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The role of pericytes in hyperemia-induced capillary de-recruitment following stenosis

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Abstract

Purpose: The microvascular capillary network is ensheathed by cells called pericytes - a heterogeneous population of mural cells derived from multiple lineages. Pericytes play a multifaceted role in the body, including in vascular structure and permeability, regulation of local blood flow, immune and wound healing functions, induction of angiogenesis, and generation of various progenitor cells. Here, we consider the role of pericytes in capillary de-recruitment, a pathophysiologic phenomenon that is observed following hyperemic stimuli in the presence of a stenosis and attenuates the hyperemic response.

Recent Findings: We discuss recent observations that conclusively demonstrate pericytes to be the cellular structures that contract in response to hyperemic stimuli when an upstream arterial stenosis is present. This response constricts capillaries, which is likely aimed at maintaining capillary hydrostatic pressure, an important factor in tissue homeostasis. Nonetheless, the ensuing attenuation of the hyperemic response can lead to a decrease in energy supply and negatively impact tissue health.

Summary: Therapeutics aimed at preventing pericyte-mediated capillary de-recruitment may prove beneficial in conditions such as coronary stenosis and peripheral arterial disease by reducing restriction in hyperemic flow. Identification of the pericyte subtypes involved in this de-recruitment and the underlying molecular mechanisms regulating this process will greatly assist this purpose.

Keywords

pericyte; arterial stenosis; microvascular blood flow; capillary; capillary de-recruitment; myocardial ischemia; coronary stenosis; peripheral arterial disease

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Introduction

The principles of tissue homeostatis were defined by Starling in 1896 and were further refined over the years [1]. The four starling forces that govern tissue fluid homeostasis are the hydrostatic and oncotic pressures in the capillary and interstitium, respectively, and their balance defines net fluid filtration as well as cell size. Of these forces, the one most likely to fluctuate acutely is the capillary hydrostatic pressure (CHP) because it can be influenced by systemic pressure. In order to maintain a constant CHP at a mean of about 30 mmHg, the upstream resistance arterioles, 100–300 μm in diameter, change their tone in response to aortic pressure. Thus, they dilate when aortic pressure falls and constrict when the aortic pressure rises, in order to maintain constant CHP and blood flow, a phenomenon termed autoregulation [2, 3]. This phenomenon is noted in all vital organs, including the heart, and serves to maintain constant pressure within capillaries. In conditions of hyperemia under stenosis, this drive to maintain CHP results in attenuation of hyperemic blood flow. This review focuses on what is known about the cellular structures that control capillary contractility and hence CHP, namely pericytes, and points towards future research directions necessary to better understand the molecular mechanisms regulating this process with a view towards developing therapeutics for conditions featuring stenosis.

Relationship between aortic pressure and capillary hydrostatic pressure

In the heart, autoregulation maintains a constant CHP when the mean aortic pressure (and thus, the mean epicardial coronary pressure) ranges from approximately 45 mmHg to 120 mmHg, the physiologic autoregulatory range. At 45 mmHg aortic pressure, the low end of this range, the arterioles are fully dilated and cannot dilate anymore, while at the high end - 120 mmHg - they are fully constricted and cannot constrict anymore [4]. At these extremes, the flow through the coronary vasculature is driven directly by aortic pressure in comparison to the autoregulatory range where flow is maintained constant despite variations in aortic pressure.

Stenosis and capillary de-recruitment

In the presence of a non-critical stenosis, the hyperemic response is attenuated without alterations in resting perfusion pressure (Figure 1) [5]. This occurs because autoregulation decreases downstream vascular resistance in a manner inversely proportional to the increase in resistance caused by the stenosis. In this setting, the total resistance does not change but the decrease in arteriolar resistance allows maintenance of CHP. When hyperemia is induced by exercise or exogenously administered vasodilators, the increased flow through the stenosis causes a pressure drop beyond it, thus imperiling CHP. In response, a phenomenon we termed capillary ‘de-recruitment’ is observed [6*]. Capillary de-recruitment under physiological or pharmacological stress results in a reversible perfusion defect on myocardial contrast echocardiography (Figure 2) [7–9] and other imaging modalities [10**], which allows their use in detecting physiologically significant coronary artery disease. Presumably, this de-recruitment increases capillary resistance, which helps maintain CHP, but the ensuing attenuation of hyperemic blood flow through the tissue is likely to have a negative impact on tissue metabolism and health. Although ‘pre-capillary sphincters’ had

