The Dynamic Vasa Vasorum

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Abstract

The function of vasa vasorum is both to deliver nutrients and oxygen to arterial and venous walls and to remove "waste" products, either produced by cells in the wall or introduced by diffusional transport through the endothelium of the artery or vein. Although the relationship between changes in vasa vasorum characteristics and the development of atheromatous plaques is well documented, the role of vasa vasorum, especially in terms of their appearance and disappearance in disease processes such as atherosclerosis, are still not clearly understood in terms of their being causative or merely reactive. However, even if their proliferation is merely reactive, these new microvessels may be a source of disease progression by virtue of endothelial impairment and as a pathway for monocytic cells to migrate to sites of early disease. As both these features are aspects of the vasa vasorum function, this Review focuses on the following issues: 1) acute modulation of vasa vasorum patency due to surrounding compressive forces within vessel wall and due to variable tone in the smooth muscle within proximal vasa vasorum and 2) chronic angiogenic responses due to local cytokine accumulations such as occur in the wall of arteries in the presence of hypertension, hypercholesterolemia, accumulation of lipids, extravasated blood products (e.g., red blood cells, macrophages, inflammatory products) which attract monocytes, and response of vasa vasorum to pharmacological stimuli.

Keywords

Angiogenesis; Arteries; Atherosclerosis; Coronary disease; Inflammation

1. Introduction

Vasa vasorum consist of small arteries which enter the vascular wall either from the abluminal surface (vasa vasorum externa) or from the luminal surfaces (vasa vasorum interna) and then arborize to the outer media. Venous vasa vasorum drain a network of capillaries/venules laid down around the outer media to veins in close proximity to the arteries. In humans, vessels with walls less than 29-cell layers thick [1] normally do not have vasa [2] and, in general, vessels less than 0.5 mm lumen diameter [3] (all normal vessels in mice and intramyocardial vessels in humans) do not have vasa vasorum. In larger vessels diffusion of solutes to the media from the vessel lumen is supplemented by vasa vasorum [4,5].

The vasa vasorum have been the subject of considerable interest for more than a century [6] because of their possible role in, atherogenesis [7-12], coronary interventions [13-15], and in response to risk factors for atherosclerosis, such as hypercholesterolemia [16-20] and hypertension [21-23]. Although many studies have described the anatomy of the vasa vasorum in a qualitative manner [24-28], the more recently described detailed 3D architecture of the vasa vasorum network (due to the availability of micro-CT imaging capabilities [29,30]) has made more quantitative information available. In addition, it is becoming increasingly clear that vasa vasorum are dynamic in that they can be transiently compressed by the surrounding arterial wall and/or undergo vasodilation and vasoconstriction as well as increase in number (e.g., angiogenesis). Thus, these capabilities of the vasa vasorum underscore their dynamic role in the regulation of vascular wall perfusion.

2. Anatomy and Function of Vasa Vasorum

2.1 Vasa Vasorum Branching Geometry

The vasa vasorum have been shown to function as end arteries [30], possibly due to the pressure distribution within the arterial wall which could compress most of the vasa vasorum. An arterial injection of the silicon polymer Microfil® results in high pressure in the arterial lumen and consequently within the arterial wall consistent with Lame's Law [31]. This intramural pressure gradient can result in compression of some of the vasa vasorum. As illustrated in Figure 1, this phenomenon is demonstrated when Microfil® is injected into the concomitant vein so that the coronary artery is filled retrogradely via the intramyocardial capillaries and the arterial vasa vasorum are filled retrogradely via the venous vasa vasorum which empty directly into the concomitant vein and are therefore also exposed to the Microfil® injection pressure. Hence, the luminal pressure in the artery is much reduced, resulting in a less distended coronary arterial lumen and the compressive force within the arterial wall is proportionally decreased. This in turn results in less compression of the vasa vasorum in the arterial wall because they are both exposed to the increased pressure in the vasa vasorum as well as to the reduced intramural pressure. Consequently, the density of perfused (and therefore opacified) vasa vasorum under these conditions is increased.

Due to the vasa vasorum both the vascular adventitia and, to a lesser extent, the media are brought into close proximity to blood cells and blood solutes. Because the blood pressure within the main arterial lumen is generally higher than the extravascular tissue pressure, the diffusion of the blood solutes would tend to be from the main lumen towards the adventitia, as described by Darcy's Law [32] which links diffusion of a solute through a porous medium subjected to a pressure gradient. The only way that those solutes can leave the vessel wall is via the venous vasa vasorum and any lymphatics that may be present in the wall.

The branching structures of the vasa vasorum have also been explored [4,33,34], but little has been done to use that structure to explore the fluid dynamic conductive characteristics of the vasa vasorum [29,30,35].

