Effect of Changing Heart Rate on Cardiovascular Function in the Conscious Dog

By Mark I. M. Noble, Ph.D., B.Sc., M.B., B.S., Diana Trenchard, B.Sc., and Abraham Guz, M.B., B.S., M.R.C.P.

ABSTRACT

The effect of heart rate on the cardiovascular system of the conscious dog was studied by pacing the heart with an implanted right atrial electrode. Left ventricular outflow was measured by an electromagnetic flowmeter with a chronically implanted transducer on the ascending aorta. As heart rate increased, stroke volume fell, and this was linearly related to heart rate over the entire range studied. Peak flow rate and maximum acceleration decreased as heart rate increased, but the change was small compared with that in stroke volume. The decrease in stroke volume resulted principally from a loss of volume ejected in late systole. An increase in heart rate sometimes resulted in a rise of cardiac output, and when this occurred mean arterial pressure rose; when cardiac output did not increase, mean arterial pressure also remained unchanged. The data suggest that there is a pressure for the systemic circulation analogous to the "critical closing pressure" of peripheral vascular beds. It was shown that in these circumstances changes in calculated systemic resistance may not reflect any real alterations in the peripheral vascular beds.

ADDITIONAL KEY WORDS: blood flow, cardiac output, blood pressure, stroke volume, aortic flow acceleration, unanesthetized dogs, atrial pacing.

Methods

Eight mongrel dogs, weighing 22 to 31 kg were used. A left thoractomy was performed under halothane anaesthesia with full aseptic precautions. A flowmeter transducer was implanted around the ascending aorta, a bipolar electrode was sewn to the right atrial appendage, and catheters were inserted into the right atrium or ventricle, left atrium or ventricle, and pulmonary artery. The chest was closed, and an incision made in the neck to expose the left common carotid artery. A Teflon catheter was inserted into the exposed artery by the Seldinger technique. All catheters and leads were brought out at the back of the neck. No studies were done for a week after surgery, during which time the dogs returned to health and the transducer became fixed to the aorta by fibrosis.

The dogs were trained to lie quietly so that a slow spontaneous heart rate was present. Heart rate was then controlled by electrical pacing using the implanted right atrial electrode. The lowest rate that could be achieved depended on the spontaneous heart rate since control was possible only with a pacemaker frequency that was higher than the spontaneous rate. The highest heart rate that could be studied was limited in most cases by the 'pacing artifact' (fig. 1), a deflection of the flow signal caused by the stimulus voltage of the pacemaker. At low heart rates this artifact occurred in diastole and could be ignored; at high heart rates the stimulus for one beat occurred during the ejection of the previous beat rendering measurement of stroke volume impossible. The range of heart rate to be explored having been established, the pacemaker frequency was either altered progressively over the range from low to high or high to low rates, or the rate was altered randomly. A new steady state for stroke volume, peak flow, maximum acceleration and arterial pressure was established within three
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Comparison of the aortic blood flow curves (AF) of one dog, no. 60, upper record, heart paced at 122 beats/min; lower record at 182 beats/min. Deflection during backflow in the lower beat is an artifact due to the pacing stimulus for the following beat.

Beats following a change of heart rate. All measurements were made from 5 to 20 sec after the imposition of a new heart rate. The entire study was completed within a period of 5 min during which time the dog remained resting quietly.

In one dog, no. 60, the pacing artifact was sufficiently small to ignore and heart rates up to 214 beats/min were studied; in the remainder the upper limit of heart rate studied ranged from 117 to 159 beats/min. In another dog, no. 39, an additional study was done under light thiopentone anaesthesia (12 mg/kg) during which the heart rate was slowed to less than the spontaneous rate by electrical stimulation of the right vagus nerve in the neck below a lignocaine block. The range of heart rate studied in this experiment was 55 to 150 beats/min. In two dogs left ventricular pressure was measured during changes in heart rate. A Statham SF1 catheter tip manometer was inserted into the right brachial artery, which had been exposed under local anaesthesia. The catheter was then advanced until left ventricular pressure was obtained.

