Interaction of interval-force relationship with aortic pressure and stroke volume

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Powers, Eric R., James R. Foster, and William John Powell, Jr. Interaction of interval-force relationship with aortic pressure and stroke volume. Am. J. Physiol. 230(4): 893-900. 1976. — The modification by aortic pressure and stroke volume of the response in cardiac performance to increases in heart rate (interval-force relationship) has not been previously studied. To investigate this interaction, 30 adrenergically blocked anesthetized dogs on right heart bypass were studied. At constant low aortic pressure and stroke volume, increasing heart rate (over the entire range 60-180) is associated with a continuously increasing stroke power, decreasing systolic ejection period, and an unchanging left ventricular end-diastolic pressure and circumference. At increased aortic pressure or stroke volume at low rates (60-120), increases in heart rate were associated with an increased performance. However, at increased aortic pressure or stroke volume at high rates (120-180), increases in heart rate were associated with a leveling or decrease in performance. Thus, an increase in aortic pressure or stroke volume results in an accentuation of the improvement in cardiac performance observed with increases in heart rate, but this response is limited to a low heart rate range. Therefore, the hemodynamic response to given increases in heart rate is critically dependent on aortic pressure and stroke volume.

METHODS

Mongrel dogs of either sex weighing between 25 and 35 kg were anesthetized with intravenous chloralose (60 mg/kg) and urethan (600 mg/kg). Tracheal intubation was performed and respiration was achieved with a Harvard respirator using a gas mixture of 97% O₂, 3% CO₂. A median sternotomy was performed. A modified right heart bypass preparation was used (Fig. 1). After the intravenous administration of heparin (3 mg/kg), the superior and inferior venae cavae were canulated and the azygos vein was divided. The caval return was directed to a reservoir through a bubble oxygenator and heat exchanger (37 ± 0.5°C) and was returned through a variable-speed calibrated roller pump to the pulmonary artery. Left ventricular output was controlled by the pulmonary artery inflow. A ligature placed around the pulmonary artery completed isolation of the right heart, which then received only coronary venous drainage.

Total coronary flow (minus left ventricular Thebesian flow) was led by siphon drainage from the cannulated right atrium and ventricle to the venous reservoir. Timed volumetric collections of coronary venous blood allowed quantitation of total coronary blood flow. Right ventricular and right atrial pressures were not monitored, but both chambers were observed to remain flaccid without visible distension throughout all experiments.

Aortic pressure was controlled by a second separate roller pump from the heat exchanger to the femoral
arteries. This permitted pumping of blood either to or from the animals' systemic circulation to maintain mean aortic pressure constant (within 1-2 mmHg). Left ventricular pressure and left ventricular diastolic pressure were monitored using a short, wide-bore, Y-shaped polyethylene catheter inserted through the apex of the left ventricle. The proximal aortic pressure was monitored with a short, wide-bore polyethylene catheter inserted into the aortic arch through the left carotid artery. All pressures were monitored with Statham P23Db pressure transducers; the frequency response of the pressure measurement system is linear up to 30 cycles/s.

All measured variables were recorded on a multichannel Sanborn direct-writing oscillograph. After the sinoatrial node was crushed, heart rate was controlled by atrial pacing. Mecamylamine hydrochloride (Inversine) (100 mg in 10 ml normal saline) was given intravenously during a 1-min infusion to the experimental animals prior to study. Propranolol (Inderal) (1 mg/kg in normal saline) was given intravenously prior to the experiment. Maintenance of beta blockade was tested by isoproterenol (Isuprel) injections (2.5 µg in 1-3 ml saline in the pulmonary artery or 0.2 µg directly into the left coronary perfusion line) at the end of every experiment. Prior to the administration of propranolol, this amount of isoproterenol produced a substantial lowering of left ventricular end-diastolic pressure (LVEDP). After beta blockade there was no response to the injection of isoproterenol.

Experiments were conducted by increasing heart rate sequentially from 60 to 180 beats/min when possible. In a few dogs low heart rates were unobtainable because of the animals' faster intrinsic rate. For each series of heart rates, mean aortic pressure and stroke volume were maintained constant. Similar sequences of increasing heart rate were conducted at increased aortic pressure or ventricular filling (stroke volume). Heart rate sequences with identical aortic pressure and stroke volume were conducted at the beginning and end of every experiment (pre and postcontrol) to document the stability of the preparation. With the institution of each heart rate change, adequate time (at least 4-5 min) was allowed for hemodynamic stability to be achieved.

