The Influence of Heart Rate on Pulmonary Arterial-Left Ventricular Pressure Relationships at End-diastole

YALE ENSON, M.D., JOHN A. WOOD, M.D., NORDAL B. MANTARAS, B.S., AND RÉJANE M. HARVEY, M.D.

SUMMARY Increased resistance to blood flow stemming from structural and functional abnormalities of the lungs may cause pressure in the pulmonary artery to exceed that in the left ventricle at the end of ventricular diastole. This study explores the possible contribution of heart rate to the diastolic pressure gradient observed in the presence of acutely induced hypoxia. Pulmonary hemodynamics were examined in mongrel dogs with chronic atrioventricular dissociation and norepinephrine in man. Circ Res 36: 174, 1975

AS A CONSEQUENCE of increased resistance to pulmonary blood flow, pulmonary arterial pressure exceeds that in the left ventricle at the end of diastole in certain cardiopulmonary disorders. In some patients this diastolic pressure gradient may be ascribed to external encroachment on the bed by diffuse parenchymal disease or to obstruction of the bed from within by thromboemboli or other pulmonary vascular lesions. In other patients the vasoconstrictor effects of alveolar hypoxia and acidemia contribute to the gradient. In a previous consideration of factors regulating the gradient in patients with chronic obstructive lung disease, 61% of the observed variation in the gradient could be ascribed to abnormal gas exchange. While heart rate also appeared to be related to the level of the gradient, addition of this factor to multiple regression analysis of the determinants of the

From the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York.

Supported in part by Grants HL 17813, HL 07018 and 5 K06 HL 16603 from the National Heart, Lung and Blood Institute.

Address for reprints: Yale Eson, M.D., Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 W. 168th Street, New York, New York 10032.

Received March 31, 1977; revision accepted May 18, 1977.


10. Akhtar N, Mikulic E, Cohn JN, Chaudhry MH: Hemodynamic effect of dobutamine in patients with severe heart failure. Am J Cardiol 36: 202, 177


16. Sarnoff SJ: Myocardial contractility as described by ventricular function curves; observations on Starling's law of the heart. Physiol Rev 35: 107, 1955


gradient did not effect a significant reduction in unexplained variance (unpublished observations). We consider it possible that this failure stemmed from the relatively narrow range of rates encountered in our series.

A contribution of heart rate to the level of the diastolic pressure gradient is suggested by the data of other workers. Bouchard and associates examined the relationship between pulmonary arterial and left ventricular pressures at the end of diastole as heart rate was increased by intracardiac pacing in 16 patients undergoing diagnostic cardiac catheterization. When heart rate rose from an average value of 74 beats/min to 124, left ventricular diastolic pressure fell while that in the pulmonary artery rose. Cardiac output was not measured in this study, hence its contribution to the increment in diastolic pressure gradient cannot be defined.

Earlier, Escher and others studying the hemodynamic effects of intracardiac pacing in patients with complete atrioventricular block reported a rise in pulmonary arterial diastolic pressure as well as an increase in cardiac output with faster rates. Segal and others also studied patients with complete atrioventricular block during intracardiac pacing. Mean pulmonary wedge pressure and pulmonary diastolic pressure were measured. They found no change on the average in the former while on the average the latter rose as heart rate increased. The cardiac output increased with the heart rate, reaching its highest level when the heart rate lay between 70 and 83 beats/min. Further increase in rate (85–100) produced no substantial rise in cardiac output or even a fall, while the pulmonary arterial diastolic pressure continued to rise. These latter data suggest that the rise in pulmonary arterial diastolic pressure was independent of the change in pulmonary blood flow.

The purpose of the present study was to explore the possible contribution of heart rate to the diastolic pressure gradient observed in the presence of hypoxia and to attempt to separate the effect of an increase in heart rate from that of an increase in blood flow on the gradient.

Methods

To circumvent the effects of anesthesia on heart rate and to induce rates by electrical pacing which are commonly encountered during acute or chronic hypoxia in man, chronic complete atrioventricular dissociation was produced in mongrel dogs. Two protocols were utilized. In one, pulmonary hemodynamics were examined at two different heart rates with and without hypoxia, while in the second protocol the effect of sequential increments in heart rate were studied while the animals breathed room air.

