Influence of Inotropic Alteration on the Severity of Myocardial Ischemia after Experimental Coronary Occlusion

Tan WATANABE, M.D., Fujio SHINTANI, M.D., Longtai Fu, M.D., Junichi Fujii, M.D., Hiroshi WATANABE, M.D., and Kazuzo KATO, M.D.

SUMMARY

The effects of propranolol (0.5–2 mg./Kg.) and isoproterenol (0.2 μg./Kg./min.) on the severity and extent of ischemic injury after acute coronary occlusion in experimental dogs were determined from the average S-T segment elevation (E-ST) and the number of sites where S-T elevation exceeded 2 mV. (N-ST) in 12 to 20 left ventricular (LV) epicardial sites. The mappings were obtained 15 min. after repetitive occlusions of a main branch of the left anterior descending coronary artery. In 5 dogs propranolol decreased E-ST from 4.0±0.8 during simple control occlusion to 1.5±0.3 mV. (SEM) (p<0.01) and N-ST from 9.2±1.0 to 4.2±0.5 (p<0.01). At this time, LV myocardial contractility expressed by dP/dt/IIT decreased from 2,320±280 to 1,460±230 (p<0.01) along with significant reduction of cardiac output (CO). LV developed tension assessed from LV TTI/min. fell slightly and insignificantly. In contrast, in 5 dogs the infusion of isoproterenol increased E-ST from 1.5±0.2 to 3.1±0.7 mV. and N-ST from 6.6±0.6 to 9.4±1.1 (both, p<0.01). The value of dP/dt/IIT increased from 1,980±440 to 4,610±920 (p<0.01) with concomitant increment in CO. LV TTI/min. elevated slightly and again insignificantly. It was concluded that, in beating in situ heart the severity and extent of acute myocardial ischemic injury can be altered by the changes in LV contractile state, even in the absence of changes in LV wall tension.

Additional Indexing Words:

Epicardial mapping Propranolol Isoproterenol Myocardial oxygen demand and supply Wall tension Contractile state

The balance between local myocardial oxygen demand and supply appears to be an important determinant of the extent of ischemic injury or damage following an acute coronary occlusion.1)-4) It is also clear that myocardial contractile state and left ventricular tension are the crucial factors which alter the myocardial oxygen requirements.5)-10) Recent experimental studies have shown that the extent and severity of myocardial ischemic injury after coronary occlusion...
occlusion can be affected by a variety of pharmacologic and hemodynamic interventions. For example, isoproterenol, given prior to repeated occlusion, increased the severity and extent of ischemic injury comparing to its preceding simple occlusion, whereas propranolol decreased it. These results or facts are considered not due to the specific effects of the drugs used, but due to the changes in contractile state of the myocardium, the left ventricular developed tension, or the coronary blood flow. Accordingly, the purpose of the present study was to clarify which of these factors would predominate over the interrelationship of the myocardial oxygen demand and supply during an acute coronary occlusion under the influence of hemodynamic alterations induced by inotropic agents.

**Materials and Methods**

Studies were carried out in 10 mongrel dogs weighing between 10 to 16 Kg. and anesthetized with 25 mg./Kg. of sodium pentobarbital. Respiration was maintained with a Harvard respirator, and the heart was exposed through a left thoracotomy and suspended in a pericardial cradle. One or two main branches of the left anterior descending coronary artery were dissected free from the surrounding tissues for the purpose of repeated occlusions.

Aortic and left ventricular (LV) pressures were measured through metal cannulae inserted via the left carotid artery and LV apical dimple, respectively, and connected to Statham P23 Db transducers. The first derivative of the LV pressure pulse (LV dP/dt) was obtained with an analog differentiating circuit.* A flow transducer was placed around the ascending aorta, and blood flow velocity was recorded with a gated sine wave electromagnetic flowmeter.** All variables, including the epicardial electrogram, were recorded on a multichannel oscillographic recorder*** at a paper speed of 125 mm./sec.

The severity and extent of myocardial ischemic injury following coronary occlusion were assessed by epicardial mapping technique described in detail by Maroko et al. Using a cotton wick soaked in normal saline and impacted in the hollow metallic cylinder of 2 mm. in diameter, electrogram was recorded with use of the central terminal system of Wilson et al. Twelve to twenty sites on the anterior surface of the left ventricle were chosen for epicardial electrography. Sites for mapping were selected within the area supplied by the occluded branch, in area adjacent to this zone, as well as remote portions where were considered to be adequately perfused by unaffected coronary arteries. Since the mappings from each site had to be made several times in one experiment, sites were selected near the bifurcation of the vessels so that the electrode could be easily and correctly repositioned at the same location. The schematic illustration is shown in Fig. 1.

The sites at which myocardial ischemic injury was considered to exist were those where the junctional elevation of S-T segment exceeded 2 mV. when recorded 15 min. after occlusion. In each experiment, the magnitude of S-T segment elevations in mV. from such the sites were added, then divided by the total number of sites, and this value, E-ST, served as an overall index of the severity of ischemic
injury in any given experiment. As well, the number of sites at which S-T segment was significantly elevated (N-ST) served as an index of the extent of the injury. Changes in both the ES-T and N-ST for a group of experiments were analyzed by the paired t-test to determine the effects of interventions on the myocardial ischemic injury.

