Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia

AKIRA IDO, NAOYUKI HASEBE, HIRONOBU MATSUHASHI, AND KENJIRO KIKUCHI
First Department of Internal Medicine, Asahikawa Medical College, Asahikawa 078-8510, Japan

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Ido, Akira, Naoyuki Hasebe, Hironobu Matsuhashi, and Kenjiro Kikuchi. Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia. Am J Physiol Heart Circ Physiol 280: H1361–H1367, 2001.—On the hypothesis that coronary sinus occlusion (CSO) may reduce myocardial ischemia, we examined the effects of CSO on coronary collateral blood flow and on the distribution of regional myocardial blood flow (RMBF) in dogs. Thirty-eight anesthetized dogs underwent occlusion of the left anterior descending coronary artery with or without CSO and intact vasomotor tone. We measured RMBF and intramyocardial pressure (IMP) in the subendocardium (Endo) and subepicardium (Epi) separately. With intact vasomotor tone, CSO during ischemia significantly increased RMBF in the ischemic region (IR), particularly in Endo from 0.17 ± 0.03 to 0.33 ± 0.05 ml·min⁻¹·g⁻¹ (P < 0.05), and increased the Endo/Epi from 0.59 ± 0.10 to 1.15 ± 0.15 (P < 0.01). These effects of CSO were partially abolished by adenosine. However, the Endo/Epi was still increased from 0.90 ± 0.13 to 2.09 ± 0.30 (P < 0.01). The changes in RMBF in IR were significantly correlated with the peak CS pressure during CSO. The Endo/Epi of IMP in IR was significantly decreased during CSO. In conclusion, CSO potentially enhances coronary collateral flow, and preserves the ischemic myocardium, especially in Endo.

METHODS

Animal Preparation and Experimental Measurement

Thirty-eight adult mongrel dogs (9–16 kg body wt) were anesthetized by an intravenous injection of pentobarbital sodium (25 mg/kg), intubated with an endotracheal tube, and connected to a respirator (model 613, Harvard). Ventilation was controlled to maintain the physiological level of blood gases. A thoracotomy was performed via a bilateral, transsternal incision through the fifth intercostal space. The heart was suspended in a pericardial cradle. A schematic illustration of the instrumentation is shown in Fig. 1. A 7-Fr balloon catheter with a specially designed tip was manually inserted from the right external carotid vein and advanced into the coronary sinus. The catheter was positioned as close as possible to the orifice of the coronary sinus and secured to prevent dislodgment when the balloon was inflated. We tested and repeated inflation and deflation of the balloon. This catheter allowed occlusion and reperfusion of the coronary sinus. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: N. Hasebe, First Dept. of Internal Medicine, Asahikawa Medical College, 2-1-1 Midorigaoka Higashi, Asahikawa 078-8510 Japan (E-mail: haselove @asahikawa-med.ac.jp).

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Coronary sinus pressure (CSP) was measured by using a pressure transducer (model MPU 0.5, Nihon Kohden). A snare occluder was placed just proximal to the first diagonal branch of the left anterior descending coronary artery (LAD), and an ultrasonic Doppler blood flow probe, which fit the diameter of the coronary artery, was placed proximal to the occluder to measure LAD blood flow using a Doppler flow meter (model VF-1, Valpey-Fisher). The control velocity of blood flow before LAD occlusion and the peak velocity of blood flow associated with reactive hyperemia after reperfusion of the LAD were measured, and the ratio of these values (the coronary reserve equals the peak velocity of blood flow to the control velocity of blood flow) was used as an index of the severity of ischemia (7). Electrocardiogram, aortic pressure (AoP), left ventricular (LV) pressure (LVP), and other hemodynamic variables were monitored simultaneously and continuously, and recorded on an 8-channel polygraph (polygraph system RM6200, Nihon Kohden). IMP was measured in a separate group of nine dogs in both the Endo and subepicardium (Epi) in the ischemic region using needle tip pressure transducers (5-Fr; model SPR-230; Millar). One set of needle-tip transducers was advanced into the myocardium. One was placed superficially as the Epi transducer, and the other was deeply advanced as the Endo transducer. The order of protocols 1–3 was randomized to avoid the influence of repeated ischemia, which may affect collateral flow and RMBF distribution. At least 20 min elapsed between each protocol. We confirmed that all hemodynamic parameters returned to the baseline control level before starting the next protocol. The same protocols of the three conditions described above were repeated under adenosine administration (1 mg·kg⁻¹·min⁻¹) in another group of 10 dogs to assess the effects of maximum vasodilation on RMBF (21).