Flow measurements were made in the resting unsedated dogs by the method outlined by Guz et al.2 The electromagnetic flowmeter used was that described by Elliott et al.,3 which was modified in order to reduce the noise level from 5% of the signal to 1%. The amplitude frequency response of the modified instrument was flat to 30 cycles/sec and the phase shift was linearly related to frequency. Acetylcholine arrest of the heart has shown that zero flow occurs in late diastole;2 in this study zero flow has been assumed to occur in late diastole. The flowmeter was calibrated in vivo for each transducer implantation by making simultaneous measurements of flow with the flowmeter and with dye dilution curves immediately after each experiment.2

Stroke volumes were obtained by planimetry from the area under flow curves recorded at a paper speed of 100 mm/sec. A continuous beat-by-beat record of stroke volume was obtained by electrical integration of the flow signal, using a Philbrick operational amplifier with a simple analogue circuit. Accuracy of stroke volume measurements was within 0.5 ml. Acceleration and left ventricular dp/dt were measured by continuous electrical differentiation of the flow and left ventricular pressure signals and calibrated by correlation with simultaneous oscilloscope photographs of the primary signals recorded at a film speed of 10 inches/sec.

Pressures were measured through the implanted catheters by Statham 23Db strain gauges. Mean arterial pressure was obtained by planimetry of the undamped pressure trace or by using an electronic mean. The d-c carrier amplifiers were provided in a 12-channel pen recorder (Cardiac Recorders Ltd.). The signals were monitored on a two-channel cathode ray oscilloscope (Cardiac Recorders Ltd.). Fast records were obtained by photographing the screen of this oscilloscope using a Cossor camera and a film speed of 10 inches/sec. The stimulator used to pace the heart and to stimulate the vagus nerve has been described elsewhere.4

Results

All the results of a change of heart rate were independent of the sequence of rates imposed.

CHANGES IN LEFT VENTRICULAR EJECTION WITH DIFFERENT HEART RATES

An increase in heart rate was associated with a much greater reduction of stroke volume than of peak flow or maximum acceleration (table 1). A corresponding change in the shape of the flow curve was found (fig. 1); the flow was little affected in early systole but was reduced in late systole.

EFFECT OF HEART RATE ON STROKE VOLUME AND CARDIAC OUTPUT

The relationship between stroke volume (SV) and heart rate (HR) appeared linear over the range studied (table 2). The data can be expressed in the general form:

$$SV = -a \cdot (HR) + b \quad (1)$$

where $-a$ = the decrement in stroke volume per beat/min rise in heart rate, and $b =$...
TABLE 1

Haemodynamic Effects of Changes in Heart Rate

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Paced heart rate</th>
<th>Stroke volume</th>
<th>Peak aortic flow</th>
<th>Maximum acceleration</th>
<th>Mean left atrial pressure or left ventricular end diastolic pressure change from lowest to highest rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
<td>Highest</td>
<td>Decrease during change from lowest to highest rate</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>29</td>
<td>96</td>
<td>140</td>
<td>29</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>37</td>
<td>100</td>
<td>155</td>
<td>22</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>38</td>
<td>95</td>
<td>155</td>
<td>25</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>39</td>
<td>78.5</td>
<td>144</td>
<td>33</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>42</td>
<td>117</td>
<td>159</td>
<td>23</td>
<td>11.5</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>89</td>
<td>144</td>
<td>31</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>46</td>
<td>71</td>
<td>117</td>
<td>21.5</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>125</td>
<td>214</td>
<td>44.5</td>
<td>21</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Mean left atrial pressure or left ventricular end diastolic pressure change from lowest to highest rate:

+2.0 LV
+1.5 LV
-2.0 LA
-5 LA
-3.3 LA

TABLE 2

Regressions of Stroke Volume in ml (SV) on Heart Rate in Beats/Min (HR)

