Observations on the Regulation of Cerebral Blood Flow in Complete Heart Block

By William Shapiro, M.D., and N. P. S. Chawla, M. B.

SUMMARY

The simultaneous effects of right ventricular pacing on cerebral blood flow (CBF) and cardiac function in complete heart block have not been reported. Catheters in the jugular bulb, right ventricle, and pulmonary and brachial arteries of five patients, aged 49 to 78 years, allowed studies at initial rates of 30 to 40 and during the tenth minute of pacing at 60, 70, 90, and 100 per minute. Mean initial cardiac output (CO) was 2.8 L per minute and increased 29% to 3.6 at a rate of 60 per minute (P < 0.01). Simultaneous mean control CBF was also low, but rose to 118% of control with pacing (P < 0.05). Systemic, cerebral, and pulmonary vascular resistances declined with these increases in flow as the elevated mean venous and arterial pressures remained stable. Mean arterial oxygen and carbon dioxide tensions and pH were normal at all rates. The parameters measured were not materially altered by pacing at rates above 60 per minute. The changes in CBF were well correlated with those of CO (r = 0.81, P < 0.01) and unrelated to simultaneous mean arterial or cerebral perfusion pressures. The alterations in CO were also unrelated to these pressures. The data clearly demonstrate a disturbance in CBF autoregulation, which may be a function of the low CO state.

Additional Indexing Words:
Circulatory dynamics during pacing
Cerebral perfusion pressure  Cerebral blood flow equivalent  Blood gas  pH

AUTOREGULATION OF THE human cerebral vasculature when the mean arterial blood pressure exceeds approximately 70 mm Hg is a well-established concept.² The occurrence of reversible mental symptoms in patients with complete heart block and normal arterial blood pressures suggests associated underlying inadequate cerebral perfusion. Cerebral blood flow and metabolism in patients with profound congestive heart failure are reportedly reduced⁴ despite a normal arterial blood pressure and normal arterial carbon dioxide tension; vascular resistance was thought to be markedly elevated in these subjects, and the resistance in cerebral vessels participated in this over-all vasoconstriction. Pacemaker-induced restoration of heart rate has been reported to be accompanied, after varying lengths of time, by increases in regional cerebral blood flow and improvement in the electroencephalogram in subjects with complete heart block.⁷ The simultaneous alterations in cardiac output and intravascular pressures were unreported in these heart block patients, but it is well known that cardiac output is often reduced in this condition. Shenkin and Novack⁸ suggested that a critical reduction in cardiac output forces cerebral arterial blood vessels to constrict in order to participate in the maintenance of an appropriately elevated peripheral resistance. This mechanism would limit intrinsic cerebrovascular control, and the enforced cerebral vasoconstriction may be expected to lead to diminution in cerebral blood flow.

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This study was supported by a research grant from the National Institutes of Health, National Institute of Neurological Diseases and Stroke, U. S. Public Health Service, and by the Dallas Heart Association.

An abstract of a portion of this work has appeared.¹
The purpose of the present study was to examine the interrelations of cerebral blood flow, cardiac output, mean arterial blood pressure, and heart rate in patients with complete heart block. By means of catheterization techniques, arterial and pulmonary vascular pressures, cardiac output, and cerebral blood flow were measured during complete heart block and the alterations in these parameters were noted after increased heart rates were induced by right ventricular pacing.

**Methods**

Five patients with complete heart block whose average age was 65.2 years (range 49 to 78) were studied. Prior to the placement of permanent pacemakers, these patients volunteered to undergo investigation of the circulatory effects resulting from increasing their heart rates.

Under local anesthesia and with the subjects in the postabsorptive state, the following intubations were made by conventional methods: (1) percutaneous passage of a no. 6 Cournand catheter into the femoral vein and placement of the tip in the internal jugular bulb; (2) placement of a pacemaker catheter via an antecubital vein or by means of the cephalic vein approach in the apex of the right ventricle; (3) passage of a no. 6 or 7 Cournand catheter through a superficial antecubital vein into the pulmonary artery; (4) percutaneous passage of a short radiopaque catheter into the brachial artery.

The routine use of light barbiturate anesthesia and occasional use of additional analgesics as necessary precluded precise observations concerning change in mental status during the interventions that were performed.

The following measurements were made in the control state at heart rates of 30 to 40: mean internal jugular venous, pulmonary wedge (in three subjects), pulmonary artery, and brachial arterial pressures; cardiac output by the indicator-dilution technic with use of indocyanine-green dye and a Beckman cardiodensitometer; oxygen saturation of blood from the brachial artery, the pulmonary artery, and the internal jugular bulb.