We evaluated the effects of the CSP elevation induced by CSO during myocardial ischemia on the coronary collateral blood flow and on the distribution of myocardial blood flow in the Endo and Epi. In addition, we studied the relationship between CSP and ΔRMBF caused by CSO during myocardial ischemia, as well as the coronary reserve, which was evaluated in protocol 3 after release of CSO.

The present study was reviewed and approved by Committee of the Ethics on Animal Experiments in Asahikawa Medical College and according to The Law (No. 105) and Notification (No. 6) of the Japanese Government.

Statistical Analysis

All results are expressed as means ± SE. The significance of differences in group mean values was assessed by the one-way ANOVA. The correlation was tested using Pearson's correlation coefficient. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Hemodynamics

Heart rate, systemic blood pressure, and LVP were not significantly different among any of the protocols (See Table 1). CSO produced a pulsatile, gradual increase in coronary sinus systolic pressure (12, 26), which increased from 4 ± 1 mmHg and reached a...
plateau of 34 ± 3 mmHg (P < 0.01). During 25 s of CSO, CSP in all of the animals exceeded 11 mmHg, which is the approximate pressure of the coronary venous waterfall (5, 29). Adenosine administration significantly decreased systolic AoP from 151 ± 13 to 115 ± 11 mmHg and diastolic AoP from 106 ± 9 to 68 ± 10 mmHg.

**Coronary Collateral Blood Flow**

Collateral blood flow under the intact vasomotor tone. Control RMBF was 0.98 ± 0.09 ml·min⁻¹·g⁻¹ in the ischemic region and 1.16 ± 0.09 ml·min⁻¹·g⁻¹ in the nonischemic region. (See Fig. 2 for an example.) There was no significant difference between the ischemic and nonischemic region.

During LAO, RMBF was 0.25 ± 0.03 ml·min⁻¹·g⁻¹ in the ischemic region, which was significantly lower than control RMBF (P < 0.01). In the nonischemic region, RMBF during LAO was 1.40 ± 0.13 ml·min⁻¹·g⁻¹, which was significantly higher than the control RMBF (P < 0.01).

During LAO+CSO, RMBF in the ischemic region, 0.31 ± 0.05 ml·min⁻¹·g⁻¹, was significantly greater compared with that during LAO alone, 0.25 ± 0.03 ml·min⁻¹·g⁻¹ (P < 0.05). RMBF in the nonischemic region during LAO+CSO tended to be lower than that during LAO alone, but the difference was not statistically significant. In addition, the correlation between RMBF during LAO and ∆RMBF induced by LAO+CSO was significant and positive in the ischemic region (r = 0.74, P < 0.01).

**Collateral blood flow under the vasodilation with adenosine.** Control RMBF increased in both the ischemic (2.55 ± 0.28 ml·min⁻¹·g⁻¹) and the nonischemic (2.69 ± 0.22 ml·min⁻¹·g⁻¹) regions (P < 0.01, respectively) compared with control RMBF without adenosine administration. See Fig. 3 for an example. There was no significant difference between the ischemic and nonischemic region.

During LAO, RMBF in the ischemic region was 0.14 ± 0.03 ml·min⁻¹·g⁻¹, which was significantly lower than that under the condition without adenosine administration (P < 0.01).

During LAO+CSO, RMBF in the ischemic region (0.12 ± 0.04 ml·min⁻¹·g⁻¹) did not increase compared with that during LAO alone. RMBF in the nonischemic region did not show any statistically significant change during LAO and LAO+CSO.

