Phasic Coronary Blood Flow Patterns as Related to the Balance between Oxygen Demand and Supply in the Myocardium

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Summary

To explore possible relationship between changing coronary arterial flow patterns and states of coronary circulation, the left circumflex arterial flow (mean and phasic) was measured simultaneously with the oxygen saturation of the great cardiac vein blood ($S_{GCV}O_2$) in anesthetized open-chest dogs. Coronary vasomotion was altered either with administration of drugs or with mechanical interventions. The “intermittent” flow pattern observed in the resting state persisted as far as $S_{GCV}O_2$ remained unchanged or lowered regardless of changes in coronary flow, aortic pressure or heart rate. On the other hand, when increase in circumflex flow occurred simultaneously with elevation of $S_{GCV}O_2$, a “continuous” flow pattern of the circumflex flow was noticed. We suggest that (1) the “intermittent” flow pattern would indicate that efficient $O_2$ uptake from the supplied arterial blood is taking place in the myocardium and (2) the “continuous” flow pattern would indicate presence of arterial flow excess to the myocardial requirement, rendering the increased coronary blood flow less effective for its amount in terms of $O_2$ supply to the myocardium.

Additional Indexing Words:
Oxygen saturation of the coronary vein blood   Intermittent vs. continuous flow pattern   Coronary flow pathways

Blood flow through the coronary circulation is modified principally by 1) changes in aortic pressure, 2) coronary vasomotion, and 3) extravascular compression of the intramyocardial coronary vessels from myocardial contraction. The intermittent compression from rhythmic myocardial contraction impedes blood flow during systole and is responsible for the phasic nature of coronary blood flow.\(^{1,2}\) In normal resting condition, the blood flow through the left coronary artery has a phasic pattern characterized by a major diastolic and minor systolic flow, and its flow rate reaches zero or near-zero at the onset and/or end of ventricular systole.\(^{3}\) Thus, dominance in
diastolic flow with intermittence in flow pattern is one of the major characteristics of the normal coronary circulation. This intermittent flow pattern, however, is not always seen in conditions with altered coronary vasomotion induced by some pharmacological or hemodynamic interventions.

The purpose of the present investigation is to explore possible relationship between flow patterns and the state of coronary circulation with special attention to the balance between myocardial oxygen demand and supply.

**Method**

Twenty-two mongrel dogs weighing 10 to 16 Kg (mean 13.5 Kg) were anesthetized with 25 mg/Kg of sodium pentobarbital given intravenously. Respiration was controlled by a Harvard pump delivering room air via an endotracheal tube. A thoracotomy was performed in the fourth left intercostal space and the pericardium was opened. The circumflex coronary artery was dissected free and an electromagnetic flow probe (1.5—2.5 mm, i.d.) was placed just distal to the left anterior atrial branch artery. The mean and phasic coronary flow were measured simultaneously with a Statham SP 201 electromagnetic flowmeter. Teflon catheters (3 mm, o.d.) were inserted via the left and right carotid arteries into the left ventricle and the root of the aorta, respectively. Each end of the catheters was connected to a Statham P23Db pressure transducer. The dog was then heparinized intravenously (5,000 U).

A curved Kifa green catheter (2.5 mm, o.d.) with 4 side-holes at its tip was inserted via the right atrial appendage into the great cardiac vein 2 cm apart from the coronary sinus and secured in place. The other end was connected to a Gilford cuvette oximeter R103 for measuring oxygen saturation of the great cardiac vein blood. Withdrawal of the venous blood was carried out with the same amount of blood transfusion by use of a Harvard Infusion-Withdrawal Pump to prevent arterial pressure changes. Contamination of the right atrial blood was carefully prevented by adjusting the withdrawl rate not to exceed the circumflex flow. The oxygen saturation of the venous blood was expressed in percent of that of arterial blood. Hematocrit of the coronary vein blood was determined on several occasions to confirm absence of significant variation during the course of each observation. In experiments with aortic insufficiency, another electromagnetic flow-probe (12—16 mm, i.d.) was placed around the root of the aorta to measure aortic flow. All measurements were recorded on a direct-writing oscillographic polygraph (Brush Clevite M-2600) at a paper speed of 125 mm/min or 25 mm/sec.

