Limitation of Myocardial Function by Reduced Coronary Blood Flow during Isoproterenol Action

By Herman B. Daniell, Ph.D., Ervin E. Bagwell, Ph.D., and Robert P. Walton, M.D., Ph.D.

ABSTRACT

The interpolated decrease in heart force or isometric systolic tension that occurs during isoproterenol stimulation has been examined in terms of changes in coronary flow and myocardial metabolism. In 67 open-chest dogs under pentobarbital anesthesia, determinations were made of lactate, pyruvate, Po₂ and Pco₂ in arterial and coronary sinus blood; coronary flow was measured with an electromagnetic flow transducer and ventricular force with a strain gauge arch. Although the characteristic, uncomplicated effect of isoproterenol is a marked increase in coronary flow and contractile force, this is briefly interrupted by a sharp decrease in these functions, and the decrease is associated with evidence of anaerobic metabolism. This decrease is concomitant with decreased coronary perfusion pressure and is intensified by sustained infusion of isoproterenol or by lowered oxygen concentrations in the inspired air. The stage of depressed function is counteracted by mechanical maintenance of high aortic pressure or by slow, controlled heart rate. When uncontrolled, tachycardia due to isoproterenol continues without phasic interruption. The intermediate period of depressed function is interpreted in terms of sharply decreased oxygen delivery when both cardiac rate and force are increased. The hemodynamic and metabolic values for these acutely occurring, reversible extremes have been specified.

ADDITIONAL KEY WORDS contractile force oxygen extraction triphasic response excess lactate anaerobic metabolism anesthetized dogs

Isoproterenol increases coronary flow when coronary perfusion pressure is maintained constant by artificial systems (1, 2). With the circulation intact, however, the initial marked increase in coronary flow is often interrupted by a sharp decrease in flow to near control levels, and this can occur when other effects of isoproterenol such as heart rate are reaching peak level. At this stage, ventricular force measured by the strain gauge arch is also sharply decreased, even below control levels, despite the intense, positive inotropism that normally occurs under a steady state of coronary flow. Typically, in the intact animal, force and coronary flow both return for a period to high levels as the systemic arterial pressure returns to control levels (3). This triphasic sequence of change in force is not unique with isoproterenol but occurs with other drugs which simultaneously lower arterial pressure and increase rate and force (4). It can be assumed that systemic arterial hypotension reduces coronary flow sufficiently to make oxygen delivery to the myocardium inadequate to meet these simultaneously increased demands. This provides, under relatively natural conditions, an acutely occurring, reversible condition which presents some of the limiting conditions of oxygen delivery and myocardial function.
These relations have been examined in the present experiments, and further metabolic data have been obtained. Such studies can be expected to provide a more quantitative recognition of the factors operating during acute onset and recovery from a condition in which myocardial function deteriorates because of a rapidly developed disparity between oxygen supply and demands.

Myocardial function in the present studies was measured by recording peak development of isometric systolic tension by a strain gauge arch attached to a representative segment of the myocardium. Bacaner et al. (5) recorded a similar function for the entire ventricular mass of an isolated heart preparation and they observed a close correspondence of this myocardial function and coronary flow. Nakano (6), on the other hand, observed parallelism only during stepwise decreases in coronary flow and not during supernormal flow; function was estimated by a strain gauge arch sutured to the area of the ventricle being perfused. These two studies of coronary blood flow as a determinant of myocardial function clearly differ in method from the several studies in which myocardial oxygen consumption was the chief point of interest and other hemodynamic functions were monitored.

