

EDITORIAL COMMENT

## Myocardial Capillaries and Coronary Flow Reserve\*

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The general assumption among cardiologists is that myocardial ischemia occurs only in the presence of obstructive coronary artery disease. This is based on the misconception that abnormal coronary flow reserve (CFR) is associated only with coronary stenosis and results from the increased resistance offered by the stenosis. We showed some time ago that when the normal coronary vasculature is maximally dilated with adenosine, the capillaries (which do not have smooth muscle and hence do not vasodilate) are the bottleneck to hyperemic flow (1). Thus, although the capillaries provide only one-quarter of the total microvascular resistance (MVR) at rest, they offer three-quarters of the total MVR during hyperemia, despite the total MVR decreasing by one-half during hyperemia from arteriolar and venous vasodilation.

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Even in the presence of an epicardial luminal diameter stenosis of <85% to 90% the attenuation of the hyperemic response is due mainly to the capillaries and not the stenosis itself. At rest, the total MVR decreases in the presence of a noncritical stenosis (depending on the degree of stenosis) because of autoregulation, with no change in capillary resistance (1). During hyperemia, the coronary artery pressure distal to the stenosis decreases, leading to capillary derecruitment to maintain a constant capillary hydrostatic pressure (2). Thus, unlike the normal coronary circulation where total MVR decreases during hyperemia, in the presence of a stenosis, it increases (1). In this situation, because arteriolar and venular resistances are already minimal, the increase in MVR is due to increased capillary resistance caused by derecruitment, making it the predominant component of the total MVR.

An individual capillary is approximately 0.5 mm long and 0.7  $\mu\text{m}$  in diameter (3). On the basis of its diameter alone

it offers very high resistance ( $R = 8\eta l/\pi r^4$ , where  $\eta$  = viscosity, and  $l$  and  $r$  are length and radius of the vessel, respectively). Luckily, our 8 million myocardial capillaries are placed in parallel such that total capillary resistance is reduced to an acceptable level. Thus, the normal CFR of 5 would increase if we had more capillaries and decrease if we had fewer capillaries (Online Appendix).

There are many conditions that are associated with reduced myocardial capillary density (MCD) and, hence, lower CFR, such as myocardial infarction (4), hypertension (5), and diabetes (6). In this issue of the *Journal*, Tsagalou et al. (7) describe an association between reduced MCD and CFR in a carefully studied cohort of patients with end-stage idiopathic dilated cardiomyopathy (IDC). In their study, not only was the MCD reduced, but the capillary diameter (D) was also smaller.

Our model (Jayaweera et al. [1], Online Appendix) predicts a relation between MCD and CFR, when capillary D is unchanged, that is shown by the blue line in Figure 1. The green line denotes the expected results if capillary D were reduced from 7 to 5  $\mu\text{m}$ , as noted by Tsagalou et al. (7) in their study. The red line and the regression equation depict the actual relation between MCD and CFR based on the data in Table 2 of their article (depicted as red data points in Fig. 1). Their actual data lie somewhere between the blue and green lines. The scatter shown in their data can be attributed to the imprecision of morphometric measurements of myocardial capillaries in fixed tissue. Shown in Figure 2 is the model-derived relation between MCD, capillary D, and CFR (Jayaweera et al. [1], Online Appendix). Because flow is related to the fourth power of D, a decrease in capillary D affects CFR more than does a decrease in MCD.

Partial exhaustion of autoregulation can also cause a decrease in CFR in IDC for which there are 3 putative mechanisms, all of them based on compensatory vasodilation at rest. First, the decrease in MCD and capillary D result in increased capillary resistance that is compensated by some arteriolar and venular vasodilation to maintain normal resting coronary flow (Online Appendix). Second, increased wall stress in IDC leads to increased myocardial oxygen demand that is met by increased coronary flow via arteriolar and venular vasodilation. Finally, the central aortic (and arterial pressure) may be low in end-stage IDC, which could also cause arteriolar and venular dilation in order to maintain a constant myocardial capillary hydrostatic pressure.

CFR is related to the coronary driving pressure ( $\Delta P$ , difference between mean aortic and right atrial pressures) according to the formula  $\text{CFR} = \Delta P / (Q_r \times R_{\text{min}})$  where  $Q_r$  is resting coronary flow and  $R_{\text{min}}$  is the MVR during hyperemia.  $\Delta P$  may decrease if either aortic pressure decreases or right atrial pressure increases, both of which can occur in IDC. If one plots hyperemic  $\Delta P$  against CFR from the data presented in Table 2 of the article by Tsagalou et al. (7), not unexpectedly, one notices a worsening of the

