

## Original Research

## Preservation of Coronary Sinus Flow After Complete Ligation of All Coronary Arteries

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## Key words:

**Coronary sinus, collateral blood flow, coronary artery ligation.**

**Introduction:** The contribution of the collateral network to myocardial oxygenation under normal circumstances is not clear. However, it is possible that in diseased myocardium this network may be activated and contributes significantly to cardiac blood supply. The purpose of this study was to examine the coronary sinus flow after acute, synchronous, complete occlusion of all epicardial coronary arteries and to investigate methods to increase the flow in the setting of ischaemia.

**Methods:** In 8 pigs, the coronary sinus flow was measured after complete ligation of all coronary arteries. In two of the 8 experiments adrenaline and dobutamine were infused into the left ventricular cavity, while clamping of the ascending aorta was performed in another three animals in an effort to increase left ventricular systolic pressure.

**Results:** The mean coronary sinus flow decreased from  $36.06 \pm 11.01$  ml/min to  $5.61 \pm 6.96$  ml/min ( $p < 0.001$ ) after ligation of the coronary arteries. A 67% mean reduction of coronary sinus flow at the first minute after ligation was observed and a progressive decrease of coronary sinus outflow to almost zero within 60 minutes was seen in some experiments. Neither infusion of adrenaline and dobutamine nor ascending aorta clamping increased the coronary sinus flow.

**Conclusions:** The preservation of coronary sinus flow after the complete occlusion of all coronary arteries indicates that retrograde flow through the collateral network from cardiac chambers may exist. Methods that increase the blood flow through the collateral network may contribute to the improvement of myocardial perfusion in severe coronary insufficiency.

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**T**he cardiac network of vessels comprises the epicardial arteries and veins as well as a complex network of collateral channels, which is composed of arterio-luminal, arterio-sinusoidal vessels, Thebesian veins and numerous other intra- and extracardiac anastomoses. Thus the myocardium can be perfused by the epicardial arteries as well as directly from the cardiac chambers via the collateral network.<sup>1</sup> It has been estimated that only 50% of the coronary venous blood is drained via the coronary sinus, whereas

23% is drained directly to the right atrium via the anterior cardiac veins. In the remaining 27% of the coronary venous drainage the role of the Thebesian veins is of pivotal importance.<sup>2</sup> The contribution of the collateral network to myocardial oxygenation under normal circumstances has not been clarified. However, it is theoretically possible that in diseased myocardium this network can be activated and could contribute significantly to the cardiac blood supply.<sup>3</sup> Numerous unverified questions arise after the complete ligation

ation of all epicardial coronary arteries. First, is there any blood flow in the coronary sinus from the collateral network, and for how long? Second, is this flow adequate to maintain a minimal supply of energy to the myocardial cells and metabolism to ensure haemodynamic stability? Third, are there great variations between experiments?

The aim of this study was to examine the coronary sinus flow after acute, synchronous, complete occlusion of all epicardial coronary arteries and to investigate methods to increase this flow in the setting of ischaemia.

## Materials and methods

### *Animals and surgical preparation*

The study material consisted of 13 pigs weighing 28-30 kg. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and was approved by the Scientific Committee of the "Alexandra" University Hospital. Eight experiments were successful, whereas two were not completed because of surgical incidents and another three because of unsuccessful recovery from ventricular fibrillation immediately after the complete and synchronous ligation of all coronary arteries.

The animals were sedated with intramuscular administration of midazolam 0.08-1 mg/kg, anaesthetised with intravenous thiopental sodium 3-5 mg/kg, intubated, and controlled by mechanical ventilator. Anaesthesia was maintained with intravenous propofol 0.1-0.2 mg/kg. The chest was opened through a median sternotomy and pericardiotomy was performed. The left main coronary artery, if its length was sufficient, and the right coronary arteries were carefully isolated. If the length of the left main coronary artery was not sufficient, the left anterior descending branch, before the first diagonal, and the left circumflex were used instead. Loose sutures of 4-0 were placed around the vessels. The ends of each suture were threaded through a piece of tubing, forming a snare that was tightened to occlude the artery. Left ventricular pressure was gauged through a 5F pigtail catheter placed through the left atrial appendage. Another catheter was placed in the ascending aorta through the left internal carotid artery, for the estimation of central arterial pressures. The right internal jugular vein was used for the administration of parenteral fluids. A suture was placed and tight-