Methods

Experiments were performed on 67 open-chest dogs under anesthesia with sodium pentobarbital (30 mg/kg iv). Animals of both sexes were used after examination showed them to be free of Dirofilaria immitis and to have hematocrit values greater than 35%. After tracheal intubation, the animals were ventilated with room air using a Harvard positive pressure respirator unless otherwise noted. A precalibrated strain gauge arch with adjustable length was sutured directly to the left or right ventricle or both for assessment of changes in ventricular force (isometric systolic tension). Most of the recordings were made from the right ventricle because of its more ready accessibility and because preliminary investigations showed that the response to isoproterenol occurred in both ventricles simultaneously and was of similar magnitude and pattern. Attachment of the arch on the right ventricle was in a line parallel to the base of the heart and on the left ventricle was perpendicular to the interventricular septum; by extending the length of the arch, the muscle segment was stretched by about 30% of its original end-diastolic length (7). In some instances, an isotonic strain gauge arch to record alterations in heart size was attached to the ventricular wall parallel to the isometric gauge. Polyethylene catheters were inserted in both right and left femoral arteries and advanced centrally until their tips were near the right atrium; these were used for intravenous injections and pressure recordings. For sampling coronary venous blood the coronary sinus was cannulated near the ostium by external puncture, as described by Rayford et al. (8), and the cannula was secured in place with a purse string suture. Continuous recordings of coronary blood flow were made from either the main left coronary artery or the anterior descending branch with a Medicon sine-wave electromagnetic flow transducer. Aortic flow was monitored by a Carolina Medical Electronics square-wave electromagnetic flow transducer placed around the ascending aorta. In some experiments, coronary sinus flow was measured by diverting the blood through an extracorporeal square-wave flow transducer and back into the systemic circulation by way of the right jugular vein. Prior to initial experimentation, all flow transducers were calibrated with blood on appropriate vessel segments by a gravity system or by cannulating a blood vessel in an intact animal distal to the transducer and collecting the blood in graduated cylinders several times for fixed intervals. The calibrations were repeated at intervals of 2 to 3 months, and the results were reproducible within ±5%. Heart rate was recorded electromechanically, and mean blood pressure was obtained by electrical damping of systolic and diastolic pressure impulses. The recording instrument was a model 5B Grass Polygraph.

Prior to experimentation, the respiratory rate was adjusted so that the arterial pH was within the range of 7.35 to 7.45. Simultaneous blood samples taken from the aorta and coronary sinus before the isoproterenol injection served as controls. Isoproterenol was either rapidly injected intravenously in a dose of 1 μg/kg or infused at the rate of 12 μg/kg/min; simultaneous blood samples again were taken during the nadir of the coronary flow response. These samples were analyzed for pH, Pco₂, and P0₂ with an Instrumentation Laboratory blood gas analyzer; for lactate by the method of Segal et al. (9); and for
Sequential comparison of effects of 1 μg/kg isoproterenol and 1 μg/kg norepinephrine in open-chest dog under pentobarbital anesthesia. Contractile force was recorded from the right ventricle while coronary and aortic flow rates were recorded respectively from sine-wave and square-wave electromagnetic flow transducers. With isoproterenol, the initial sharp increase in force is followed by a brief period of severe depression associated with decreased coronary flow and aortic pressure and a markedly increased rate.

Changes in optical density for the lactate and pyruvate determinations were obtained with a Beckman DU Spectrophotometer, and changes in "excess lactate" were calculated by Huckabee's formula (11). In a few experiments, an indwelling PO₂ electrode (Instrumentation Laboratory) was inserted into the coronary sinus, and the PO₂ of the coronary venous blood was monitored continuously. Oxygen and CO₂ contents of the samples were determined by use of a blood gas analyzer (F&M Scientific Corporation model 450). Blood withdrawn for samples was replaced with blood from a donor dog.

In 9 dogs complete heart block (12) was produced by cauterizing the bundle of His (modification of heart block procedure developed by Pruett and Woods of this laboratory), and the hearts were paced at various rates by electrical stimulation during the isoproterenol response.

In 11 animals, a section of the descending aorta was isolated near the diaphragm and a strip of umbilical tape placed around the isolated segment. By gently lifting the strip of tape while observing the blood pressure recordings, the desired degree of occlusion was obtained to maintain constant coronary perfusion pressure throughout the isoproterenol response.

Three animals were given 5 mg/kg of hexamethonium. A spinal block was induced in one other animal with 0.5% procaine massively infused epidurally after laminectomy (13). Sym pathetic block was considered complete when occlusion of the carotid arteries failed to cause a reflex increase in blood pressure and when no change in cardiac force, arterial pressure, or heart rate could be obtained by infusion of additional amounts of procaine.