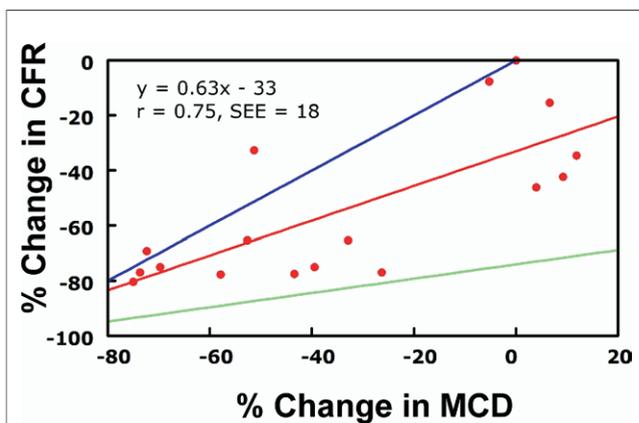
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coronary vasodilatory capacity with decreasing  $\Delta P$ .  $R_{\min}$  might also increase in IDC because of increased extravascular myocardial compressive forces associated with increased wall stress.

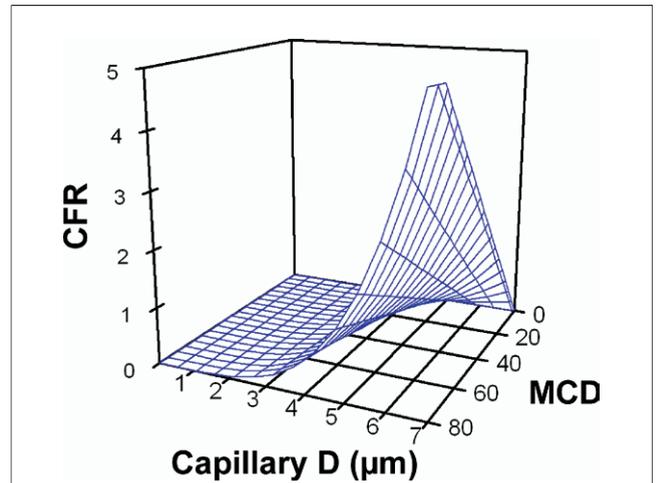
There are other possible reasons for the decrease in CFR as alluded to by Tsagalou et al. (7). Because the capillaries are the bottleneck to hyperemic flow, viscosity becomes very important, primarily because of erythrocyte mobility within the capillaries (8). Erythrocyte diameter is larger than that of the capillaries and therefore erythrocytes have to fold upon themselves in order to pass through capillaries. Factors such as erythrocyte deformability and charge can affect erythrocyte mobility and hence viscosity and CFR (9). Although the authors did not measure blood viscosity and its determinants, it will not be surprising if later studies find alterations in blood viscosity in patients with IDC. The common causes that can affect blood viscosity, such as hematocrit (8) and lipids (10), were not increased in patients with IDC in this study.

Whereas it is not possible to imply causation between reduced CFR and end-stage IDC, one can speculate on a contributing role of reduced CFR in the etiopathogenesis of IDC. Reduced CFR could lead to repeated episodes of ischemia and contribute to the fibrosis that may have been initiated during the primary insult. Ischemia is even more likely to occur in dilated hearts that exhibit increased myocardial oxygen demand because of increased wall stress, contributing to the vicious cycle of left ventricular dilation, poor wall thickening, and increased left ventricular end-diastolic pressure. Finally, the myocardial dyssynchrony often seen in IDC (11) may compromise perfusion in parts of the myocardium that may still be contracting when the aortic valve is closed and coronary filling is occurring.



**Figure 1** Relationship Between Percent Decrease in MCD (X-Axis) and CFR (Y-Axis)

The **blue line** depicts the model-derived relation when capillary diameter (D) is unchanged, and the **green line** depicts the model-derived relation when the capillary D has been reduced from 7 to 5  $\mu\text{m}$ . **Red data points and line fit** (along with the regression equation) denote actual data from Table 2 of the article by Tsagalou et al. (7). See text and Online Appendix for details. CFR = coronary flow reserve; MCD = myocardial capillary density.



**Figure 2** Model-Derived Relation Between Capillary D (X-Axis), MCD (Z-Axis), and CFR (Y-Axis)

See text and Online Appendix for details. Abbreviations as in Figure 1.

In summary, myocardial capillaries are the primary determinant of CFR. There are many cardiac conditions that affect capillary structure and function as well as microvascular rheology. This must be kept in mind when assessing the clinical and prognostic implications of reduced CFR in individual patients. Therapeutic attempts at altering capillary structure, function, and rheology could be beneficial to patients by augmenting CFR (12). It should be remembered, however, that any increase in capillary density should not occur in a haphazard manner. Capillaries must be laid in parallel for them to positively affect CFR.

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**Key Words:** dilated cardiomyopathy ■ microcirculation ■ capillary density ■ flow reserve.

 **APPENDIX**

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**For equations, please see the online version of this article.**