Coronary circulation was altered either with administration of drugs or with mechanical or electrical interventions described below.

The drugs employed were nitroglycerin, acetylcholine, dipyridamole, angiotensin (Hypertensin, Ciba), propranolol, and pitressin. They were diluted in 0.9% normal saline and 1—2 ml of which were administered intravenously through a polyethylene catheter inserted via the left external jugular vein into the right atrium. Some of them were also given selectively into the left common coronary artery through a fine polyethylene catheter (P.E. #10, 0.61 mm, o.d.) which was inserted in a small distal branch of the left anterior descending artery up to the left coronary
ostium. A volume of 0.1 or 0.2 ml was given in 5 sec for intracoronary injections.

Mechanical interventions included 1) aortic constriction by constricting an umbilical tape passed around the descending aorta, 2) aortic valve insufficiency induced with an umbrella-type valve-spreading catheter, 3) A-V fistula placed between the left subclavian artery and the left external jugular vein, and 4) bleeding out 100 ml of arterial blood. Heart rate was increased with electrical stimulation of the right atrial appendage.

Each intervention was repeated twice with different recording paper speeds; first with 125 mm/min, next with 25 mm/sec.

RESULTS

The oxygen saturation of the great cardiac vein blood (hereafter referred to as “coronary vein blood”) remained almost constant under basal conditions in a given animal, although some interindividual differences were noted (19–34%, average 26%). It was either elevated, unchanged or lowered with alterations in coronary circulation. Since the primary interest was to explore possible relationship between changing coronary flow patterns and states of myocardial oxygen balance, the results are presented according to the response pattern in the oxygen saturation of the coronary vein blood induced by interventions.

A. Situations with elevated oxygen saturation of the coronary vein blood

A selective intracoronary injection of 30 μg of nitroglycerin (Fig. 1) or 2 μg of acetylcholine produced a transient increase in coronary blood flow which was accompanied by a similar course of elevation in oxygen saturation of the coronary vein blood with little changes in aortic pressure and heart rate (Table I). Following an intravenous injection of 5 mg of dipyridamole, a sustained increase in coronary flow occurred in parallel with that of oxygen saturation of the coronary vein blood as shown in Fig. 2. The increased coronary flow with these 3 vasodilating agents was seen both in systole and diastole, and the lowest point of the coronary flow curve was significantly higher than 0-flow level throughout the cardiac cycle. This flow pattern is referred to as “continuous” flow pattern since some fraction of coronary arterial blood is continuously running through the myocardium without interruption, giving rise to contrast with that of “intermittent” flow pattern observed during the control state.

The augmented circumflex blood flow following the release of a 15 sec occlusion was accompanied by a significant elevation in oxygen saturation of the coronary vein blood, having a “continuous” flow pattern, very similar to that observed following intravenous dipyridamole (Fig. 3).
Fig. 1. Response to an intracoronary injection of 30 µg of nitroglycerin. Arrow on the top indicates the dose of the drug and the time it was given. The time lag of 8 sec indicated below the tracing of the oxygen saturation of great cardiac vein blood ($S_{GCVO_2}$) was mostly due to the transit delay of the venous blood from the cannulated site to the oximeter. The circumflex (Cx) flow patterns shown in the bottom row were derived from another recording with a paper speed of 25 mm/sec. The numericals below these shaded areas indicate coronary blood flow during one cardiac cycle. 1 = control state; 2 = maximally increased coronary flow; 3 = return toward the control.

Thus, interventions that elevated the oxygen saturation of the coronary vein blood were always accompanied by increased coronary flow having a "continuous" flow pattern.