Conditions as in Figure 1 but at a paper speed 10 times faster. The vertical line marks the beginning of the increase in coronary flow. Decrease in coronary flow precedes the decline in force and increase in flow precedes late increase in force.
Relation Between Systemic Blood Pressure, Coronary Flow, Ventricular Force, and Heart Rate during Isoproterenol Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Coronary flow (ml/min)</th>
<th>Ventricular force (g)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>114 ± 3</td>
<td>27 ± 2</td>
<td>96 ± 5</td>
<td>132 ± 5</td>
</tr>
<tr>
<td>1st Phase</td>
<td>93 ± 7*</td>
<td>50 ± 6*</td>
<td>246 ± 8*</td>
<td>170 ± 4*</td>
</tr>
<tr>
<td>2d Phase</td>
<td>71 ± 3*</td>
<td>28 ± 4</td>
<td>153 ± 8*</td>
<td>198 ± 6*</td>
</tr>
<tr>
<td>3d Phase</td>
<td>97 ± 11</td>
<td>50 ± 5*</td>
<td>202 ± 7*</td>
<td>174 ± 3*</td>
</tr>
</tbody>
</table>

Single injections of 1 μg/kg (46 experiments)

Infusions of 12 μg/kg per min (10 experiments)

Control 117 ± 11 33 ± 3 78 ± 8 130 ± 4
1st Phase 92 ± 8 64 ± 4* 224 ± 7* 164 ± 5*
2d Phase 67 ± 7* 35 ± 4 90 ± 6 203 ± 6*
3d Phase 90 ± 10 59 ± 7* 162 ± 7* 169 ± 4*

Values = Mean ± SE. 1st Phase = initial increase in coronary flow; 2d Phase = nadir of coronary flow; 3d Phase = second elevation in coronary flow.
*Significant difference from control (P < .05).
†Measurements made 3 min after the beginning of infusion.
‡Measurements made at peak response after termination of infusion.

Seventeen injections of isoproterenol were given to 5 dogs while they were being ventilated with different concentrations of oxygen and nitrogen by an Ohio anesthesia machine connected to a positive pressure respirator. Seven experiments were performed while the oxygen concentration of the inspired gas was 12 to 13%; 5 when it was 20 to 25%; and 5 when it was 100%. The sequence of the procedure was varied randomly. In one experiment at low oxygen concentration, coronary perfusion pressure was kept constant during the drug response by partial aortic occlusion. In an effort to keep systemic blood pressure constant at the different oxygen concentrations, each animal was given 1 mg/kg of phentolamine before the experiment.

Calculations of standard error, correlation coefficient, and Student's t-test were made according to Snedecor (14) with a P value < 0.05, indicating significance.

Results

Figure 1 compares the effects of isoproterenol and norepinephrine on cardiovascular responses. The influence of systemic perfusion pressure on coronary flow is clearly evident in both sets of tracings, as well as the relation between coronary blood flow and ventricular contractile force. Figure 2 illustrates the response obtained from isoproterenol at a faster paper speed in a different animal. The first response was a slight increase in coronary flow, which was followed in about 4 sec by an increase in contractile force and a concomitant rapid elevation in coronary flow. As systemic perfusion pressure declined, coronary flow decreased to levels near control values (Table 1), and the alteration in flow was followed in about 8 sec by a reduction from peak values in contractile force. When systemic perfusion pressure returned toward control values, coronary flow increased; the increase in flow preceded the elevation in force. In animals whose systemic blood pressure did not fall appreciably, coronary flow increased and remained well above control values throughout the period of the response, and a period of reduced contractile force did not occur. There was a correlation at the 1% level of significance between the level to which systemic blood pressure fell and the reduction from peak ventricular force values (n = 46, r = .556).

Table 1 summarizes the relation between aortic blood pressure, coronary flow, and ventricular force during isoproterenol stimulation. Infusions of the drug resulted in a prolonged nadir phase of the response, and both coronary flow and force remained at a lower level of stimulation as long as the drug was being infused and as long as the systemic hypotension persisted. The fact that force approached preinjection values during the
nadir of the coronary flow response should not be interpreted as indicating that the heart was not in a stimulated state at that time; heart rate was elevated from control values of $132 \pm 5$ (SE) to $198 \pm 6$ (SE) and thus the total tension developed by the myocardium per unit of time was well above control levels.