ened around the left hemiazygous vein, which in pigs opens directly into the coronary sinus, and ligation of this vein was performed. Then, a three-lumen retrograde cardioplegia balloon catheter was introduced via the right atrial appendage to the ostium of the coronary sinus and stabilised by a suture around the coronary sinus. Position was confirmed by palpation and a rise in coronary sinus pressure measured at the distal tip of the catheter during balloon inflation. The catheter allowed the pressure and flow in the coronary sinus to be recorded. The flow was determined by measuring the volume of blood freely flowing in a volumetric tube held at the level of the right atrium for three consecutive minutes during baseline conditions and then every minute after the complete occlusion of the coronary arteries, until sustained ventricular fibrillation or electromechanical dissociation intervened. All the catheters of the coronary sinus, left ventricle and aorta were connected to a multi-channel system for monitoring and recording of the pressures and lead II of the ECG. The blood volume from the coronary sinus was transfused to the superior *vena cava* via a transfusion system.

In an attempt to increase blood flow via the collateral network in the setting of ischaemia, inotropic stimulation (dobutamine or adrenaline) or a mechanical increase of left ventricular systolic pressure by clamping of the ascending aorta were used indicatively.

### *Experimental protocol*

The animals were allowed to stabilise for 15 min after surgical preparation and insertion of the catheters. Following intravenous administration of 5000 units heparin, baseline haemodynamics were obtained. The volume of the blood flow of the coronary sinus every minute for three consecutive minutes was measured and the mean value was calculated. Meanwhile, the systolic and diastolic pressure of the left ventricle and aorta and the ECG were recorded simultaneously. Then, acute and complete occlusion of all epicardial coronary arteries was performed simultaneously. Every minute after the complete occlusion of the coronary arteries the coronary sinus volume was measured, until sustained ventricular fibrillation or electromechanical dissociation intervened.

### *Statistical analysis*

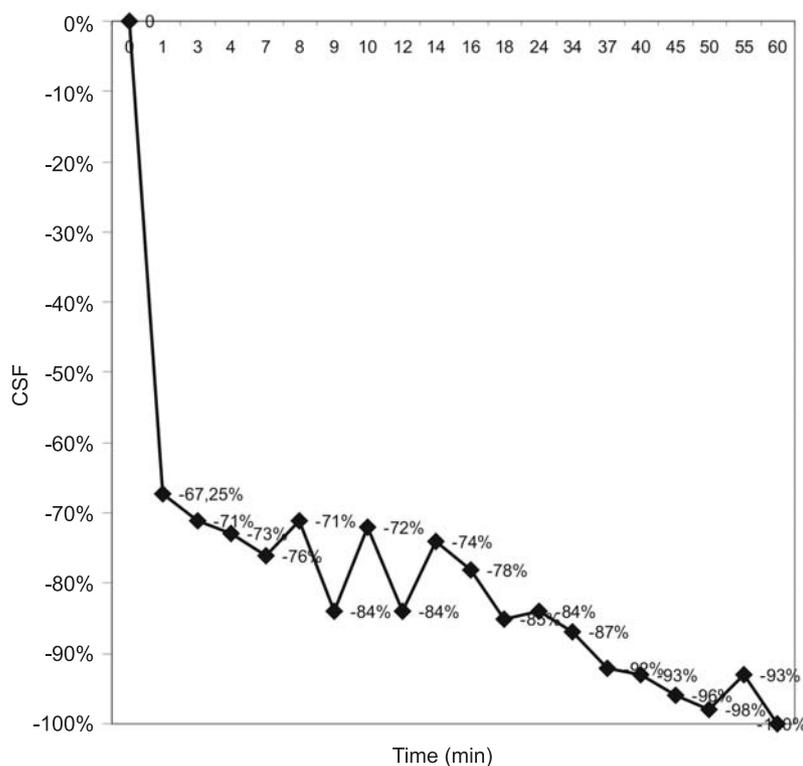
Data for each parameter from all experiments are expressed as mean value  $\pm$  standard deviation. Coronary

sinus flow, heart rate, systolic and diastolic left ventricular pressure were included in the statistical analysis. The Student t-test, Pearson's correlation and multivariate regression techniques were used in the processing of the data (statistical package SPSS 10.0).

