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REVIEW

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The coronary capillary bed and its role in blood flow and oxygen delivery: A review

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Abstract

The assumption that the coronary capillary blood flow is exclusively regulated by precapillary vessels is not supported by recent data. Rather, the complex coronary capillary bed has unique structural and geometric characteristics that invalidate many assumptions regarding red blood cell (RBC) transport, for example, data based on a single capillary or that increases in flow are the result of capillary recruitment. It is now recognized that all coronary capillaries are open and that their variations in flow are due to structural differences, local O_2 demand and delivery, and variations in hematocrit. Recent data reveal that local mechanisms within the capillary bed regulate flow via signaling mechanisms involving RBC signaling and endothelial-associated pericytes that contract and relax in response to humoral and neural signaling. The discovery that pericytes respond to vasoactive signals (e.g., nitric oxide, phenylephrine, and adenosine) underscores the role of these cells in regulating capillary diameter and consequently RBC flux and oxygen delivery. RBCs also affect blood flow by sensing P_{O_2} and releasing nitric oxide to facilitate relaxation of pericytes and a consequential capillary dilation. New data indicate that these signaling mechanisms allow control of blood flow in specific coronary capillaries according to their oxygen requirements. In conclusion, mechanisms in the coronary capillary bed facilitate RBC density and transit time, hematocrit, blood flow and O_2 delivery, factors that decrease capillary heterogeneity. These findings have important clinical implications for myocardial ischemia and infarction, as well as other vascular diseases.

KEYWORDS

coronary circulation, pericytes, oxygen, erythrocytes, endothelium

1 | INTRODUCTION

The primary function of the cardiovascular system is the transportation of oxygen to cells, and "it is in the microcirculation where the final local determinant of oxygen supply, oxygen demand and their regulation are decided" (Pittman, 2013). Coronary blood flow is closely connected to myocardial contraction and is influenced by

metabolic and myogenic autoregulation. Increases in O_2 demand, as occur during exercise, are mostly met by increases in coronary blood flow. Unlike other organs, arterial flow is almost exclusively diastolic, whereas venous flow is predominantly systolic (Chilian & Marcus, 1982), and endo-myocardial flow is more complex than epi-myocardial flow due to the higher surrounding interstitial pressure (Fibich et al., 1993). Since the coronary capillary flow is heterogeneous, oxygen diffusion in the microcirculation needs to be considered because it is likely the primary determinant when the flow is impaired (reviewed by Zuurbier et al., 1999).

Because the capillary network is the final pathway for oxygen delivery to cardiomyocytes, understanding the regulation of this pathway may explain the heterogeneities in red blood cell (RBC) fluxes and oxygen supply. Recent evidence reveals an active role for capillaries in regional dilation and constriction, which affects blood flow, RBC density distribution and velocity, and consequently oxygen delivery (Clavica et al., 2016; Lee et al., 2021; Schmid et al., 2015; Špiranec et al., 2018; Zhao et al., 2020).

A greater O_2 extraction for a given level of arterial flow can be achieved by an increase in the arteriolar content of O_2, which is the product of hemoglobin concentration and O_2 saturation, and a small amount dissolved in the plasma. Other important considerations are erythrocyte transit time in the capillaries, hematocrit, the geometry and density of the capillary bed, and the heterogeneity of capillary perfusion. O_2 delivery in the myocardial capillary bed is more complex than in most other organs, because of the effects of extravascular forces and high O_2 demand. This review addresses the roles of structural and functional components of the coronary capillary bed and presents recent evidence that the coronary capillaries play a regulatory role in their regional blood flow and O_2 delivery to the cardiomyocyte.

2 | CAPILLARY MORPHOLOGY AND GEOMETRY

Myocardial blood flow and oxygen delivery are facilitated by the morphology, geometry, and organization of the capillary bed. Accordingly, these characteristics are closely linked to our understanding the physiology and mechanics of the capillary circulation and are discussed in this section of the review.

2.1 | Morphometric characteristics

Because of its dependence on aerobic metabolism and its high metabolic demand, the myocardium is characterized by a very extensive capillary network, a topic reviewed by Tomanek (2013, pp 73–74), and several morphometric parameters that provide insights into capillary functional parameters. Capillary length density (L_V), rather than numerical density (N_V), is the best quantitative measure of the capillary bed (Tomanek et al., 1991). Capillary diameter and volume density (V_v) are morphological parameters related to capillary perfusion, while surface density (S_v) is a key parameter for oxygen delivery. Extracellular regions between capillaries and cardiomyocytes seen in micrographs are usually artifacts associated with tissue processing. Capillaries abut cardiomyocytes and often indent into cardiomyocytes (Figure 1a,b). By indenting into the surface of a cardiomyocyte, the size of a capillary domain (the region of cardiomyocytes that receives O_2 from a capillary) is reduced. This feature is an adaptation most notable in hearts exposed to chronic hypoxia (Lund & Tomanek, 1980).