Following the control measurements, the pacemaker was turned to the minimum stimulus level that would capture at a rate of 60 beats per minute. This was maintained for 10 minutes; the measurements were repeated during the last minute. These measurements were repeated again during the tenth minute of pacing at rates of 70, 90, and 100 beats per minute.

Estimates of cerebral blood flow and cerebrovascular resistance were made by the $1/(A-V)O_2$ technic previously described.\(^9\),\(^10\) This technic is quantitatively precise in the steady state with constant cerebral oxygen consumption,\(^9\) but it will underestimate cerebral flow during interventions associated with rises in cerebral oxygen uptake.\(^11\) Cerebral blood flow equivalent was calculated as described by Cotev, Lee, and Severinghaus.\(^12\)

Standard methods for statistical analysis of the data were employed.\(^13\) Actual calculations were performed on an Olivetti Model no. 101 computer.

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**Table 1**

**Mean Values for Blood Oxygen Saturation, Arterial Blood Gases, and pH during Heart Block and Paced Heart Rates**

<table>
<thead>
<tr>
<th>Blood value (mean ± SE)</th>
<th>Control*</th>
<th>60</th>
<th>70</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jugular venous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$O_2$ sat %</td>
<td>50 ± 5</td>
<td>58 ± 3</td>
<td>58 ± 2</td>
<td>58 ± 2</td>
<td>59 ± 3</td>
</tr>
<tr>
<td><strong>Pulmonary artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$O_2$ sat %</td>
<td>65 ± 3</td>
<td>68 ± 3</td>
<td>67 ± 4</td>
<td>68 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td><strong>Arterial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$O_2$ sat %</td>
<td>97 ± .7</td>
<td>96 ± .9</td>
<td>96 ± .7</td>
<td>96 ± .6</td>
<td>97 ± 1</td>
</tr>
<tr>
<td>$P_O_2$ mm Hg</td>
<td>88 ± 2</td>
<td>88 ± 4</td>
<td>86 ± 6</td>
<td>85 ± 2</td>
<td>89 ± 8</td>
</tr>
<tr>
<td>$P_CO_2$ mm Hg</td>
<td>38 ± 3</td>
<td>41 ± 1</td>
<td>40 ± 2</td>
<td>41 ± 2</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td>7.47 ± .03</td>
<td>7.43 ± .00</td>
<td>7.44 ± .01</td>
<td>7.43 ± .01</td>
<td>7.44 ± .01</td>
</tr>
<tr>
<td>Cerebral A-V $O_2$ †</td>
<td>7.7 ± 0.8</td>
<td>6.5 ± 0.4</td>
<td>6.5 ± 0.2</td>
<td>6.6 ± 0.3</td>
<td>6.4 ± 0.5</td>
</tr>
<tr>
<td>Vol %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 30 to 40 beats per minute.
† Brachial artery—jugular bulb $O_2$ content difference in volumes per cent.
**Results**

**General and Regional Circulatory Effects of Pacing**

Table 1 shows the normal and nearly constant mean values for arterial pH and oxygen and carbon dioxide tensions throughout the study. One patient exhibited hypocapnia during the control state, but this returned to normal during all paced races (fig. 1).

The mean per cent oxygen saturation in the jugular bulb, and in the pulmonary and the brachial arteries throughout the study are also shown in table 1. The consistently lower values from the jugular bulb as compared to the pulmonary artery may be considered to confirm the accurate placement of the catheter tip in the jugular bulb. The mean arterial oxygen saturation was normal, and during all paced rates the systemic arterial-pulmonary artery oxygen differences were narrowed when compared to control as were the systemic arterial-jugular venous oxygen saturation differences.

The jugular venous and pulmonary artery pressures were elevated above normal (table 2), consistent with the presence of biventricular heart failure in these patients; brachial artery mean pressure was somewhat elevated and increased slightly during the several pacing rates. Control cardiac output was $2.8 \pm 0.05$ L per minute. The inference may be made from the control values for the cerebral arteriovenous oxygen difference and cerebral blood flow equivalent that the cerebral blood flow was also well below normal during complete heart block (table 1, fig. 2).

Significant increases in both cardiac output ($P < 0.01$) and cerebral blood flow ($P < 0.05$) occurred at the paced rate of 60 beats per minute (table 2, fig. 3); however, no further changes were recorded at the higher pacing rates in this series. Although the changes in the several vascular resistances were not statistically significant, they all declined during pacing at 60 per minute and showed little change thereafter, save at the rate of 100 when slight increases in both cerebrovascular and systemic vascular resistances were encountered (fig. 4; table 2).

