Stimulating Extracardiac Collaterals via Right Internal Mammary Artery Occlusion
Another Step Into an Undiscovered Country

Morton J. Kern, MD; Arnold H. Seto, MD, MPA

But that the dread of something after death,
The undiscovered country from whose bourn [boundary] No traveler returns, puzzles the will
—The Tragedy of Hamlet Prince of Denmark, Act III, Scene I
—William Shakespeare (1564–1616)

In their search to find ways to reduce ischemia and possibly prevent death in patients with refractory angina, Stoller and Seiler, in 2014, moved into an undiscovered country and advanced a novel therapeutic strategy involving stimulation of extracardiac collaterals through occlusion of the internal mammary artery. In this issue of Circulation: Cardiovascular Interventions, Stoller and Seiler2 take another step from temporary internal mammary artery (IMA) occlusion now to report on the effects of permanent percutaneous right internal mammary artery (RIMA) occlusion.

See Article by Stoller and Seiler

In the current study, 50 patients with coronary disease underwent 1-minute serial right and left coronary artery balloon occlusion at baseline and then again 6 weeks after placement of a distal RIMA vascular occluding device. The primary end point was the change in collateral flow index (CFI) derived from pressure, \( CFI_{\text{pressure}} = \frac{P_{\text{occlusion}} - P_{\text{venous}}}{P_{\text{aorta}} - P_{\text{venous}}} \), using a pressure sensor guidewire distal to the balloon occlusion. Secondary end points included fractional flow reserve, degree of ST-segment elevation from an intracoronary electrogram, and anginal symptoms during the 1-minute occlusion of coronary with coronary occlusion.

After 6 weeks of follow-up, CFI increased in the right coronary artery (RCA) after RIMA occlusion (from 0.071±0.08 to 0.132±0.12; \( P<0.0001 \)), whereas the left anterior descending coronary artery CFI was unchanged (0.11±0.09 to 0.08±0.08; \( P=\text{NS} \)). Concomitant with the increased RCA CFI was a decrease in the intracoronary ST-segment elevation during RCA occlusion, a response not demonstrated in the left anterior descending artery. Likewise, angina tended to be less in the follow-up 1 minute coronary occlusion. Stoller and Seiler, thus, show that a permanent RIMA distal occlusion seems to augment extracardiac pericardiophrenic collateral anastomoses to ipsilateral native coronary arteries and reduce signs of ischemia in adjacent myocardial territories. This effect was demonstrated with temporary IMA occlusion previously and for the first time seems to be durable, at least in the short term.

Before addressing some of the strengths and weakness of this unique experiment, it is worthwhile to briefly review the foundational studies that led us to this point. Extracardiac collaterals were truly undiscovered until the first description by Hudson et al in 1932. At postmortem examination of cardiac patients, Hudson injected India ink into the occluded native vessels and traced the opacified microvessels over the aorta, pericardiophrenic connectors, and other vascular networks in proximity to the heart. Little was done with this information until the 1950s and 60s, when investigators tried surgical IMA occlusion as a potential treatment for angina, but because of several factors and equivocal results, these experiments failed. Over subsequent decades, sporadic rare cases suggested that IMA pericardiophrenic branches could be called forth. After years of fruitless research by early investigators, Stoller et al resurrected the extracardiac collateral concept in a remarkable experiment in 2014. By using temporary balloon occlusion of the ipsilateral IMA and inducing temporary ischemia in the native coronary also by balloon occlusion while quantifying the CFI, they found that IMA occlusion increased RCA CFI while LIMA occlusion increased left anterior descending artery CFI. Because of the variable dominance and myocardial supply region, neither IMA occlusion improved circumflex CFI. These data, summarized in the Figure, not only demonstrated the existence and inducibility of the collateral supply but led to the current clinical pilot trial of permanent IMA occlusion and CFI responses over time as a potential for a new method to relieve ischemia for the end-stage refractory angina patient.

Questions Raised

While we must compliment the investigators on a truly unique experiment, certainly one of a kind in ischemia research, this study raises several issues which will need to be addressed before the concept becomes clinically applicable. Central to these new observations is (1) through what mechanism does IMA occlusion produce, elicit, or enhance collaterals to heart? Temporary 1-minute induced ischemia during coronary balloon occlusion elicits native coronary–coronary collaterals,
but how and why should the pericardiophrenic network be called into play? And (2) what is the anti-ischemic threshold of the extracardiac collaterals? Is a CFI of 0.132 sufficient to reduce the ischemia of daily life? Finally, (3) where is the best location to occluded the IMA, and what is its long-term effect?