## Results

The mean coronary sinus blood flow before the ligation was  $36.06 \pm 11.01$  ml/min, ranging from 18 ml/min to 144 ml/min. Following complete ligation of the coronary arteries, the myocardium became cyanotic after approximately one minute of occlusion and expanded with each heartbeat. A 67% acute reduction in coronary sinus flow was observed during the first minute. In the following 60 minutes the blood flow diminished gradually to zero (Figure 1). The persis-

tence of blood flow varied greatly between the experiments. In the eight animals the duration of flow was 2, 5, 9, 14, 14, 18, 50, 60 minutes and the total amount of blood derived from the coronary sinus was 5, 42, 90, 30, 953, 31, 189, and 356 ml, respectively. The reduction of mean blood flow 60 minutes after the ligation ( $5.61 \pm 6.96$  ml/min) was statistically significant ( $p < 0.001$ ) compared to the mean blood flow before the ligation ( $36.06 \pm 11.01$ ). The mean systolic pressure of the left ventricle after the ligation decreased significantly from  $108.25 \pm 18.51$  mmHg before ligation to  $20.90 \pm 16.31$  mmHg after ( $p < 0.001$ ). Conversely, the mean diastolic pressure of the left ventricle increased significantly from  $1.58 \pm 1.56$  mmHg to  $7.73 \pm 7.81$  mmHg ( $p < 0.001$ ) (Table 1). The mean heart rate decreased significantly ( $151.87 \pm 22.82$  beats/min before and  $77.00 \pm 34.10$  beats/min after



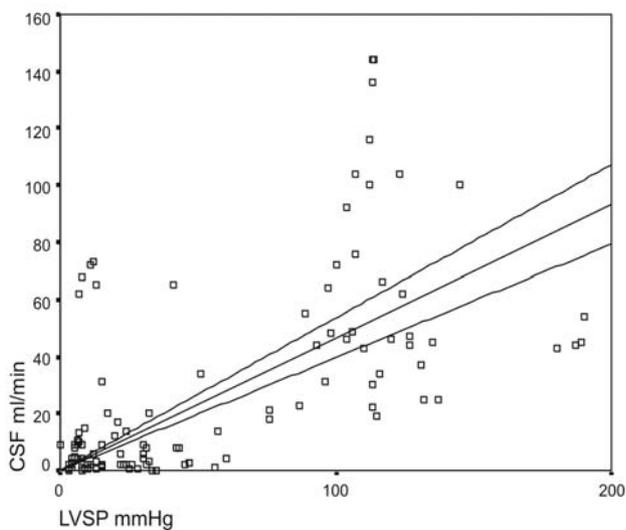
**Figure 1.** Percentage change in coronary sinus flow (CSF) over time after ligation of all coronary arteries.

