Pressure-Flow Characteristics of the Coronary Collateral Circulation During Cardiopulmonary Bypass

Effects of Ventricular Fibrillation

LEONARD H. KLEINMAN, M.D. AND ANDREW S. WECHSLER, M.D.

SUMMARY Even though ventricular fibrillation is used frequently during cardiopulmonary bypass (CPB), the effects of fibrillation on myocardial regions supplied by collateral vessels have not been determined. To study these effects, nine dogs with left ventricles (anterior model) consisting of a region of myocardium supplied by collateral vessels (CR) and a region supplied by normal coronary arteries (NR) were subjected to normothermic CPB at two perfusion pressures. In both the empty beating heart (EBH) and empty fibrillating heart (EFH) regional myocardial flow was determined by tracer microspheres. Retrograde coronary pressure was measured via cannulation of the circumflex artery distal to the amniotic induced occlusion. When perfusion pressure was maintained at 80 mm Hg, retrograde coronary pressure was similar in the EBH (46 ± 4 mm Hg) and in the EFH (48 ± 3 mm Hg). During fibrillation subendocardial flow in the CR was unchanged, while flow in the NR increased (P < 0.02). In addition, the endo/epi was greater in the NR than in the CR (P < 0.01), a difference which did not exist in the EBH. The flow response to fibrillation in the CR could be produced in the NR by reducing the perfusion pressure to 50 mm Hg. These data suggest that during CPB, fibrillation exaggerates existing subendocardial perfusion deficits in collateral regions and the impaired flow response appears to be related to a low regional intravascular pressure.

INCREASINGLY, PATIENTS with myocardial regions supplied by collateral vessels are being selected for cardiac surgery. During cardiopulmonary bypass (CPB), elective ventricular fibrillation is used frequently and repetitively to facilitate operative exposure and prevent air embolization.1,2 The effects of this intervention have been documented in normal and hypertrophied ventricles supplied by normal coronary arteries as well as in normal ventricles following an acute critical coronary stenosis.3-6 However, the effects of ventricular fibrillation on myocardial regions supplied by collateral vessels have not been investigated. A more complete understanding of the way in which collateralized myocardial regions are affected by interventions utilized during extracorporeal circulation may allow more appropriate use of these techniques, and thus reduce the incidence of perioperative myocardial injury. This study compares the pressure-flow relationship in regions of myocardium supplied by collateral vessels to regions of myocardium supplied by normal coronary arteries in the empty beating heart (EBH) and empty fibrillating heart (EFH) at various CPB pressures.

Methods

Adult mongrel dogs (18-22.5 kg) were anesthetized with thiamylal sodium, intubated and ventilated with a Harvard respirator. Under sterile conditions, left thoracotomy was performed and the left main coronary artery including the bifurcation exposed. An amniotic constrictor,7 (2.5 or 2.77 mm i.d., Threepoint Products, Montreal, Canada), was placed around the proximal circumflex artery.

Four to five weeks following amniotic placement, the dogs were anesthetized with sodium pentobarbital (0.5 ml/kg) and ventilated with room air. Median sternotomy was performed, the pericardium opened and epicardial electrodes sutured to the left ventricle. The circumflex artery distal to the amniotic constrictor was exposed and cannulated with a Longweld teflon catheter (18G) for recording retrograde coronary pressure. Polyvinyl chloride catheters (16G) were positioned in the innominate artery, aorta and left ventricle. Aortic and retrograde coronary pressures were measured with model 1280 matched Hewlett-Packard transducers. Pressures and epicardial electrocardiogram were monitored utilizing Hewlett-Packard amplifiers and an 8-channel Mechanics for Electronics recorder. Heparin (200 units/kg) was administered and an arterial perfusion cannula placed in the left axillary artery, as venous drainage was obtained through a cannula placed in the right atrium. Total normothermic CPB was initiated utilizing a Sarns model 1900 pump console and Harvey bubble oxygenator (H200) primed with heparinized fresh whole blood. Following apical venting of the left ventricle, intracavitary pressures remained below 0 mm Hg. Hematocrit was maintained between 35-40% and pH was maintained between 7.35-7.48. PO2 ranged between 150-200 mm Hg, and perfusion pressure was maintained by adjusting pump flow between 70-100
ml/kg/min. Pharmacologic agents were not used to alter pressure.