**Pericardiophrenic Collaterals**

The anatomic vascular networks fed from the IMA can connect to the coronary circulation via the second IMA branch also called the pericardiacophrenic artery, which arises at approximately the second intercostal space and supplies the pericardium. During IMA angiography, this branch is recognizable as the only branch moving with the heart. The pericardiophrenic artery also has branches to the atria or the epicardial coronary circulation. It may be postulated that these connections become functional with altered local hemodynamics from coronary occlusion, coupled in some way to the ischemic myocardium producing some kind of angiogenic signal.

**IMA Occlusion Location and Late Patency**

Where is the best location of IMA occlusion? The IMA connects distally to ipsilateral external iliac artery. The site of IMA occlusion was selected as distal to the second intercostal artery away from the bifurcation of the pericardiophrenic branch because of the connections to the pericardiophrenic network and its proximity to the heart. It may be challenging to test if other locations would serve as well. However, it is noteworthy that in 4 cases in which the pericardiophrenic branch was dissected and occluded, CFI did not increase.
Permanent IMA device closure theoretically carries a risk for ischemia in the dependent zone of the chest, reducing the patient’s physical arm activity. No such symptoms were reported, and although RIMA graft use is uncommon in most clinical practices, chest wall ischemia is nearly unheard of related to single RIMA or LIMA bypass surgery. A CFI of the IMA during balloon occlusion is =0.75 to 0.80, meaning that the external iliac artery supplies >75% of perfusion beyond the IMA occlusion, likely explaining for the most part the absence of clinical sequela.

One puzzling observation is that 11 patients (22%) had a patent IMA after vascular plug insertion at follow-up, and yet, the net CFI remained significantly higher at 6 weeks. Whether this means that the LIMA occlusion and collateral recruitment can continue without a completely occlusive stimulus or whether the small but positive changes in CFI are coincidental remains to be seen. The use of IMA occlusion to elicit extracardiac collaterals in an animal model was unsuccessful, and the rarity of extracardiac collaterals in clinical patient reports makes the unique responses in Stoller and Seiler’s work even more curious.

**Ischemic CFI Threshold**

Is a CFI increase to 0.132±0.117 sufficient to make a difference in clinical ischemia and the patient’s life? According to the initial reports of Seiler et al., a CFI of >0.30 has a 75% sensitivity and 92% specificity to predict absence of ischemia during coronary occlusion. In that study, 11 of 51 patients without ECG signs of ischemia during coronary balloon occlusion with CFI >0.30 had sufficient collaterals to prevent ischemic ST changes, with relative collateral flow of 46% determined both by Doppler and pressure wire. Patients with CFI <0.30 had insufficient collaterals, with relative collateral flow values of 18%. Patients with and without ischemia had CFI of 0.17±0.09 and 0.44±0.16, respectively. The RCA CFI response to RIMA occlusion in this study (0.132±0.117) exceeded the RCA CFI of 0.116±0.079 of temporary occlusion in their prior study. The CFI value was also comparable to CFI seen with other novel potential anti-ischemic treatments such as granulocyte colony-stimulating factor (CFI, 0.12–0.17 posttreatment; Δ+0.049), Ivabradine infusion (0.11–0.15 posttreatment; Δ+0.040), and endurance training (0.16–0.20; Δ+0.04 in the exercise group [P<0.03]; in the sedentary group, CFI was 0.19–0.21; Δ+0.02 on 3-month follow-up [P=ns]). Whether this is an endorsement of significant collateral-related reduction of clinical ischemia cannot be determined. However, both IC ST changes and follow-up fractional flow reserve added more evidence of a favorable influence of increased collateral flow. Not only did the ischemic ST elevation statistically decrease but also the repeat fractional flow reserve (native artery stenosis not yet treated) at the follow-up was higher than baseline fractional flow reserve, suggesting that more functional collateral flow was produced, despite lower CFI values than prior reports of nonischemic CFI.

To be clinically relevant, coronary collaterals should be a sustainable and sufficiently large source of myocardial perfusion and reduce ischemia in daily life. It is conceivable that improved extracardiac collateral flow has the potential to be exactly that. Novel approaches to stimulate or develop the extracardiac collateral supply to the heart may ultimately assist those with severe diffuse atherosclerosis and those with chronic arterial occlusions who are refractory to maximal anti-ischemic medical therapy. This unique exploration is worthy of our attention to understand the how and why of collateral protection in this undiscovered country.

**Disclosures**

Dr Kern is a speaker and consultant for companies making the pressure wire used in this study to include Philips Volcano, Abbott St. Jude, Acist Medical, Opsens Inc. Dr Seto is a speaker for Acist Medical and received research grants from Philips Volcano and Acist Medical.

**References**


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