Protocol I

Complete atrioventricular dissociation was induced in fifteen mongrel dogs weighing 16.4–26.4 kg using the technique of Steiner and Kovalik which requires a right thoracotomy and the injection of formaldehyde into the region of the atrioventricular node. The animals were studied three weeks later. The atria maintained a sinus rhythm. Only one dog had clinical evidence of congestion which was confirmed at necropsy when bilateral pleural effusion and ascites were found. Eight others which also were autopsied following completion of the studies showed only patchy discoloration in the posterior aspects of the lower lobes.

Anesthesia was induced with intravenous sodium pentobarbital, 25 mg/kg. The level of anesthesia was maintained for the remainder of the study with small intravenous doses of sodium pentobarbital adjusted to maintain an active inner corneal reflex. The animals were intubated with a cuffed oroendotracheal tube and breathed spontaneously throughout the study. Electrocardiographic leads were applied for recording heart rate. Under fluoroscopic control a French catheter was introduced into the right atrium via a femoral vein for injection of indicators for measurement of cardiac output and pulmonary mean transit time. A angiographic catheter (Elecath) was placed in the left ventricle through the left carotid artery for recording left ventricular pressures. A French catheter was introduced into the pulmonary artery via the right jugular vein for recording pulmonary arterial pressures. A bipolar pacemaker electrode (1-NBHI) catheter was placed through the same jugular vein into the apex of the right ventricle for pacing the heart utilizing a Medtronic Model 5800 pacemaker. A femoral artery was cannulated for sampling blood for gas analysis and measurement of cardiac output.

Following the placement of the catheters, 2 ml of heparin were administered intravenously to prevent clotting of blood samples. All studies were performed with the dogs supine.

Four periods comprised the experimental protocol. During one period the animal spontaneously breathed room air; during a second period while inspiring room air, heart rate was increased by intracardiac pacing; in a third period the animals were not paced and inspired 10% oxygen; in a fourth period the animals were paced and breathed 10% oxygen. The order of the periods was varied as follows:

<table>
<thead>
<tr>
<th>No. of dogs</th>
<th>Period A</th>
<th>Period B</th>
<th>Period C</th>
<th>Period D</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>21% O₂</td>
<td>21% O₂</td>
<td>10% O₂</td>
<td>10% O₂</td>
</tr>
<tr>
<td></td>
<td>paced</td>
<td>paced</td>
<td></td>
<td>paced</td>
</tr>
<tr>
<td>4</td>
<td>21% O₂</td>
<td>21% O₂</td>
<td>10% O₂</td>
<td>10% O₂</td>
</tr>
<tr>
<td></td>
<td>paced</td>
<td>paced</td>
<td></td>
<td>paced</td>
</tr>
<tr>
<td>3</td>
<td>10% O₂</td>
<td>10% O₂</td>
<td>21% O₂</td>
<td>21% O₂</td>
</tr>
<tr>
<td></td>
<td>paced</td>
<td>paced</td>
<td></td>
<td>paced</td>
</tr>
<tr>
<td>2</td>
<td>21% O₂</td>
<td>10% O₂</td>
<td>10% O₂</td>
<td>21% O₂</td>
</tr>
<tr>
<td></td>
<td>paced</td>
<td>paced</td>
<td></td>
<td>paced</td>
</tr>
<tr>
<td>1</td>
<td>21% O₂</td>
<td>10% O₂</td>
<td>21% O₂</td>
<td>10% O₂</td>
</tr>
<tr>
<td></td>
<td>paced</td>
<td>paced</td>
<td></td>
<td>paced</td>
</tr>
</tbody>
</table>

The periods lasted approximately 15 minutes. Pulmonary arterial and left ventricular pressures and the electrocardiogram were recorded every 3 to 5 min during each period. Pressure values used in compiling the data in table 1 are those which were recorded closest in time to the measurement of blood flow. Cardiac output, pulmonary blood volume, blood gases and pH were measured toward the end of each period.

Pulmonary arterial and left ventricular pressure curves were recorded simultaneously by Statham P23Db strain gauges with identically calibrated sensitivities on an Electronics for Medicine DR 8 recorder. High sensitivities were utilized for measurement of left ventricular end-diastolic
and pulmonary artery pressures and a lower one for measurement of left ventricular systolic pressure. End-diastolic pressure in the left ventricle and pulmonary artery was measured at the time of onset of ventricular systole as illustrated in Figure 1.

