



# Immediate recruitment of dormant coronary collaterals can provide more than half of normal resting perfusion during coronary occlusion in patients with coronary artery disease

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**Background.** Dormant coronary collaterals are highly prevalent and clinically beneficial in cases of coronary occlusion. However, the magnitude of myocardial perfusion provided by immediate coronary collateral recruitment during acute occlusion is unknown. We aimed to quantify collateral myocardial perfusion during balloon occlusion in patients with coronary artery disease (CAD).

**Methods.** Patients without angiographically visible collaterals undergoing elective percutaneous transluminal coronary angioplasty (PTCA) to a single epicardial vessel underwent two scans with <sup>99m</sup>Tc-sestamibi myocardial perfusion single-photon emission computed tomography (SPECT). All subjects underwent at least three minutes of angiographically verified complete balloon occlusion, at which time an intravenous injection of the radiotracer was administered, followed by SPECT imaging. A second radiotracer injection followed by SPECT imaging was performed 24 h after PTCA.

**Results.** The study included 22 patients (median [interquartile range] age 68 [54-72] years. The perfusion defect extent was 19 [11-38] % of the LV, and the collateral perfusion at rest was 64 [58-67] % of normal.

**Conclusion.** This is the first study to describe the magnitude of short-term changes in coronary microvascular collateral perfusion in patients with CAD. On average, despite coronary

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**occlusion and an absence of angiographically visible collateral vessels, collaterals provided more than half of the normal perfusion. (J Nucl Cardiol 2023;30:2338–45.)**

**Key Words: Coronary angiography • coronary physiology • collateral flow**

**Abbreviations**

CAD	Coronary artery disease
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
LV	Left ventricle
PTCA	Percutaneous transluminal coronary angioplasty
RCA	Right coronary artery
SPECT	Single-photon emission computed tomography
STEMI	ST-elevation myocardial infarction
<sup>99m</sup> Tc	Technetium-99 m

**See related editorial, pp. 2346–2348**

**BACKGROUND**

The coronary collateral circulation is a preformed network of anastomotic connections between epicardial arteries acting as a “natural bypass” mechanism.<sup>1,2</sup> The presence of robust coronary collateral circulation is known to be associated with improved survival and left ventricular function in the setting of ST-elevation myocardial infarction (STEMI).<sup>3</sup>

Whilst the prevalence of collaterals varies between species, approximately 25% of patients have angiographically visible robust collaterals at the time of ST elevation myocardial infarction.<sup>4</sup> Short-term changes in collateral flow in humans have been described angiographically by Rentrop et al.<sup>1</sup> In that study, patients with stable angina and single-vessel disease were studied by contralateral coronary artery contrast injection during balloon inflation. Most patients had no collateral filling at baseline, while all but one patient showed improved collateral filling upon balloon occlusion. This suggests a high prevalence of dormant collaterals, but does not provide reliable information on magnitude of the resultant perfusion.

Importantly, collateral vessels smaller than approximately 100 μm are not visibly detectable by invasive angiography.<sup>5</sup> However, relative myocardial perfusion can be quantified by <sup>99m</sup>Tc-sestamibi single-photon emission computed tomography (SPECT) regardless of vessel size. <sup>99m</sup>Tc-sestamibi uptake is proportional to myocardial perfusion,<sup>6</sup> and it exhibits minimal redistribution after initial uptake.<sup>7</sup> While the contribution of collateral flow has been thoroughly described in canine models using microsphere techniques,<sup>8-13</sup> there is no quantitative data on short-term changes in collateral

perfusion in man. Of note, infarct biology cannot be readily translated from canine models to man,<sup>14</sup> and an understanding of human basic coronary physiology is essential to cardiovascular medicine. Therefore, the aim of the study was to quantify collateral myocardial perfusion during coronary balloon occlusion in patients with CAD using <sup>99m</sup>Tc-sestamibi SPECT.