2.2 | Organization of the capillary bed

As seen in Figures 1c,d, collateral branches in the coronary capillary bed are common and affect the flow and hematocrit distribution, as discussed subsequently in this review. A critical organizational feature of the capillary channels is that no cardiomyocyte is devoid of an arteriolar portion (relatively O_2-rich) adjacent capillary. This arrangement, illustrated in Figure 2, indicates that at any given level of a cardiomyocyte both venular and arteriolar portions of capillaries are present, an arrangement that facilitates a more even O_2 availability for each cardiomyocyte. A second, compensatory structural feature for minimizing the longitudinal variation in capillary P_{O_2} is that the capillary network of venous capillaries is denser than their arterial counterparts, and therefore facilitates a more homogeneous tissue oxygenation (Batra et al., 1989; Lücker et al., 2015; Rakusan et al., 1997). These data suggest that such a structural arrangement in microvascular design theoretically provides improved geometrical conditions.

2.3 | Structural complexity of the capillary bed and heterogeneity of capillary spacing and perfusion

Heterogeneity of blood flow and myocardial oxygenation are consequences of capillary spacing heterogeneity (Hoofd et al., 1987; Rakusan & Turek, 1985), as well as the heterogeneities of RBC distribution and O_2 supply, all of which "leads to heterogeneity in microvascular perfusion and unique hemodynamic effects" (Goldman (2008).

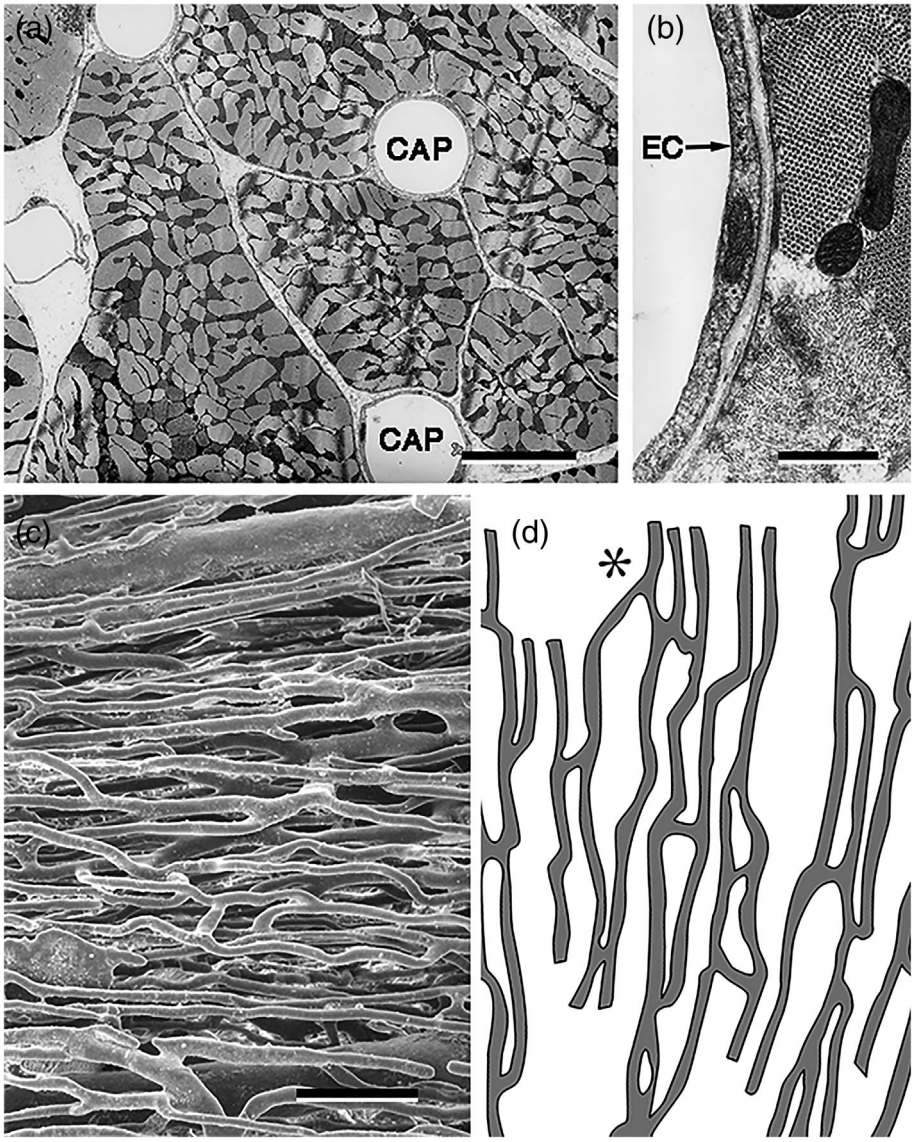

FIGURE 1 Myocardial capillaries in electron micrographs (a,b) reveal capillary (CAP) endothelial cells (EC) abutting the sarcolemma of cardiomyocytes (canine heart). A capillary network seen in a rat ventricle is displayed by the coronary cast technique after digestion of all tissue (c). Note the branching and anastomoses of the network, which is provided in tracings of selective portions of the cast (d); multiple anastomoses are seen at the asterisk. The bar length represents 10 μm in a, 0.5 μm in b and 50 μm in c

Moreover, the myocardial capillary bed is characterized by segments with bifurcations and anastomoses (Figure 1c,d), an architecture that significantly affects hemodynamics and perfusion, including flow velocity, RBC distribution, shear rate, and partial oxygen pressure (Pries & Secomb, 2003).