An important consequence of the anatomic location and branching architecture of the vasa vasorum, which enter the arterial wall via the adventitia, is that flow through the vasa cannot proceed far into the media due to the compressive force (P_w) within the arterial wall, at location R, as described by Lamé's Law [31]:

$$\text{Lamé's Law:} \quad \frac{P_w(R)}{P_\ell} = a^2 \left[\frac{1 - (b/R)^2}{b^2 - a^2} \right] \tag{1}$$

Where: P_ℓ is the pressure in the coronary artery lumen, 'a' is radius of coronary artery lumen, 'b' is the radius of the outer adventitia, R is the radial distance (from the endothelial surface) within the coronary arterial wall.

This law indicates that the local compressive pressure within the vessel wall is equal to lumenal blood pressure in the sub-endothelial layer (i.e., $R \approx a$) but falls-off hyperbolically towards to adventitia (i.e., $R \approx b$). As a consequence, at the radial location at which the pressure inside the parent vessel wall exceeds the pressure in the vasa vasorum lumen (determined largely by pressure drop (ΔP_i) along the vasa vasorum as described by Poiseuille's Law [36]), no perfusion of the wall can occur closer to the main lumen.

$$\text{Poiseuille's Law: } \Delta P_i \propto L_i \big/ r_i^4 \tag{2}$$

Where: P_i is pressure in lumen of vasa vasorum at distance L from the origin of the vasa vasorum. Where: 'r_i' is the radius of the 'proximal' vasa vasorum lumen and L_i is the distance along the vasa vasorum to the point-of-interest within the wall.

The vascular resistance to flow in the vasa vasorum is high because the radii of the vasa vasorum are much smaller than the parent vessel lumen, hence the pressure within the distal vasa vasorum close to the media must be lower than the coronary arterial lumen pressure – hence this intima-medial zone must be where the compressive pressure within the wall can exceed the blood pressure within the vasa vasorum at that location. However, these considerations assume steady state. It is conceivable that as the systolic pressure pulse progresses along the vasa vasorum its arrival in the terminal vasa vasorum is delayed relative to the transient increase of systolic pressure propagated within the arterial wall. Consequently, the extent of transmural perfusion by vasa vasorum may be underestimated by a steady-state assumption.

Darcy's Law [32] describes the driving force for diffusion of extra-vascular solutes to migrate across a vessel wall in the direction of the pressure gradient within the wall.

$$\text{Darcy's Law: } \frac{f_\ell}{f_{vv}} \propto \left(\frac{Area_\ell}{Area_{vv}} \right) \left(\frac{R+T}{R} \right)^3 \tag{3}$$

Where: f_ℓ and f_{vv} are the fluxes of solutes from the coronary arterial lumen and into the venous vasa vasorum respectively. $Area_\ell$ is the coronary arterial endothelial surface area across which solute flux occurs and $Area_{vv}$ being the area of the vasa endothelial surface within the wall at distance R within the wall. T is the distance from the endothelium towards the outer surface of the adventitia (i.e., R-a).

This law implies that for the venous vasa vasorum to match the flux across the main lumen's endothelium, the venous vasa vasorum endothelial permeability surface area product must be large enough to cope with this transmural flux from the main lumen. Thus, ligating venous vasa vasorum should result in build-up of solutes such as fatty compounds [7,11,37].

As veins also have vasa vasorum [38,39], it is of interest that veins generally do not develop atherosclerosis except when they are exposed to increased lumen pressure. This is observed when they are used as arterial shunts (such as saphenous vein bypass grafts [40-42]) which often undergo accelerated intimal thickening and plaque formation after three years. Although the accelerated venous atherosclerosis may in part be due to damage to the vasa vasorum at the time of harvesting and transplant of the vein segment, the combination of the presence of vasa and high intra-vascular blood pressure [42,43] or very high plasma lipid concentrations [44] appear to be necessary for development of atherosclerotic plaques.

The "footprints" of coronary vasa vasorum perfusion territories (Figure 2) have also been studied [30]. Microembolization reduced vasa vasorum densities significantly and increased the size of low-vasa-vasorum-density territories. Consequently, under normal conditions coronary vasa vasorum are functional end-arteries, even though they may end up being connected via an anatomic plexus. This characteristic may have a significant impact on the spatial distribution of perfusion and drainage of the coronary vessel wall. If the heterogeneous distribution of both coronary atherosclerosis and of the vasa vasorum along the coronary vascular tree are anatomically coincident, this would more directly support the potential role of the vasa vasorum in the disease process.

2.2 Physiologic Reactivity of Vasa Vasorum

The proximal vasa vasorum display a regularly layered vascular structure of endothelial cells, vascular smooth muscle cells, and surrounding connective tissue. These characteristics are important since they imply that the vasa vasorum may regulate their own tone and vascular perfusion [5,45,46] in a manner similar to small coronary arteries, as was demonstrated by Scotland et al., [47,48].

Vasa vasorum, isolated from porcine aorta, respond to the endothelium-dependent vasodilators substance P and bradykinin similar to the host vessel response. Although vascular reactivity of the vasa vasorum in different vascular beds is not known, any differences in reactivity conceivably contribute to the different susceptibilities of different vascular beds, (such as coronary versus peripheral arteries) to atherosclerosis [49-51].

