Induction of ST-Segment Elevation by Regional Myocardial Stretch in Normal Canine Hearts *in Vivo*

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The purpose of this study was to evaluate ST-segment elevation induced by regional myocardial stretch without myocardial ischemia in canine hearts. A strain gauge arch (TH-601T) was sutured to the left ventricular epicardium, parallel to the short axis, to shorten the end-diastolic length of the myocardium beneath the arch (stretch zone; SZ) and to produce regional myocardial stretch in each of 6 dogs. An increase in preload caused by altering the height of a saline-filled reservoir affected prolongation or shortening of the myocardium both in the SZ and outside the arch (normal zone; NZ) to increase myocardial stretch. An epicardial electrocardiogram was recorded in both the SZ and the NZ. After suture of the strain gauge arch, the ST segment was elevated in the SZ. An increase in preload augmented stretch during systole in the SZ, resulting in additional ST-segment elevation. These results suggest that regional myocardial stretch itself plays an important role in ST-segment elevation.

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Key Words: Regional myocardial stretch; Strain gauge arch; ST-segment elevation; Systolic bulging; Mechano-electrical feedback

In clinical electrocardiology, the mechanism of ST-segment elevation in acute myocardial infarction has been elucidated by studies of the injury current from the normal area to an ischemic area.¹ Non-ischemic ST-segment elevation is sometimes observed in ventricular aneurysm and in exercise tests after an old myocardial infarction.^{2,3} It is possible that myocardial stretching of a dyskinetic ventricle may alter transmembrane potential, causing ST-segment elevation. Whether regional myocardial stretch influences electrocardiographic change in the normal heart *in vivo* has not been determined.

We developed a model of regional myocardial stretch in a canine heart *in vivo*. When a stiff tension gauge is sutured to the surface of the left ventricle to shorten segment length, the developed systolic tension of the muscle under the gauge is less than that of muscles outside the gauge. Thus, muscle under the gauge is stretched by intraventricular systolic pressure

developed by muscle outside the gauge, and the gauge measures the systolic force of the stretch. The difference between the developed forces inside and outside the gauge can be changed by altering the diastolic load of the ventricle. We evaluated electrocardiographic changes induced by regional myocardial stretch in canine hearts *in vivo* to investigate mechanically induced ST-segment elevation without myocardial ischemia.

Materials and Methods

Experimental Preparations and Procedures

Six mongrel dogs of either sex weighing 10–20 kg were sedated with 1–1.5 mg/kg body weight droperidol intramuscularly and anesthetized with 25–30 mg/kg pentobarbital intravenously. Respiration was controlled by a Harvard pump (Harvard Apparatus, South Natick, MA), which provided a mixture of room

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Fig 1. Schematic diagram of the preparation. Ao, aorta; LV, left ventricle; RV, right ventricle.

Fig 2. Schematic representation of experimental preparation. The strain gauge arch was sutured to the left ventricular (LV) wall by thin sutures to shorten the end-diastolic length of the myocardium between the ends of the arch.

air and 1.0 L/min oxygen. After thoracotomy, the epicardium was opened and a catheter was inserted through a femoral vein for intravenous infusion. Aortic pressure was monitored through a catheter inserted through a femoral artery. Left ventricular (LV) pressure was measured through a short catheter inserted from the apex. A silicone tube (8 mm diameter) filled

with heparinized normal saline was inserted through the left appendage and connected to a reservoir that could be used to alter the preload by changing its height. An epicardial electrocardiogram (ECG) was monitored using a contact electrode at the left anterior descending (LAD) perfused area, and using a Wilson central terminal as the indifferent electrode.

Table 1 Hemodynamic Variables in All Procedures

	Control	Gauge (+)	Preload increase
HR (/min)	117.2±12.0	114.8±12.3	108.2±12.3
MAP (mmHg)	74.2±5.2	73.8±6.9	75.6±5.8
LVSP (mmHg)	87.8±5.1	86.3±5.1	102.7±10.8
LVEDP (mmHg)	3.0±1.8	5.5±2.1	10.6±2.2*

HR, heart rate; MAP, mean aortic pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure

* $p < 0.05$ vs control

Fig 3. Hemodynamic tracing in a representative case. Suture of the strain gauge arch to the LV wall induced ST-segment elevation in the epicardial ECG in the SZ, and additional ST-segment elevation was observed in the SZ after a preload increase created by altering the height of the reservoir. Gauge, strain gauge arch; NZ-ECG, epicardial ECG in the normal zone; SZ-ECG, epicardial ECG in the stretch zone; AoP, aortic pressure; LVP, left ventricular pressure; gW, gram weight.