2.4 | Increased blood flow is not a consequence of capillary recruitment

The assumption that all capillaries in the heart are not perfused during resting conditions was originally based on rat heart experiments that identified open capillaries on the basis the presence of an RBC (Bourdeau-Martini et al., 1974; Henquell & Honig, 1976; Korecky et al., 1982), and led to the conclusion that inter-capillary distances decreased when O_2 demand increased during hypoxia and increased when O_2 demand decreased during hyperoxemia. Because intracapillary spacing between RBCs (termed plasma gaps) varies considerably with one-third of the gaps exceeding 5 μm (Honig et al., 1989), the distribution variability is now well accepted (Schmid et al., 2015) and the absence of an RBC in a capillary cross-section does not signify a flow-free channel. Indeed, by using fluorochromes to study perfusion in hearts during rest and during hypoxia, Vetterlein et al. (1982), established that, although plasma passage is inhomogeneous, (1) all capillaries are labeled within 5 s, and (2) hypoxia did not increase the number of perfused capillaries containing the label. Moreover, rodent studies (Vetterlein et al., 1989; Vetterlein & Schmidt, 1984) provided data documenting that increases in coronary blood flow in response to epinephrine or hypoxia caused elongation of cardiomyocytes and thereby increased the numerical density of both cardiomyocytes, but not their numerical ratio. Thus, the decrease in cardiomyocyte

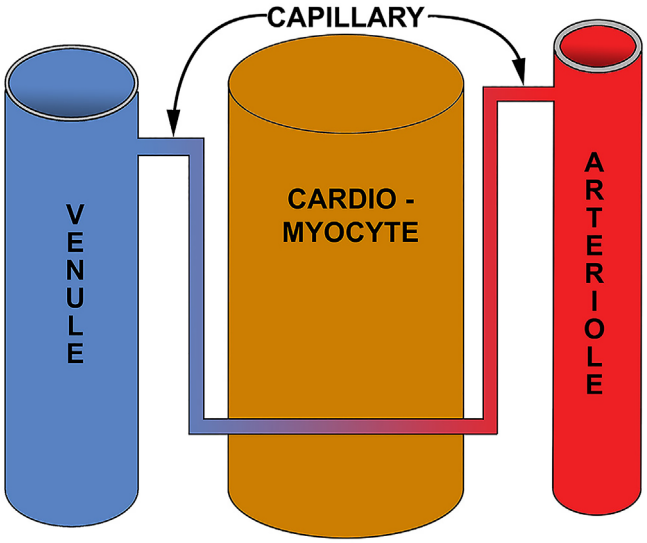

FIGURE 2 Venular and arteriolar capillary segments are staggered along the length of a cardiomyocyte providing a more optimal level of oxygen. As illustrated here, both types of segments are seen along the side of the cardiomyocyte

diameters decreased the distances between capillaries. Their work also documented that the number of capillaries (revealed by basement membrane labeling) and the number of perfused capillaries (fluorescein plasma labeling) were identical. Moreover, even a seven-fold increase in coronary flow of the canine heart did not result in the recruitment of additional capillaries (Eliasen & Amtorp, 1985a), which further supports the conclusion that increases in myocardial capillary perfusion are not a consequence of capillary recruitment.

2.5 | Capillary bifurcations

Capillary RBC heterogeneity and flow distribution are due, in large part, to a nonuniform partitioning or "phase separation" of RBCs at bifurcations of the network (Klitzman & Johnson, 1982). Moreover, the RBC decrease at bifurcations is more pronounced as the angle of the bifurcation increases (McHedlishvili & Varazashvili, 1982). The importance of bifurcation angle and daughter vessel diameter in the distribution of RBCs has been documented by data indicating that more RBCs tend to enter the high flow ratio daughter branch, whereas the low flow branch tends to draw a higher proportion of plasma (Hyakutake & Nagai, 2015; Secomb, 2016). These data illustrate how structural factors contribute to heterogeneity of RBCs in the microcirculation (Figure 3).

The recognition that capillary flow, although variable, does not cease in coronary capillaries, indicates that attention can now focus on the mechanisms within the capillary bed that regulate flow and cardiomyocyte oxygenation. As detailed in this review, these mechanisms facilitate increases in hematocrit, blood flow, and blood flow homogenization (Angleys & Østergaard, 2020; Østergaard, 2020). Even in skeletal muscle, noted a decade ago, a longitudinal RBC flux, rather than capillary recruitment is the major factor in meeting O_2 demand (Poole et al., 2011).

3 | CAPILLARY REGULATION OF BLOOD FLOW AND OXYGEN EXTRACTION

Since the length density of capillaries in the heart is more than 100 units greater than arterioles, as documented in animal models (Chen et al., 1994; Dedkov et al., 2014; Lamping et al., 2005; Wang et al., 2003), and humans (Dedkov et al., 2006), cardiomyocytes are nearly totally dependent on oxygen derived from capillaries. It is well known that capillaries function in coupling blood flow and muscle metabolism (Murrant & Sarelius, 2000), a coupling that occurs by not one, but several mechanisms, as described in this review. Although coronary capillaries do not close, they display vasomotion in response to vasoactive substances via their closely associated contractile pericytes, a process that only recently has been recognized.