**B. Situations with unchanged oxygen saturation of the coronary vein blood**

Following an intravenous injection of 300 µg of nitroglycerin, a minor and transient increase in coronary flow was observed at the period when the
aortic pressure started to decline (Fig. 4). The coronary flow then remained decreased than that of the control as long as hypotension persisted. The time course in the changes in the oxygen saturation of the coronary vein blood was similar to that in the flow. Throughout the course of the drug response the coronary flow pattern was "intermittent" and its systolic maximum flow velocity was increased during hypotension.5) 

Along with the elevation in aortic pressure induced by aortic constriction, the coronary blood flow was significantly increased (Fig. 5). Oxygen saturation, on the other hand, remained unchanged except some initial fluctuations. Although increased coronary flow occurred both in systole and diastole, its phasic flow velocity reached near zero-flow level at the onset of ventricular contraction, which was in strong contrast to that observed following intravenous dipyridamole in which coronary flow was also greatly increased (Fig. 2). Thus the phasic flow pattern of the increased coronary flow in aortic constriction could be "intermittent".
Fig. 3. Reactive hyperemia following the release of a 15 sec occlusion of the circumflex artery (L.A.D. was not occluded). 1=control; 2=early stage of reactive hyperemia. Flow pattern is very similar to that seen in Fig. 2.

Regurgitant aortic flow in aortic insufficiency is known to be compensated for to some extent by augmented stroke volume, and coronary blood flow is increased in response to increased cardiac work load. The aortic insufficiency with 32% regurgitant fraction (Fig. 6) was accompanied by significantly increased coronary blood flow in the presence of lowered mean aortic pressure. Changes in the oxygen saturation of the coronary vein blood was insignificant and the phasic coronary flow pattern remained “intermittent”.

Oxygen saturation of the coronary vein blood remained almost unchanged with such interventions as (1) electrical pacing of the heart (heart rate from average of 155 to 199/min), (2) lowering of aortic pressure either by opening the A-V fistula or by withdrawal of 100 ml of arterial blood in 10 min, and (3) β-blockade with 1 mg/Kg of propranolol, although changes were variable
Table I. Effects of Various Interventions on Heart Rate, Mean Aortic Pressure, Circumflex Arterial Flow and Oxygen Saturation of the Great Cardiac Vein Blood

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Times observed</th>
<th>H.R. b.p.m.</th>
<th>M.A.P. mmHg</th>
<th>Cx. Flow ml/min</th>
<th>SGCVO₂ %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Nitroglycerin, i.c., 30 µg(a)</td>
<td>10</td>
<td>139</td>
<td>138</td>
<td>95</td>
<td>93**</td>
</tr>
<tr>
<td>Acetylcholine, i.c., 2 µg(b)</td>
<td>10</td>
<td>152</td>
<td>152</td>
<td>99</td>
<td>91**</td>
</tr>
<tr>
<td>Dipyridamole, i.v., 5 mg(a)</td>
<td>4</td>
<td>141</td>
<td>136</td>
<td>96</td>
<td>88*</td>
</tr>
<tr>
<td>Reactive hyperemia(a) (15 sec occlusion)</td>
<td>7</td>
<td>144</td>
<td>141*</td>
<td>102</td>
<td>99**</td>
</tr>
<tr>
<td>Nitroglycerin, i.v., 300 µg(c)</td>
<td>9</td>
<td>142</td>
<td>142</td>
<td>107</td>
<td>86**</td>
</tr>
<tr>
<td>Aortic constriction(e)</td>
<td>8</td>
<td>151</td>
<td>141**</td>
<td>92</td>
<td>139**</td>
</tr>
<tr>
<td>Aortic insufficiency(g) (R.F. 32±3%)</td>
<td>8</td>
<td>187</td>
<td>190</td>
<td>102</td>
<td>86**</td>
</tr>
<tr>
<td>R.A. Pacing(e)</td>
<td>9</td>
<td>155</td>
<td>198**</td>
<td>106</td>
<td>102</td>
</tr>
<tr>
<td>A-V fistula(e)</td>
<td>2</td>
<td>192</td>
<td>197</td>
<td>105</td>
<td>89</td>
</tr>
<tr>
<td>Propranolol, i.v., 1 mg/Kg(d)</td>
<td>2</td>
<td>158</td>
<td>140</td>
<td>95</td>
<td>90</td>
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<tr>
<td>Bleeding, 100 ml(b)</td>
<td>4</td>
<td>161</td>
<td>171</td>
<td>94</td>
<td>52**</td>
</tr>
<tr>
<td>Angiotensin, i.c., 1 µg(b)</td>
<td>9</td>
<td>153</td>
<td>150</td>
<td>98</td>
<td>113**</td>
</tr>
<tr>
<td>Angiotensin, i.v., 20 µg(e)</td>
<td>5</td>
<td>157</td>
<td>180</td>
<td>92</td>
<td>139**</td>
</tr>
<tr>
<td>Pitressin, i.c., 2 U(b)</td>
<td>7</td>
<td>150</td>
<td>148**</td>
<td>90</td>
<td>94</td>
</tr>
</tbody>
</table>