After control recording of hemodynamic parameters and epicardial ECG, a strain gauge arch⁴ (TH-601T; Nihon Kohden, Tokyo) was sutured to the left ventricular epicardium parallel to the short axis (Fig 1). The arch recorded the sum of 2 opposing forces: one developed by contraction of the myocardium between the 2 ends of the strain gauge arch [stretch zone (SZ)] and the other developed by contraction of the myocardium outside the arch [normal zone (NZ)]⁵ (Fig 2). When the SZ was stretched by the NZ, the force was recorded as a negative wave form that serves as an index of the force (stretch) pulling the ends of the arch apart. In order to obtain regional myocardial

stretch in the SZ, the strain gauge arch was sutured to shorten the end-diastolic length of the SZ. The muscular segment in the SZ was then released and folded between the ends of the arch, and the SZ was stretched by the NZ during systole. An epicardial ECG was monitored in both the SZ and the NZ.

After recording the hemodynamic variables and epicardial ECG changes before and after suture of the strain gauge arch, we elevated the reservoir to increase the preload. After about 500 ml of heparinized normal saline had been infused for 10–20 sec and the epicardial ECG and hemodynamic parameters had been recorded at 1 min after reservoir use, the ST-segment

Fig 4. Change in ST-segment elevation after preload increase. ST-segment elevation was more prominent in the terminal ST-segment. Time, measuring point for ST-segment elevation after the beginning of the QRS complex.

Fig 5. ST-segment elevation during all experimental procedures. After suture of the strain gauge arch, ST-segment elevation was induced in the SZ. The preload increase augmented regional stretch in the SZ, and was accompanied by an additional ST-segment elevation in all 6 dogs. In the NZ, ST-segment elevation was also induced after an increase in preload. Δ ST, Change of ST segment from control level. ST-segment elevation was measured 160 msec after the beginning of the QRS complex. ●, SZ; ○, NZ.

elevation in the epicardial ECG was measured, with the flat portion of the PR segment defined as zero level. The difference between ST-segment elevation and the control level was expressed as Δ ST. The data were recorded on a polygraph (Nihon Kohden) at paper speeds of 25 and 100 mm/sec.

Statistics

Data are expressed as mean $\pm$ standard error. A paired t test was used to compare mean values between groups. Differences were considered statisti-

Fig 6. Relationship between ST-segment elevation and regional myocardial stretch. Increase in regional myocardial stretch induced additional ST-segment elevation in the SZ in all 6 dogs. gW, gram weight.

cally significant when $p < 0.05$.

Results

Hemodynamic variables in the control and experimental procedures are summarized in Table 1. Heart rate, mean aortic pressure, and left ventricular systolic pressure were unchanged in all procedures. Left ventricular end-diastolic pressure increased significantly after a preload increase induced by changing the height of the reservoir.

Just after the strain gauge arch had been sutured to the epicardium, the force recorded by the arch showed a negative wave form during systole, indicating stretch resulting from muscle shortening outside the arch (see Fig 3 for representative data from 1 dog). ST-segment elevation was augmented in the epicardial ECG in the SZ but not in the NZ. After the increase in preload, LV systolic pressure increased from 87.5 to 92.5 mmHg and LV end-diastolic pressure (LVEDP) increased from 11.2 to 16.3 mmHg. Mechanical changes in the LV produced by an increased preload affected the lengthening or shortening of the SZ and the NZ, and this increase in mechanical change from 26.4 to 45.1 g weight (gW) induced further ST-segment elevation in the SZ.

Mean ST-segment elevation in the SZ for all dogs after an increase in preload was calculated (Fig 4). ST-segment elevation was significant in the SZ, and was more prominent in the terminal ST segment. Fig 5 shows ST-segment change for each dog 160 msec after the onset of the QRS complex in the epicardial ECG following suture of the strain gauge arch and an increase in preload. After suture of the arch, ST-segment elevation was induced in the SZ but not

in the NZ. Increasing the preload caused additional ST-segment elevation in the SZ, but also in the NZ. The relationship between regional myocardial stretch and ST-segment elevation in the SZ was determined in all 6 dogs (Fig 6). The degree of ST-segment elevation and regional myocardial stretch differed in each dog, but there was a similar tendency for stretch to cause ST-segment elevation in all dogs.