In four dogs left coronary blood flow was held constant throughout the experiment. This was accomplished by ligating a Gregg cannula into the ostium of the main left coronary artery and perfusing this artery with a separate calibrated roller pump.

An additional five dogs were studied by maintaining heart rate constant and constructing ventricular function curves from data obtained by increasing left ventricular output. This procedure was followed at each of several heart rates, a postcontrol ventricular function curve being obtained in each experiment.

Myocardial oxygen consumption (MV\textsubscript{O2}) was measured in all but one animal. The coronary arteriovenous oxygen content difference was obtained from an online Guyton (A-V\textsubscript{O2}) analyzer (Oxford Instrument Co., Jackson, Miss.) which was calibrated for every experiment by comparison with multiple manometric determinations (method of Van Slyke and Neill (27)). MV\textsubscript{O2} was calculated as the coronary arterial minus venous oxygen content difference.

Three dogs were pretreated with intravenous reserpine (0.5 mg/kg per day) for 2 days prior to study. Adequacy of catecholamine depletion was tested by the intracoronary injection of 10 mg of tyramine hydrochloride. No response to this injection was seen in the reserpinized animals. A similar dose in nonreserpinized animals resulted in a substantial lowering of LVEDP.

In nine experiments left ventricular circumference was measured by mercury-in-Silastic variable resistance strain gauges following the techniques previously outlined by Hawthorne (9) and Rushmer (15). These circumferential gauges provided measurements during the cardiac cycle of that portion of the left ventricular muscle (including the interventricular septum) which was surrounded. The gauge was fastened to the ventricular wall under slight tension at three equidistant points. Each gauge was calibrated prior to and subsequent to each experiment.

Stroke power was calculated as the product of mean systolic pressure (cmH\textsubscript{2}O) minus LVEDP (cmH\textsubscript{2}O) times stroke volume times 100 divided by the systolic ejection period.

**RESULTS**

The response in cardiac performance to increases in heart rate and the modification of this response by increases in aortic pressure are shown in Fig. 2, A and B. These are the mean data from 10 experiments. Stroke volume is constant. In this plot and the mean plots that follow, the mean data at heart rates of 60, 100, 140, and
PRELOAD AND AFTERLOAD AND INTERVAL-FORCE RELATIONSHIP

Higher pressures a given increment in heart rate results in a greater increase in stroke power than at the lower pressure. At the highest pressure studied (125–150 mmHg), the stroke power curve has a greater slope only for the heart rate ranges 60–100 and 100–140 beats/min. Increases in heart rate above this level result in a failure of stroke power to increase.

For the low and moderate aortic pressures, the systolic ejection period falls as heart rate is raised over the entire heart rate range (Fig. 2B). Furthermore, the two curves relating ejection period to heart rate at these two low aortic pressure ranges are nearly parallel. At any given heart rate, an increase in aortic pressure results in a decrease in the ejection period which has not been previously appreciated (5). Also, for the low and moderate pressure, the responses of LVEDP to increases in heart rate are parallel. Left ventricular end-diastolic pressure is nearly constant over the entire heart rate range for both.

At the high pressures the systolic ejection period falls in parallel with the curves at lower pressure only over the low heart rates. With increases in heart rate above 100 beats/min, the ejection period falls less at the high pressures. Furthermore, left ventricular end-diastolic pressure falls with increases in heart rate over the low heart rates, then becomes constant, and then increases considerably over the high heart rate range.

To rule out the possibility that the augmentation of the frequency-force relationship observed at high aortic pressures and over the low heart rate range is due to an increased coronary blood flow, four experiments were conducted with left coronary blood flow held constant. The mean data for these experiments are given in Table 1. As can be seen, the data with coronary blood flow held constant are similar to those obtained with uncontrolled coronary flow.

The mean data for eight experiments conducted at various stroke volumes (SV) are given in Fig. 3. As can be seen, increases in stroke volume result in greater increases in stroke power for a given increment in heart rate over the low heart rate range. However, this tendency is abolished at higher heart rates. At the high stroke volumes (25, 30 ml/beat), increases in heart rate

TABLE 1. Effect of varying aortic pressure on hemodynamic response to increases in heart rate at constant coronary flow

<table>
<thead>
<tr>
<th>AP, mmHg</th>
<th>60-100</th>
<th>100-140</th>
<th>140-180</th>
<th>60-100</th>
<th>100-140</th>
<th>140-180</th>
<th>60-100</th>
<th>100-140</th>
<th>140-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;125</td>
<td>12.0</td>
<td>16.0</td>
<td>30.0</td>
<td>.015</td>
<td>.015</td>
<td>.00</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>125-150</td>
<td>12.0</td>
<td>16.0</td>
<td>30.0</td>
<td>.015</td>
<td>.015</td>
<td>.00</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Values are means ± SE from four experiments. * One experiment. † P < .05 (compared to data obtained at the lowest AP).