The animals were divided into 2 groups, in which experimental protocol was similar. Epicardial mappings were obtained before and 15 min. after each occlusion. A control simple occlusion was at first carried out. After release of the occlusion and return of the each hemodynamic parameter along with epicardial electrograms to pre-occlusion control state, following interventions were employed. In the first group (5 dogs), cardiac depression was induced by the intravenous administration of propranolol (0.5-2.0 mg./Kg.) 5 min. prior to repeated occlusion. In the second group (5 dogs), contractile state was augmented by isoproterenol. A constant rate infusion of isoproterenol (0.2 µg./Kg./min.) was started 5 min. before occlusion and maintained during the repeated occlusions.

* Electronics for Medicine SGA-2 Preamplifier.
** Statham M4001.
*** Brush Clevite 260.
RESULTS

Overall data during the occlusions are summarized in Table I.

Table I.

<table>
<thead>
<tr>
<th></th>
<th>E-ST (mV)</th>
<th>N-ST</th>
<th>CO(%)**</th>
<th>LV TTI (mm.Hg/sec.)</th>
<th>dp/dt/JIT</th>
<th>LVEDP (mm.Hg/sec/min.)</th>
<th>PPI (mm.Hg/sec/min.)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>15' after Control Oclusion</td>
<td>4.0±0.8*</td>
<td>9.2±1.0</td>
<td>94± 2</td>
<td>2,930±250</td>
<td>2,320±280</td>
<td>4.9±1.3</td>
<td>4,290±160</td>
</tr>
<tr>
<td>15' after Oclusion after Propranolol</td>
<td>1.5±0.3*</td>
<td>4.2±0.5*</td>
<td>69±2*</td>
<td>2,660±260</td>
<td>1,460±230</td>
<td>6.4±1.9</td>
<td>4,300±280</td>
</tr>
<tr>
<td>15' after Control Oclusion</td>
<td>1.5±0.2</td>
<td>6.6±0.6</td>
<td>88± 5</td>
<td>3,420±270</td>
<td>1,980±440</td>
<td>2.8±0.7</td>
<td>4,630±280</td>
</tr>
<tr>
<td>15' after Oclusion during Isoproterenol</td>
<td>3.1±0.7*</td>
<td>9.4±1.1*</td>
<td>121±12*</td>
<td>3,680±340</td>
<td>4,610±920</td>
<td>2.7±0.7</td>
<td>4,710±340</td>
</tr>
</tbody>
</table>

# Mean±SEM
+ not significant
* p < 0.01 (by Student's paired t-test)
** cardiac output expressed by percent of pre-occlusion value
*** coronary perfusion pressure index: see text

Severity and extent of ischemic injury

In the first group (5 dogs), 15 min. after control simple occlusion, mean value of average S-T segment elevation, (E-ST) an index of severity of ischemic injury, was 4.0±0.8 mV.* Also, the number of sites with S-T segment elevation exceeding 2 mV., (N-ST) an index of the extent of ischemic zone, was 9.2±1.0. Repeated coronary occlusion carried out after the intravenous administration of propranolol (0.5–2.0 mg./Kg.) resulted in a significant decrease in mean value of E-ST from the control value to 1.5±0.3 mV. (p < 0.01). N-ST also decreased from the control value to 4.2±0.5 (p < 0.01).

In the second group (5 dogs), during continuous infusion of isoproterenol (0.2 μg./Kg./min.), the average E-ST increased 15 min. after occlusion from 1.5±0.2 during control occlusion to 3.1±0.7 mV. along with a significant increase in N-ST from 6.6±0.6 to 9.4±1.1 (both p < 0.01). These are shown in Fig. 2-A and B.

* Standard error of mean.
Fig. 2. A. Effects of propranolol and isoproterenol on the average S-T segment elevation (E-ST) 15 min. after coronary occlusion. Bars represent standard errors of mean. White column = control simple occlusion; Striped column = occlusion after propranolol; Hatched column = occlusion during isoproterenol. Symbols are the same hereafter.  

B. Effects of propranolol and isoproterenol on the average number of sites with S-T segment elevation (N-ST).

Hemodynamic alterations

Heart rate was reduced after propranolol from an average control value of 156 ± 14 to 130 ± 8 beats/min. It was increased from an average of 153 ± 7 to 199 ± 9 during isoproterenol infusion. LV end-diastolic pressure was elevated slightly after cardiac depression by propranolol and lowered slightly by isoproterenol, but changes were significant in neither. Mean systemic arterial blood pressure was not significantly altered following any interventions.

Cardiac output was assessed by the product of heart rate and stroke volume measured with a flow probe around the aortic root, and expressed as a percent of the initial value obtained from tracings just prior to the control occlusion. As shown in Fig. 3, cardiac output decreased as an average value from 94 ± 2% during control occlusion to 69 ± 2% after propranolol, whereas it increased from 88 ± 5 to 121 ± 12% by isoproterenol.