**Cerebral Blood Flow Equivalent**

Figure 2 depicts the effects of the induced increase in heart rate on the cerebral blood flow equivalent (milliliters of cerebral blood flow per milliliter of cerebral oxygen consumption). These data would be precisely correct if the cerebral metabolic rates for oxygen (not directly measured) were assumed to remain constant. If cerebral oxygen uptake were to have increased in association with the other measured benefits of pacing, the data would underestimate actual values. The points represent the mean ± 1 standard error of the mean in the control state and at the end of each of the various pacing periods. The cerebral blood flow equivalent was significantly increased during pacing at 60 beats per minute ($P < 0.05$), reflecting the narrowed arteriovenous oxygen difference (table 1).

**Correlations Between Mean Arterial Pressure, Cerebral Perfusion Pressure, Cardiac Output, and Cerebral Blood Flow**

When all observed changes in cardiac output expressed as per cent of control were plotted against the simultaneous changes in values for cerebral blood flow during pacing, a good correlation was present as seen in figure 5. The r value was 0.81; this was significant.
Table 2

Mean Values for Pressures, Flows, and Resistances Measured during Heart Block and Paced Heart Rates

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control*</th>
<th>60</th>
<th>70</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular venous mean (mm Hg)</td>
<td>12 ± 2†</td>
<td>13 ± 3</td>
<td>13 ± 3</td>
<td>13 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Pulmonary artery mean (mm Hg)</td>
<td>29 ± 9</td>
<td>34 ± 11</td>
<td>32 ± 11</td>
<td>34 ± 11</td>
<td>32 ± 9</td>
</tr>
<tr>
<td>Brachial artery mean (mm Hg)</td>
<td>105 ± 13</td>
<td>109 ± 17</td>
<td>112 ± 16</td>
<td>110 ± 12</td>
<td>111 ± 7</td>
</tr>
<tr>
<td>Flows:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.8 ± .05</td>
<td>3.6 ± 0.6‡</td>
<td>3.4 ± .6</td>
<td>3.4 ± .5</td>
<td>3.6 ± .7</td>
</tr>
<tr>
<td>Cerebral blood flow (% control)</td>
<td>100</td>
<td>118 ± 6§</td>
<td>118 ± 12</td>
<td>118 ± 11</td>
<td>124 ± 16</td>
</tr>
<tr>
<td>Resistances:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular (units)</td>
<td>37 ± 4</td>
<td>30 ± 3</td>
<td>33 ± 4</td>
<td>29 ± 2.3</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>Total pulmonary (units)</td>
<td>14 ± 7</td>
<td>11 ± 4</td>
<td>10 ± 4</td>
<td>10 ± 3</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Cerebrovascular (% control)</td>
<td>100</td>
<td>88 ± 9</td>
<td>94 ± 12</td>
<td>93 ± 9</td>
<td>98 ± 18</td>
</tr>
</tbody>
</table>

*30 to 40 beats per minute.
† ± Standard error of the mean.
‡ P < 0.01.
§ P < 0.05.

Figure 2

The initial cerebral blood flow equivalent (ml blood flow per ml O₂ uptake) was low and rose to a plateau with pacing at 60, 70, and 90 per minute. A slight further rise was seen at 100 per minute.

Figure 3

The significant alterations in cardiac output (C.O.) and cerebral blood flow (C.B.F.) occurred with the change in heart rate from 30 to 40 to 60 per minute. Slight rises were again seen at 100 per minute.
The systemic (SVR), cerebral (CVR), and total pulmonary (TPR) vascular resistances declined together with pacing at 60 per minute. CVR and SVR rose slightly at 100 per minute.

Figure 4

The absence of correlation between simultaneous values for cerebral perfusion pressure and cerebral blood flow (closed circles) is seen. Control values are represented by the open circle.

Figure 6

The correlation between all simultaneous paced values for cardiac output and cerebral blood flow (closed circles) was significant, P < 0.01. The control values are represented by the open circle.

(P < 0.01). Linear regression revealed cerebral blood flow = 0.98 cardiac output + (-2.431) when both were expressed in terms of per cent of the control value (assigned 100%) in this study.

The absence of correlation between the cerebral blood flow and the cerebral perfusion pressure (mean arterial pressure-mean jugular venous pressure) under the conditions of the present study (r = 0.28). When mean arterial blood pressure was substituted for cerebral perfusion pressure, there was no improvement in correlation (r = 0.23).

Figure 7 presents the relation between all the observed changes in the cardiac output and the mean arterial pressure expressed as per cent of the control value. There was a lack of correlation (r = 0.3, not significant), and there was no correlation between the per cent changes in cerebral perfusion pressure and the changes in cardiac output (r = 0.33).