3.1 | Capillary transit time, diameter, and hematocrit

3.1.1 | RBC capillary transit time is a major determinant of O_2 delivery

As noted in canine hearts, a large transient time heterogeneity becomes homogeneous only during maximal vasodilation (Rose & Goresky, 1976), and the time spent by RBCs traversing the microcirculation in rabbit hearts is a major determinant of O_2 transport to cardiomyocytes (Allard et al., 1993). Moreover, experiments in closed-chest dogs revealed that cardiac metabolic activation prolonged capillary RBC transit times and thereby decreased their heterogeneity (Cousineau et al., 1983). Normal cardiac function depends on the balance between O_2 supply and demand, and this balance is regulated in large part by capillary transit time (Østergaard et al., 2014; Østergaard (2020). To affect capillary flow homogeneity and adequate tissue oxygen, high blood flow must be accompanied by a decrease in transit time heterogeneity. Thus, the distribution of capillary transit times is a major determinant of the extraction of diffusible substances and

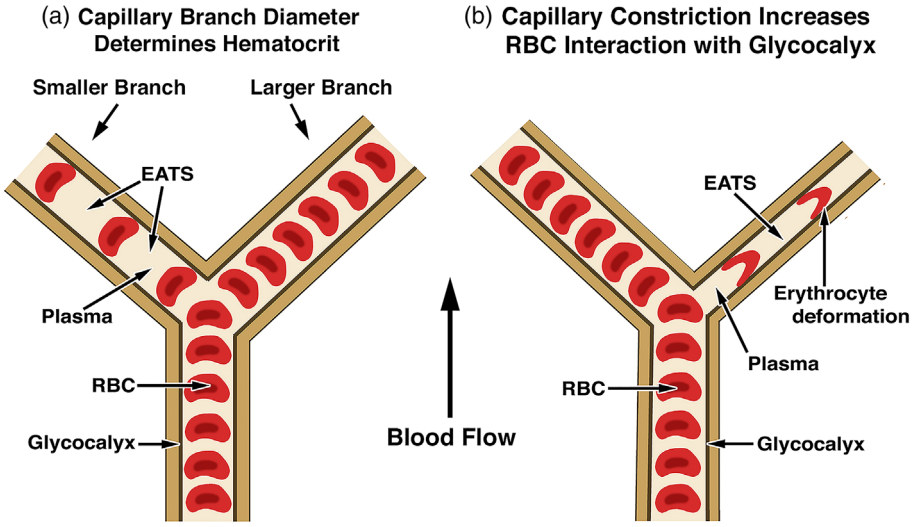

FIGURE 3 The effect of capillary diameter on red blood cell (RBC) spacing is a determinant of hematocrit. As seen in (a) the smaller (left) branch has a lower hematocrit due to more plasma between RBCs known as erythrocyte associated transients (EATS), which theoretically indicates lower P_{O_2} gradients between RBCs. As seen in B, a reduction in capillary diameter via constriction (right branch) that is sufficient to cause RBC deformation, enhances RBC interaction with the glycocalyx of the endothelium and activates mechanical stresses that act on RBCs. The glycocalyx–RBC interaction enhances RBC deformability and oxygen release, a mechanism that compensates, in part, for the lower hematocrit due to fewer RBCs per unit capillary length

indicates that a single capillary transit time is not representative of the whole. This finding underscores the significance of longer myocardial transit times and higher O_2 extraction levels with lower blood flow and higher vascular resistance in highly trained athletes (Heinonen et al., 2014).

3.1.2 | Role of capillary diameter in perfusion

In vitro experiments, utilizing models of cerebral microvascular networks, suggest that capillary dilation causes increases in RBC line density and residency time in the dilated segment of the network, and thus, facilitates a greater oxygen supply to the corresponding tissue (Clavica et al., 2016). Moreover, a significant dilatory response of canine epicardial coronary capillaries occurs during reactive hyperemia (Kiyooka et al., 2005). Thus, the larger capillary diameter facilitates a greater volume of blood flow through the capillary and thereby increases O_2 delivery (Korpisalo et al., 2011).

3.1.3 | Microvascular hematocrit

An increase in RBC density is associated with a higher hematocrit and consequently a better O_2 delivery/consumption, as occurs in men adapted to high altitude (Grover, 1973). They were found to have a 30% increase in O_2 extraction from coronary blood, associated with a higher RBC volume, compared to a sea-level control group. The fact that in the distal portions of coronary capillaries, the distances between RBCs is decreased provides a compensatory mechanism for minimizing the drop in VO_2 (Silverman & Rakusan, 1996). In dogs, the importance of hematocrit distal to a coronary artery with a decreased blood flow revealed that both hematocrit and oxygen delivery to the myocardium in the stenotic distal artery was lower than control values and was accompanied by an increase in the fraction of plasma volume (Eliasen & Amtorp, 1985b). Moreover, graded coronary stenosis in the porcine left ventricle caused a progressively heterogeneous mismatch of regional O_2 delivery/consumption (Alders et al., 2015). These findings indicate that during ischemia the myocardium suffers the consequences not only a diminished blood supply, but also is perfused with blood containing a smaller number of RBCs, and therefore has a lowered oxygen delivery capacity.