Regional myocardial blood flow was determined by microspheres (3M Manufacturing Company, Minneapolis, Minnesota) 7-10 μ in diameter labeled with 113Ce, 85Sr, 46Sc, and 51Cr. For each measurement, 3 x 10^6 microspheres suspended in one ml of dextran solution were injected with vigorous mixing into the arterial line over 15 seconds, while arterial reference samples were collected from the innominate artery catheter for 3 minutes utilizing a calibrated Harvard peristaltic withdrawal pump.

Hemodynamic data were recorded before cardiopulmonary bypass (CPB) and were monitored throughout the bypass period. Regional myocardial blood flow was determined following four specific time periods during CPB: 1) the EBH perfused at 80 mm Hg for 30 minutes, 2) after 30 minutes of fibrillation with a perfusion pressure of 80 mm Hg, 3) when perfusion pressure was reduced to 50 mm Hg for 20 minutes with the heart in the empty beating state, and 4) after 20 minutes of fibrillation with a perfusion pressure of 50 mm Hg.

At the conclusion of each study, the heart was excised with the retrograde coronary pressure catheter in situ. Under fluoroscopic control, the degree of constriction of the circumflex artery by the ameroid was determined by injecting renografin into the left main coronary artery at a pressure of 180-200 mm Hg. A second renografin injection delineated the distal circumflex arterial bed. Incomplete closure warranted exclusion from the study. Gross or histologic evidence of myocardial infarction also resulted in exclusion from the study.

Figure 1 shows the left ventricular free wall divided into three regions: 1) anterior papillary muscle supplied by normal coronary arteries (normal region); 2) lateral wall supplied by both normal coronary arteries and collateral vessels (border region); and 3) posterior papillary muscle supplied predominantly by collateral vessels (collateral region). Each myocardial region was sectioned into a subendocardial, midmyocardial and subepicardial layer; a 1.5-2 g sample of the respective layers was analyzed for gamma radioactivity using a Beckman Biogamma Counter. An IBM digital computer was utilized in computing regional transmural flow. Flow data from the midmyocardial layer were discarded for clearer separation of subendocardial and subepicardial blood flows. Statistical analysis of hemodynamic and myocardial blood flow data (mean ± SEM) was performed using Student's t test for paired data.

Results

Before CPB heart rate was 148 ± 8 beats/min, aortic pressure was 112 ± 5/82 ± 4 mm Hg and retrograde coronary pressure was 89 ± 5/81 ± 6 mm Hg (fig. 2). After the onset of CPB, heart rate was 134 ± 7 beats/min in the EBH at a perfusion pressure of 80 mm Hg and was essentially unchanged as the perfusion pressure was reduced to 50 mm Hg.

Responses of retrograde coronary pressure to alterations in perfusion pressure and mechanical state of the heart are shown in table 1. Diastolic retrograde coronary pressure is given in the EBH, and mean retrograde coronary pressure in the EFH. At a perfusion pressure of 80 mm Hg, retrograde coronary pressure was 46 ± 4 mm Hg in the EBH and was not altered significantly with the onset of ventricular fibrillation. Retrograde coronary pressure decreased in both the EBH (P < 0.001) and EFH (P < 0.001) as perfusion pressure was reduced from 80 to 50 mm Hg. Retrograde coronary pressure, which was 26 ± 3 mm Hg in the EBH, increased to 30 ± 3 mm Hg during ventricular fibrillation.