been suggested as mediating capillary de-recruitment [6*], the exact nature of these sphincters and, hence, the mechanism responsible for capillary de-recruitment under stenosis remained elusive until recently, largely because of a lack of knowledge regarding the cellular structures that impart contractility to capillaries.

Pericytes

Pericytes were first described by Rouget in 1874, two decades before Starling published his paper on tissue homeostasis, as cells that form the contractile tunic of the vessels [11]. Half a century later, in 1923, Zimmerman assigned them the name ‘pericytes’ based on their location and described them as cells that clung to the outside of capillaries [12]. During this same period, Krogh’s Nobel prize winning work had already established that capillary diameter could change independent of their upstream arteries to regulate local blood flow [13, 14] and pericytes were proposed as the cellular substrate mediating these changes [15]. Despite these seminal observations, pericytes were overlooked in vascular physiology research for a large part of the twentieth century. Fortunately, they have enjoyed a renewed interest in the last few decades, producing a flourishing body of work on pericyte phenotype and biology, including their contribution to vascular structure and permeability, blood flow regulation, immune and wound healing functions, progenitor capacity, and, in the central nervous system (CNS), maintenance of the blood-brain barrier [16–26].

Pericytes can be identified by their relatively high expression of the platelet-derived growth factor receptor β (PDGFRβ) and neuron-glia antigen 2 (NG2), a chondroitin sulfate proteoglycan [23]. Pericytes also express desmin (also found in myocytes), CD13 and CD146 [24, 27–31]. Although these markers are not entirely unique to pericytes, they can nonetheless be used to reliably identify pericytes in conjunction with their morphology and location along the vascular tree. Unlike vascular smooth muscle cells, which cover the arterioles in a contiguous fashion, pericytes are located on capillaries as individual cells with a bump-on-a-log morphology, where their soma appear as bumps along the vasculature at approximately 30 μm intervals in the brain and retina [21, 24], and 60 μm intervals in the heart [32*] (Figure 3). Indeed, the characterization of these markers has driven the development of many tools that allow the study of pericytes more widely, e.g. mice expressing fluorescent reporters under the PDGFRβ or NG2 promoters are now commonly used in pericyte research [33–35].

Organizational heterogeneity of pericytes

Zimmermann classified pericytes into three distinct classes based on their organization along the vascular tree and their corresponding morphology, namely precapillary pericytes, capillary pericytes and postcapillary pericytes (schematized in Figure 3A) [12]. These pericytes have been described in more detail in recent studies [36, 37]. Precapillary pericytes, also known as ensheathing or mesh pericytes, exist at the transitional zone between arteriole and capillaries, extend circumferential processes that wrap the vessel, and express alpha smooth muscle actin (α-SMA) [23, 36, 38]. A further subset of these are located at the transitional branch-points from arterioles to capillaries and are proposed to be the cellular substrates of pre-capillary sphincters [39]. Precapillary pericytes play an active

role in microvascular regulation. At least in the CNS, they are shown to regulate activity-dependent changes in regional blood flow [17, 21, 40] and to constrict in response to ischemia and other injuries [21, 22, 41, 42]. These precapillary pericytes also harbor other specializations that contribute to their hemodynamic function. For example, although all CNS pericytes express Kir6.1 channels [43], which is involved in regulating resting perfusion [44], Kir6.1 channels in pericytes proximal to retinal arterioles were much more weakly rectifying compared to those closer to venules due to intracellular regulation [45]. The loss of this rectification gradient across the capillary network important in diabetic retinopathy [45], a condition characterized by capillary dysfunction, suggests that it is for microvascular dynamics.