**Table 1.** Effect of coronary artery ligation on heart rate, left ventricular pressure and coronary sinus flow

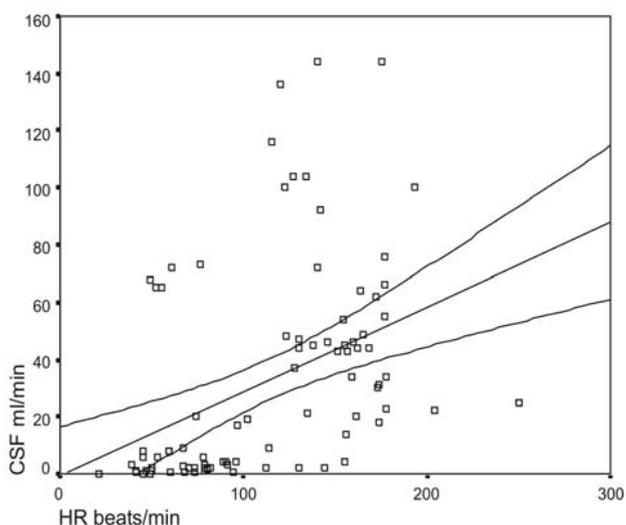
	Before ligation	After ligation	p <
Heart rate (beats/min)	$151.87 \pm 22.82$	$77.00 \pm 34.10$	0.001
LVSP (mmHg)	$108.25 \pm 18.51$	$20.90 \pm 16.31$	0.001
LVDP (mmHg)	$1.58 \pm 1.56$	$7.73 \pm 7.81$	0.001
Csf (ml/min)	$36.06 \pm 11.01$	$5.61 \pm 6.96$	0.001

Csf – Coronary sinus flow; LVDP – left ventricular diastolic pressure; LVSP – left ventricular systolic pressure.

ligation,  $p < 0.001$ ). All animals were in sinus rhythm. The coronary sinus flow showed an overall positive correlation with left ventricular systolic pressure ( $r = 0.66$ ,  $p < 0.001$ ), and heart rate ( $r = 0.47$ ,  $p < 0.001$ ) (Figures 2 & 3). Multivariate regression analysis revealed that heart rate and left ventricular systolic pressure were the only independent predictors of coronary sinus blood flow before the ligation ( $r = 0.971$ ,  $F = 65.72$ ,  $p < 0.001$ ), whereas after the ligation only the systolic pressure of the left ventricle was an independent predictor ( $r = 0.58$ ,  $F = 8.24$ ,  $p < 0.011$ ); excluded variables were the left ventricular diastolic



**Figure 2.** Correlation between coronary sinus flow (CSF) and left ventricular systolic pressure (LVSP).



**Figure 3.** Correlation between coronary sinus flow (CSF) and heart rate (HR).

pressure, and the heart rate (Figures 2 & 3).

In the experiments in which adrenaline and dobutamine were infused in the left ventricle or clamping of the ascending aorta was performed after ligation, neither left ventricular pressure nor coronary sinus flow were affected significantly.

## Discussion

The role of the coronary venous network is not only the drainage of the coronary blood received from the coronary arteries through the capillaries. Experimental studies have proved the connection between the coronary venous network and the collateral network of vessels and indicated its potential contribution to the coronary blood supply.<sup>4</sup> The infusion of contrast agents into the great coronary vein after the occlusion of the left anterior descending artery in dogs resulted in the retrograde opacification of the entire ischaemic zone. Furthermore, contrast echocardiography confirmed the presence of shunts between coronary vessels and cardiac chambers by detecting contrast in the latter.<sup>4</sup>

The most important conclusion of our experiment was the persistence of blood flow through the coronary sinus after the complete occlusion of all coronary arteries, which does not allow any blood supply through this route to the myocardium and the coronary veins. In the first minute after the occlusion the coronary sinus blood flow decreased by approximately 70%, becoming zero only after several minutes. During that period of time, the ECG showed sinus bradycardia, probably due to ischaemia of the sinus node, usually culminating in sustained ventricular fibrillation or electromechanical dissociation. Gregg et al showed that after occlusion of the left and right coronary arteries there was blood flow inside the great cardiac vein corresponding to 5-10% of the flow before the ligation.<sup>5</sup> It seems that this minimal flow, capable of sustaining a minimal supply of energy to the myocardial cells and metabolism, arises from the cardiac chambers through the system of Thebesian veins.<sup>1</sup> The Thebesian veins are vessels of small calibre, situated deep in the myocardium, and open into the cardiac chambers where their diameter is of the order of 1 mm.<sup>6</sup> These veins form a collateral network between the distal ends of capillaries and the cardiac chambers, especially in the myocardium of the right heart, less in the myocardium of the left ventricle, and much less in the myocardium of the left atrium.<sup>7,8</sup>