**METHODS**

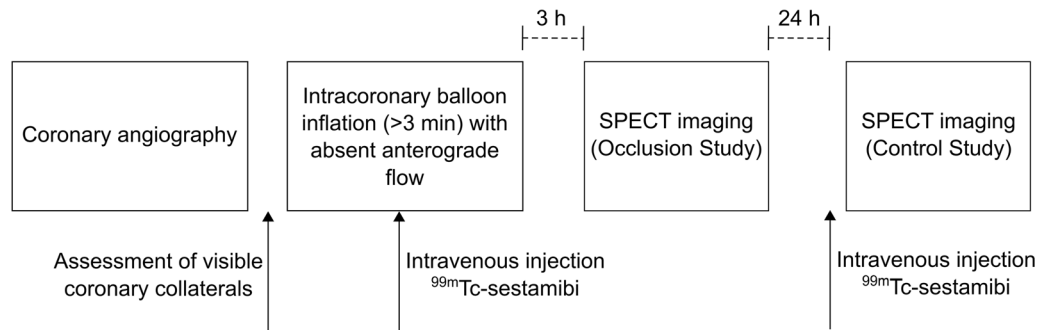
**Study design**

To quantify the amount of collateral perfusion in CAD patients, two myocardial perfusion single-photon emission computed tomography (SPECT) scans were performed in all patients. One of them after isotope injection during complete coronary occlusion (Occlusion study), and one at rest (Control study). The difference in myocardial perfusion between the Occlusion study and the Control study reflects the difference in perfusion between a state of immediate and complete coronary artery balloon occlusion and a non-occluded state, respectively. Patients with angiographically visible collaterals were excluded, and the difference in perfusion can thus be considered to be an effect of recruitment of dormant collaterals, recruited immediately upon coronary occlusion.

The current study was a retrospective substudy of a previously published larger cohort.<sup>15</sup> In that study, 42 patients with obstructive, single-vessel coronary artery disease underwent elective prolonged balloon inflation during percutaneous transluminal coronary angioplasty (PTCA), and two myocardial perfusion SPECT scans between September 1995 and April 1996 with radioactive tracer injections during coronary occlusion and at rest the subsequent day.<sup>15</sup> A flow-chart of the study protocol is presented in Figure 1.

Due to either technical problems, unsuccessful injections, or prior coronary artery bypass surgery to the balloon-occluded artery, 7 patients were excluded from the original study. For the purpose of this study, patients with angiographically visible collaterals, prior infarction, or coronary artery bypass surgery (not only to the balloon-occluded artery) were further excluded (n = 13).

The study was undertaken at Charleston Area Medical Center, Charleston, West Virginia, USA, and was approved by the local Investigational Review Board. Ethical permission was granted based on prior favorable clinical, pilot experience with the



**Figure 1.** A flow-chart of the study protocol. Abbreviations: *h*, hours; *SPECT*, single photon emission computed tomography; *Tc*, Technetium.

methodology, and that subjects all could provide informed consent for this elective procedure, which was obtained for all participants.

### SPECT imaging

For each patient, when the angioplasty balloon was angiographically verified as being fully inflated during PTCA, with absence of anterograde blood flow, 1100 MBq (30 mCi)  $^{99m}\text{Tc}$ -sestamibi was injected intravenously. The intracoronary balloon inflation lasted for at least three minutes in all patients, which allowed for adequate clearance of  $^{99m}\text{Tc}$ -sestamibi from the bloodstream.<sup>16</sup> Immediately following PTCA, the interventional cardiologist performing the procedure recorded the location of balloon occlusion and the duration of balloon inflation. Also, at the conclusion of the procedure, the interventional cardiologist noted whether angiographically visible collateral circulation was considered to be present upon review of the angiographic images of all coronary vessels. Within three hours following angioplasty, the patient was brought to the nuclear medicine laboratory to acquire SPECT imaging data (Occlusion study). On the day following PTCA, a second intravenous injection with 1100 MBq of  $^{99m}\text{Tc}$ -sestamibi was administered intravenously, followed by SPECT imaging within three hours (Control study). Each patient in the study was clinically stable throughout both processes.