**Regional Myocardial Blood Flow**

**RMBF under intact vasomotor tone.** Control RMBF in the Endo tended to be higher than that in the Epi in the ischemic and nonischemic regions. See Table 2 and Fig. 4A for examples.

During LAO, RMBF in the ischemic region decreased in both the Endo and Epi, but to a significantly greater extent in the former (P < 0.01). The Endo/Epi RMBF ratio during LAO, 0.59 ± 0.10, was significantly smaller than that in the control, 1.09 ± 0.07 (P < 0.01). In contrast, RMBF in the nonischemic region during LAO tended to increase compared with control RMBF in both the Endo and Epi.

RMBF in the Endo during LAO+CSO increased significantly compared with LAO alone in the ischemic region. 

**Table 1. Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LAO</th>
<th>LAO + CSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>154 ± 5</td>
<td>159 ± 5</td>
<td>152 ± 6</td>
</tr>
<tr>
<td>Mean AoP, mmHg</td>
<td>107 ± 7</td>
<td>110 ± 7</td>
<td>116 ± 6</td>
</tr>
<tr>
<td>Systolic LVP, mmHg</td>
<td>134 ± 8</td>
<td>138 ± 8</td>
<td>136 ± 7</td>
</tr>
<tr>
<td>Systolic CSP, mmHg</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>34 ± 3*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LAO, during left anterior descending coronary artery (LAD) occlusion; LAO + CSO, during LAD occlusion and coronary sinus occlusion; AoP, aortic pressure; LVP, left ventricular pressure; CSP, coronary sinus pressure. *P < 0.01 vs. control and LAO.

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Fig. 2. Changes in the regional myocardial blood flow (RMBF). A: ischemic region; B: nonischemic region. Control, blood flow without intervention; LAO, blood flow during LAD occlusion; LAO + CSO, blood flow during LAO and coronary sinus occlusion (CSO). All results are means ± SE; n = 19, *P < 0.01 vs. control. n.s., Not significant.

Fig. 3. Changes in RMBF (ΔRMBF) with adenosine. A: ischemic region; B: nonischemic region. Control, blood flow without intervention; LAO, blood flow during LAD occlusion; LAO + CSO, the blood flow during LAD occlusion and CSO. All results are means ± SE; n = 10, *P < 0.01 vs. control.
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CSO ENHANCES COLLATERAL AND REDUCES ISCHEMIA

Table 2. Distribution of regional myocardial blood flow in ischemic and nonischemic regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Myocardial blood flow, ml/min/g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control LAO LAO + CSO</td>
</tr>
<tr>
<td>Ischemic region</td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1.02 ± 0.11 0.17 ± 0.03‡ 0.33 ± 0.05†</td>
</tr>
<tr>
<td>Epi</td>
<td>0.92 ± 0.08 0.33 ± 0.04a 0.29 ± 0.04a</td>
</tr>
<tr>
<td>Endo/Epi</td>
<td>1.09 ± 0.07 0.59 ± 0.10a 1.15 ± 0.15†</td>
</tr>
<tr>
<td>Nonischemic region</td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1.29 ± 0.10 1.47 ± 0.15 1.37 ± 0.11</td>
</tr>
<tr>
<td>Epi</td>
<td>1.02 ± 0.11 1.33 ± 0.13a 1.08 ± 0.09a</td>
</tr>
<tr>
<td>Endo/Epi</td>
<td>1.28 ± 0.09 1.12 ± 0.06a 1.29 ± 0.10a</td>
</tr>
</tbody>
</table>

Values are means ± SE. Endo, subendocardial blood flow; Epi, subepicardial blood flow. *P < 0.05 vs. control; †P < 0.05 vs. LAO; ‡P < 0.05 vs. Epi.

region (P < 0.01). In contrast, RMBF in the Epi during LAO+CSO remained unchanged. Accordingly the Endo/Epi flow ratios during LAO+CSO, 1.15 ± 0.15, increased significantly compared with LAO alone, 0.59 ± 0.10 (P < 0.01).