The duration (2-60 min) and the amount of coro-

nary sinus blood flow (5-356 ml) after the occlusion of all coronary arteries varied between experiments. Although such volume flows of arterial blood are adequate for the metabolic needs of the potentially infarcted myocardium, it should be emphasised that there is a considerable natural variation in the ability of such an anastomotic collateral network to develop in different pigs. The mortality accompanying these coronary operations is high. Those pigs which survive complete occlusion of all coronary arteries probably represent a select group naturally endowed with a resistance to this type of procedure. Another possibility is that the blood flow through the coronary sinus could arise from the squeezing of the myocardium during the next few systoles and represent the amount of intramyocardial blood existing before the occlusion. However, in the majority of our experiments the total volume of blood coming through the coronary sinus exceeded endomyocardial coronary capacity, which is estimated to be  $0.10 \text{ ml} \times \text{mmHg}^{-1} \times 100 \text{ g}^{-1}$ .<sup>9</sup> Furthermore, it has been claimed recently that blood remains in the vascular bed for fifteen seconds immediately after the total coronary occlusion and is not squeezed out, even if wall motion of the risk area continues.<sup>10</sup>

The systolic pressure of the left ventricle seems to be the most important factor that determines the blood flow through the coronary sinus, both before and after occlusion of the coronary arteries. This finding is in keeping with previous data suggesting that the pressure and flow of the coronary veins are both maximal during systole and are further augmented in positive inotropic conditions as well as during occlusion of the aorta.<sup>3</sup> The administration of adrenaline and dobutamine and the clamping of the ascending aorta, although performed indicatively, did not change the flow in the coronary sinus, obviously because of the myocardium's inability to increase systolic left ventricular pressure in the face of minimal cellular metabolism and functioning. It is possible that other means of increasing ventricular pressure, such as intraaortic or intraventricular balloon pumping, could augment myocardial blood supply through the collateral network.

Protection of the ischaemic myocardium via the coronary sinus provides a unique approach, since it provides access to the ischaemic myocardium through a retrograde means. A variety of techniques have been developed, each with its own advantages and disadvantages. These techniques include aortovenous bypass anastomoses during cardiac surgery,<sup>11</sup> coro-

nary sinus retroperfusion of cardioplegic solution,<sup>12</sup> synchronised coronary sinus retroperfusion with arterial blood,<sup>13</sup> and pressure controlled intermittent coronary sinus occlusion.<sup>14</sup> The delivery of pharmacological agents, such as streptokinase, antiarrhythmics, inotropics, magnesium, or calcium channel blockers, through coronary venous retroperfusion could provide protective benefits during continuous coronary occlusions.<sup>15</sup> The concept of direct revascularisation of ischaemic myocardium via transmural left ventricular conduits created by laser beams was based mainly on the existence of complex anatomical connections between the coronary vasculature and cardiac chambers.<sup>16</sup> However, Thebesian veins and endomyocardial channels created with laser beams are much alike histologically. The disappointing results of this technique may be due in part to the inability of improving myocardial blood supply, either directly from the cardiac chambers or through creating connections between the left ventricle and endomyocardial vessels such as the Thebesian veins.<sup>17</sup>

### Limitations

Although the heart of the pig is anatomically similar to humans<sup>18</sup> (with a notable exception being the drainage of the left hemiazygous vein, which in our experiments was ligated, into the coronary sinus), the extrapolation of the above data to the human heart is questionable. The consistent trends of the results in all experiments probably outweigh the small number of experiments; the mortality associated with these coronary operations is in any case high. The attempts to increase blood flow via the collateral network in the setting of ischaemia by inotropic stimulation and mechanically were indicative. A separate protocol to assess cardioprotection and biochemical markers of the severity of ischaemia, in both the presence and absence of interventions, and to explore novel methods for increasing the blood flow, such as intraaortic or intraventricular balloon pumping, is needed.

### Conclusion

The preservation of coronary sinus blood flow after total, synchronous occlusion of all three coronary arteries indicates the importance of the collateral network in the blood supply of the myocardium, especially in the setting of severe ischaemia. Further investigation is warranted to establish ways of increasing the flow through the collateral network. These

methods may contribute to the improvement of blood supply in the severely diseased myocardium.