SPECT imaging was performed using a single-head gamma camera (Elscent, Haifa, Israel) with a 140 keV ( $\pm 20\%$ ) energy window. Images were acquired using a low energy high-resolution collimator in a  $64 \times 64$  matrix, 6.9 mm pixel size, using 30 projections (25 *s*/projection) over  $180^\circ$  from  $45^\circ$  right anterior oblique to  $45^\circ$  left posterior oblique. A filtered back projection with a Butterworth filter (order 5, cut-off 0.25 cycles/pixel) was used to reconstruct axial slices. The same gamma camera and image acquisition procedures were used for the Occlusion and Control studies.

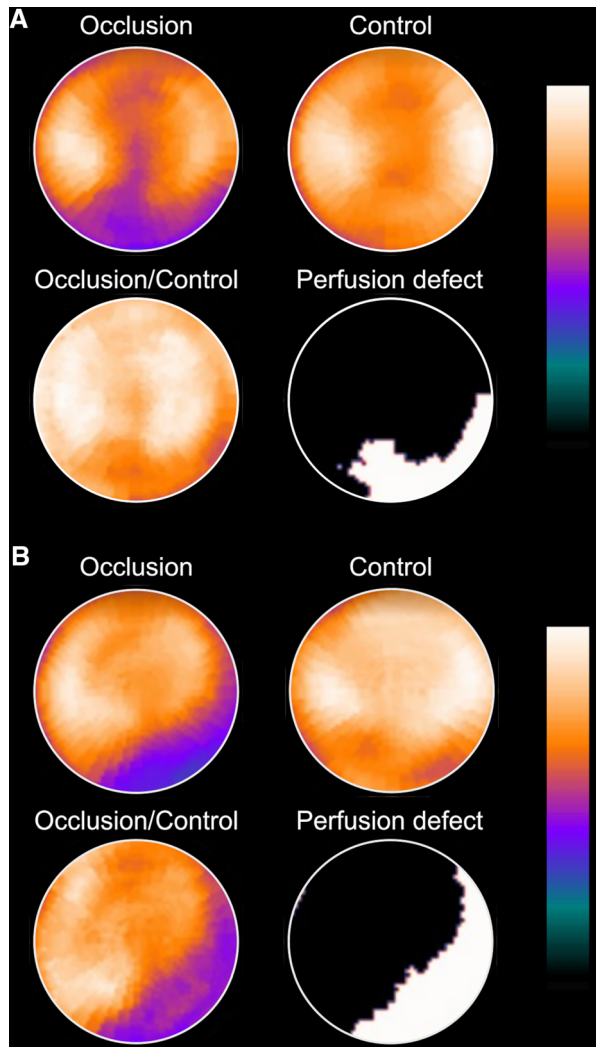
### Image Analysis

Short-axis images were reconstructed using the Cedars-Emory quantitative analysis software (CEqual), and were used to build a volume-weighted bull's eye plots.<sup>17</sup> The quantification of collateral perfusion was performed by comparing the Occlusion study to the Control study for each patient. The Control study was first corrected by taking the decay of  $^{99m}\text{Tc}$  into account (24 h,  $\text{Tc}^{99m}$  decay constant  $\lambda = 0.1151 \text{ h}^{-1}$ ). Following this process, the Occlusion study was scaled so that its average value, in the region above 90% of its maximum, was made equal to the average value of the control study in the same region of the heart. This normalization was necessary to achieve uniformity for the Control and Occlusion studies in regions not impacted by inflation-induced hypoperfusion.

The amount of residual perfusion downstream of the balloon-occluded artery, presumably due to coronary collateral flow, was quantified within the region of hypoperfusion in the following manner. First, the ratio of perfusion between the occlusion study and the control study was calculated. Secondly, the extent of the perfusion defect was identified in an extent map, and the region where the ratio of Occlusion-to-Control counts was less than 75% of tracer uptake was delineated, as previously validated.<sup>15</sup> Residual collateral perfusion, i.e. the perfusion within the perfusion defect in % of the normal perfusion within that same region, was calculated as Occlusion counts divided by Control counts (%). Representative cases are illustrated in Figure 2.