RMBF under vasodilation with adenosine. During LAO, RMBF in the ischemic region decreased in both the Endo and Epi, and the Endo/Epi RMBF ratio during LAO (0.90 ± 0.13) did not show a significant change compared with that in the control (1.16 ± 0.16). See Table 3 for an example. However, the Endo/Epi flow ratios during LAO+CSO (2.09 ± 0.30) increased significantly compared with LAO alone (P < 0.01). The Endo/Epi flow ratios in the nonischemic region did not show any statistically significant change during LAO and LAO+CSO.

Alterations of IMP in Ischemic Region

Control systolic IMP in the ischemic region was 112 ± 7 mmHg in the Endo and 82 ± 6 mmHg in the Epi. See Fig. 4B for an example. The control Endo/Epi ratio of systolic IMP was 1.39 ± 0.06, indicating that IMP was significantly higher in the Endo in the control (P < 0.01). Systolic IMP during LAO was 105 ± 9 mmHg in the Endo and 53 ± 5 mmHg in the Epi. Accordingly, the Endo/Epi of systolic IMP during LAO, 2.13 ± 0.22, was significantly higher than that in the control (P < 0.01). Systolic IMP during LAO+CSO was 81 ± 11 mmHg in the Endo and 65 ± 7 mmHg in the Epi. Thus the Endo/Epi of systolic IMP during LAO+CSO, 1.36 ± 0.21, decreased significantly compared with that during LAO (P < 0.05).

On the other hand, control diastolic IMP in the ischemic region was 11 ± 2 mmHg in the Endo and 10 ± 2 mmHg in the Epi. Diastolic IMP during LAO was 9 ± 2 mmHg in the Endo and 7 ± 2 mmHg in the Epi and that during LAO+CSO was 7 ± 3 mmHg in the Endo and 8 ± 3 mmHg in the Epi. The Endo/Epi of diastolic IMP in the ischemic region did not show any statistically significant change during LAO and LAO+CSO.

Relationship Between CSP and RMBF

Under the intact vasomotor tone, during LAO+CSO, there was a significant positive correlation between the peak CSP and ∆RMBF in the ischemic region (r = 0.56, P < 0.05) (Fig. 5). In contrast, there was no significant relationship between the peak CSP and ∆RMBF in the nonischemic region.

Fig. 4. Changes in the endocardial (Endo)/epicardial (Epi) blood flow ratios (A) and Endo/Epi intramyocardial pressure (IMP) ratios (B). Control, Endo/Epi flow and IMP ratios without intervention; LAO, Endo/Epi flow and IMP ratios during LAO occlusion; LAO+CSO, Endo/Epi flow and IMP ratios during LAO occlusion and CSO. Endo/Epi flow (n = 19) decreased, and the Endo/Epi IMP ratios (n = 9) increased significantly compared with control during LAO. These differences were returned to the control level during LAO+CSO.

Fig. 5. Relation between ∆RMBF in the ischemic region and the peak CSP during CSO. During LAO+CSO, there was a significant positive correlation between the peak CSP and ∆RMBF in the ischemic region. r = 0.56, y = -0.12 + 0.01x, P < 0.05, n = 19 dogs.
In the ischemic region, the peak CSP positively correlated with ΔRMBF in the Endo \( (r = 0.61, P < 0.01) \) but not in the Epi.

Relationship Between Reactive Hyperemia and RMBF and Between Reactive Hyperemia and CSP

Under the intact vasomotor tone, during LAO+CSO, the coronary reserve and ΔRMBF correlated significantly and negatively in the ischemic region \( (r = -0.49, P < 0.05; \text{Fig. 6}) \). Moreover, the coronary reserve negatively correlated with the peak CSP \( (r = -0.59, P < 0.01; \text{Fig. 7}) \).

DISCUSSION

The retrograde treatment of myocardial ischemia via the coronary venous system has been investigated in relation to acute myocardial infarction, coronary revascularization, and open heart surgery \( (1, 10, 14) \). The mechanisms of its cardioprotective effects remain controversial. Mohl et al. \( (15) \) and Moser et al. \( (16) \) considered that the washout of accumulated toxic metabolites formed during ischemia and an improvement in myocardial edema are involved. However, experiments \( (6, 28) \) conducted in pigs, which do not have preformed coronary collaterals, failed to demonstrate efficacy of the retrograde treatment of myocardial ischemia. These findings indicate that coronary collaterals play an important role in the myocardial protective effects of the retrograde treatment of myocardial ischemia.