Regional myocardial blood flow at a perfusion pressure of 80 mm Hg is displayed in table 2. In the EBH, subendocardial flow in the normal region was...
CORONARY COLLATERALS DURING CPB/Kleinman and Wechsler

**Table 1. Retrograde Coronary Pressure During Cardiopulmonary Bypass**

<table>
<thead>
<tr>
<th>Dog</th>
<th>80 mm Hg CPB</th>
<th>50 mm Hg CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>35</td>
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<tr>
<td>5</td>
<td>38</td>
<td>28</td>
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<td>6</td>
<td>63</td>
<td>50</td>
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<td>7</td>
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<td>65</td>
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<td>8</td>
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<td>9</td>
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<td>28</td>
</tr>
<tr>
<td>Mean</td>
<td>62</td>
<td>46</td>
</tr>
<tr>
<td>SEM</td>
<td>±5</td>
<td>±4</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EBH = empty beating heart; EFH = empty fibrillating heart; CPB = cardiopulmonary bypass; NS = no statistically significant difference.

**Figure 2.** Representative direct recording of electrocardiogram, aortic pressure and retrograde coronary pressures. Control is the open chest preparation before cardiopulmonary bypass (CPB). The lower panels compare retrograde coronary pressure in the empty beating heart (EBH) with that measured in empty fibrillating heart (EFH) at a perfusion pressure of 80 mm Hg (left) and 50 mm Hg (right). Measurements comparing diastolic retrograde coronary pressure in EBH and mean retrograde coronary pressure in EFH were made from this and similar tracings at a paper speed of 50 mm/sec.

greater than subendocardial flow in either the border or collateral region. In addition, the normal region received more subepicardial flow than the collateral region. As the EBH was fibrillated while perfusion pressure was maintained at 80 mm Hg, subepicardial flow increased in the normal and border regions. However, fibrillation did not result in a significant flow increase in the subendocardium of the collateral region. Therefore, the subendocardial flow difference between the normal and collateral regions, observed in the EBH, was exaggerated in the EFH (fig. 3). In addition, the subendocardial flow difference between normal and border regions increased during fibrillation. Subepicardial flow increased to all regions during fibrillation (table 2). However, the subepicardial flow difference between regions was essentially unchanged as the EBH was fibrillated.

Regional myocardial blood flow decreased in all
regions as perfusion pressure was reduced from 80 to 50 mm Hg ($P < 0.05$). Subendocardial flow in the EBH at a perfusion pressure of 50 mm Hg was greater in the normal region than in the border or collateral regions, while subepicardial flow was similar in all regions (table 3). Although flow tended to increase during ventricular fibrillation, this intervention, at a reduced perfusion pressure, was not accompanied by a statistically significant change in either subendocardial or subepicardial flow (table 3, fig. 4).

The endocardial-to-epicardial ratio in the EBH at a perfusion pressure of 80 mm Hg was similar in all regions. However, after 30 minutes of ventricular fibrillation, the endocardial-to-epicardial ratio in the normal region was greater than that observed in the border ($P < 0.05$) or collateral ($P < 0.05$) regions (fig. 5). Moreover, when the EBH was fibrillated at a perfusion pressure of 50 mm Hg, the endocardial-to-epicardial ratio was $0.91 \pm 0.08$ in the normal region and $0.42 \pm 0.10$ in the collateral region ($P < 0.01$).

**Table 2.** Myocardial Blood Flow at a Cardiopulmonary Bypass Perfusion Pressure of 80 mm Hg ($N = 9$)

<table>
<thead>
<tr>
<th>Layer</th>
<th>Anterior papillary muscle Normal region</th>
<th>Lateral free wall Border region</th>
<th>Posterior papillary muscle Collateral region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBH EFH $P$</td>
<td>EBH EFH $P$</td>
<td>EBH EFH $P$</td>
</tr>
<tr>
<td></td>
<td>ml/min/g</td>
<td>ml/min/g</td>
<td>ml/min/g</td>
</tr>
<tr>
<td>Subepicardium</td>
<td>1.05 1.81 0.88 1.53 0.71 1.37</td>
<td>$\pm 0.04$ $\pm 0.28$ &lt;0.02</td>
<td>$\pm 0.07$ $\pm 0.18$ &lt;0.02 $\pm 0.07$ $\pm 0.28$ &lt;0.02</td>
</tr>
<tr>
<td>Subendocardium</td>
<td>0.99 1.91 0.68 1.13 0.55 0.88</td>
<td>$\pm 0.13$ $\pm 0.26$ &lt;0.02</td>
<td>$\pm 0.07$ $\pm 0.17$ &lt;0.02 $\pm 0.10$ $\pm 0.20$ NS</td>
</tr>
</tbody>
</table>

$P$ NS NS NS <0.05 <0.05 <0.05 <0.05

Abbreviations: EBH = empty beating heart; EFH = empty fibrillating heart; NS = no statistically significant difference.