Cardiac output was measured by an indicator-dilution

**Table 1. Hemodynamic Effects of Intracardiac Pacing and/or Inspiration of 10% Oxygen in 15 Dogs with Complete Atrioventricular Block**

<table>
<thead>
<tr>
<th></th>
<th>Mean Value for Each Period and One Standard Deviation</th>
<th>P Value for Significance of Difference between Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>50 ± 11</td>
<td>133 ± 12</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg)</td>
<td>148 ± 44</td>
<td>214 ± 66</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>81 ± 9</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>Pulmonary blood volume* (ml/kg)</td>
<td>7.9 ± 2.2</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>Left ventricular pressures (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>153 ± 24</td>
<td>143 ± 25</td>
</tr>
<tr>
<td>diastolic</td>
<td>9 ± 4</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>Pulmonary arterial pressures (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>45 ± 12</td>
<td>32 ± 11</td>
</tr>
<tr>
<td>diastolic</td>
<td>8 ± 4</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>mean</td>
<td>15 ± 5</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>PDG† (mm Hg)</td>
<td>-1 ± 2</td>
<td>6 ± 4</td>
</tr>
</tbody>
</table>

*Pulmonary blood volume measured in 10 dogs.
†PDG: Pulmonary diastolic pressure gradient; difference between pulmonary arterial and left ventricular pressures measured at the end of ventricular diastole.

**Figure 1.** Pulmonary arterial (PA) and left ventricular (LV) pressure contours recorded with catheter tip pressure transducers set at equal sensitivity and common baseline. Left ventricular end diastole is indicated by the appropriate arrow. Calibration in mm Hg is indicated at the left. Electrocardiogram, at the top, indicates complete A-V dissociation with electronically paced ventricular rate at 80/min (panel A) and 120/min (panel B). Time lines 0.1 second, paper speed 50 mm/second.
method using indocyanine green dye. A mixed bolus of approximately 40 μCi of iodinated 131I serum albumin and 1.25 mg indocyanine green dye diluted to 0.5 ml saline was preloaded from a semi-automatic syringe into the injection catheter. Salt poor human albumin was added to the dye solution in an amount of 0.1 g/mg dye. Injectate was delivered by flushing the lumen with 5 ml saline. Dye curves were inscribed by sampling through a Gilford Densitometer (Model 103 IR) at the rate of one ml/sec with a Harvard constant speed withdrawal pump. The curves were calibrated utilizing the technique of Caldwell and associates.\(^7\)

Mean pulmonary transit time was determined by the radiographic technique of Giuntini and associates.\(^8\) Pulmonary blood volume was calculated by multiplying the mean transit time in heart cycles by the stroke volume. Arterial blood samples were obtained after each blood flow determination and analyzed immediately utilizing a microanalyzer for pH, PO\(_2\), and PCO\(_2\). Blood was reinforced at the end of each period following the determination of cardiac output and the last measurement of blood pressures.

The data presented in tables 1 and 2 and figure 2 are arranged irrespective of the order of the individual protocols and are grouped according to the experimental manipulations. Statistical analysis for the significance of difference between paired observations was performed with the Student's \(t\)-test.

**Protocol II**

This protocol differed from the first in several respects. Five dogs were studied only on room air. Pulmonary blood volume was not measured. Catheter-tip pressure transducers (Millar Mikro-Tip, No. 7F, PC-470) were utilized for measurement of pulmonary arterial and left ventricular pressures. These catheters have a lumen with a side opening 4 mm proximal to the sensor which permits external pressure monitoring. The micromanometers and a Statham P23Db strain gauge were calibrated and set at equal sensitivities. Prior to each simultaneous recording of pulmonary arterial and left ventricular pressures from the micromanometers, the pressure pulse derived from the micromanometer and that from the Statham gauge were recorded to make certain that the position of the former had not changed in relation to the reference level of the latter.