We hypothesized that CSO increases the coronary collateral blood flow and alters the distribution of RMBF in the ischemic myocardium.

Two major findings were obtained from the present study. First, collateral blood flow was significantly enhanced by CSO in the presence of intact vasomotor tone. Second, CSO reduced subendocardial ischemia in the presence of intact vasomotor tone as well as in the absence of it induced by adenosine infusion.

CSO significantly increased collateral blood flow under the intact vasomotor tone. However, it was abol-ished under the maximum vasodilation with adenosine. It is generally accepted that vasodilators such as adenosine induce coronary steal of collateral blood flow \( (3, 17) \). In fact, RMBF was significantly increased in the nonischemic region and decreased in the ischemic region indicating coronary steal phenomenon induced by adenosine in the present study. These results indicate that the effect of CSO on the enhancement of coronary collateral flow requires the intact vasomotor tone; in other words, CSO is not so powerful to overcome the coronary steal phenomenon induced by adenosine. However, the local effect of CSO on the distribution of RMBF in the ischemic region is still observed under the maximum vasodilation with adenosine.

The changes in the collateral blood flow and the peak CSP during CSO showed a significant positive correlation. We used the coronary reserve as an index of the severity of myocardial ischemia \( (7) \) and found that it negatively correlated with the increment in CSP. Regional perfusion pressure in the ischemic region decreases as a consequence of reductions in both coronary artery blood flow and myocardial contractility \( (16) \). The obstructive effects of CSO on the coronary flow into the nonischemic region \( (12) \) may promote a shift of blood flow to the ischemic region, which is exposed to a lower tissue perfusion pressure. In this case, the alternative interpretation of pressure dependence of resistances also should be considered \( (27) \). If the collateral vessels originate from the circumflex coronary artery so that there is proximal resistance, collateral flow would increase because of the increase in driving pressure at the origin of the collateral vessels \( (25) \). In the present study, coronary collateral flow was higher in the presence of intact vasomotor tone than under the maximum vasodilation. This is consistent with the collateral source being proximal to the resistance vessels in the nonischemic region. The obstructive effects of CSO should be sufficiently powerful, and the increment in CSP seems to be a major determinant of CSO effectiveness.

![Graph](http://ajpheart.physiology.org/DownloadedfromH1365)

**Fig. 6.** Relation between ΔRMBF in the ischemic region and the coronary reserve after CSO. During LAO+CSO, there was a significant negative correlation between the coronary reserve and ΔRMBF in the ischemic region. \( r = -0.49, y = 0.18 - 0.02x, P < 0.05, n = 19 \) dogs.

![Graph](http://ajpheart.physiology.org/DownloadedfromH1365)

**Fig. 7.** Relation between the peak CSP and the coronary reserve after CSO. During LAO+CSO, there was a significant negative correlation between the coronary reserve and the peak CSP in the ischemic region. \( r = -0.59, y = 49.60 - 3.11x, P < 0.01, n = 19 \).
One major factor that determines the degree to which CSP is increased by CSO is a route other than the coronary sinus that can drain coronary venous blood, such as Thebesian veins that connect directly with the chambers of the heart, the anterior cardiac veins that connect with the right atrium independently of the coronary sinus (19, 24), and the small coronary vein branches that connect with the right atrium distal to the site of the CSO balloon. If these extra routes are well developed, increasing the CSP becomes difficult. These may be the case in four dogs in the present study that did not demonstrate a significant increase in CSP and RMBF.

