Effect of Acute Volume Loading on Heart Rate in the Conscious Dog

By Lawrence D. Horwitz and Vernon S. Bishop

ABSTRACT

The effect on heart rate of rapid elevation of ventricular filling pressure by intravenous infusion of isotonic solution was studied in 31 conscious dogs with autonomic innervation intact and during vagal, beta-receptor, or combined vagal and beta-receptor blockade. When parasympathetic innervation was intact, heart rate always rose during infusion and there was a consistent relationship between mean left atrial pressure and heart rate described by

\[ f = f_m - (f_m - f_i) e^{-kp} \]

where \( f \) is the heart rate at any left atrial pressure, \( p \), \( f_m \) the maximum heart rate, \( f_i \) the initial heart rate, and \( k \) a rate constant. Sympathetic blockade reduced the magnitude of the response and parasympathetic blockade prevented the response. It is concluded that a steady rise in filling pressure during intravenous infusion in a normally innervated, conscious dog invariably results in a tachycardia, which is due to either reflex inhibition of the parasympathetic nervous system or direct mechanical stimulation of the sinoatrial node.

KEY WORDS reflex tachycardia ventricular filling pressure beta-receptor blockade stretch receptor Bainbridge reflex vagal blockade

In 1915, Bainbridge described an increase in heart rate during intravenous infusions and attributed the tachycardia to reflex inhibition of vagal tone (1). Subsequently, the findings of some investigators have supported Bainbridge's findings (2), but others have been unable to consistently demonstrate the reflex he described (3–7). These latter studies of heart rate during volume loading used anesthetized dogs or did not ensure that the rate of infusion was sufficient to increase ventricular filling pressures.

This communication reports the effect on heart rate of rapid elevation in ventricular filling pressure by intravenous infusion of an isotonic solution in 31 conscious dogs. One or more infusions were performed with autonomic innervation intact, and during vagal, beta-receptor, or combined vagal and beta-receptor blockade. When vagal innervation was unimpaired, the heart rate invariably increased during infusions, and a quantitative relationship was demonstrable between heart rate and filling pressure.

Methods

In 31 mongrel dogs a left thoracotomy was performed. An 18-gauge polyvinyl catheter was inserted into the left atrium through the atrial appendage. In some animals, which were instrumented for other studies, an electromagnetic flow probe was affixed around the ascending aorta, and a solid state pressure transducer (Whittaker model 1017) or sonomicrometer transducers for measurement of left ventricular internal transverse diameter (8) were implanted in the left ventricle. At thoracotomy, or a few days later, a 10-gauge polyvinyl catheter was inserted into the superior vena cava through the left jugular vein. In some animals, an 18-gauge polyvinyl catheter was inserted into the aorta through the left internal mammary artery. Two weeks were allowed for recovery after thoracotomy and to
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accustom the dogs to the experimental environment before experiments began. During experiments, the animals lay on their right sides, unsedated and lightly restrained. The animals were familiar with the environment and displayed no overt evidence of excitement or distress during infusions.

All measurements were inscribed on a Beckman-Offner paper oscillograph and an Ampex FR1300 magnetic tape recorder. Left atrial and aortic pressures were measured with Statham P23Db transducers zeroed to the midline of the sternum with the animal lying on its right side. Aortic flow was measured with a Medicon K2000 electromagnetic flowmeter (9). The electrocardiogram was obtained with subcutaneous electrodes placed in the sternal region.

Tyrode's solution, heated to 37.5°C, was infused through the catheter in the jugular vein from a pressure bottle. The rate of infusion was adjusted to ensure a steady rise in left atrial pressure. Infusions were given over a period of 3-6 minutes until the cardiac output reached a constant level which was not exceeded despite further rise in left atrial pressure; the total infusion volume was 300-800 ml (9). Hemodynamic measurements were continuously recorded during each infusion. At least 2 days of rest were allowed between infusions.

In 16 animals beta-receptor blockade was accomplished by intravenous administration of 0.75-1.0 mg/kg propranolol prior to the infusion. In 8 animals parasympathetic blockade was performed by intravenous administration of atropine (0.05-0.10 mg/kg) and in 9 other animals by passing alcohol cooled to −30°C through a metal coil implanted around the right vagus nerve after the left vagus nerve had been transected (10). Combined beta-receptor and parasympathetic blockade was obtained with propranolol and atropine in 2 dogs and propranolol and vagal cooling in 4 dogs.

Results

Eighty infusions were performed in 31 dogs in the normally innervated, resting state and, as shown in Figure 1, in every case the heart rate increased. A similar increase in heart rate occurred in all of 24 infusions performed in 16 dogs during beta-receptor blockade (Fig 2). Thirty-eight infusions were performed in 17 dogs with vagal blockade. During this parasympathetic blockade the heart rate response was variable with either small increases, decreases, or no change noted (Fig 2). Combined beta-receptor and parasympathetic blockade was studied during
18 infusions in 6 dogs. Combined blockade resulted in a small increase in heart rate in 15 infusions, with 2 showing no change and 1 decreasing slightly (Fig. 2).