3.1.4 | RBC distribution, properties, and signaling

About half of the resistance to O_2 transfer occurs in the capillaries (Hellums, 1977), and the critical maximum distance between RBCs is four-cell lengths, whereas RBC

separation distance cannot exceed one cell length during maximal O_2 consumption (Federspiel & Sarelius, 1984). P_{O_2} gradients between RBCs are manifested as rapid P_{O_2} fluctuations or EATs. However, mechanisms in the microvasculature that increase O_2 release from RBCs have been shown to compensate for the drop in P_{O_2} associated with hemodilution (Barker et al., 2007). Although O_2 supply in the vasculature is influenced by the unequal partition of flow and RBC distributions, capillary dilation and constriction provide a mechanism that can alter the distribution of RBCs locally and thus regulate O_2 delivery (Schmid et al., 2015). Adaptations to hypoxia include an increase in hemoglobin–oxygen (Hb–O_2) affinity, which has been shown to enhance O_2 delivery to hypoxic regions in the heart and brain (Yalcin & Cabrales, 2012). A recent review of the topic concluded that "high Hb–O_2 affinity is a potentially advantageous adaptation to high altitude in several animal species" and that high Hb–O_2 affinity in humans is associated with a smaller increase in heart rate during exercise and a higher arterial O_2 saturation at rest (Webb et al., 2022). Low-oxygen tensions in hypoxic tissues are sensed by RBCs and they subsequently release signaling molecules (e.g., nitric oxide and ATP) that affect changes in blood flow (Richardson et al., 2020). The authors proposed that the deformation of RBCs, as occurs in response to shear stress and cell deformation, facilitates the release of the vasoactive molecules, a view consistent with the finding that erythrocyte flexibility (deformability) facilitates microvascular P_{O_2}, and O_2 uploading in the lungs and downloading in tissues (Cabrales, 2007).

3.1.5 | Capillary endothelial cell glycocalyx in blood flow regulation

The seminal observation by Luft (1966) of a coating on luminal endothelial surfaces that has a high affinity for acidic mucopolysaccharides and constitutes a glycocalyx opened the door for investigations regarding its role in capillary perfusion **(**Figure 3**)**. A review of the mechanical and biochemical properties of the glycocalyx indicates that this luminal surface layer undergoes deformation from fluid shear stress and transduces the fluid shear stress into the intracellular cytoskeleton of endothelial cells (Weinbaum et al., 2007; Zhou et al., 2014). Moreover, the glycocalyx interacts with red blood cells and functions in the regulation of blood flow and oxygen transport in capillaries (Pries et al., 2000), by modulating RBC motion (Damiano, 1998) and thereby enables a more homogeneous blood flow (McClatchey et al., 2016). As illustrated in Figure 3b, the mechanical stimulation by the capillary wall enhances the RBC's flexibility facilitating its passage through the narrow capillary segment by activating mechano-sensitive channels, most likely the non-selective Piezo 1 channel (Danielczok et al., 2017). Activation of the channel results in a loss water and a shrinking of the RBC.

3.2 | Capillary blood flow and oxygen heterogeneity

As discussed in a recent review (Premont et al., 2020), oxygen supply to tissues in the microvasculature involves a complex interplay between hemoglobin, oxygen, carbon dioxide, and nitric oxide (three gas respiratory cycle). Both oxygen consumption and local blood flow in the myocardium are heterogeneous, as documented in dogs (Loncar et al., 1998) and rabbits (Schwanke et al., 2000). These studies indicate that when inflow is unrestricted, O_2 supply to low-flow regions meets metabolic demand, whereas high-flow regions reflect a high O_2 demand. As oxygen sensors, RBCs can regulate vascular tone by releasing ATP, which stimulates the synthesis and release of multiple endothelial cell vasodilators (reviewed in Ellsworth et al., 2009). Nearly, four decades ago, Cousineau et al. (1983) increased oxygen consumption and coronary flow in dogs by coronary sinus pacing and found that capillary heterogeneity, characteristic of the control dogs, declined substantially, while capillary permeability-surface product (a measure of the area available for O_2 diffusion) increased. They concluded that these two factors amplify the capacity of increased flow to deliver substrates to muscle.

3.2.1 | Signals from RBCs regulate blood flow and oxygen delivery

By sensing physiological oxygen and facilitating vasoconstriction under high P_{O_2} and vasodilation under low P_{O_2}, RBCs play a key role in microvascular blood flow (Ellsworth et al., 1995). Thus, erythrocyte signaling provides for an increase in O_2 delivery to a local area in need. One mechanism by which heterogeneity of blood flow in capillaries may be reduced is by release of ATP from RBCs in response to low P_{O_2}, which in hamster cheek pouch muscle has been shown to increase capillary RBC supply by 31% and 81% in the arteriolar and venular portions of capillaries respectively (Ellsworth et al., 1995). In addition to increasing the number of RBCs in capillaries, the nitric oxide produced by RBCs inhibits cell adhesion and increases RBC deformability,