The experimental protocol consisted of 5 to 7 periods each of 10 min duration. Intracardiac pacing during the initial period was at the lowest rate sufficient to capture the ventricular rate (60-67 beats/min). In one animal the idioventricular rate was so rapid (77 beats/min) that the initial period began at this rate. The pacing rate in each subsequent period was increased by approximately 10 beats/min until a rate of approximately 120 was achieved. During each period pressure pulses and the electrocardiogram were recorded at the fourth minute, followed by measurement of cardiac output, systemic arterial blood gas and pH and a second recording of pressures and the electrocardiogram. In four animals duplicate measurements of cardiac output were made in

---

**Table 2. Effects of Intracardiac Pacing and/or Inspiration of 10% Oxygen on Blood Gases in 15 Dogs with Complete Atrioventricular Block**

<table>
<thead>
<tr>
<th></th>
<th>Mean Value of Each Period and One Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>PaO(_2) (mm Hg)</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>PaCO(_2) (mm Hg)</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>[H(_+)] (μM/Eq/L)</td>
<td>44.44 ± 3.92</td>
</tr>
</tbody>
</table>

|                     | A and B  | A and C   | B and D   | C and D   |
| Heart rate (beats/min) | <0.001   | <0.001   | NS        | NS        |
| PaO\(_2\) (mm Hg)      | NS       | <0.001   | <0.001    | NS        |
| PaCO\(_2\) (mm Hg)     | NS       | <0.001   | <0.001    | NS        |
| [H\(_+\)] (μM/Eq/L)   | NS       | <0.001   | <0.001    | NS        |

Abbreviations as in Table 1.

---

**Figure 2.** Mean values for heart rate, cardiac output, left ventricular (LVD) and pulmonary arterial (PAD) pressures at the end of ventricular diastole, and blood gases in 15 mongrel dogs with chronic atrioventricular dissociation while (A) normoxic with idioventricular rhythm; (B) normoxic with electrically paced rhythm; (C) hypoxic with idioventricular rhythm; (D) hypoxic with electrically paced rhythm.
rapid sequence every other period; the averages of these values are presented in figure 3.

Results

Protocol I

Periods A & B

Comparison of values while the animals inspired room air showed that increasing heart rate produced a significant difference in the diastolic pressure gradient; pulmonary arterial diastolic pressure rose, while that in the left ventricle fell. Both left ventricular and pulmonary arterial systolic pressures were lower during pacing, while the mean pulmonary arterial pressure did not change significantly. Cardiac output was higher during tachycardia, while stroke volume was lower. There were no significant differences in blood gases, blood hydrogen ion concentration or pulmonary blood volume.

Periods A & C

There were several differences between observations made while the dogs breathed 10% oxygen as compared with 21% oxygen during idioventricular rhythm. During hypoxia PaO₂, PaCO₂ and blood hydrogen concentration were lower, heart rate was slightly but significantly higher, and pulmonary arterial diastolic and mean pressures and the diastolic pressure gradient were slightly but significantly higher. There were no significant differences in cardiac output, stroke volume, pulmonary blood volume, left ventricular pressure and pulmonary arterial systolic pressure.

Periods B & D

When the animals were being paced, PaO₂, PaCO₂ and hydrogen ion concentration were lower during hypoxia than normoxia. Pulmonary diastolic and mean pressures were significantly higher and the diastolic pressure gradient was larger during hypoxia; the systolic pressure remained the same. There were no significant differences in cardiac output, stroke volume, pulmonary blood volume or left ventricular pressures.

Periods C & D

In the presence of hypoxia, the faster heart rate induced by pacing was associated with a larger cardiac output and a smaller stroke volume as compared with values secured while an idioventricular rhythm was present. Left ventricular systolic and diastolic pressures and pulmonary arterial systolic pressure were lower during pacing. The pulmonary arterial diastolic pressure was higher and the diastolic gradient larger during pacing; the mean pressure did not change. There were no significant differences in pulmonary blood volume.

Protocol II

The initial and final mean values (and one standard deviation) for the hemodynamic variables and blood gases were as follows: cardiac output (ml/min/kg) 135 ± 15 and 160 ± 18; left ventricular end-diastolic pressure (mm Hg) 11 ± 4 and 4 ± 3; pulmonary arterial diastolic pressure (mm Hg) 9 ± 4 and 12 ± 4; pulmonary diastolic pressure gradient (mm Hg) −2 ± 2.0 and 8 ± 2; PaO₂ (mm Hg) 77 ± 7 and 76 ± 11; PaCO₂ (mm Hg) 40 ± 4 and 38 ± 4; pH 7.38 ± 0.05 and 7.39 ± 0.06.

As shown in figure 3 heart rate ranged from 60 to 122 beats per minute, cardiac output from 115 to 181 ml/min/kg and the pulmonary diastolic pressure gradient from −5 to +11 mm Hg.