During the second, or nadir, phase lactate utilization by the heart decreased significantly with single injections of the drug, and metabolism became anaerobic in the myocardium in approximately 25% of the experiments, as indicated by the formation of "excess lactate." When the second phase of the coronary flow response was prolonged, as with infusion of isoproterenol, myocardial excess lactate was formed in each experiment. These data along with other myocardial metabolic changes are shown in Table 2. Coronary venous $P_{CO_2}$ was slightly elevated during the nadir of the coronary flow response, and this elevation became significant when this phase of the response was extended. Coronary venous pH was significantly lower than arterial pH and became progressively lower with continued administration of the drug.

When the drug infusion was terminated and coronary flow increased to higher levels, the coronary venous pH returned toward preinjection values. Statistically significant correlations, however, were not found between either the coronary sinus pH or coronary sinus $P_{CO_2}$ and the extent of the reduction in ventricular force; a significant correlation was found between the decreased myocardial lactate utilization and the reduction from peak values in ventricular force.

Mean values for 40 determinations showed no significant change in coronary venous $P_{O_2}$ during the second phase of the response when single injections of the drug were administered; whereas, when isoproterenol was infused, a significant reduction from control values in coronary venous $P_{O_2}$ did occur. However, control values for this series of experiments were higher, and the level to which the $P_{O_2}$ fell was not significantly different from the single injection studies (Table 2). In a few experiments, continuous recordings of coronary sinus $P_{O_2}$ were obtained with an indwelling electrode. An example of the tracing obtained is shown in Figure 3.

**Influence of Other Variables.**—The above

### Table 2

**Alterations in Myocardial Metabolism during Period of Reduced Coronary Flow with Isoproterenol Stimulation**

<table>
<thead>
<tr>
<th></th>
<th>Aortic blood</th>
<th>Coronary venous blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Isoproterenol</td>
</tr>
<tr>
<td>Lactate (mg/100 ml)</td>
<td>16.17 ± 1.30</td>
<td>16.74 ± 1.36</td>
</tr>
<tr>
<td>Pyruvate (mg/100 ml)</td>
<td>1.24 ± 0.09</td>
<td>0.96 ± 0.08*</td>
</tr>
<tr>
<td>$P_{O_2}$ (mm Hg)</td>
<td>72.0 ± 2.5</td>
<td>64.0 ± 2.0</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mm Hg)</td>
<td>25.0 ± 0.7</td>
<td>31.0 ± 0.8</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.01</td>
<td>7.40 ± 0.01*</td>
</tr>
</tbody>
</table>

Single injections of 1 μg/kg (40 experiments)

| Lactate (mg/100 ml) | 15.45 ± 2.03  | 17.96 ± 1.75  | 10.05 ± 1.45 | 22.28 ± 1.78* |
| Pyruvate (mg/100 ml) | 1.18 ± 0.15   | 1.22 ± 0.08  | 0.97 ± 0.17  | 1.13 ± 0.12  |
| $P_{O_2}$ (mm Hg)     | 64.0 ± 1.0    | 62.0 ± 2.0   | 27.0 ± 1.0   | 23.0 ± 1.0*  |
| $P_{CO_2}$ (mm Hg)    | 39.0 ± 1.0    | 47.0 ± 1.0*  | 47.0 ± 1.0*  | 69.0 ± 2.0*  |
| pH                | 7.41 ± 0.01   | 7.43 ± 0.01* | 7.37 ± 0.01  | 7.24 ± 0.01* |

Infusions of 12 μg/kg per min (10 experiments)

Values = Mean ± SE.

*Significant difference from control.