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Body wt. kg</th>
<th>Regression equations</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>31</td>
<td>SV = -0.22 HR + 55</td>
<td>0.98</td>
</tr>
<tr>
<td>37</td>
<td>27</td>
<td>SV = -0.22 HR + 81</td>
<td>0.93</td>
</tr>
<tr>
<td>38</td>
<td>25</td>
<td>SV = -0.21 HR + 65</td>
<td>0.92</td>
</tr>
<tr>
<td>39</td>
<td>23</td>
<td>SV = -0.20 HR + 53</td>
<td>0.92</td>
</tr>
<tr>
<td>42</td>
<td>22</td>
<td>SV = -0.21 HR + 59</td>
<td>0.98</td>
</tr>
<tr>
<td>45</td>
<td>23</td>
<td>SV = -0.18 HR + 53</td>
<td>0.98</td>
</tr>
<tr>
<td>46</td>
<td>30</td>
<td>SV = -0.13 HR + 37</td>
<td>0.97</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>SV = -0.16 HR + 58</td>
<td>0.98</td>
</tr>
</tbody>
</table>

The positive intercept on the stroke volume axis. This intercept, b, has no biological meaning but is necessary to define the position of the SV/HR regression line relative to the SV axis. The cardiac output (CO) was therefore related to heart rate by the expression:

\[ CO = -a \cdot (HR)^2 + b \cdot (HR) \]  

Equations 1 and 2 are expressed graphically in figure 2 with units from dog no. 45 as an example. Depending on the values for a and b and the range of heart rate explored, cardiac output may rise with increasing heart rate (the ascending limb of the curve in fig. 2) or there may be little change in cardiac output (the apex of the curve in fig. 2). The apex of the curve occurred in the range of heart rate 120 to 138 beats/min in four dogs, in dog no. 46 the apex was at 113 to 117 beats/min and in dog no. 60 at 187 to 214 beats/min. In no experiment was the pacing frequency high enough to explore the theoretical descending limb in figure 2.

EFFECT OF THE CHANGE IN CARDIAC OUTPUT ON ARTERIAL PRESSURE

In those experiments in which cardiac output increased, mean arterial pressure also increased (fig. 3) and the correlations between...
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**FIGURE 3**
Effect of heart rate in one dog, no. 39, on stroke volume, cardiac output, arterial pressure and peripheral resistance (mean arterial pressure divided by cardiac output). Open circles in arterial pressure indicate mean values obtained by planimeter.

**TABLE 3**
Regressions of Mean Arterial Pressure in mm Hg (MAP) on Cardiac Output in Liters/Min (CO)

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Regression equations</th>
<th>r</th>
<th>P(1)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>MAP = 14.8 (CO) + 31</td>
<td>0.73</td>
<td>0.1</td>
</tr>
<tr>
<td>38</td>
<td>MAP = 10.0 (CO) + 47</td>
<td>0.57</td>
<td>0.05</td>
</tr>
<tr>
<td>39</td>
<td>MAP = 22.7 (CO) + 40</td>
<td>0.80</td>
<td>0.1</td>
</tr>
<tr>
<td>39†</td>
<td>MAP = 15.8 (CO) + 49</td>
<td>0.89</td>
<td>0.001</td>
</tr>
<tr>
<td>45</td>
<td>MAP = 18.0 (CO) + 30</td>
<td>0.77</td>
<td>0.025</td>
</tr>
<tr>
<td>46</td>
<td>MAP = 13.7 (CO) + 62</td>
<td>0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>60</td>
<td>MAP = 12.3 (CO) + 35</td>
<td>0.80</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*P(1)*: probability that the intercept on the mean arterial pressure axis is not different from zero. Coefficients of cardiac output (CO) in regression equations represent the dynamic resistances and these values were always lower than peripheral resistance because of positive intercept on the pressure axis.

Light thiopentone anaesthesia and right efferent vagus stimulation.

Cardiac output and mean arterial pressure are shown in table 3. The positive intercept on the mean arterial pressure axis was significantly different from zero in five out of seven studies (figs. 4 and 6, table 3).