## References

1. Ansari A: Anatomy and clinical significance of ventricular Thebesian veins. *Clin Anat* 2001; 14: 102-110.
2. Lüdinghausen v.M: Anatomy of the coronary arteries and veins, in Mohl W, Wolner E, Glogar D (eds.): *The Coronary Sinus. Proceedings of the 1st International Symposium on Myocardial Protection Via the Coronary Sinus*. Springer-Verlag, New York, 1984; pp 5-7.
3. Klassen GA, Armour JA: Coronary venous pressure and flow: effects of vagal stimulation, aortic occlusion, and vasodilators. *Can J Physiol* 1983; 62: 531-538.
4. Maurer G, Punzengruber C, Haendchen RV, Torres MAR, Meerbaum S, Corday E: Penetration of coronary venous injections into ischemic myocardium. In: Mohl W, Wolner E, Glogar D (eds). *The Coronary Sinus. Proceedings of the 1st International Symposium on Myocardial Protection Via the Coronary Sinus*. Springer-Verlag, New York, 1984; pp 167-175.
5. Gregg DE: *Coronary circulation in health and disease*. Lea & Febiger, Philadelphia, 1950; pp 79-89.
6. Esperanca Pina JA, Correia M, O'Neill JG: Morphological study of the right cavities in the dog. *Acta Anat* 1975; 92: 310-320.
7. Maurer G, Punzengruber C, Haendchen RV, et al: Retrograde coronary venous contrast echocardiography: assessment of shunting and delineation of the regional myocardium in the normal and ischemic canine heart. *J Am Coll Cardiol* 1984; 4: 577-586.
8. Shiki K, Masuda M, Yonenaga K, Asou T, Tokunaga K: Myocardial distribution of retrograde flow through the coronary sinus of the excised normal canine heart. *Ann Thorac Surg* 1986; 41: 265-271.
9. Chilian WM, Marcus ML: Coronary venous outflow persists after cessation of coronary arterial inflow. *Am J Physiol* 1984; 247: H984-H990.
10. Otani K, Beppu S, Ibaraki K, et al: Is blood squeezed from the microcirculation soon after coronary occlusion?: real time myocardial contrast echocardiographic study. *J Cardiol* 2003; 41: 13-19.
11. Arealis EG, Volder JGR, Kolff WJ: Arterialization of the coronary vein coming from an ischemic area. *Chest* 1973; 63: 462-463.
12. Tian G, Xiang B, Dai G, et al: Retrograde cardioplegia. *J Thorac Cardiovasc Surg* 2003; 125: 872-880.
13. Aldea GS, Zhang X, Rivers S, Shemin RJ: Salvage of ischemic myocardium with simplified and even delayed coronary sinus retroperfusion. *Ann Thorac Surg* 1996; 62: 9-15.
14. Lazar HL: Advantages of pressure-controlled intermittent coronary sinus occlusion over left ventricle-powered coronary sinus retroperfusion. *Ann Thorac Surg* 2001; 71: 402.
15. Yamamoto K, Bando S: Effects of verapamil and magnesium sulfate on electrophysiologic changes during acute myocardial ischemia and following reperfusion in dogs: comparative effects of administration by intravenous and coronary sinus retroperfusion routes. *Angiology* 1996; 47: 557-568.
16. Moosdorf R, Rybinski L, Hoffken H, Funck RC, Maisch B: Transmyocardial laser revascularization in stable and unstable angina pectoris. *Herz* 1997; 22: 198-204.
17. Kanellopoulos GK, Svindland A, Ilebekk A, Goverud I, Kvernebo K: Transventricular non-transmural laser treatment of hypoperfused porcine myocardium acutely reduces left ventricular contractile function. *Eur J Cardiothorac Surg* 1999; 16: 135-143.
18. Swindle MM, Horneffer PJ, Gardner TJ, et al: Anatomic and anesthetic considerations in experimental cardiopulmonary surgery in swine. *Lab Anim Sci* 1986; 36: 357-361.