What is the significance of “collateral dependent perfusion”?

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In their study published in this issue of the *Journal*, Sabe and colleagues¹ used their well-established hypercholesterolemic swine model of chronic regional ischemia to investigate the effect of low- and high-dose calpain inhibition 3 weeks after chronic left circumflex coronary artery occlusion. Calpain has been shown to regulate the integration of neovascular networks and cleaves protein targets that regulate cytoskeletal organization, cell adhesion, and cell migration.^{2,3} In mouse models (skin and hypoxic retinopathy), the inhibition of calpain has demonstrated improved neovascular network integration and perfusion (specifically vascular endothelial growth factor–driven pathologic angiogenesis), corrected pathologic neovascularization, and improved functional neovasculature.^{2,3} Sabe and colleagues¹ fed pigs a high-cholesterol diet for 4 weeks, followed by placement of an ameroid constrictor on the left circumflex coronary artery. Three weeks later, low- or high-dose calpain inhibition was administered. Five weeks after drug administration, angiographic assessment of collateral flow by a cardiologist was performed, as well as microvessel reactivity, assessment for capillary density and arteriolar density, assessment of proangiogenic proteins, and assessment of myocardial perfusion with microspheres. Interestingly, Sabe and colleagues¹ found that capillary density and arteriolar counts were increased in the low- and high-dose inhibition groups relative to controls, that there was a significant increase in several proangiogenic proteins in the ischemic myocardium, and that myocardial perfusion ratios were significantly improved in the high-dose inhibition group relative to controls. This work is intriguing and could potentially lead to pharmacologic mechanisms to improve neovascularity in ischemic territories after myocardial infarction in human patients in the future.

These results also raise additional questions for future exploration and experimentation.

Why was there no statistically significant increase in collateral vessel formation on the blinded angiograms? We as heart surgeons would consider this the most clinically relevant finding in such a study. In their Figure 1, Sabe and colleagues¹ noted a “trend,” with an increase seen when comparing low-dose inhibition with high-dose inhibition;

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Central Message

Oral calpain inhibition shows promising early results in chronically ischemic hypercholesterolemic swine model.

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however, the control animals were in the middle, with a *P* value of .34 for the differences between groups. Is 5 weeks long enough to establish collateral vessel formation visible on angiography? Longer term studies would be very interesting. Are the new capillary density and arteriolar count observations enough to be clinically relevant or to prevent ischemia? Ischemia in the territory could be measured and compared with that in controls in future work.

What are the calpain levels over the course of the experiment? Ischemia alone likely increases calpain, which should be increased in all animals (ameroid constriction), and this is presumably harmful. What is the half-life of calpain? Can levels be measured over the course of the experiment? Does pharmacologic inhibition cause a decrease in calpain that is detectable in the animals?

Is there also an increase in capillary density and arteriolar counts in the normal myocardial territories? If so, then this would be an important finding that could be exploited in the future.

What is the ideal dose of the calpain inhibitor and does toxicity exist at high doses? Sabe and colleagues¹ noted conflicting data as some benefits were demonstrated in the low dose group but not the high dose group; whereas other benefits were demonstrated in the high dose but not the low dose group. Dose-response experiments could shed light on these findings.

Finally, what is the mechanism of this upregulation of proangiogenic proteins, capillary density, and arteriolar counts? Sabe and colleagues¹ present a very

exciting and interesting group of observations in hypercholesterolemic swine with chronic myocardial ischemia. These findings could potentially provide mechanisms to increase blood flow to ischemic myocardial territories, which would be profoundly clinically relevant. It is to be hoped that Sabe and colleagues¹ will continue to investigate their findings. Fortunately, many scientific observations such as these often lead to many more hypotheses. In the words of George Bernard Shaw, “Science is always wrong. And science

never solves a problem without raising ten more problems to confront us.”

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