This figure also depicts the relationship between the gradient and both heart rate and cardiac output. At lower

**FIGURE 3.** Graphic representation of relationship between the pulmonary diastolic pressure gradient and heart rate (Panel A) and cardiac output (Panel B).
heart rates, left ventricular pressure exceeded or was equal to that in the pulmonary artery, while at the more rapid rates, this relationship was reversed.

Partial correlation analysis of the relationships among the gradient, cardiac output and heart rate indicates that heart rate explains 58% of the observed variation in the gradient which is not explained by cardiac output alone (P < 0.001), while cardiac output explained only 14% of the observed variation in the gradient which heart rate alone had failed to explain (P < 0.05).

Discussion

This study confirms the work of others who have demonstrated that an increase in heart rate induced by electrical pacing can result in an increase in cardiac output, a fall in left ventricular end-diastolic pressure and a rise in pulmonary arterial diastolic pressure. This conclusion may also be inferred from the studies of Rushmer and of Miller who found a reduction in the diastolic size of the heart during tachycardia. A lower left ventricular end-diastolic pressure has also been found when atrial systole does not precede ventricular systole. However, this latter possibility cannot be considered a factor in these experiments since atrial systole bore no consistent relationship to ventricular systole during either the idioventricular rhythm or ventricular pacing.

It is unlikely that the elevation of the pulmonary arterial diastolic pressure during tachycardia resulted from an elevation of left atrial pressure during diastole. Wallace and associates explored the relationship between left atrial and left ventricular pressures during pacing and found that the mean diastolic pressure difference between atrium and ventricle was not altered by changes in heart rate although the mean left atrial pressure may rise. The rise in left atrial mean pressure stems primarily from the occurrence of atrial systole against a closed or partially closed mitral valve resulting in large A waves.

Could closure of some segments of the pulmonary vascular be responsible for the gradient as left ventricular diastolic pressure fell? This is unlikely since the pulmonary arterial diastolic pressure did not fall together with that in the left ventricle, but on the contrary, rose. If closure were indeed the mechanism for production of the gradient one would expect the pulmonary arterial diastolic pressure to fall as did that in the left ventricle until a critical level had been reached, after which the pulmonary arterial diastolic pressure would no longer fall and would exceed that in the left ventricle.

From the studies conducted with Protocol I, it is not possible to separate the effect of cardiac output on the gradient from that of heart rate. However, with sequential pacing, the role of each could be identified. Heart rate proved to be of more importance than blood flow in determining the magnitude of the gradient. Presumably the shortened diastole at faster rates interfered with egress of blood from the pulmonary arterial tree causing the diastolic pressure in the pulmonary artery to rise while that in the left ventricle was declining.

Pulmonary blood volume (that volume between the pulmonic valve and some portion of the left atrium) showed no significant change during pacing and/or hypoxia. Since the volume of blood in the pulmonary arterial tree is only a small fraction (30%) of pulmonary blood volume, it could increase without our being able to detect it by measuring overall volume.

These studies confirm the conclusions of Bouchard and associates that heart rate can affect the level of the pulmonary diastolic pressure gradient across the lung. Changes in rate will have to be considered when pulmonary hemodynamics are being investigated. It may be that the variability of pressure response to exercise, hypoxia or drugs reflects, in part, the magnitude of the change in heart rate. Since an increase in rate is a common accomplishment of diseases which structurally or functionally affect the pulmonary vascular bed, its importance will have to be defined when the origins of pulmonary hypertension are being explored and the effects of therapy examined.

Acknowledgment

The authors wish to thank Miss Dorothy Rice, R.N., for her expert help in the conduct of these studies.

References

15. Miller DE, Gleason WL, Whalen RE, Morris JJ Jr, McIntosh HD:
18. Lasry JE, Benchimol A, Baronofsky ID, Carvalho FR: Cardiovascular hemodynamics and the internally placed cardiac pacemaker. Am J Cardiol 11: 399, 1963
44. Feisal KA, Soni J, Dubois AB: Pulmonary arterial circulation time, pulmonary arterial blood volume and the ratio of gas to tissue volume in the lungs of dogs. J Clin Invest 41: 390, 1962
The influence of heart rate on pulmonary arterial-left ventricular pressure relationships at end-diastole.
Y Enson, J A Wood, N B Mantaras and R M Harvey

Circulation. 1977;56:533-539
doi: 10.1161/01.CIR.56.4.533
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/4/533

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/