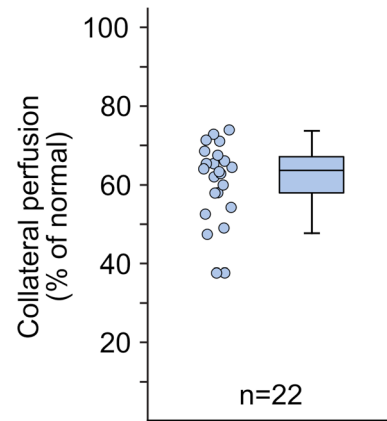
### Statistical Analysis

Non-normally distributed data are presented as median [interquartile range]. Differences between groups were tested using the Wilcoxon test. Linear correlations were described using Spearman's rank correlation coefficient  $\rho$ . A two-sided *P*-value less than 0.05 was considered statistically significant. All



**Figure 2.** Visualization of collateral perfusion to the left ventricular myocardium during elective percutaneous transluminal coronary angioplasty (PTCA) in patients with coronary artery disease. Polar plots show left ventricular (LV) myocardial perfusion by  $^{99m}\text{Tc}$ -sestamibi SPECT. **A** Balloon-occluded right coronary artery. **B** Balloon-occluded left circumflex coronary artery. Images show the myocardial perfusion during balloon occlusion (upper left images within A and B respectively, “Occlusion”), and 24 h later at rest (upper right images within A and B respectively, “Control”). First, the occlusion study was normalized to the control study (see text). A new polar plot was then constructed (lower left images, “Occlusion/Control”) by calculating the ratio between the Occlusion study and the Control study. Based on the new polar plot, a perfusion defect (lower right images, “Perfusion defect”) was defined as the region where the Occlusion/Control ratio was less than 75%<sup>4</sup>. Residual myocardial perfusion, i.e. collateral perfusion, within that defect was quantified as Occlusion counts divided by Control counts, expressed in percent.

statistical analysis was performed using the software R (version 4.0.4, R Core Team, R Foundation for Statistical Computing, Vienna, Austria).



**Figure 3.** Quantification of collateral perfusion to myocardium during elective PTCA in patients with CAD. Box and whiskers plot show the collateral perfusion in all patients ( $n = 22$ , median [interquartile range], 64 [58-67] %).

## RESULTS

The study included 22 patients (age 68 [54-72] years, 10 (45%) female). The degree of diameter stenosis of treated vessels ranged from 60 to 99%, with successful PTCA performed with a mean balloon occlusion time of 5 min (range 3-7 min), resulting in  $\leq 20\%$  residual stenosis in all cases. Ten patients underwent stent implantation as part of the procedure. The vessels undergoing PTCA were 6 (27%) in the left anterior descending artery (LAD) [4 proximal], 7 (32%) in the left circumflex coronary artery (LCx) [5 proximal] and 9 (41%) in the right coronary artery (RCA) [4 proximal].

For the entire cohort, the median extent of the perfusion defect was 19 [11-38] % of the left ventricle. The extent of perfusion defects was larger in patients with LAD occlusion (47 [42-50] %), compared to RCA or LCx occlusion (14<sup>7-22</sup> %),  $P < 0.001$ . The residual collateral perfusion was 64 [58-67] % [Figure 3], 51 [48-54] % in LAD occlusion, and 65 [63-69] % in RCA or LCx occlusion ( $P < 0.001$ ). Collateral perfusion was negatively correlated with perfusion defect size ( $\rho = -0.82$ ,  $P < 0.001$ ), but did not differ by sex (males 62 [54-66] vs females 65 [61-68] %,  $P = 0.34$ ) and was not correlated to age ( $\rho = -0.18$ ,  $P = 0.42$ ).