Discussion

The present study clearly shows that in the presence of heart block associated with biventricular failure, both cerebral blood flow and cardiac output are reduced, and both
cardiac output and cerebral blood flow were significantly increased by pacing at 60 beats per minute; pulmonary, systemic, and cerebrovascular resistances declined pari passu as a result of these increases in flow. The simultaneous mean arterial pressures and cerebral perfusion pressures were not materially altered. Further, the increases in cerebral blood flow correlated well with the increases in cardiac output and were unrelated to the minor observed changes in mean arterial blood pressure or cerebral perfusion pressure. Mean blood gases were nearly constant throughout this series of observations, save in one patient who was hypocapnic prior to pacing (fig. 1).

Eisenberg, Madison, and Sensenbach have shown distinct reductions in cerebral blood flow and in the cerebral metabolic rate for oxygen in patients with clinically profound heart failure accompanied by obvious mental dysfunction such as disorientation or coma. Arterial blood pressure, arterial blood gas tensions, and pH were not found to be deranged in those studies, thus allowing for the conclusion that the gross (though unmeasured) reductions in cardiac output that must have been present were perhaps responsible for the observed disturbances in cerebral blood flow and metabolism. Although these important investigations revealed increased cerebral flow, decreased cerebrovascular resistance, and unchanged cerebral oxygen uptake, the studies of Novack and his associates demonstrated cerebral blood flow to be normal when cardiac output was normal, increased, or slightly reduced, but they also found a diminution in cerebral blood flow when cardiac output was markedly reduced. Low regional cerebral blood flow in the heart block state followed by slight (approximately 10%) improvement toward normal in the days or weeks after implantation of a pacemaker has recently been reported. Studies of the simultaneous general hemodynamic effects (cardiac output, cerebral perfusion pressure, etc.) were not made.

The concept of cerebral autoregulation implies intrinsic cerebrovascular regulation mediated by well-known humoral agents when the cardiac output is adequate and the mean arterial blood pressure exceeds 60 to 70 mm Hg. When the arterial blood pressure is experimentally reduced below a mean level of approximately 70 mm Hg, the cerebral blood flow tends to vary directly with the variations in the lowered levels of arterial pressure, and the expected responses to alterations in its principal normal regulator, arterial carbon dioxide tension, are blunted. Exceptions in the behavior of this vasculature predicted on the basis of studies on normal human volunteers or suitable experimental animals have been found in certain human disease states. Conditions such as cerebral trauma, stroke, brain tumor, the coma of St. Louis encephalitis, anemia, and diabetic acidosis have revealed disturbances in these relationships manifested by relatively or absolutely increased cerebral blood flow, diminished cerebral oxygen uptake, normal arterial blood pressure, and frequent hypocapnia.

The results obtained in the present study appear to show that changes in cerebral blood flow parallel alterations in cardiac output.
induced by pacing independent of changes in blood pressure or arterial blood gases and pH. The nature of the cerebral circulatory disturbance then differs from those found in the diseases listed above but is presumably similar to that found in profound congestive heart failure by Eisenberg and colleagues.5 Here, the initially low cerebral blood flow increased significantly toward normal in the absence of important associated change in perfusion pressure or blood gases. One explanation may be the hypothesis of Shenkin and Novack,9 who thought that marked increases in peripheral resistance might ultimately force an increase in the cerebrovascular resistance and result in decreases in cerebral blood flow as the cerebral vessels were forced to constrict by this mechanism in the presence of grossly diminished cardiac output. This hypothesis requires that the cerebral vessels resist the dilator effects of the local increases in arterial or “tissue” carbon dioxide tension and decreases in oxygen tension that would be expected when the cerebral blood flow falls. Insensitivity to the usual effects of carbon dioxide has been described when the arterial blood pressure of laboratory animals has been lowered below the critical threshold.14 Alternatively, however, the possibility of reflex vasoconstriction of the cerebral vessels, possibly activated by myocardial or pulmonary vascular distention, is not necessarily ruled out. Sensitive control of the cerebral vasculature by reflex means is not widely accepted, but some evidence in support of such a concept continues to be reported.19 Impressive evidence for the presence of reflexes linking the myocardium and the canine limb circulation has been under active investigation.20

The method of estimation of cerebral blood flow employed in this study does not directly measure the cerebral oxygen uptake. The method has been accurate in the presence of a constant cerebral metabolic rate for oxygen,8,10 and may be considered an indicator of direction of change, if not absolutely quantitative, even when the cerebral oxygen uptake is unknown.12 This method of measurement would tend to underestimate increases in cerebral blood flow if arteriovenous oxygen difference narrowed and cerebral metabolic rate for oxygen increased.11 Since cerebral oxygen uptake has been found to be decreased in profound heart failure,8 it may well be that the absolute changes in cerebral blood flow under the conditions of this study were larger than those indicated by the results in table 2.

References
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WILLIAM SHAPIRO and N. P. S. CHAWLA

Circulation. 1969;40:863-870
doi: 10.1161/01.CIR.40.6.863

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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