†Response sample taken 3 min after beginning of infusion.
results suggested that a transient relative coronary insufficiency was associated with an attenuation of the positive inotropic response to isoproterenol. It became apparent, however, that other variables including heart rate, aortic blood pressure, and perhaps reflex activity, could have contributed to the period of lessened positive inotropism. Therefore we determined the effects of isoproterenol on myocardial functions when one or more of these variables were held constant. We also determined the effects of changes in arterial oxygen tensions on the inotropic response to the drug.

Controlled Rate.—Figure 4 shows tracings obtained from an animal with complete heart block. The characteristic triphasic response of contractile force did not occur during stimulation when the heart was paced at a slow rate. The reduction in arterial blood pressure during heart block was not as pronounced as that before the block; however, control blood pressure was lower after the block, and the level to which mean blood pressure decreased was approximately the same before and after the block. Mean values for anterior descending coronary flow during stimulation at fixed heart rates of 136/min...
TABLE 3

Metabolic Responses to Isoproterenol during Heart Block

<table>
<thead>
<tr>
<th></th>
<th>Control (12 dogs)</th>
<th>Paced heart rate 136 ± 8/min (8 dogs)</th>
<th>Paced heart rate 200/min (4 dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>7.40 ± 0.01</td>
<td>7.40 ± 0.01</td>
<td>7.37 ± 0.02*</td>
</tr>
<tr>
<td>Coronary venous pH</td>
<td>7.36 ± 0.01</td>
<td>7.35 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Arterial O₂ content</td>
<td>18.0 ± 0.6</td>
<td>18.0 ± 0.7</td>
<td>18.0 ± 0.7</td>
</tr>
<tr>
<td>Coronary venous O₂</td>
<td>5.0 ± 0.5</td>
<td>5.0 ± 0.3</td>
<td>3.0 ± 0.3*</td>
</tr>
<tr>
<td>content (ml/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial CO₂ content</td>
<td>42.0 ± 3.0</td>
<td>45.0 ± 3.0</td>
<td>49.0 ± 3.0</td>
</tr>
<tr>
<td>Coronary venous CO₂</td>
<td>56.0 ± 2.0</td>
<td>57.0 ± 3.0</td>
<td>64.0 ± 6.0</td>
</tr>
<tr>
<td>content (ml/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial lactate</td>
<td>24.84 ± 3.71</td>
<td>25.48 ± 3.79</td>
<td>26.71 ± 3.74</td>
</tr>
<tr>
<td>Coronary venous lactate</td>
<td>13.92 ± 2.07</td>
<td>16.78 ± 3.11</td>
<td>26.21 ± 5.32*</td>
</tr>
<tr>
<td>(mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pyruvate</td>
<td>1.47 ± 0.25</td>
<td>1.13 ± 0.14</td>
<td>0.90 ± 0.06</td>
</tr>
<tr>
<td>Coronary venous pyruvate</td>
<td>0.95 ± 0.07</td>
<td>1.02 ± 0.10</td>
<td>0.85 ± 0.26</td>
</tr>
<tr>
<td>(mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values = mean ± se. Isoproterenol dose = 1 μg/kg iv.
*Differs significantly from control.
†Differs significantly from response obtained at rates below 200/min.

TABLE 4

Hemodynamic Responses to Isoproterenol during Maintenance of a Constant Perfusion Pressure by Aortic Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Control (10 dogs)</th>
<th>Isoproterenol (10 dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractile force (g)</td>
<td>93 ± 7</td>
<td>338 ± 25*</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg)</td>
<td>92 ± 2</td>
<td>96 ± 5</td>
</tr>
<tr>
<td>Heart rate (per min)</td>
<td>123 ± 7</td>
<td>190 ± 7*</td>
</tr>
<tr>
<td>Aortic flow (ml/min)</td>
<td>1034 ± 117</td>
<td>2304 ± 250*</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>27 ± 2</td>
<td>76 ± 6*</td>
</tr>
</tbody>
</table>

Values = mean ± se. Isoproterenol dose = 1 μg/kg iv.
*Differs significantly from control.