180 are shown. The standard error bars refer to the changes in stroke power for given increments in heart rate between the mean data points. This emphasizes and compares variations in the slopes of the mean curves with changes in load.

Figure 2A shows the effect of increases in heart rate (HR) on stroke power (SP) over three aortic pressure (AP) ranges. An increase in aortic pressure from the low (60–80 mmHg) to the moderate (80–125 mmHg) range results in a significant increase in the slope of the stroke power curve for all heart rates examined. Thus, at the higher pressures a given increment in heart rate results in an increase in stroke power at constant coronary flow. Left ventricular end-diastolic pressure is nearly constant over the entire heart rate range for both.

The mean data for six experiments conducted at various stroke volumes (SV) are given in Fig. 3. As can be seen, increases in stroke volume result in greater increases in stroke power for a given increment in heart rate over the low heart rate range. However, this tendency is abolished at higher heart rates. At the high stroke volumes (25, 30 ml/beat), increases in heart rate...
myocardial oxygen consumption and the modification of this effect by changes in aortic pressure and stroke volume are shown in Fig. 4. Increases in heart rate always increase myocardial oxygen consumption at any aortic pressure and stroke volume. At any given heart rate an increase in aortic pressure or stroke volume also increases oxygen consumption. It should be noted that an increase in heart rate from 140 to 180 beats/min at high aortic pressure or stroke volume is associated with a large increase in oxygen consumption. This occurs despite the inability of the heart to increase stroke power for this heart rate increase.

Irrespective of whether left ventricular end-diastolic pressure was elevated by increasing stroke volume or by increasing mean aortic pressure, a decrease in left ventricular end-diastolic pressure was invariably observed with a heart rate increment from 60 to 100 beats/min when initial left ventricular end-diastolic pressure was greater than 12 cmH2O. Furthermore, in individual experiments this phenomenon was accentuated at progressively higher initial left ventricular end-diastolic pressures. Table 2 gives the mean data for all experiments and is divided into those in which the initial left ventricular end-diastolic pressure was less than 12, 12-16, or 16-26 cmH2O. The fall in left ventricular end-diastolic pressure is progressively greater for each group as heart rate is raised from 60 to 100 beats/min. Each curve obtained by increasing heart rate in the left ventricular end-diastolic pressure versus heart rate plot of Fig. 3 is constructed at constant stroke volume and aortic pressure, and thus nearly constant stroke work (SW). The greater range and higher values of left ventricular end-diastolic pressure at low (60) and high (180) heart rate compared to those at moderate heart rate (100-140) implies a depression of the stroke work versus left ventricular end-diastolic pressure ventricu-
TABLE 2. Effect on end-diastolic pressure of increasing heart rate from 60 to 100 beats/min

<table>
<thead>
<tr>
<th>Control LVEDP at 60 beats/min, cmH₂O</th>
<th>ΔLVEDP, cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>12-16</td>
<td>-1.6 ± 0.4*</td>
</tr>
<tr>
<td>16-26</td>
<td>-3.8 ± 0.8*</td>
</tr>
</tbody>
</table>

*Significantly greater (P < .05) than ΔLVEDP from initial LVEDP of 0-12 cmH₂O. † Significantly greater (P < .05) than ΔLVEDP from initial LVEDP of 12-16 cmH₂O.

Three dogs were studied after reserpine pretreatment. A representative experiment is demonstrated in Fig. 7, A and B. As can be seen, the effects of aortic pressure and stroke volume on the relationship between stroke power, systolic ejection period, end-diastolic pressure (and end-diastolic circumference), and heart rate are unaffected by reserpine.

DISCUSSION

The present study demonstrates the important interaction of heart rate with aortic pressure and stroke...
ing stroke power, systolic ejection period, and left ventricular end-diastolic pressure and circumference. The changes in stroke power with increases in heart rate are dependent on the changes in the systolic ejection period. The extent to which stroke power increases is dependent on the ability of the heart to decrease ejection period with an increase in heart rate. As shown by the present data, the loading condition will determine the extent to which the ejection period will decrease. In addition, to date it has not been appreciated that increases in aortic pressure decrease the systolic ejection period. The finding that the ejection period is decreased at a given heart rate also contributes to the increase in steepness of the stroke power curves at higher aortic pressures.

