar before and after phenol application. This early systolic expansion and prolonged contraction was not observed during NE infusion. Pressure-length loops during sympathetic stimulation before and after phenol application are shown in Fig. 3. In the control period (solid lines), all loops showed counter-clockwise rotation and the patterns during rapid pressure generation were similar in the anterior and the posterior walls. Following sympathetic stimulation (broken

lines), end-systolic points shifted upward and to the left both in the anterior and posterior walls (panel A). After phenol application (panel B), there were marked alterations in pressure-length loops. In the anterior wall, early systolic expansion was observed with the pressure rise but the end-systolic point was not shifted to the left and prolonged shortening occurred, while the posterior wall showed a normal segmental shortening pattern. The changes in pressure-length loops were further exaggerated following sympathetic stimulation. These results were not found during NE infusion (panel C), i.e., early systolic expansion disappeared and the end-systolic point shifted upward and to the left.

Plasma norepinephrine data

In the control period, arterial blood NE concentration did not significantly change by

Fig.3. Pressure-length loops of the two segments in dog No. 8. Upper and lower panel show the response of anterior and posterior walls, respectively. Before denervation (panel A), loops for both anterior and posterior walls rotate counterclockwise during control period (solid lines). Following sympathetic stimulation (broken lines), end-systolic points ($\triangleleft$) shifted upwards and to the left. After phenol application (panel B), the posterior wall (lower middle panel) showed a normal shortening pattern during control and following sympathetic stimulation. In the anterior wall (upper middle panel), early systolic expansion was observed with pressure rise, the end-systolic point did not shift to the left and prolonged shortening occurred following sympathetic stimulation (broken line). In contrast, NE infusion (panel C) did not produce asynchronous contraction in the phenol treated anterior wall (dashed-dotted line). LV, left ventricle.

sympathetic stimulation (0.25 ± 0.09 to 0.32 ± 0.06 ng/ml) but GCV blood NE concentration increased from 0.12 ± 0.03 to 1.23 ± 0.21 ng/ml, indicating NE uptake (-0.09 ± 0.04 ng/ml) in the control period and NE overflow (0.91 ± 0.21 ng/ml) during sympathetic stimulation. After phenol application, NE uptake was similar to that of the control period (-0.10 ± 0.04 ng/ml), but NE overflow during sympathetic stimulation significantly decreased (0.45 ± 0.14 ng/ml, $p < 0.01$) due to a smaller increase in GCV blood NE concentration.

DISCUSSION

It has been reported that in anesthetized dogs there is a significant NE overflow in response to supramaximal sympathetic nerve stimulation at a frequency of 8 Hz⁸. Peak NE overflow occurred between the first and second minutes of stimulation and the rate of NE overflow declined rapidly thereafter. When the cardiac sympathetics were stimulated at lower frequency, the cardiovascular response attained peak values in about 1 min and then maintained a steady state for 10 min. In the present study, we performed sympathetic stimulation at a frequency of 4 Hz

and blood sampling from the GCV was made 90 seconds after the onset of stimulation. Therefore, our data may show nearly peak liberation of NE.

As described above, at the baseline condition, NE uptake was not significantly different between before and after phenol application, indicating that topical application of phenol has no influence on cardiac NE uptake. After phenol application, however, NE overflow following sympathetic stimulation significantly decreased, suggesting that sympathetic efferent nerve conduction was locally interrupted in the anterior wall of the left ventricle.

Left ventricular systolic pressure and peak dP/dt increased following sympathetic stimulation both before and after phenol application, but the magnitude of the increase in peak dP/dt was significantly smaller than that during the control period. It was possible that the diminished response of peak dP/dt to sympathetic stimulation was due to the depressant effect of phenol to the myocardium. Pace et al⁹ studied the effects of 85% phenol application on left ventricular performance using the ventricular function curve in anesthetized dogs. They reported that the ventricular function curve ob-

tained immediately after phenol application was shifted downward and to the right, indicating depressed left ventricular contractility. But 20 min later, ventricular function had returned to the control state. Also Randall et al¹⁰ showed in their histological examination of phenol treated hearts that tissue destruction is very superficial, being confined within 0.25 mm of the epicardial surface. In our experiment, phenol was painted over a narrow stripe of epicardium along the coronary artery, so that the extent of the coagulation necrosis might be limited to the epicardium. Therefore, the diminished response of peak dP/dt to sympathetic stimulation was not caused by myocardial damage but by ventricular asynchrony due to interruption of sympathetic nerve conduction.

Rushmer¹¹ summarized the effects of sympathetic stimulation on left ventricular dimensions as follows: 1) reduced diastolic size; 2) faster ejection; 3) more complete ejection; 4) faster early filling. In the present study, regional wall motion showed reduced EDL and ESL and increased %dL following sympathetic stimulation. After phenol application, pressure-length loop in the lateral wall was similar to that obtained before phenol application. On the other hand, the phenol treated sympathectomized region expanded in the early systolic phase, contraction continued over end-systole, and the end-systolic point in the pressure-length loop shifted upward but not to the left (see Table I, end-systolic length does not change following sympathetic stimulation). These findings are consistent with asynchronous contraction in this region. Several investigators have shown that ventricular pacing results in an early shortening in the region close to the pacemaker site and the segment produces a bulge in the opposing, not yet activated region.¹²⁻¹⁴ Furthermore, the late contracted segment in turn produces late systolic lengthening in the early activated segment, and this interaction is dependent on the disparity of activation time between the stimulating site and the opposing region. In the present study, early systolic expansion and prolonged contraction observed in phenol treated area displayed a motion similar to asynchronous contraction induced by ventricular pacing. But beta receptor stimulation has no effect on the ventricular specialized conduction system, and sympathetic stimulation does not significantly affect ventricular muscle conduction. Therefore, the early systolic expansion observed in the phenol treated

region seems not to be related to interruption of the specialized conduction system.

Reuter¹⁵ reported in his experiment of perfused calf ventricular trabecula that NE causes an increase in isometric tension and decreases in time to peak tension and time to half maximal relaxation. In our experiment, peak dP/dt following sympathetic stimulation increased 3 times as much as the control value and %dL increased from 11.8 ± 1.3 to 20.2 ± 1.9 , indicating an increase in left ventricular performance and pressure generation. But in locally sympathectomized hearts, peak dP/dt following sympathetic stimulation increased by only 2.4 times the control value, suggesting that tension development was not influenced by sympathetic stimulation in the phenol treated area. In the present study, locally sympathectomized myocardium expanded early systole so that the anterior wall may not contribute on pressure rise. In contrast, NE infusion did not produce asynchronous contraction in the locally sympathectomized region, signifying that phenol interrupted sympathetic nerve conduction in epicardial surface but maintained myocardial beta receptor intact. It was therefore considered that the early systolic expansion and prolonged contraction observed in the anterior wall were originated from a disparity of tension development.

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