## DISCUSSION

The main finding of the study was that immediate recruitment of dormant collaterals after balloon occlusion of an epicardial coronary artery results in substantial myocardial perfusion, averaging 64% of normal perfusion. This is the first study to describe the magnitude of short-term changes in collateral perfusion

in human subjects with CAD. A high prevalence of short-term changes in collateral flow was described angiographically by Rentrop, et al., using contralateral contrast injections during balloon inflation, with improvement in angiographic collateral filling grade in all but one patient.<sup>1</sup> However, angiographic visualization of coronary vessels does not necessarily equal myocardial perfusion.<sup>18</sup> We add to the existing knowledge by providing quantification of the myocardial perfusion resulting from coronary collateral recruitment. Our findings are in agreement with previous findings that collateral flow, in some cases, can be enough to prevent short-term ischemia and anginal symptoms.<sup>19</sup>

Although the observation of significant collateral perfusion upon acute coronary occlusion does not provide immediate clinical implications, an understanding of the underlying physiological processes related to acute ischemic heart disease provide an essential foundation for future clinical innovation. This study provides a basis for further research in this area, e.g. regarding how collateral perfusion affects clinical outcomes, what factors affect its magnitude, and how/if different therapies affect the magnitude of collateral perfusion.

### **COLLATERAL CORONARY PERFUSION IN HUMANS**

The magnitude of collateral perfusion in our study was greater than previously described. Collateral perfusion has been evaluated in patients with successfully reperfused STEMI, and found to provide incremental information on final infarct size, beyond myocardium at risk, time to reperfusion, and infarct location.<sup>20</sup> In that study, 89 patients were injected with <sup>99m</sup>Tc-sestamibi prior to revascularization by PTCA or thrombolysis. Collateral myocardial perfusion was estimated by comparing the counts within the perfusion defect to the maximal value within the same short-axis slice, and was found to be approximately 27%, which is less than in our study. Of note, in contrast to our methodology, the authors did not evaluate the collateral perfusion in reference to the normal perfusion within the affected myocardial region, but rather it was compared to remote myocardium in the same slice. Furthermore, that study reported the magnitude of collateral perfusion in a clinical cohort before emergent revascularization, after on average 5 h of acute coronary occlusion and ongoing myocardial infarction. In contrast to the results of that study, the current is the first study to report the magnitude of perfusion in relation to normal perfusion that can be accomplished by collateral vessel recruitment in an immediate (3-5 min) response to coronary occlusion without the confounding pathophysiology of ongoing acute myocardial infarction which involves a

significantly longer duration of coronary occlusion. Our data stems from previous research in which the correlation between ST-segment changes and myocardial ischemia during coronary occlusion was evaluated.<sup>16</sup> Although the severity of ischemia was described in that paper, the current study included patients without visible coronary collaterals only, thus it provides specific insights into recruitment of dormant collateral coronary vessels.

### **COLLATERAL PERFUSION IN ANIMAL MODELS**

By comparison, Reimer, et al., have reported from experimental studies in the dog, that collateral flow decreases over time in coronary occlusion, especially in subendocardial regions.<sup>8,12</sup>

The magnitude of collateral perfusion in humans, as shown in our study, is higher than in animal models.<sup>8-10</sup> Reimer, et al., found variable but consistently lower collateral flow in dogs with a proximally occluded LCx, ranging from 12 to 31% in subendocardial vs. subepicardial layers of the myocardium, in reference to normally perfused myocardium,<sup>8</sup> and even values as low as 6% have been reported.<sup>10</sup> By comparison, the current study found more than twofold greater collateral perfusion in patients with CAD, likely due to a combination of biological differences between species, age, and the presence of CAD.

### **TECHNICAL CONSIDERATIONS**

The current study showed a negative correlation between perfusion defect size and the magnitude of collateral perfusion. In other words, smaller perfusion defects had greater collateral perfusion than larger perfusion defects. Phantom studies have shown that residual activity in perfusion defects is influenced not only by the collateral flow to that region, but also by pixel size, collimator resolution, type of orbit, defect size, and location. With the SPECT technology used in this study, a significant overestimation can be expected in defect sizes < 10%, but the effect is of less importance with larger defect sizes.<sup>21</sup> By excluding those with an extent < 10% the median residual collateral perfusion was still substantial (62%). The difference in the extent of perfusion defects between LAD and RCA or LCx occlusions likely contributes to the observed differences in residual perfusion between different ischemic locations. Taken together, these results suggest that although technical aspects can have influenced the results, there may be a limit to the distance over which collaterals can effectively perfuse into the core of a perfusion defect.