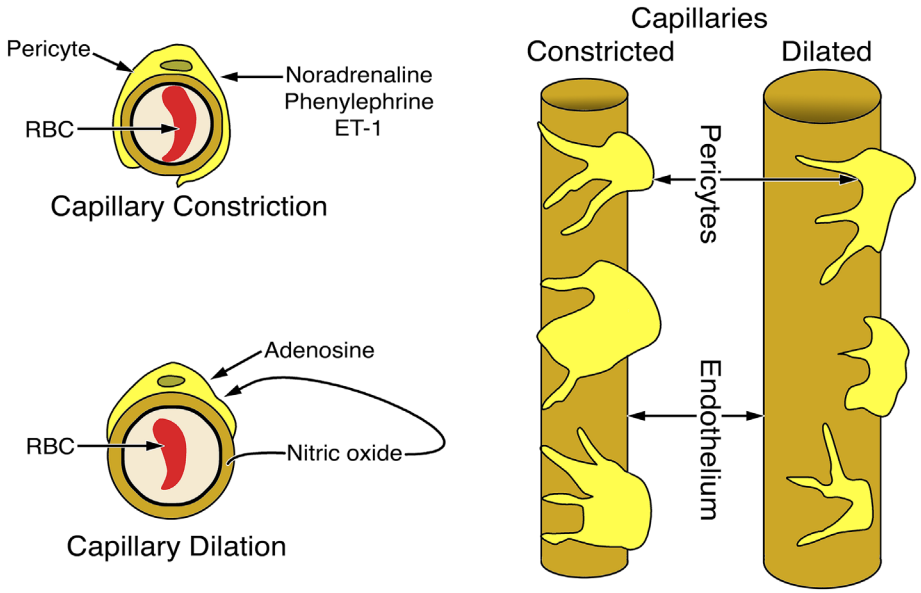

FIGURE 4 Pericytes (contractile cells) on the abluminal surface of endothelium play a key role in regulating the diameters of capillary segments, as they have receptors for vasoactive molecules. Capillary constriction occurs when pericyte calcium levels increase via vasoactive substances, such as noradrenaline, phenylephrine, or endothelin-1 (ET-1). In contrast, capillary dilation occurs when calcium levels fall in response to adenosine or nitric oxide. Note the less extensive distribution of pericyte processes in the dilated capillary

factors which promote blood flow in capillaries (reviewed by Simmonds et al., 2014). Activation of RBC nitric oxide facilitates deformability of RBCs, as evidenced by data that documented impaired RBC deformability when the RBC proteins were modified (Grau et al., 2013; Zhao et al., 2018). Moreover, RBC release of nitric oxide from a coronary capillary facilitates local oxygen delivery during hypoxia (Zhao et al., 2018), which can occur by two pathways, that is, one that facilitates Hb releasing O_2 or the other that improves RCB deformability (Premont et al., 2020).

3.2.2 | Capillary outflow saturation heterogeneity

Because P_{O_2} distribution at the ends of capillaries is a key determinant of tissue oxygenation, its heterogeneity indicates the oxygen supply to tissue regions most vulnerable to hypoxia (Lücker, Secomb, Barrett, et al., 2018). However, data from mouse somatosensory cortex revealed that the diffusive O_2 exchange among capillaries (diffusive interaction), that is, oxygen provided by adjacent capillaries, significantly reduces capillary outflow saturation interaction heterogeneity (Lücker, Secomb, Weber, & Jenny, 2018. This finding indicates that "diffusive interaction contributes greatly to the microcirculation's ability to achieve tissue oxygenation despite heterogeneous capillary transit time and hematocrit distribution." Such an adaptation allows the microcirculation to achieve adequate tissue oxygenation despite heterogeneous capillary transit time and hematocrit distribution.

4 | PERICYTES REGULATE CAPILLARY BLOOD FLOW

4.1 | Pericytes are contractile cells

As illustrated in Figure 4, pericytes lie within the basal lamina of capillaries where their numerous extensions encircle the endothelium and regulate capillary diameter. As demonstrated in artificial networks, capillary dilation/constriction constitutes a mechanism for altering RBC distribution and consequently the local regulation of O_2 (Schmid et al., 2015). Contractile activity of pericytes is controlled by changes in cytosolic free Ca^{2+} concentration (reviewed in Burdyga & Borysova, 2018), and their morphology and function has recently been detailed (Alarcon-Martinez et al., 2021). That capillary pericytes contract and relax in response to neural or humoral stimuli and regulate regional flow within the capillary bed is well documented (Almaça et al., 2018; Hall et al., 2014; Hamilton et al., 2010; Methner et al., 2019; Špiranec et al., 2018). Endothelial cell-derived agents, such as endothelin-1, thromboxane A_2, and angiotensin II trigger constriction (reviewed by Hamilton et al., 2010), whereas nitric oxide and adenosine, two major vasodilators of capillaries, facilitate pericyte relaxation by increasing K^+ (Hamilton et al., 2010). As documented in rat brain, capillary dilatation occurs in response to prostaglandin E_2 via its EP_4 receptor (Hall et al., 2014. Taken together, these studies, which focused on various circulations (brain, pancreas, leg, and cremaster muscle) indicate that pericytes are major regulators of capillary regional blood flow, as well as RBC transit time, and O_2 delivery.