**EFFECT OF A CHANGE OF HEART RATE ON MAXIMUM LEFT VENTRICULAR dp/dt**

The maximum rate of rise of left ventricular pressure was unaffected by the change of heart rate in the two studies using the catheter tip manometer (fig. 5); no measurements of this parameter were made with any other type of catheter.

**Discussion**

Previous work in conscious dogs with heart block and in anaesthetised dogs has shown that stroke volume decreases when heart rate increases. However, no previous studies of the stroke volume/heart rate relationship have been done in conscious dogs with normal atrioventricular conduction and contraction sequences. In addition, the use of an electromagnetic flowmeter in the present study has made possible precise beat-by-beat measure-
ment of left ventricular stroke volume including the details of the left ventricular ejection pattern during changes in heart rate. This method has also permitted the study to be done so quickly that fluctuations in the circulatory state of the dog would be minimal. In spite of the rapidity with which the study was done, care was taken to ensure that a steady state was established after any change of heart rate. This steady state occurred within three beats and this is not surprising because the intervention merely changes the frequency of oscillation of the arterial system; this system is known to be highly damped.8

The surprising finding in the present study was the closeness of the linear relationship between stroke volume and heart rate (table 3). The reason for the reduction of stroke volume with increasing heart rate is not known. It has been established that when the heart rate rises, end diastolic volume and end diastolic diameter decline.7,9,10 This reduction of end diastolic volume is difficult to explain because the greater part of left ventricular filling occurs in early diastole.11

In the present study, a change of the ejection pattern was found during an increase of heart rate. This effect, namely preservation of early systolic flow and reduction of late systolic flow, is typical of the response to reduced end diastolic volume or initial fibre length resulting from a postural change.12 The decline of stroke volume with increase of heart rate may therefore be purely secondary to the

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reduction in initial fibre length. Such a mechanism would not explain the remarkable linearity between stroke volume and heart rate; this linearity may only hold over the range observed.

The lack of change in the early systolic left ventricular ejection pattern with increase of heart rate is interesting because Rushmer has suggested that early systole, the initial ventricular impulse, is a good index of myocardial performance. Similarly, Guz et al. concluded that the maximum acceleration was a very sensitive index of the contractile state of cardiac muscle. The observation that maximum acceleration was little affected in the present study suggests therefore that myocardial contractility was unchanged by the change of heart rate. It is generally accepted, however, that increased heart rate is associated with a positive inotropic effect. Sonnenblick for instance, showed that in the isolated papillary muscle, an increased frequency of contraction resulted in a greater initial velocity of shortening. Mitchell et al. studied the effect of heart rate on the maximum rate of rise of left ventricular pressure in anaesthetised dogs in which the right side of the heart had been bypassed. They showed that maximum dp/dt was greater at higher heart rates. However, in the present study, no change in maximum dp/dt was observed in the two dogs in which this measurement was made. It is not clear why the preparations used by Mitchell et al. should behave in a different way from the intact conscious dog. The effect described by Sonnenblick was demonstrated over a range of contraction frequency of 10 to 60/min and little further change appeared at frequencies above this. It is therefore likely that in the physiological range in conscious dogs, changing heart rate has little, if any, effect on myocardial contractility. This agrees with the results of Cotton who showed that change in heart rate did not have any effect on ventricular contractile force measured with a strain gauge arch sewn to the ventricle.