Figures 3 and 4 show the relationship between mean left atrial pressure and heart rate during six infusions in a single animal with intact autonomic innervation. As left atrial pressure is steadily increased by the infusion there is a simultaneous increase in heart rate until a maximum, or plateau, heart rate is reached which remains constant despite further elevation in atrial pressure. If \( f \) is the heart rate at any left atrial pressure, \( f_m \) is the maximum heart rate, and \( f_i \) is the initial heart rate, heart rate increases exponentially as left atrial pressure increases, as shown by the linear semilogarithmic plot of change in mean left atrial pressure (\( p \)) versus \( (f_m - f)/(f_m - f_i) \) in Figure 3. Therefore,

\[
(df/dp) = k / (f_m - f),
\]

where \( k \) is a constant in mm Hg\(^{-1}\). This equation states that for any heart rate during the infusion the instantaneous rate of change in heart rate with respect to change in mean left atrial pressure is proportional to the difference between that rate and the maximum heart rate.

The solution of Eq. 1 is

\[
f = f_m - (f_m - f_i) e^{-kp},
\]

(2)

This equation permits calculation of the instantaneous heart rate, \( f \), at any left atrial pressure, \( p \), given the maximum and initial heart rates and the rate constant, \( k \). In Figure 4 are plotted the measured values for heart rate versus change in mean left atrial pressure and the mathematically derived theoretical curve described by Eq. 2. The two curves agree closely, with the theoretical points well within the standard error of the actual values. Use of the absolute change in atrial pressure rather than the actual atrial pressure gives a slightly better fit to the equation by eliminating the slight variation in resting atrial pressures.
In Figure 5 are plotted the averaged results in six dogs in each of which infusions were performed under conditions of intact autonomic innervation, beta-receptor blockade, vagal blockade, and combined beta-receptor and vagal blockade. Curves with autonomic innervation intact are considered control curves for comparison with those done during the various types of autonomic blockade. The averaged control curve resembles the curve in Figure 4 and is well described by Eq. 2. With beta-receptor blockade the curve was of similar shape, but the initial and maximum heart rates were reduced and the maximum rate of change of heart rate with respect to pressure was also reduced. Vagal blockade produced a very high initial rate, significantly greater than the maximum control heart rate; the rate did not change significantly during the infusion. Combined blockade resulted in a high initial heart rate which increased slightly during the infusion, with the maximum rate approximating that of the control curve.

A digital computer analysis of the curves in Figure 5 is summarized in Table 1. The best-fit exponential curve was obtained by a combination of Newton's method and the least-squares method (11). Regression coefficients for log \((f_m - f_i)/(f_m - f_i)\) versus mean left atrial pressure showed excellent fits for control infusions and infusions during beta-receptor blockade and a slightly poorer fit for infusions during combined blockade. Curves during vagal blockade are not described by Eqs. 1 and 2. Group comparisons showed significant statistical differences for \(k\) between control and beta-receptor blockade \((P<0.01)\), control and combined blockade \((P<0.01)\), and beta-receptor blockade and combined blockade \((P<0.001)\). Differences in \(f_m\) and maximal rate of change of heart rate \((df/dp)\) also were statistically significant for these three comparisons. The range in heart rate \((f_m - f_i)\) was greater in control infusions than in infusions during beta-receptor blockade in all animals, but by variable amounts which were not statistically significant, although control versus combined blockade and beta-receptor blockade versus combined blockade were significantly different \((both P<0.01)\).

In those infusions in which mean left atrial and left ventricular end-diastolic pressures were simultaneously measured, the two pressures agreed closely, always being well described by a linear regression line which passed through, or near, zero. Therefore, the mean left atrial pressure may, for practical purposes, be considered an accurate index to ventricular filling pressure under the conditions of this study. In almost all infusions in all states studied, the rise in atrial pressure and heart rate was accompanied by rises in stroke volume and left ventricular end-diastolic diameter as described previously (12). Therefore, acute volume loading results in a substantial increment in cardiac output not only through an increase in heart rate but also in stroke volume. Mean arterial pressure usually rose slightly during infusions, but there was no consistent relationship between the rise in arterial pressure and the rise in heart rate.
TABLE 1

Heart Rate Response to Acute Volume Loading in Six Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>k ± sd</th>
<th>f_i</th>
<th>f_m</th>
<th>max df/dp</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.14 ± 0.04</td>
<td>92 ± 11</td>
<td>158 ± 29</td>
<td>8.9</td>
<td>0.984</td>
</tr>
<tr>
<td>Beta-receptor blockade</td>
<td>0.10 ± 0.03</td>
<td>81 ± 16</td>
<td>125 ± 26</td>
<td>4.6</td>
<td>0.989</td>
</tr>
<tr>
<td>Beta-receptor + vagal blockade</td>
<td>0.05 ± 0.01</td>
<td>148 ± 26</td>
<td>180 ± 26</td>
<td>0.7</td>
<td>0.938</td>
</tr>
<tr>
<td>Vagal blockade</td>
<td>213 ± 27</td>
<td>205 ± 21</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means = sd. k = rate constant in mm Hg^-1; f_i = initial heart rate in beats/min; f_m = final heart rate in beats/min; df/dp = maximum rate of change in heart rate in beats min^-1 mm Hg^-1; r = regression coefficient for log (f — f_i)/(f_m — f_i) versus atrial pressure.