4.2 | Pericytes modulate local capillary blood flow

Pericytes modulate capillary diameter in response to neuronal activity and are sensitive to damage during pathological insults, such as ischemia, Alzheimer disease, and diabetic retinopathy (reviewed by Hamilton et al., 2010). Capillary dilation, as occurs by nitric oxide inhibition of pericyte constriction, is a major determinant of capillary blood flow (Hall et al., 2014). Brain capillaries dilate before arterioles and are estimated to produce 84% of the increase in blood flow. Similar data, from pancreatic islets, revealed that adenosine is the mediator of capillary dilation (Almaça et al., 2018). Endothelial C-type natriuretic peptide has been shown to regulate microcirculatory flow in mouse cremaster muscle and retina by affecting two pericyte pathways: (a) activation of cGMP-dependent protein kinase I to activate downstream vasodilators and (b) inhibition of cAMP levels that increase pericyte calcium (Špiranec et al., 2018). Ca^{2+} mediates pericyte constriction, whereas K^+ mediates pericyte relaxation (Gonzales et al., 2020). The elevation of pericyte Ca^{2+} that occurs during ischemia in mice retinas persists after recanalization (Alarcon-Martinez et al., 2019), and thereby prolongs the ischemic period. Subsequent work from their laboratory (Alarcon-Martinez et al., 2020) documented the presence of nanotube-like pericyte processes that form a functional network on capillaries connected by gap junctions and serve as conduits for intercellular Ca^{2+} waves. The network is not limited to single capillaries but extends to adjacent ones. Using a model of mouse skeletal muscle hyperemia following femoral artery constriction, the role of pericytes in capillary constriction was addressed (Methner et al., 2019). In transgenic mice with partial pericyte depletion, the number of capillary segments that constricted was only 14% compared to a 33% capillary segment number in wild-type littermate controls. These data support selective flow regulation in the capillary bed, via diameter changes and implicate pericytes as key mediators that facilitate metabolic demand with capillary blood flow in several organs, especially skeletal muscle (reviewed by Attrill et al., 2020).

4.3 | Cardiac pericytes

Recent evidence documents the abundance of pericytes (Figure 4) in the heart where they perform tissue-specific functions (Lee et al., 2021; Lee & Chintalgattu, 2019). Their position within the basement membranes of endothelial cells underscores a system of intimate communication that is a prerequisite for "conducted vasodilation," that is, rapid transmission of electronic dilation signals within the microvasculature (Lee & Chintalgattu, 2019; Nees, Weiss, & Juchem, 2013; Nees, Weiss, Partsch, & Juchem, 2013). Pericytes are also important for endothelial integrity, as a decrease in their number causes a decrease in coronary flow (Lee & Chintalgattu, 2019). Their role in the no-reflow phenomenon, that occurs after coronary ischemia and reperfusion, was shown to be the result of pericyte constriction of capillaries and was associated with a 37% reduction in capillary diameter in the affected region where pericytes were present on the capillary wall (O'Farrell et al., 2017). Administration of the pericyte relaxant adenosine increased capillary diameter by 21% and perfusion volume by 57%. Because of its clinical significance, that is, ischemia and infarct expansion, the role of pericytes in the no-reflow phenomenon in the microcirculation, and especially the capillary bed, deserves attention (Costa et al., 2018).

Most recently, Lee et al., 2021) documented the cardiac pericyte cell's role in capillary constriction and dilation under normal physiological conditions. They established that cardiac pericytes express α-adrenergic activation of calcium flux for contraction, and contract in response to phenylephrine via the alpha-adrenergic activation pathway proteins and relax in response to adenosine and nitric oxide. Cardiac pericytes are the second most nonmyocyte cell in the heart and communicate with endothelial cells via their specialized intracellular junctions which link the two cell types (Su et al., 2021). Pericyte motility is influenced by several cytokines from endothelial cells. A feedback mechanism for restoring ATP levels in cardiomyocytes has been documented in a model of mouse papillary muscle (Zhao et al., 2020), and is illustrated in Figure 5. When ATP consumption exceeds its production, openings in K_{ATP} channels are increased and cardiomyocytes are electrically biased toward hyperpolarization, which triggers relative hyperpolarization of electrically connected cells, namely capillary endothelial cells and pericytes, as well as smooth muscle cells. The consequential drop in Ca^{2+} in these cells facilitates an increase in microvascular blood flow. Opening of K_{ATP} channels by pinocidil and activation of "electro-metabolic signaling" revealed that capillaries and small arterioles dilate via relaxation of pericytes and smooth muscle cells. This recently discovered system explains how cardiomyocyte ATP can be rapidly restored by increased blood flow in the microcirculation. Noteworthy is the fact that the inner mitochondrial membrane of cardiomyocytes contains several K^+ channel types including those that are ATP-sensitive and voltage-regulated (Kulawiak et al., 2021).