In contrast, mid-capillary pericytes located in the capillary bed possess long spindly processes that twist around the endothelial tube, aptly renamed thin strand/helical pericytes [36]. In the CNS, mid-capillary pericytes are most studied in the context of blood-brain barrier development and maintenance [19, 46]. They are believed not to regulate blood flow largely due to their lack of smooth muscle actin [38], but this view has been challenged by a recent study that reported that α-SMA is indeed expressed in mid-capillary pericytes, albeit at low levels, which renders it difficult to detect using traditional fixation methods [47]. Another study reports that capillaries in the mid-capillary bed are contractile but with slower dynamics than ensheathing pericytes, regardless of branching order or α-SMA expression [48]. Indeed, mid-capillary pericytes may express actin isoforms other than α-SMA [49], such as the β- or γ-SMA as shown in the retina [50] and the heart [32*], and clearly contain other proteins such as myosins [38, 51] and tropomyosin [52] that bestow contractility. Indeed, their role in regulating blood flow has also been demonstrated in the skeletal and renal microcirculation [53, 54**].

Much less is known about the function of postcapillary pericytes on the venules, but regulation of immune extravasation has been proposed. Postcapillary pericytes often reside on top of the endothelial cell junctions on venules (and sometimes on capillaries as well) [26]. Upon stimulation by inflammatory mediators, pericytes migrate along the venule to cap the endothelial junction openings even further to limit [25, 55, 56] or regulate [57] extravasation of immune cells.

Functional heterogeneity of pericytes

Pericyte heterogeneity and distribution also depends on which part of the body is under study. Studies in human and equine samples show that distal capillaries further away from the heart have more pericytes than those closer to the heart [58, 59], with pericytes increasing in both number and coverage in a head-to-foot direction. This observation holds true within at least two different organ systems, the skin and skeletal muscle, although variation exists between organs in pericyte numbers and coverage. This prompts the hypothesis that perhaps the higher pericyte investment of capillaries further away from the heart is necessary to maintain physiologic capillary blood flow under increased hydrostatic pressure [58], although this idea has yet to be tested empirically. It is also noteworthy that pericyte coverage depends on the organ system: capillaries in the skin possess more pericytes and are more completely ensheathed than are capillaries in the skeletal muscle

[58]. The skin microvascular bears a higher internal pressure compared to skeletal muscle capillaries [58], which may necessitate this higher pericyte coverage. The skin also plays a crucial role in the regulation of body temperature via dilation and constriction of the dermal capillary bed; hence, it is tempting to speculate that perhaps the higher pericyte coverage of skin capillaries is necessary for thermoregulation.

Even within the same tissue system, pericytes may differ in their functional specialization. Recently, pericytes from several organ systems–skeletal muscle, lung, heart, kidney, spinal cord and heart–were reported to classify into two main sub-types: type 1 pericytes that are NG2+/Nestin− and type 2 pericytes that are NG2+/Nestin+ [60, 61]. Type 1 pericytes tend to contribute to fibrosis in most organs, but their collagen producing ability is organ-dependent [61, 62]. Similarly, in the spinal cord, a subset of pericytes that are negative for contractile proteins have been shown to contribute to scar tissue formation [63], cementing their role in wound healing [64]. This is perhaps one reason why wound healing is slowed in conditions like diabetes, where pericyte loss is observed. Type 2 pericyte, on the other hand, tended to induce angiogenesis *in vivo* [65]. Further, both pericyte subtypes could give rise to α-SMA+ contractile pericytes, but only the type 2 cells could be guided to generate Tuj1+ cells lacking α-SMA that are reminiscent of neural progenitors under some *in vitro* conditions [60]. The attempts at pericyte classification thus far are commendable, yet the fact that the scar-forming pericytes in the spinal cord are α-SMA negative while type 1 pericytes that are fibrotic in other organ systems are more closely related to α-SMA positive cells suggests that the work is far from over.