(Fig. 4, B) showed an increase to 64 ± 6 (se) ml/min from control values of 28 ± 2 (se) ml/min during the initial phase of the response. Flow decreased to 32 ± 6 (se) ml/min at the nadir of the response and again increased as the third phase occurred. As these results show, the triphasic pattern of the flow response during isoproterenol stimulation was similar to that before the block. Metabolic responses to isoproterenol stimulation after heart block are shown in Table 3. No significant differences from control values occurred when the heart was paced at a rate of 136 beats/min throughout the response. But, when the pacing was increased to 200/min during stimulation, oxygen extraction increased, lactate utilization decreased, and a phase of reduced contractility occurred. In 2 of the 4 experiments at the higher heart rate, myocardial excess lactate was formed.

When the heart was being paced at rates under 100 beats/min, isoproterenol caused the heart to escape the pacing. On those occasions, heart rate increased to approximately the same rates as those during stimu-
**Maintenance of Coronary Perfusion Pressure.**—Table 4 is a summary of hemodynamic alterations during isoproterenol stimulation when coronary perfusion pressure remained constant, and Figure 5 shows typical tracings obtained in these experiments. Note that during control stimulation, a triphasic response occurred not only in contractile force and coronary flow but also in heart size recorded with an isotonic strain gauge arch on the same ventricle.

The increase in contractile force when aortic pressure was maintained was not significantly different from peak responses to isoproterenol before partial aortic occlusion.

![Figure 5](image)

**Conditions as before with additionally an indication of changes in heart size indicated by an isotonic strain gauge attached to the right ventricle. Aorta occ. = aortic or perfusion pressure maintained constant by manually adjusted aortic occlusion; the period of reduced coronary flow and right ventricular force did not occur in this instance.**

![Figure 6](image)

**Conditions as before with recordings of left ventricular force and other variables during injection of 1 μg/kg isoproterenol before and after the institution of sympathetic blockade by epidural infusion of 0.5% procaine hydrochloride. Elimination of sympathetic reflexes prolonged the depressor phase of arterial pressure with corresponding reductions in force and coronary flow. Rate was not similarly affected.**
The tracings in Figure 5 show that when coronary perfusion pressure was kept constant and coronary flow remained elevated, there was not a period of reduced contractile force during the isoproterenol response, even though heart rate increased to levels that were attained during the control response. The prevention of hypotension during stimulation had little if any affect on heart rate. The rates attained at constant aortic pressure and during control responses were not significantly different.

With constant perfusion pressure, the peak increase in coronary flow was not significantly different from peak responses obtained when the blood pressure fell, but the duration of the peak flow was lengthened and there was no period of reduced flow. Aortic flow was significantly higher at constant systemic pressure than the flow responses obtained when hypotension occurred. This failure of peak coronary flow to increase despite a higher aortic pressure occurred consistently in all experiments.

Table 5 represents a summary of the effects of isoproterenol on myocardial metabolism during constant coronary perfusion pressure. The data from this table demonstrate that myocardial metabolism was not significantly altered when coronary flow remained elevated during the drug response; as in the controlled rate experiments, there was neither myocardial anaerobic metabolism nor a phase of reduced contractility.

**Examining Sympathetic Reflex Component in Third Phase.**—Tracings obtained during isoproterenol stimulation after spinal block are shown in Figure 6. Blockade of reflex activity by either hexamethonium or spinal block resulted in a prolongation of the systemic hypotensive phase of the isoproterenol response and an associated lengthening of the nadir of the response of contractile force. Also, the character of the response of coronary blood flow was altered by blockade of reflex activity. After increasing from control values of 22 ml/min to 70 ml/min, flow decreased to 36 ml/min and tended to remain in this relatively steady state throughout the greater portion of the isoproterenol response. These data are insufficient to determine if the failure of coronary flow to demonstrate the usual triphasic pattern was due to blockade of reflex activity, which affects the coronary vessels directly, or was a result of the prolonged systemic hypotension. At any rate, this experiment offers evidence that, for the most part, the second increase in contractile force was not mediated through reflex activity. It further demonstrated the relation between heart rate, contractile force, and coronary flow. If one arbitrarily uses the product of heart rate and peak contractile force as an indication of the total tension developed by the myocardium...
Figure 7 shows tracings of such effects. The degree of reduction in force at the nadir of the isoproterenol response was directly related to the arterial oxygen concentration. While the animals were being ventilated with 100% oxygen, the mean force was 288% of control during the second phase of the response; with 20 to 50% oxygen, mean force was 170% of control at the nadir of the response; with 12 to 13% oxygen, force was 70% of control values during this second phase. Calculations of t showed that significant differences existed between the degree of reduction in force at each of the oxygen tensions studied. Under the conditions of
this study, the responses of systemic blood pressure and coronary flow were similar at the different oxygen tensions. Also, no statistical difference was found between heart rates attained during stimulation at any of the oxygen tensions studied.