**Figure 3.** Panel A: Comparison of the subendocardial flow difference between normal and collateral regions in the empty beating heart (EBH) with that observed in the empty fibrillating heart (EFH). A similar comparison was made of the subendocardial flow difference between normal and border regions and between border and collateral regions. Panel B: Comparison of the subepicardial flow difference between normal and collateral regions in the EBH with that observed in the EFH. A similar comparison was made of the subepicardial flow difference between normal and border regions and between border and collateral regions. N-C = flow in normal region minus flow in collateral region; N-B = flow in normal region minus flow in border region; B-C = flow in border regions minus flow in collateral region; NS = no statistically significant difference. Perfusion pressure was maintained at 80 mm Hg ($N = 9$).
Table 3. Myocardial Blood Flow at a Cardiopulmonary Bypass Pressure of 50 mm Hg (N = 9)

<table>
<thead>
<tr>
<th>Layer</th>
<th>Anterior papillary muscle Normal region</th>
<th>Lateral free wall Border region</th>
<th>Posterior papillary muscle Collateral region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBH</td>
<td>EFH</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>ml/min/g</td>
<td>ml/min/g</td>
<td></td>
</tr>
<tr>
<td>Subepicardium</td>
<td>0.62</td>
<td>1.10</td>
<td>=0.07</td>
</tr>
<tr>
<td></td>
<td>±0.37 NS</td>
<td>±0.03 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Subendocardium</td>
<td>0.58</td>
<td>0.89</td>
<td>=0.04</td>
</tr>
<tr>
<td></td>
<td>±0.18 NS</td>
<td>±0.03 NS</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: EBH = empty beating heart; EFH = empty fibrillating heart; NS = no statistically significant difference.

Discussion

In the absence of myocardial infarction, ameroid constriction of a coronary artery results in extensive morphologic transformation of pre-existing collaterals which is associated with increasing retrograde coronary flows,\(10,11\) increasing retrograde coronary pressures\(12\) and decreasing collateral resistances.\(13\)

In the present study, the pressure-flow characteristics in viable collateralized myocardium were determined in the empty beating and empty fibrillating state. Data were obtained three to five weeks after ameroid placement, since the diastolic retrograde pressure measured at this stage of development in the canine collateral circulation most closely approximates that observed in man.\(14,15\) At a perfusion pressure of 80 mm Hg in the EBH, subendocardial flow is greater in the normal region than in the collateral region. With the onset of fibrillation, subendocardial flow in the normal region increases significantly. However, the expected subendocardial flow increase in regions of myocardium supplied by collateral vessels is attenuated markedly.\(8\) Subepicardial flow increases similarly in both regions. Thus, in the collateral region the onset of ventricular fibrillation is associated with a redistribution of transmural myocardial perfusion away from the subendocardium, resulting in an exaggeration of the existing subendocardial perfusion deficit.

Why was the subendocardial flow increase in the collateral regions less than that observed in normal regions as the EBH was fibrillated? By experimental design, flow through the arterial line was adjusted manually to maintain a perfusion pressure of 80 mm Hg and intracavitary pressure was held constant at 0 mm Hg. Since retrograde coronary pressure essentially remains unchanged as the mechanical state of the heart is altered, fibrillation is accompanied by a