Pericytes have also long been proposed to have immune functions [66], and this idea is now supported by several studies demonstrating that subsets of pericytes can give rise to microglia-like cells following injury [67, 68]. Further, brain pericytes can sense systemic inflammation and secrete chemokines to alter brain function [69] and activate local microglia [70]. Even more interestingly, a sub-population of pericytes in the CNS and the skin vasculature are generated from myeloid cells [71, 72], further stressing their heterogeneity in both lineage and function. The remainder of this review will focus on the role of pericytes in capillary flow regulation during arterial stenosis; however, the diversity of pericytes must be kept in mind when studying and interpreting their functions.

Pericytes in the coronary vasculature

Pericytes are also an integral component of the capillary network in the heart and other organs (Figure 3B). Most studies relating to heart pericytes have focused on cardiac regeneration, immune surveillance, and cardiotoxicity induced by cancer therapies [73–75]. The role of pericytes in controlling coronary blood flow has not been described as extensively. Similar to brain pericytes, approximately 40% of heart pericytes also express alpha smooth muscle actin [32]. A much larger proportion have been found to also express beta and gamma smooth muscle actins (~60% and ~80% of pericytes, respectively) [32, 50], suggesting that pericyte contractility in the heart may be mediated by multiple actin isoforms, potentially in a location dependent manner.

Pericytes in capillary de-recruitment

Two recent studies have suggested that pericyte-dependent capillary constriction may be a mechanism underlying capillary de-recruitment. O'Farrell et al. reported capillary constrictions in regions apposed to pericytes after acute myocardial infarction and suggested this constriction to be the underlying cause of no reflow [32*]. However, this study examined ischemic myocardial tissue and did not differentiate whether capillary constriction was due to direct effect of ischemia on pericytes or due to the pericytes sensing the change in perfusion pressure induced by coronary occlusion and actively responding by de-recruiting the capillaries.

Ideally, visualization of the pericyte contractions during coronary stenosis would be invaluable to prove the active role of these cells in capillary de-recruitment; however, this is near impossible to image in the heart due to the tissue movement caused by the heartbeat. Hence, in a recent study, we used a skeletal muscle preparation as a substitute system to conclusively show that capillary de-recruitment is caused by contraction of pericytes [54**]. When a stenosis was produced in the femoral artery and hyperemic challenge administered, a significant reduction in red blood cell flux through the downstream capillary bed resulted, reflecting capillary de-recruitment. *In-vivo* 2-photon microscopy demonstrated a significant increase in the number of constricting capillaries under these conditions. Importantly, the capillary regions that constricted were invested with pericytes and capillary de-recruitment was prevented in a transgenic mouse model featuring partial pericyte depletion. This was the first direct *in vivo* visualization of hyperemia-induced capillary de-recruitment distal to an arterial stenosis and the results establish pericytes as the contractile cell responsible for capillary de-recruitment.

In cases of coronary stenosis, similarly, a pressure drop would occur distal to the stenosis at baseline. Hyperemic stimulation under this situation, such as exercise, is expected to cause capillary constriction due to pericyte contraction, which would attenuate hyperemic blood flow in the myocardial at the time most necessary to sustain function. Such a response would cause undue metabolic stress on cardiac tissue over time and increase the likelihood of developing heart failure due to repetitive episodes of myocardial stunning [76]. Therefore, targeting pericytes to increase myocardial perfusion and restore energy supply to active cardiac tissue should be considered a viable therapeutic target for future study. Further, although the first indications that capillary de-recruitment contributes to vascular defects following stenosis came from observations made in the coronary system [6, 77], the findings discussed above [54**] suggest that this phenomenon likely also contributes to reduced peripheral perfusion observed in peripheral arterial disease, a common condition in older patients with diabetes, atherosclerosis and other cardiovascular morbidities [78, 79]. Hence, therapeutics aimed at preventing pericyte-mediated capillary de-recruitment may also prove beneficial in peripheral arterial disease [80]. Whether such capillary de-recruitment is mediated by all pericytes equally or whether only certain subpopulations of pericytes are involved remains unknown. Further studies to identify these pericyte populations and the mechanisms that trigger them to de-recruit capillaries will prove imperative in this endeavor.