The myocardium did not form excess lactate during any of the control periods nor during the isoproterenol response at the two higher oxygen tensions studied; however, in 5 of the 6 experiments conducted at the lower oxygen tension, excess lactate was formed during the nadir of the response. The percent oxygen extracted by the myocardium remained essentially unchanged during control and stimulation at the two higher oxygen tensions. The range was 68 to 74%. When the animals were ventilated with the lower oxygen concentrations, arterial oxygen content fell to $12.9 \pm 0.9$ (SE) ml/100 ml, and myocardial oxygen extraction increased to 77%. During the second phase of the isoproterenol response of the low oxygen experiments, oxygen extraction increased to 83% with a resulting reduction in oxygen content of the coronary sinus blood from control values of $3.0 \pm 0.3$ (SE) ml/100 ml, and this difference was significant.

Isoproterenol was infused at the rate of 12 μg/kg per min in two animals being ventilated with 100% oxygen. Myocardial excess lactate was not formed during either phase of the response and only a slight reduction in force occurred. In another animal being ventilated with 12% oxygen, perfusion pressure was kept constant by aortic occlusion during the drug response, and in this experiment the myocardium did not form excess lactate, and an interposed period of reduction in force did not occur.

Discussion

This investigation has specified conditions produced by isoproterenol in which reduced coronary flow appears to act as a limiting factor to reduce the characteristic positive inotropic effect of this drug but not its chronotropic action; indeed the increased rate contributes to the disparity between oxygen demands and supply. The concurrent tachycardia and hypotension (with reduced coronary flow rates) has the effect of briefly reducing contractile force (peak isometric systolic tension), at times below the initial control levels, and the effect is manifested as an interposed phase of reduced force between first and third stages of markedly increased force. A study of the time sequence of events indicated that a slight initial increase in coronary flow resulted from direct vasodilatory effects of isoproterenol since this change occurred prior to any detectable change in rate or force. The rapid increase in flow simultaneously with the initial positive inotropism probably was due to the action of the drug in increasing mechanical activity and thereby increasing oxygen demand within the myocardium. This investigation showed that when systemic perfusion pressure decreased, a reduction from peak values in coronary flow preceded a reduction in contractile force, and force remained low as long as flow was low and heart rate was high. A second increase in force occurred when either coronary flow increased or heart rate decreased. These data do not imply that the positive inotropism observed during isoproterenol stimulation was due to an increased coronary flow, but they do imply that the degree of inotropism attained was dependent on oxygen delivery as related to oxygen demand. When oxygen demand by the myocardium was reduced by pacing the heart at a slow fixed rate (136 ±8/min), the interposed phase of force depression was reduced or eliminated. Conversely, when oxygen demands were increased by increasing the heart rate to 200/min during the stimulatory period, the interposed period of reduced force occurred typically when coronary flow decreased. When oxygen supply to the myocardium was increased by either maintaining a constant coronary perfusion pressure (Fig. 5) or by increasing the arterial oxygen content (Fig. 7), the interposed reduction in force was lessened or eliminated, even in the presence of increased heart rate.