## THE CLINICAL IMPORTANCE OF COLLATERALS

Having robust coronary collateral circulation as visualized by invasive angiography has been associated with clinical benefits, since robust collaterals allow oxygenated blood to reach the jeopardized myocardium.<sup>2,3,22</sup> Patients with robust collaterals presenting with STEMI have a lower mortality in both the short and long term, and higher left ventricular ejection fraction.<sup>3</sup> Furthermore, patients with robust collaterals are more likely to have successful percutaneous coronary intervention to treat chronic total occlusion.<sup>22</sup> Future studies on coronary collateral circulation could incorporate quantification of the myocardial perfusion contributed by collaterals using myocardial perfusion imaging methods.

## Limitations

The data used in this study stem from a study performed during the years 1995-1996. Since then, myocardial perfusion imaging has undergone substantial technical, radiopharmaceutical, and computational advances.<sup>23-28</sup> However, any technical limitation present would have equally affected both the Occlusion and Control study, and not necessarily had a sizable impact on the magnitude of collateral coronary perfusion detected in the current study. Nonetheless, future studies evaluating immediate coronary collateral recruitment, and seeking to replicate the current findings, would be of value, using modern, state-of-the-art imaging techniques.

The access to data from complete epicardial coronary artery balloon occlusion and simultaneous radioactive tracer injection with control imaging in human subjects is unique. If the results are cautiously interpreted, significant knowledge can be gained from these records, despite apparent limitations.

Of note, concluding that the residual perfusion within the perfusion defect can be explained by immediate recruitment of dormant collaterals relies on the hypothesis that the resting perfusion obtained the day after PTCA would equal the perfusion conditions prior to PTCA. Possibly, small collaterals that were not angiographically detectable may have been present. Also, regional overlap of coronary circulation in the border regions of the myocardium may have affected the uptake within the defined perfusion defect, falsely attributing all residual uptake to collateral perfusion. However, this would likely have had a minor impact on the larger perfusion defects, which still showed substantial residual perfusion.

Uptake of <sup>99m</sup>Tc-sestamibi following balloon deflation could potentially falsely increase the estimation of collateral perfusion. However, < 5% of the activity remains in the blood stream at 5 min after intravenous

injection.<sup>29</sup> Since mean balloon inflation time in our study was 5 min, this likely had minimal impact on our results.

Furthermore, contralateral vessel angiography was not performed during balloon inflation in this study. Thus, it is only known that collateral vessels could not be visualized prior to balloon occlusion, but it is not known if collateral vessels could be angiographically visualized during balloon occlusion, which otherwise would be the case for example in the assessment of chronic total coronary occlusion. Regardless, the angiographic visualization of collateral vessels was performed under clinical conditions, and the current results highlight that angiographic visualization under clinical conditions does not visualize a sizable portion of perfusion that can reach myocardium subtended by a given artery should it become occluded. Also, SPECT images were not corrected for attenuation, which may affect accuracy, albeit not substantially,<sup>30</sup> and with minimal impact since the same attenuating properties would be at play during both the Occlusion and Control study.

Some degree of collateral perfusion was present in all patients in this study, but the sample size is small and the study lacks information on detailed clinical characteristics to conclude which factors affect the magnitude of collateral perfusion.

## CONCLUSIONS

This is the first study to quantify myocardial perfusion after immediate collateral recruitment following coronary occlusion in patients with CAD. On average, collaterals provided more than half of normal myocardial perfusion in patients with CAD. Future research on diagnosis and therapy in CAD could consider quantification of collateral perfusion beyond angiographic visualization.

## NEW KNOWLEDGE GAINED

Short-term changes in collateral flow in humans have been described angiographically but the magnitude of myocardial perfusion provided by immediate coronary collateral recruitment during acute occlusion is unknown. In patients with coronary artery disease who underwent complete coronary balloon occlusion collaterals provided more than half of normal myocardial perfusion.

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## Disclosures

All authors have no relevant conflicts of interest.

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