Conclusions

Pericytes are a heterogeneous population of mural contractile cells that play a multifaceted role in tissue homeostasis. Unlike the brain and the retina, where the role of pericytes in blood flow control has been investigated over the past decade or two, the role of pericytes in the control of myocardial hemostasis is still largely ignored. The recent development of new tools and techniques allow better specificity in terms of pericyte identification in tissue as well as cell culture, thus opening the doors to future research in elucidating the role of pericytes in capillary blood flow and hydrostatic pressure maintenance not only in coronary stenosis but also in ischemic injury and peripheral arterial disease. Sparse but tantalizing recent discoveries imply pericyte contraction in capillary de-recruitment following coronary stenosis and myocardial ischemia. We believe that pericytes could play a very important role in local regulation of myocardial and skeletal muscle blood flow during both rest and under stress. Pharmacological manipulation of pericytes could prove to be of enormous benefit for human health and, as such, efforts towards identifying the molecular mechanisms by which pericytes regulate microvascular blood flow should be the focus of much future research.

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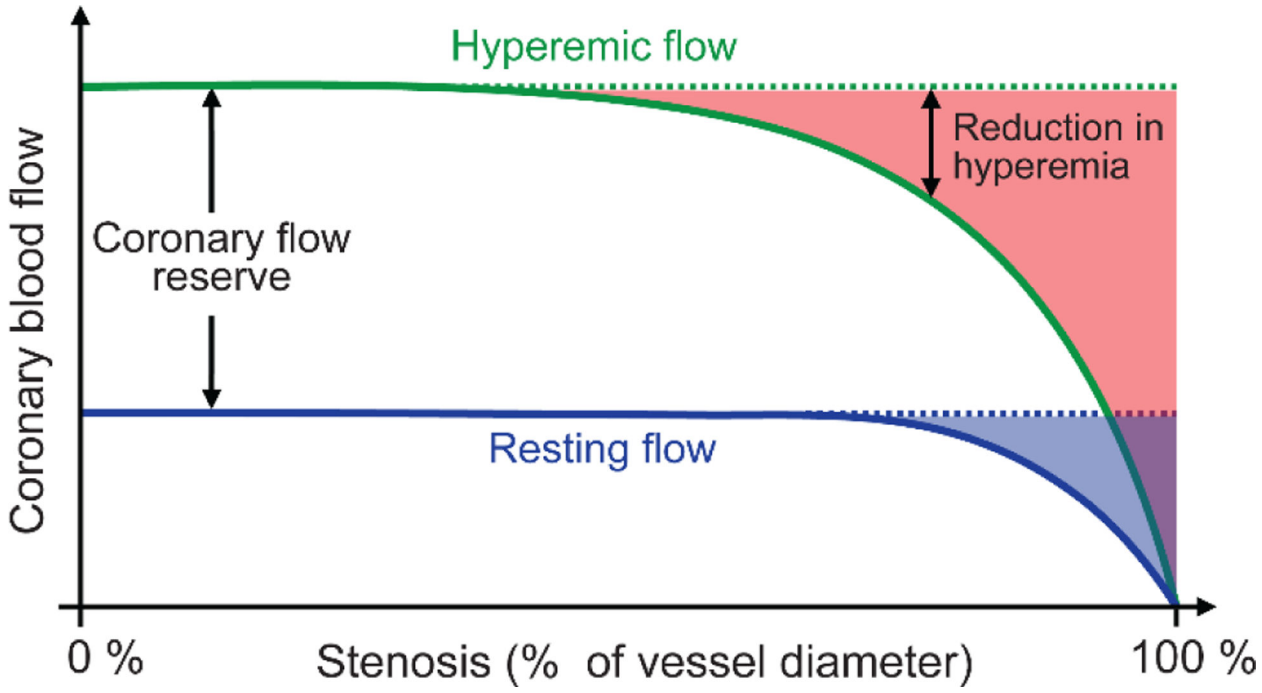

Figure 1.