H.R.=heart rate; M.A.P.=mean aortic pressure; Cx. F.=circumflex arterial flow; SGCV0₂=oxygen saturation of the great cardiac vein blood; i.c.=intracoronary; i.v.=intravenous; R.F.=regurgitant fraction; I=values at control states; II=values following interventions (they were measured at different points indicated by (a): at the peak coronary flow increase, (b): at the bottom of coronary flow decrease, (c): at 90 sec following injection, (d): at 10 min following injection, (e): at the time when a steady-state was obtained). The significance in differences between I and II was evaluated by a paired t-test (*=p<0.05, **=p<0.01).

in heart rate, aortic pressure, and coronary blood flow (Table I). The phasic coronary flow pattern under these interventions remained essentially "intermittent", not different from that of the control states.

C. Situations with lowered oxygen saturation of the coronary vein blood

A selective intracoronary injection of 1 µg of angiotensin, an agent with potent vasoconstricting and positive inotropic property, was followed by a
Fig. 4. Response to an intravenous injection of nitroglycerin (300 μg).  
1 = control; 2 = transient increase; 3 = transition from 2 to 4. Pressure is 
declining. 4 = at the bottom of hypotension; 5 = return toward the control.

gradual elevation in aortic pressure (Fig. 7). At first, coronary blood flow 
was decreased remarkably by direct vasoconstricting action of the agent on 
the coronary bed, then increased later, possibly in response to an augmented 
cardiac activity. The oxygen saturation of the coronary vein blood became 
greatly lowered at the period of coronary flow reduction. The flow pattern 
was “intermittent” throughout.

An intravenously administered angiotensin (20 μg) was followed by a 
remarkable elevation in aortic pressure in parallel with that in coronary blood 
flow (Fig. 8). The oxygen saturation of the coronary vein blood was lowered 
remarkably, which indicated that the myocardial oxygen requirement was 
not met by the increased coronary blood flow. A doubled coronary flow at 
the point 4 in Fig. 8 showed an “intermittent” pattern and is dissimilar to
Fig. 5. Response to aortic constriction. 1=control; 2, 3, & 4=aorta was gradually constricted; 5=hypotensive stage following abrupt release of the constriction.

that seen following intravenous dipyridamole (Fig. 2) in which case the coronary flow was doubled as well.

On intracoronary injection of 2 units of pitressin, an agent with coronary vasoconstricting but without positive inotropic property, the coronary blood flow was decreased with little changes in heart rate and aortic pressure. The oxygen saturation of the coronary vein blood was greatly lowered and the phasic coronary blood flow pattern remained “intermittent” (Table I).

**DISCUSSION**

The oxygen extraction of the myocardium is surprisingly high and in passing through the coronary circuit, the arterial blood gives up about 70%
of its oxygen content.\textsuperscript{10} This extraction rate of oxygen is almost extreme for a living tissue with aerobic metabolism, so that an increase in myocardial oxygen demand is mostly met by an increase in coronary flow, resulting in a fairly constant oxygen extraction rate.\textsuperscript{10} Should an increase in flow be limited, the extraction rate might further be increased before possible initiation of anaerobic metabolism. On the other hand, an excess in arterial flow might result in a decrease of the oxygen extraction. With a curvette oximeter, the continuously changing value of oxygen saturation in the coronary vein blood can be determined with reasonable precision.\textsuperscript{11} In the present experiments, the hematocrit and the oxygen saturation of the arterial blood remained unchanged during each course of interventions so that any observed change in oxygen saturation of the coronary vein blood following a given intervention could safely be interpreted to reflect an overall balance between oxygen demand and supply in the myocardium.