Taken together, the data reveal a major role for capillary dilation in the enhancement of blood flow, and a

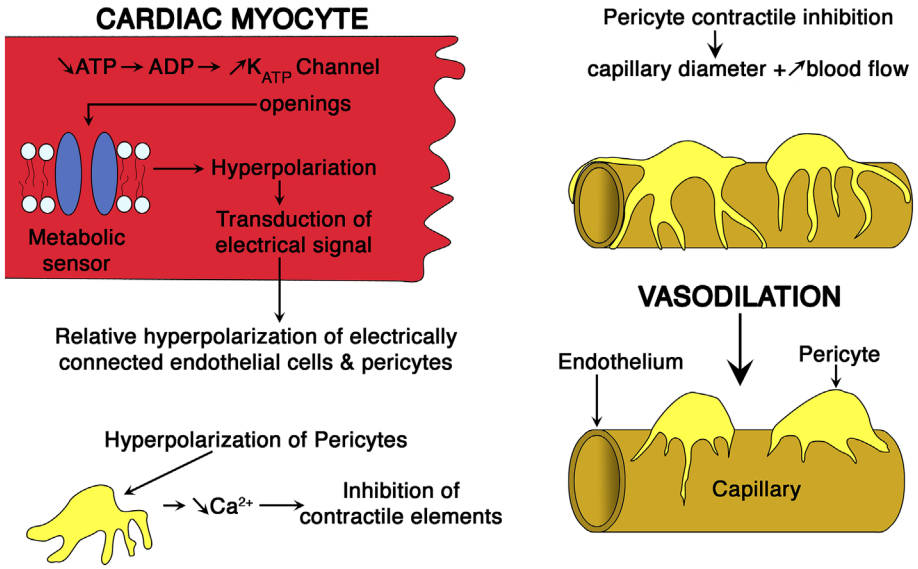

FIGURE 5 Cardiomyocyte electrical signaling regulates capillary blood flow. When cardiomyocyte ATP consumption exceeds its production, K_{ATP} openings increase, resulting in hyperpolarization of the cell. This hyperpolarization affects a relative hyperpolarization of pericytes and endothelial cells, which are adjacent to the cardiac myocardial cell, causing a drop in pericyte Ca^{2+} levels and consequently inhibition of contraction (details published by Zhao et al., 2020). As seen in the right side of the figure the extent of a capillary covered by pericytes increases or decreases substantially during constriction and dilation, respectively

more homogeneous flow distribution. Therefore, the regulation of blood perfusion and oxygen delivery by capillaries via constriction and relaxation of the pericyte cells that surround their endothelial walls is independent of arterioles. This close arrangement of the two cell types facilitates control of blood flow within small segments of a capillary bed in response to local metabolic requirements. These data support the concept that pericytes regulate flow in daughter branches by controlling the static symmetry of capillary junctions. Pericyte relaxation and the consequential increase in flow in a segment of the capillary bed diminishes resistance to flow and enhances flow homogeneity, thereby contributing to an increase in total flow of the capillary bed. This is of importance, as noted previously, because about half of the resistance to O_2 occurs in the capillary bed (Hellums, 1977). Dynamic measurements of the microcirculation and its perfusion are now possible with the development of state-of-the-art optic imaging systems (Zhao et al., 2020) and may provide insights into the role of pericytes in therapeutic approaches for diseases, for example, ischemia and infarction, stroke, diabetes Alzheimer's and various neurological diseases (Cheng et al., 2018; Hartmann et al., 2021; Nortley et al., 2019).

5 | SUMMARY/CONCLUSION

The first portion of this review addressed the structural and geometric characteristics of the coronary capillary bed, with attention to its organization, spacing, unique distribution (staggered arrangement of the arteriolar and venular capillary segments, indentation of capillaries on myocyte surfaces, diameter variations), and how these characteristics affect perfusion and oxygen delivery. The complexities of this network indicate that many assumptions regarding RBC transport through capillaries are not valid, for example, assumptions based on a single capillary and the idea that increased flow through the capillary bed is accomplished by capillary recruitment. Moreover, and of major importance, is the evidence from recent studies that flow within capillaries is not limited to regulation by arterioles. Thus, numerous recent findings, contradict the notion that the cluster of endothelial-lined channels is a passive system solely dependent on the forces of precapillary vessels.

Accordingly, emerging data reveal that there exist signaling mechanisms that allow control of blood flow in specific segments of the myocardial capillary bed, and even in individual capillaries. These mechanisms regulate the contractile elements of pericytes and control regional capillary flow when they are stimulated or inhibited, thereby decreasing or increasing capillary diameter. Signals for these responses come from several molecules, which work by activating or inhibiting Ca^{2+} Cardiac pericytes contract in response to several vasoactive substances including phenylephrine, noradrenaline, endotelin-1 and angiotensin II, and relax in response to nitric oxide and adenosine. Increases in capillary diameter, as occurs during adenosine activation, increases RBC density, hematocrit, and transit time, factors that facilitate oxygen delivery. Flow regulation is also a function of oxygen sensing RBCs and their signals, which activate or inhibit pericyte contraction and thereby activate contraction or relaxation. Moreover, the release of O_2 from hemoglobin is facilitated by the sensing of hypoxia by RBCs.

In conclusion, blood flow and oxygen delivery are influenced by regulatory mechanisms within coronary

capillaries, as well as those in arterioles. These mechanisms facilitate increases in RBC density and transit time, hematocrit, blood flow and O_2 delivery. They enable local capillary regulation as a means of increasing flow homogeneity. Moreover, the recent data indicate that local regulation by capillaries has important clinical implications for myocardial ischemia and infarction, as well as other clinical entities. Taken together the scientific evidence noted in this review indicates that regulation of the coronary microcirculation includes numerous mechanisms within the capillary channels that are independent of the precapillary vessels. Accordingly, a greater research emphasis on the coronary capillary network is indicated.

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