Relationship between percent narrowing of the coronary artery diameter (stenosis, x-axis) and coronary blood flow (y-axis) during rest (dashed blue line) and hyperemia (solid green line). The resting flow is maintained at normal levels (dotted black line) up to 85–90% stenosis because of autoregulation. During hyperemia, however, increases in flow are attenuated at 50% or greater stenosis, with more severe stenosis resulting in greater attenuation of hyperemia flow. The shaded blue region denotes the decrease in resting flow d the shaded red region denotes reduction in hyperemic flow. Adapted with permission from Gould et al. [5]†.

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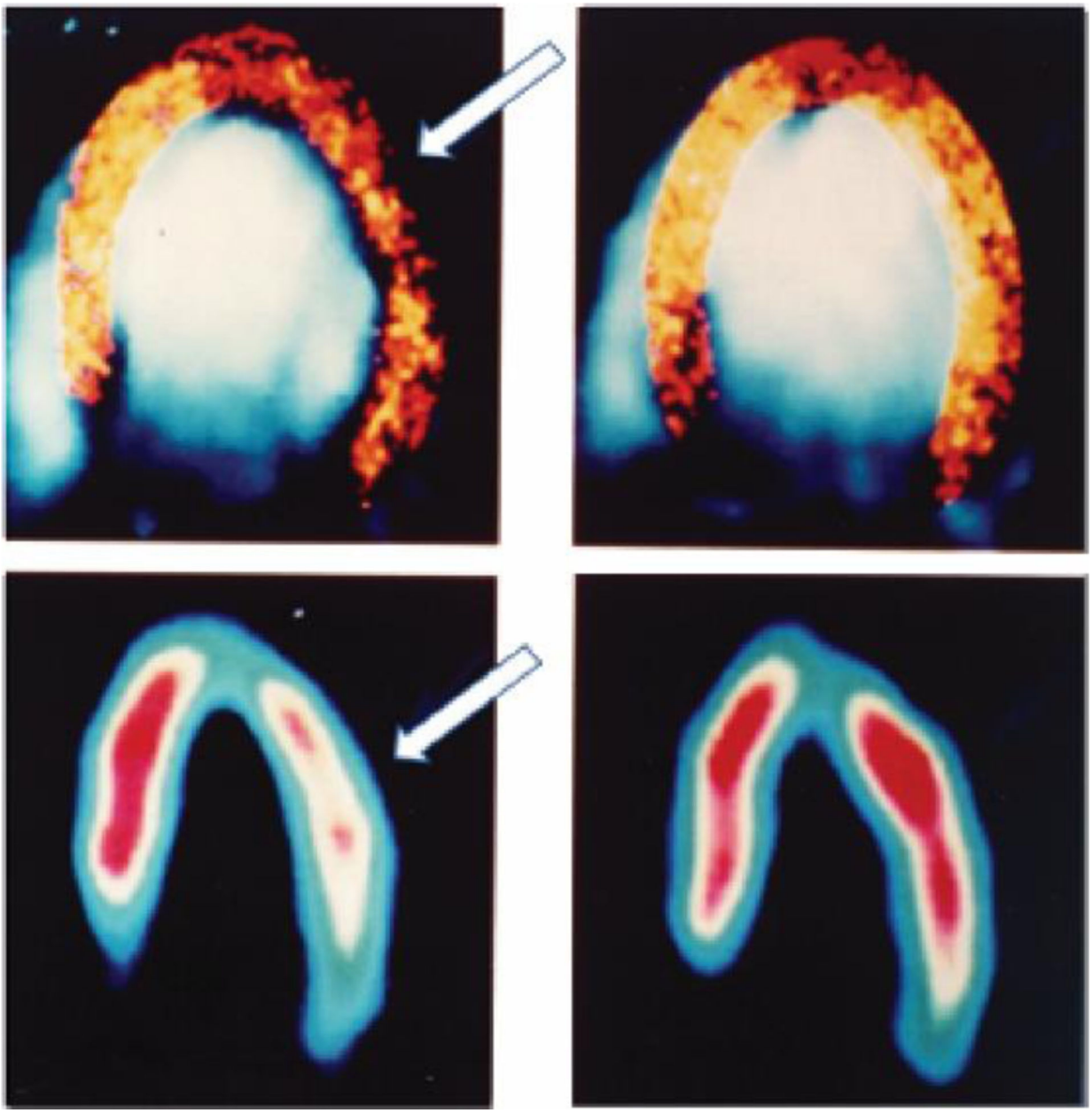