LV tension time index/min. (LV TTI) was derived from the product of heart rate and pressure area under the LV pressure curve during its active state.
Fig. 3. Effects of propranolol and isoproterenol on the average values of cardiac output, expressed by a percent of initial value 5 min. prior to simple control occlusion.

It was decreased by propranolol and increased by isoproterenol as average values from $2,930 \pm 250$ to $2,660 \pm 260$ and from $3,420 \pm 270$ to $3,680 \pm 340$ mm. Hg sec., respectively. However, as shown in Fig. 4, both of these changes were insignificant.

As an index of LV myocardial contractile state in an overall heart, dP/dt/IIT by Siegel and Sonnenblick was employed.\(^{16}\) Fig. 5 shows that propranolol significantly reduced it from an average control level of $2,320 \pm 280$ to $1,460 \pm 230$. Contrarily isoproterenol increased it from $1,980 \pm 440$ during simple occlusion to $4,610 \pm 920$ during occlusion with the drug infusion.

There were no remarkable alterations in coronary perfusion pressure indices (PPI: the product of heart rate, mean aortic pressure and duration of diastole in aortic pressure tracing) after these 2 interventions.
Factors which affect myocardial oxygen consumption have been experimentally shown to influence the magnitude and extent of S-T segment elevation following a coronary occlusion. The current studies support the hypothesis that the extent of myocardial ischemic injury during coronary ligation depends on the balance between oxygen demand and supply in the affected myocardium. It is also clear that myocardial contractile state and LV wall tension are the major determinants of oxygen requirement of the heart. In this experiment, following results appeared to be evident, as far as the indices employed in evaluating wall tension and contractile state of the heart were concerned and within the dose of the drugs used here: i) The area of myocardial ischemia decreased after cardiac depression induced by propranolol, whereas augmentation of LV myocardial contractility by isoproterenol increased it. ii) There were no significant alterations in wall tension, expressed by TTI/min.,
After the drugs. iii) In contrast, myocardial contractile state as a whole heart, assessed from dP/dt/IIT, changed significantly after both drugs to the opposite directions. iv) As far as the coronary perfusion pressure was concerned, there might be no marked differences in coronary blood supply between control states and those after both drugs. v) Therefore, these evidences indicated that the myocardial contractile state as a whole heart was the major determinant of the myocardial oxygen requirement after coronary occlusion.

Of particular interest in the present investigation is the fact that the size and severity of myocardial ischemic injury following coronary occlusion can be altered under the influence of significant changes in contractile states of an overall heart. This occurred even in the absence of any change in LV wall tension or coronary blood supply. The possibility that the contractile state of the heart might be an important determinant of myocardial oxygen demand has been examined by Sonnenblick et al., in a canine right heart bypass preparation. They observed that oxygen consumption rose while the TTI
declined after a variety of interventions increasing the myocardial contractility. In the present studies, in which spontaneously beating heart preparations, in situ, were employed, the results seemed to be in part in accordance with their observations. In our findings, however, TTI/min. rose slightly after isoproterenol due to the significant increment of heart rate. Braunwald et al. also observed increase in heart rate as much as myocardial contractility following infusion of this drug.\(^2\),\(^1\) Then studies were designed by these investigators to determine the effect of increased heart rate on the extent of S-T segment elevation during coronary occlusion. The heart was driven by electrical stimulation throughout the experiment at rates identical to those encountered during isoproterenol infusion. According to their results, coronary occlusion in paced heart produced S-T segment elevation of midway amplitude between those in the control state and those during isoproterenol infusion.\(^1\) Moreover, at least some part of these effects of increased heart rate was presumably resulted from augmented contractile state of the heart incidental to rapid action.\(^2\)\(^1\)\)\(^-\)\(^2\)\(^4\) The myocardial contractility seems to be the major determinant of the myocardial oxygen consumption in the beating heart in situ like in papillary muscle preparation.\(^2\)\(^0\) and that of the extent of S-T segment elevation during coronary occlusion as well.

Cardiac depression induced by propranolol in this experiment does not necessarily mimic the condition encountered clinically in patients with acute myocardial infarction. Extrapolation of the present data to the clinical settings could not be permitted without caution. Nevertheless, marked reduction in ischemic area after propranolol strongly suggests that the use of this drug in coronary patient without overt cardiac failure favors the affected myocardium.\(^2\)\(^5\),\(^2\)\(^6\) In contrast, positive inotropic agents, not only isoproterenol but also those such as digitalis preparations and glucagon are known to reduce viability of ischemic myocardium within marginal portion of the infarcted area.\(^1\)\(^1\),\(^2\)\(^7\),\(^2\)\(^8\) The present findings do indicate that consideration should be given whether the drug would have aggravating effects on the size and severity of the ischemic injury of myocardium prior to treatment for improving cardiac performance in patients with acute myocardial infarction.

Acknowledgements

The authors acknowledge the skill and technical assistance of Miss Eiko Ohtsu. The typing and editorial efforts of Miss Yuriko Murata are also gratefully acknowledged.

References