Constancy in oxygen saturation of the coronary vein blood in the presence of changes in coronary blood flow implies that the myocardial oxygen requirement is met by the coronary blood flow. Likewise, lowering in oxygen saturation of the coronary vein blood is the sign that the supplied blood is in short of myocardial requirement. The coronary flow patterns in these 2
situations were basically similar in that they stayed “intermittent.” The “intermittence” in phasic flow pattern is one of the basic characteristics of the normal coronary circulation and indicates that the coronary blood flow is running through the pathway that yields to the systolic myocardial compression. Intermittent flow patterns observed in these situations with unchanged or lowered oxygen saturation of the coronary vein blood also indicate that the coronary blood flow was running through such pathways that yielded to the systolic myocardial compression, even if they were loaded with a markedly increased flow. Since the oxygen saturation of the coronary vein blood was
Fig. 8. Response to an intravenous injection of 20 µg of angiotensin.
1 = control; 2 = slight and transient decrease in flow; 3 = transition from 2 to 4; 4 = flow is almost twice the control; 5 = flow at peak pressor response.

never elevated above that of the control, myocardial oxygen uptake was supposed to take place efficiently from the coronary arterial flow that was running through these pathways.

On the contrary, elevation in the oxygen saturation of the coronary vein blood indicates presence of arterial flow excess to the myocardial requirement and/or insufficient myocardial uptake. Of particular interest is that this occurred only in situations where the increased coronary blood flow had a "continuous" flow pattern, i.e., the lowest point of the coronary flow curve throughout the cardiac cycle was significantly higher than 0-flow level. Marked coronary vasodilation common to all these situations would be responsible for this continuous flow pattern, since aortic pressure and myocardial
compression on the coronary vessels, the 2 of the 3 main factors that are responsible for flow pattern determination, were not significantly changed. Therefore, a close relationship is supposed to exist among increase in coronary blood flow, continuous flow pattern and elevation in oxygen saturation of the coronary vein blood.

Judging from continuity in the flow pattern, some portion of the coronary blood was running continuously through somewhere in the myocardium even during systole when extravascular compression on the coronary vessel was normally sufficient to cause momentary cessation of coronary blood flow. It has been known that the systolic myocardial pressure that compresses the intramyocardial blood vessels and hence impedes the coronary arterial flow is greater in the subendocardial than in the subepicardial region.\textsuperscript{12)-15) Therefore, the flow that was running continuously during systole would preferably occur in the coronary pathways embedded in the outer part of the myocardium.\textsuperscript{16) These pathways would have stayed open during systole, and dilated more together with the rest of the whole coronary pathways during diastole when intramyocardial pressure was lowered, and would have allowed much more flow to pass. The concomitant elevation in the oxygen saturation of the coronary vein blood indicated that the coronary blood flow with this mode of circulation was in excess of myocardial requirement, at least in the outer part of the myocardium, so that its significant fraction could be assumed to be a kind A-V shunt flow.\textsuperscript{17) This would render the increased coronary arterial flow less effective for its amount in terms of oxygen supply to the myocardium.
In Fig. 9, the mode of coronary flow pathways through the myocardium in systole and diastole is proposed schematically, in which changes in oxygen saturation in the coronary vein blood are related to those in phasic coronary arterial flow patterns.

In conclusion, the authors suggest (1) "intermittent" flow pattern indicates that the coronary arterial blood delivered to the myocardium is running through such pathways as efficient oxygen uptake could be taken place, and (2) "continuous" flow pattern indicates that significant portion of the coronary flow is running through the subepicardial region during systole and the arterial flow delivered to the heart is in excess of myocardial requirement.

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