Figure 2.

Myocardial contrast echocardiography (top) and 99mTc-sestamibi SPECT images (bottom) at rest (right panel) and stress (left panel). White arrows depict reversible perfusion defects that are caused by capillary de-recruitment in a patient with left circumflex artery stenosis. At rest, perfusion (capillary density) was normal and equal to the contralateral left anterior descending artery bed while during hyperemia the capillary density decreased in the left circumflex compared to the left anterior descending artery bed. Reprinted with permission from Kaul et al. [9][§].

[§]Reprinted from Kaul S., Senior, R., Dittrich, H., Raval, U., Khattar, R. and Lahiri, A. *Detection of coronary artery disease with myocardial contrast echocardiography: comparison with 99mTc-sestamibi single-photon emission computed tomography*.

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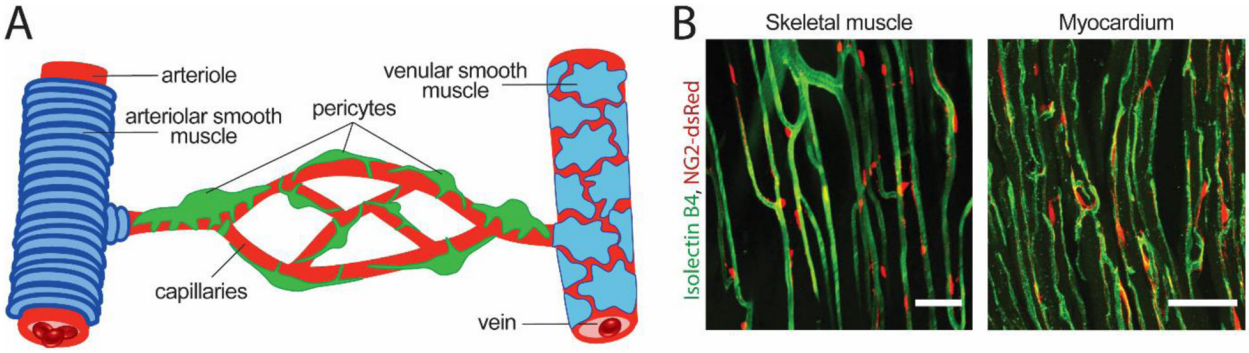

Figure 3.

Pericyte coverage of the capillary network. (A) A schematic cartoon of the vasculature showing arteriole on the left ensheathed by arteriolar smooth muscle cells (blue), the capillary network in the center enwrapped by pericytes (green) of different morphologies as described by Hartmann et al. [37], and the draining venule covered by a thin, sparse layer of smooth muscle cells on the right. (B) Images of the microvascular network in a skeletal muscle (left) and cardiac tissue (right). These images were obtained from NG2-dsRed transgenic mice in which pericytes express the red fluosrescent protein dsRed under the NG2 promoter [33] and vessels were labeled by intravascular administration of Isolectin B4 (in green) to label the vascular basement membrane. Scale bar = 50 μm.