The heart normally meets increased oxygen
demands by an increase in coronary flow (15-17). However, during stimulation with isoproterenol in the present study, coronary flow, after rising, decreased to mean control levels during the period of increased oxygen demand by the myocardium. The apparent mechanism by which coronary flow limits ventricular contractility in the isoproterenol-stimulated heart is that of a transient hypoxia. This is supported by the observation that, during the nadir of the force response, lactate utilization by the myocardium was decreased and, in 25% of the animals receiving single injections of the drug, formation of excess lactate indicated a shift to anaerobic metabolic pathways. Furthermore, when this period of suboptimal flow was prolonged by infusion of isoproterenol, excess lactate was formed in each experiment. While other investigators have shown that changes in pH (18, 19), lactate (20, 21), and carbon dioxide (21) can affect ventricular performance, significant correlations could not be found between the reduction in ventricular force and any of these variables. It is possible, however, that some of these factors contributed in a minor degree to the period of reduced force.

In the present study, coronary sinus $P_{O_2}$ was not significantly lowered at the time of apparent myocardial hypoxia (as indicated by formation of excess lactate and sharply decreased contractile force) and reduced coronary flow. In most of these experiments, the apparent shift to anaerobic metabolism occurred without significant changes in the $P_{O_2}$ of coronary sinus blood or percentage of oxygen extraction by the myocardium, although in some, coronary sinus blood showed distinct reductions in oxygen levels. The last occurred during inhalation of 12% oxygen and during artificially maintained cardiac rates of 200 beats/min. According to recognized concepts of myocardial oxygen uptake, the percent extraction is very high, in the range of exercising skeletal muscle, and increased oxygen demands are met by increased coronary flow rather than by further extraction of oxygen (15, 16). In the present experiments, when coronary flow was sharply decreased at the time of increased oxygen demands, energy requirements were presumably met by a transition to anaerobic metabolism; increased blood oxygen extraction appears to take place only when oxygen deficits are extreme. The development of glycolytic pathways, as judged by decreased utilization or by production of lactic acid, occurred without increased extraction of blood oxygen in most experiments, although increased extraction did occur under conditions of recognizably extreme oxygen deficits.

There may be additional explanations for the relative stability of coronary sinus $P_{O_2}$ in the presence of decreased coronary flow and increased oxygen demands. For instance, there may be increased opening of arteriovenous shunts and coronary sinus drainage channels with resulting admixture of blood at higher oxygen levels as described by Lafontant et al. (22) under experimental conditions. Similarly, these factors have been evaluated by Messer et al. (23) under clinical conditions. Again, there may be some unique effect of isoproterenol which directly increases glycolytic mechanisms, and Winterschied et al. (24), using isolated heart preparations, demonstrated that isoproterenol produces a shift from lactate utilization to lactate excretion during perfusions with normally oxygenated blood. They considered, however, that isoproterenol and other catecholamines produced their main metabolic effects only through increments in mechanical activity.

Under conditions somewhat parallel to those of the present experiments, Edwards et al. (25) have also reported relative constancy of coronary sinus $P_{O_2}$ and percent oxygen extraction. In hemorrhagic hypotension, coronary flow fell to about half; hemorrhagic hypotension is characterized by intensified sympathetic activity and at times by decreased contractile force (26). Whereas Edwards et al. (25) observed no significant changes in coronary sinus A-V oxygen differences, they observed that oxygen extraction in other systemic beds increased to the high
fractions of the relatively constant myocardial bed. In other studies of the hemorrhagic shock state, Doersching and Glaviano (27) reported an increase of oxygen in the coronary sinus blood from 5.7 to 8.3 ml/100 ml in the presence of a moderate decrease in coronary flow, along with a statistically significant increase in myocardial lactate. On the other hand, significantly increased percent oxygen extraction has been noted under other conditions of reduced coronary flow and probably more advanced grades of oxygen deficit in the open-chest dog (28, 29). The transition from aerobic to anaerobic mechanisms was described by Bretschneider et al. (30) as occurring at higher levels of coronary sinus Po\textsubscript{2} during high oxygen demand than during low oxygen demand. These critical values obtained in anesthetized dogs were higher than those observed by Lochner and Nasseri (31), working with unanesthetized, exercising dogs. These cited observations, along with those of the present study, provide some estimates of the degree of myocardial oxygen deficit that induces anaerobic metabolism without increasing oxygen extraction from the myocardial blood supply and, again, the more extreme deficit states that are capable of increasing the already high levels of myocardial oxygen extraction.

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References


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