The relationship between cardiac output and heart rate (fig. 2) follows from the regression of stroke volume on heart rate. However, cardiac output never decreased at high heart rates. This is contrary to the evidence from studies using ventricular pacing. Berglund et al. found reduced cardiac outputs above heart rates of 120/min in anaesthetised dogs but the stroke volumes were all low and the intercept on the stroke volume axis of the SV/HR relationship was approximately 32 ml, i.e., lower than in the present study. The stroke volume in the experiment of Berglund et al. was reduced by 0.19 ml/beat/min increase in heart rate; this is similar to the decremental stroke volume reduction in the present study. Miller et al. found a reduction in cardiac output above 100 beats/min in conscious dogs with chronic heart block. In their experiments, the intercept on the stroke volume axis of the SV/HR relationship was comparable to ours ($b = \text{approximately } 58 \text{ ml}$) but the stroke volume fell much more for each beat/min increase in heart rate ($a = 0.3 \text{ ml/beat/min}$). It is likely that the results in our experiments represent more truly the SV/HR relationship in the normal animal because anaesthesia and ventricular pacing were avoided. In this study the apex of the curvilinear cardiac output/heart rate relationship was near the upper limit of the physiological range of heart rate because stroke volume was not depressed and fell only moderately when heart rate increased. Moderate tachycardia per se does not produce therefore a reduction of cardiac output.

The observation, that mean arterial pressure always rose whenever the cardiac output increased, is interesting. The baroreceptor mechanisms were probably normal in these dogs since a small rise in arterial pressure always produced very considerable bradycardia when the heart rate was not controlled. This is not surprising because there was no surgical trauma in the region of the aortic arch baroreceptors and because only one carotid artery catheter was inserted by the Sel-dinger technique so that the lumen of the vessel was not occluded.

When the arterial pressure rose in the present study, the heart rate could not slow...
because it was under pacemaker control. The reflex control of arterial pressure was entirely dependent therefore on that part of the efferent mechanism which lowers the arterial pressure by producing vasodilatation. The results suggest that this mechanism, by itself, is inadequate for the maintenance of a normal arterial pressure.

An alternative interpretation may be that baroreceptor afferent stimulation changes very little in these experiments. The rise in mean arterial pressure was accompanied by a decrease in pulse pressure (fig. 3). It is known that a given mean carotid sinus pressure is a greater baroreceptor stimulus when that pressure is pulsatile than when it is steady. However, the quantitative contributions of mean and pulsatile pressures and the relative importance of the amplitude and rate of rise of pulse pressure have not been established. When the regression lines of mean arterial pressure on cardiac output were derived, a positive intercept on the pressure axis was consistently obtained. This could be interpreted as evidence that reflex vasodilatation did, in fact, take place because without such vasodilatation the arterial pressure might have risen more steeply, and as a result the relationship would have gone through zero. This hypothesis would require the relationship to curve off towards zero at low arterial pressure where baroreceptor stimulation would be minimal. This did not occur however even in the dog whose heart rate was slowed by vagal stimulation so that at the lowest rate, cardiac output was 1.3 litres/min and mean arterial pressure was 68 mm Hg (fig. 6). This was the experiment in which the positivity of the pressure intercept had the highest significance (P = 0.001). In addition, the pooled data suggest that the relationship is similar from dog to dog (table 3, fig. 6). A critical closing pressure, i.e., a pressure at which flow through a peripheral vascular bed ceases, has been demonstrated in some regions of the circulation. This phenomenon may be sufficiently widespread in the peripheral circulation for the effect to be detected in measurements of pressure and flow made in the aorta.

If the relationship between mean pressure and mean flow in table 3 is not appreciably influenced by reflexes, there are important consequences when attempting to calculate peripheral resistance from the formula:

\[
\text{Peripheral resistance} = \frac{\text{mean arterial pressure}}{\text{cardiac output}}
\]

The problem arises because the regression lines do not point towards the origin. Thus, in figure 6 at point A, the peripheral resistance according to this formula is the tangent of the angle AOX. At point B, the peripheral resistance is tan BOX which is a smaller value than tan AOX. This may not imply that the peripheral vascular bed has dilated; the behaviour of the calculated peripheral resistance as shown may follow simply from the pressure flow relationship. As the flow and pressure get further from the origin, this source of error becomes less important. Thus from C to D in figure 6, the apparent fall in calculated peripheral resistance is much less. These considerations suggest that there is an error in the physiological interpretation of small changes in the calculated systemic peripheral vascular resistance.

References


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