Discussion

Bainbridge reported that elevation of venous pressure by infusion of blood or saline in anesthetized dogs consistently increased heart rate through a diminution in vagal tone (1). However, Coleridge and Linden (3) and Jones (4) concluded that an increase in rate occurred only if the initial heart rate was low, whereas cardiac slowing occurred if the initial rate was high. These and other infusion studies have been unable to correlate heart rate changes to changes in venous or atrial pressure (3, 4, 7).

It was stipulated by Bainbridge that to induce quickening of the heart the volume and rate of infusion must be sufficient to elevate the venous pressure and dilate the heart. However, those studies which purport to disprove his conclusions (3-7) did not verify that these conditions were met. In addition, the relatively unstable and unphysiological state of anesthetized animals which have undergone acute surgery may account for the variability of the results in some of these studies. Many investigations with anesthetized dogs can be criticized because the anesthetics employed depressed vagal tone so severely that there was little capacity remaining for reflex efferent activity (5).

Our results show that, without exception, rapid intravenous infusion of isotonic solution (Tyrode's) increases heart rate in conscious resting dogs with intact parasympathetic innervation. A consistent quantitative relationship (Eq. 2) is present between mean left atrial pressure, or left ventricular filling pressure, and heart rate during the infusions. To obtain this response it was necessary to make the filling pressure a forcing function by regulating the rate of infusion to effectuate a steady rise in mean left atrial pressure.

Eq. 2 states that the heart rate at any mean left atrial pressure equals the maximum rate minus the product of the range in rate during the infusion (f_m — f_i) and the exponential term (e^-f_p). As the change in atrial pressure increases, the exponential term decreases and the heart rate approaches the maximum heart rate (f_m). Thus the magnitude of the change in heart rate decreases as the atrial pressure increases.

According to Eq. 1, the relationship of the instantaneous rate of change of heart rate to the difference between the maximum and the actual heart rates is linear. In contrast, Hirsch et al. (7) concluded that, during volume loading, the percent change in heart rate was linearly related to the resting heart rate. However, these authors used only initial and final heart rates and failed to ensure a steady elevation of the atrial pressure during the infusion. Therefore, their data were widely scattered and it is unlikely that they could distinguish a linear from a curvilinear relationship. Our data are well described by Eq. 1 which states that rate of change is linearly related to (f_m — f) and therefore could not be linearly related to the percent change (100 [f_m — f]/f). Thus it can be concluded that change in rate is a linear function of the initial heart rate provided left atrial pressure is increased as a constant forcing function.

Ledsome and Linden have described a reflex tachycardia from distention of balloons...
at the junction of the pulmonary vein and the left atrium (13). The increase in heart rate during volume loading may be initiated by stimulation of stretch receptors at these sites, thus explaining the relationship between left atrial pressure and heart rate. However, since end-diastolic pressure in the left ventricle is virtually identical to left atrial pressure, and pressure changes in the systemic veins, right atrium, right ventricle, and pulmonary artery are closely associated with the left atrial pressure during intravenous infusions, receptors at these locations cannot be excluded. A systemic arterial site for such receptors is unlikely, because of the lack of a consistent relationship between systemic arterial pressure and heart rate.

Because the exponential increase in heart rate with respect to atrial pressure was present in both control infusions and infusions during beta-receptor blockade, it is likely that the cardioacceleration is not primarily mediated through the sympathetic nervous system. However, the presence of sympathetic tone does appear to influence the magnitude of the heart rate response. The differences in maximal heart rate and rate constant between control curves and curves for beta-receptor blockade presumably represent the normal contribution of sympathetic tone to the rate response.

If, as seems likely, the augmentation in heart rate is due to a reflex initiated by stimulation of stretch receptors, the efferent pathway is probably the vagus nerve. However, it must be assumed that vagal withdrawal is incomplete, since the maximum heart rate without autonomic blockade was significantly less than the rate with vagal blockade.

An alternative mechanism for the cardioacceleration is through a local response to distention of the sinoatrial node (14, 15). The relatively small increase in rate during infusions in animals with combined beta-receptor and parasympathetic blockade does not rule out such a mechanism, since the high initial heart rate with combined beta-receptor and vagal blockade makes a large increase in rate during infusions unlikely.

References
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doi: 10.1161/01.RES.30.3.316

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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