Figure 4. Comparison of the flow responses to fibrillation in the normal and collateral regions at a perfusion pressure of 80 mm Hg with that observed at a perfusion pressure of 50 mm Hg. The upper panel represents subepicardial flow and the lower panel represents subendocardial flow. P values compare the flow difference between regions in the empty beating heart (EBH) with that measured during fibrillation. At a perfusion pressure of 80 mm Hg fibrillation was accompanied by a statistically significant increase in the subendocardial flow difference between the normal and collateral regions. This was not observed at a perfusion pressure of 50 mm Hg (N = 9). Solid lines represent the normal region; dotted lines represent the collateral region.
decreased resistance to flow in the subendocardium of the normal region which far exceeds that observed in the subendocardium of the collateral region. Previous studies have documented the presence of extravascular compressive forces associated with the empty fibrillating state which increase with wall depth and restrict subendocardial flows. In this study, these compressive forces may restrict flow to the subendocardium of the collateral region as a result of the low intravascular pressures despite a perfusion pressure of 80 mm Hg. In addition, partially dilated subendocardial vessels in collateral regions before fibrillation may compromise vasodilator reserve and contribute to the abnormal flow response. By flow restriction, it is implied that the expected flow increase associated with fibrillation is attenuated.

If the impaired flow responses to fibrillation are predominantly the result of relatively exaggerated compressive forces resulting from low intravascular pressure in the collateral region, then a region of myocardium supplied by normal coronary arteries with substantial vasodilator reserve should respond similarly when fibrillation is induced at a lower perfusion pressure. In the second part of this investigation, by reducing perfusion pressure to 50 mm Hg, the normal region is subjected to an intravascular pressure similar to that measured in the collateral region (48 ± 4 mm Hg) when the perfusion pressure was 80 mm Hg. The onset of fibrillation does not result in a significant increase in flow to the normal region. The failure of flow to increase during fibrillation in the normal heart subjected to low perfusion pressure has been documented and is in agreement with the present data. Thus, it appears that regional intravascular pressure is a major determinant of the regional flow response to fibrillation.

At a perfusion pressure of 80 mm Hg, subendocardial flow to the collateral region does not increase during fibrillation. In the hypertrophied left ventricle and in myocardial regions distal to an acute critical stenosis, the absence of a significant increase in subendocardial flow with the onset of fibrillation has been associated with a decrease in oxygen consumption, a decrease in intramyocardial oxygen tension and an increase in intramyocardial carbon dioxide tension. Moreover, at a perfusion pressure of 50 mm Hg, mean retrograde coronary pressure is 30 ± 3 mm Hg, a value similar to distal coronary bed pressures measured in man during coronary artery bypass surgery. This retrograde coronary pressure is associated with a subendocardial blood flow of 0.38 ± 0.10 ml/min/g, and an endocardial-to-epicardial ratio of 0.42 ± 0.10. Biochemical indices of myocardial ischemia have been documented at subendocardial flows and endocardial-to-epicardial ratios which exceed those observed in these collateral regions.

In summary, the onset of ventricular fibrillation is associated with a limited flow increase in regions of myocardium supplied by collateral vessels, despite an "adequate" aortic root perfusion pressure. The increasing flow difference between normal and collateral regions as the EBH is fibrillated appears to be related to diminished intravascular pressures in collateral regions which may result in a relative exaggeration of the extravascular compressive forces of fibrillation. The impaired flow response in collateral regions is most pronounced in the subendocardium, that layer subjected to the greatest myocardial tissue pressures and with the highest oxygen requirements. Following the onset of fibrillation, the expected subendocardial flow increase in myocardial regions supplied by normal coronary arteries is not achieved after regional intravascular pressures had been reduced to approximate intravascular pressures measured in collateral regions at higher perfusion pressures. Since retrograde coronary pressures measured in man are less than those determined in the canine collateral circulation, elective ventricular fibrillation in patients with myocardial regions supplied by collateral vessels may result in increasing regional perfusion deficits equal to or greater than those documented in this study. At the extreme, prolongation of this regional hypoperfusion may result in myocardial injury during the course of operations designed to augment total coronary blood flow. The results reported here are applicable only to normothermic perfusion. Hypothermic perfusion, which is often applied clinically, may modify these responses.
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