In the present study the frequency-force relationship was augmented by all increases of aortic pressure or stroke volume over a low heart rate range. Over a high range of heart rate, the increase in performance with increasing heart rate was augmented by moderate increases in aortic pressure but was depressed when load was raised further. Similarly, large increases in stroke volume failed to augment the frequency-force relationship over higher heart rate ranges.

At high stroke volumes, the improvement in performance with increases in heart rate from low to moderate levels and the depression in performance with increases from moderate to high levels imply that maximal performance is obtained at moderate heart rates. Thus, ventricular function curves are depressed at low and high rates compared to those at moderate heart rates. This effect is most pronounced at high preloads corresponding to the high stroke volumes. This finding is further emphasized by the tendency for end-diastolic pressure to fall with increases in heart rate over the low heart rate range and to rise over the high heart rate range while stroke work is maintained nearly constant. It can therefore be seen that the Frank-Starling mechanism is in part heart rate dependent.

The load dependence of the frequency-force relationship has not been considered by previous investigators. Mitchell et al. (12) studied the frequency-force relationship without varying loading conditions and concluded that increases in heart rate were associated with no change in left ventricular end-diastolic pressure over a heart rate range similar to that investigated in the present study. The discrepancy between this result and the observation of the present study that end-diastolic pressure is frequently dependent on heart rate is probably related to the fact that the prior studies were conducted at low end-diastolic pressures. The data in the present study demonstrate that end-diastolic pressure is frequently dependent on heart rate and is probably related to the fact that the prior studies were conducted at low end-diastolic pressures. The data in the present study demonstrate that when end-diastolic pressures are high (greater than 12 cmH$_2$O) end-diastolic pressure becomes part of a function of heart rate at constant aortic pressure and stroke volume. Furthermore, as end-diastolic pressure is increased further by given increases in stroke volume or aortic pressure, heart rate becomes an increasingly important determinant of end-diastolic pressure.

Because of the possibility that changes in ventricular compliance or coronary blood flow, limitations in myocardial oxygen delivery, or the release of endogenous
catecholamines might be responsible for some of the observations of this study, these factors were examined.

To investigate the possibility that the observed changes in end-diastolic pressure were due to compliance changes rather than to variations in ventricular volume and fiber length, recordings of end-diastolic circumference were made in several animals. Decreases in left ventricular end-diastolic pressure when heart rate was raised over the low heart rate range and increases over the high heart rate range were accompanied by directionally similar changes in end diastolic circumference. It should be noted, however, that the change in circumference for a given change in left ventricular end-diastolic pressure was smaller for increases over the high heart rate range than for decreases over the low heart rate range. This suggests that a decrease in ventricular compliance, perhaps due to incomplete relaxation, is in part, but not solely, responsible for increases in left ventricular end-diastolic pressure at high heart rate. This finding is in partial agreement with the work of Braunwald et al. (4) who demonstrated a ventricular compliance change but no change in ventricular circumference as heart rate was increased over a high heart rate range under conditions of constant stroke volume and aortic pressure.

To examine the possibility that improved performance at increased aortic pressure was secondary to increases in total coronary blood flow, experiments were conducted with left coronary blood flow held constant. In these experiments results were similar to those obtained with uncontrolled coronary flow.

Increases in myocardial oxygen consumption occur when heart rate, aortic pressure, or stroke volume is raised. This is consistent with current knowledge on the hemodynamic determinants of myocardial oxygen consumption (14, 17, 24). It is of interest that at high aortic pressure and stroke volume increases in heart rate over a high heart rate range resulted in continued large increases in oxygen consumption despite a depression of cardiac performance. This fact suggests that oxygen delivery did not limit performance in these experiments. Therefore, the inability of cardiac performance to improve at high aortic pressure or stroke volume over a high heart rate range does not seem to be related to an inability to meet the oxidative demands of the heart.

Reserpine pretreatment has no effect on the results of the present study. Thus, the augmentation of the frequency-force relationship which occurs with increases in aortic pressure or stroke volume cannot be attributed to the release of myocardial catecholamines.

The present study demonstrates that the frequency-force relationship is markedly modified by aortic pressure and ventricular filling and output. The cardiac response to increases in heart rate is critically dependent on the range of heart rate being investigated, the aortic pressure and the ventricular output, and the interaction among these three variables. This interaction will determine the magnitude of the response in performance to changes in heart rate as well as whether performance is improved or depressed. These experiments suggest the possible clinical importance of variations in aortic pressure and ventricular filling on the hemodynamic response to changes in heart rate.

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