Discussion

The major finding of this study was that regional myocardial stretch produced by the strain gauge arch induced ST-segment elevation unrelated to myocardial ischemia. However, ST-segment elevation is one of the most useful signs of acute myocardial infarction.⁶ During myocardial ischemia, electrical changes, such as shortening of the action potential, depolarization of the resting potential, and decrease in the action potential amplitude, cause abnormal injury currents to flow from normal to ischemic areas, resulting in ST-segment elevation.⁷ In addition, myocardial ischemia induces an inhomogeneous movement of the LV known as systolic bulging,⁸ which causes the myocardium to stretch during systole and to shorten late in diastole. These mechanical changes during ischemia may alter transmembrane potential, resulting in ST-segment elevation. In our previous study, ventricular dyskinesia produced by intracoronary injection of a negative inotropic agent induced ST-segment elevation without myocardial ischemia.⁹ However, the agents used may have caused a direct change in action potential, rather than one secondary to a change in myocardial contraction. In the present study, we found that an increase in myocardial stretch not associated with ischemia induced ST-segment elevation in all 6 dogs. Our results indicate that regional mechanical change in muscle contraction is one of the important regulators of electrophysiologic state. The degree of ST-segment elevation differed among the dogs, which suggests that ST-segment elevation also depended on such other conditions as LV pressure, aortic pressure, heart rate, and position of the strain gauge arch on the myocardial surface.

The electrophysiologic effect of myocardial stretch, that is mechanoelectrical feedback, is defined as a change in the mechanical state that precedes and alters the transmembrane potential.¹⁰ In preparations of frog ventricle, myocardial stretch shortens the action potential and depolarizes the resting potential, resulting in modulation of phases 2 and 3 of the action potential.¹¹ We observed that ST-segment elevation in the SZ was more prominent in the terminal ST-segment, especially

160 msec after the beginning of the QRS complex (Fig 4). The terminal ST-segment portion related to phase 2 and 3 of the action potential. Fig 3 showed that the negative force curve produced by the gauge was more prominent in the QRS phase of epicardial ECG in the SZ. It is not clear why ST elevation and force curve were conflicting, but our findings suggest that regional myocardial stretch can induce changes in the action potential that lead to an abnormal current between normal and involved parts of the myocardium, causing ST-segment elevation without myocardial ischemia.

Several factors other than myocardial ischemia influence the ST-segment level on epicardial ECGs. Because mechanical injury of the epicardial surface induced by ECG electrodes can cause elevation of the ST-segment, we used contact electrodes. Open heart surgery may alter the electrophysiologic state of the epicardial surface, as pericardial fluid is removed after pericardiotomy and changes in the electrolyte balance can affect the epicardial ST-segment. The autonomic nervous system and anesthetics also affect the electrophysiologic state. These factors could have influenced ST-T changes in the control state.

Stretch-activated ion channels are found in many animal cells.¹² In ventricular myocytes, stretch-induced depolarization may be caused by conductance increases in stretch-activated nonselective ion channels,¹³ which may explain mechanoelectrical feedback effects. In our study, regional myocardial stretch could activate more stretch channels in the SZ, leading to an abnormal current flow from the NZ to the SZ and resulting in ST-segment elevation. Proof of this hypothesis will have to come from more detailed investigations at the cellular and single-channel levels.

Adenosine triphosphate (ATP)-sensitive potassium channels may mediate the mechanoelectrical feedback effects. Gating of atrial ATP-sensitive potassium channel in rat atrial myocytes is mechanosensitive,¹⁴ and the ATP-sensitive potassium channel opener pinacidil induces ST-segment elevation.¹⁵ ATP-sensitive potassium channels may also contribute to electrophysiologic changes during myocardial ischemia;¹⁶ such channels are activated more in epicardial cells than in endocardial cells during ischemia,^{17,18} and could cause current to flow from endocardial to epicardial sites and induce ST-segment elevation. This type of mechanism may also account for stretch-induced ST-segment elevation in the NZ in our study.

Interpretation of the results of this study is subject to 3 principal limitations. First, it is unknown whether regional stretching of the myocardium from the epicardium to endocardium by the strain gauge arch was uniform. Second, we could not control the degree

of myocardial stretch by use of the reservoir. Third, it is possible that connecting the strain gauge arch to the surface of the myocardium causes elevation of the ST-segment in our model. Despite these limitations, there was a similar tendency for increased stretch induced by an increase in preload to cause additional ST-segment elevation in all 6 dogs. These results suggest that regional myocardial stretch per se played an important role in the ST-segment elevation in our model.

In conclusion, regional myocardial stretch induced by the strain gauge arch without ischemia caused ST-segment elevation, and a further increase in the stretch caused by an increase in preload augmented the elevation. Regional myocardial stretch may affect ST-segment elevation via mechanoelectrical feedback, which alters the action potential.

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