The significant positive correlation between RMBF during LAO and ΔRMBF during LAO+CSO in the ischemic region indicates that the preformed, well-developed collateral can augment the effect of CSO. This is supported by the fact that the coronary reserve showed significant negative correlations with both ΔRMBF in the ischemic region and with the peak CSP during CSO. Collateral flow is lower at higher degree of ischemia. The ischemic bed with a low-collateral flow is empty and therefore less capable of producing high peak CSP values (30). Fujita et al. (7) reported that the reactive hyperemic response (coronary reserve) after repeated transient coronary occlusion reflected the attenuation of myocardial ischemia in the occluded coronary perfusion bed. In their study, coronary reserve and the extent of myocardial ischemia progressively decreased with increment in collateral blood flow.

Endo is more susceptible to ischemia compared with the Epi (9, 20). CSO during ischemia resulted in a significant increase in the Endo blood flow and reversed the Endo/Epi blood flow ratio. This indicates that CSO may provide a myocardial protective action, especially in the Endo where ischemia is more prominent. Several mechanisms may be responsible for the Endo-protective action of CSO. The effects of elevated CSP, namely elevated coronary back pressure (22), may not be uniform in the ischemic myocardium through the Endo to Epi. The changes in vascular tonus caused by CSO may differ between the Endo and Epi. In the present study, we performed the experiments with adenosine to investigate the role of vaso-motor tone. CSO during ischemia increased Endo/Epi blood flow ratio even under the maximum vasodilation with adenosine similarly to that in the intact vasomotor tone. Thus coronary vaso tone does not seem to play a crucial role as a mechanism whereby CSO improves Endo perfusion in the ischemic region.

We also examined changes in IMP in the Endo and Epi. The Endo/Epi IMP ratios in the ischemic region were significantly decreased during CSO. This was the opposite of the relationship in RMBF, in which the Endo/Epi were significantly increased during CSO. Thus one of the mechanisms whereby blood flow shifted to the Endo by CSO might be related to the decreased IMP. Cantin and Rouleau (2) reported that CSO increased IMP and decreased blood flow in the Epi when perfusion pressure of the left circumflex coronary artery was partially restricted. Rouleau and White (22) reported that the coronary back pressure induced by CSO was higher in the Epi than in the Endo and suggested a differential intramyocardial waterfall mechanism with greater tissue pressure in the latter than in the former. Although the design of their study was different from ours in that we totally obstructed the coronary artery to mimic clinical acute myocardial infarction, our findings were consistent with the relatively lowered IMP in the Endo they reported.

There are a couple of limitations in the present study. We evaluated only the effects of a single CSO with a short duration of LAO. Because the repetition of CSO and its release may alter the benefits of a single CSO, the effects of repeated CSO should be examined with a longer duration of LAO in a future study. However, this study was designed to investigate the effect of CSO on the distribution of RMBF and to clarify the mechanism by which RMBF is modified by CSO. We applied the short duration of LAO and CSO in a randomized order to minimize ischemic myocardial damage and to evaluate the effects of several conditions repeatedly in the same dog. As a result, we detected alternative shifts of RMBF from nonischemic to ischemic regions, and could therefore evaluate the effects of CSO. Another potential problem exists in the method of IMP measurement. Artifacts may be associated with any method of intramyocardial measurement, because all sensors occupy space and may damage local muscle fibers and stretch others (18). However, Denys et al. (4) and Satoh et al. (23), by using systems similar to ours, reported that measuring IMP in both the Endo and Epi is sufficiently sensitive to detect changes under volume overload or with drug administration. We confirmed the position of each catheter at autopsy and IMP responded well to the conditional changes imposed by LAO and CSO.

The intervention via the coronary sinus may help to preserve tissue viability and improve cardiac function as a temporary substitutive treatment for acute myocardial infarction while waiting for a subsequent definitive therapy such as thrombolysis or angioplasty. It might be attractive especially as a treatment for “no reflow” phenomenon (15). However, this technique could not be directly applied for clinical use, and further studies are needed to optimize the technique, because it can lead to venous engorgement, myocardial edema, and injury to the coronary veins (13).

In conclusion, CSO potentially enhances coronary collateral flow and preserves the ischemic myocardium, especially in Endo. Further investigations are required to introduce these potential effects of the retrograde treatment of myocardial ischemia via the coronary venous system in clinical situations.

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