2.3 Role of Vasa Vasorum in Solute Transport into and from Arterial Wall

The transport physiology of aortic vasa vasorum has been explored using radiolabeled microsphere-based estimates of perfusion [5] as well as the oxygenation of the arterial wall by direct measurement [52,53] and by model-based analysis of oxygen tension [54]. These approaches show a nadir of oxygen tension of approximately 10 mmHg at about 300 μm from the lumen. Lipid transport by vasa vasorum into the parent vessel wall has been shown to be about 30% of the transintimal transport in rabbit aorta [55].

3. Role of Vasa Vasorum in Atherosclerosis

Several interacting feedback loops that plausibly involve vasa vasorum during the development of atherosclerotic plaques are provided in (Figure 3). The relative magnitude and timing of the activation and/or suppression of these feedback loops would largely determine, 1) the rate of development of plaques [56] and 2) the stability of those plaques [57].

3.1 Modification of Transport into and out of Vascular Wall

That endothelial injury and dysfunction are early features of atherosclerosis is supported by numerous experimental findings [58]. However, the hypothesis that "injured" endothelium is a causative factor begs the question as to why early atherosclerosis is not observed in small arteries, in the outer media (where vasa vasorum endothelium is present) or in undisturbed veins.

Studies involving measurement of the transport of lipids and albumin and dyes into the wall from the main lumen [44,59] generally do not consider the possible role of vasa vasorum [60] but focused exclusively on the influx of solute, endothelial permeability and local solute residence times or heat removal/delivery. Moreover, these studies also did not address the possibility that there may be circumferential variations in transmural pressure gradient. Thus, a region of wall that is not supported at its abluminal surface would have a larger pressure

gradient (which would drive diffusion into the wall via Darcy's Law) than would wall that is supported on its abluminal surface.

The reason veins and the normal pulmonary artery do not develop atherosclerosis may be due to the fact that the transmural flux of solute (as described by Darcy's Law) is diminished due to the low venous and pulmonary artery lumen pressures. In addition, with these lumen pressures generally being lower than the pressure within the arterial vasa vasorum, these vasa vasorum may never be compressed during the entire cardiac cycle, thereby maintaining adequate flow in the vasa vasorum. Nonetheless, the need for a high density of external vasa vasorum in vein walls is likely due to the fact that the venous (unlike arterial) blood in the main lumen provides little, if any, oxygen to the wall via transendothelial diffusion from the main lumen.

The early stages of histologically detectable atherogenesis have been shown to involve increased transport of low density lipoprotein (LDL) across the endothelium, preceding cellular infiltration/proliferation in the arterial wall [61-64]. Because of endothelial dysfunction in arterial vasa vasorum, delivery of LDL (and probably oxidized and inflammatory products) may occur at a rate greater than can be removed by venous vasa vasorum [17]. In addition to the increased delivery (or impaired removal) of LDL from the arterial wall by the arterial vasa vasorum [65], an early major focus on the vasa vasorum's possible role in atherogenesis has been the oxygen delivery [66-68]. Low oxygen tension has been shown to accelerate atherogenesis and interfere with LDL transport [69]. Moreover, fatty streaks, especially in diabetic situations, have been shown to increase oxygen demand [70]. We speculate that these data suggest the presence of a positive feedback process so that reduced perfusion from the vasa vasorum results in local hypoxia and in increased accumulation of fatty substances in the intima/media, which, in turn, results in further local hypoxia due to the increased local oxygen consumption.

3.2 Modification of Vasa Vasorum Function by Neovascularization

Despite the fact that atherosclerosis encroaches on the arterial lumen only at its late stage, the majority of research efforts continue to focus on the luminal side of the vascular wall. Recent evidence, however, suggests that the adventitia may play a significant role in maintaining vessel integrity, and may contribute to the initiation and/or progression of certain types of vascular disease [71,72]. Indeed, experimental studies demonstrated that manipulation of the adventitia, and more specifically of the vasa vasorum, such as handling of the vessels at surgery or deposits of talcum powder from the gloves, could lead to atherosclerotic changes of the intima [7,11, 12,73,74]. Atherosclerotic lesion formation is associated with neovascularization of the vasa vasorum [30,75,76] as illustrated in (Figure 4).

A number of autopsy-based studies highlighted that this neovascularization process occurs in the neointima, which progresses with and determines plaque extent [77]. The latter aspect was underscored by an experimental study in apoE-deficient mice, showing that anti-angiogenic therapy not only reduced plaque neovascularization but eventually plaque growth [78]. Moreover, the inhibition of angiogenesis was associated with a reduction of macrophages in the plaque and around the vasa vasorum [79-81].

3.3 Alteration of Vasa Vasorum Endothelial Function by Disease

Hypercholesterolemia and hypertension are associated with impaired endothelial function and an increase in vascular inflammation such as indicated by increased expression of the nuclear transcription factor kappaB (NF-κB) [82]. In addition, an increase of NF-κB has been shown to cause enhanced endothelial cell apoptosis [83]. Endothelial dysfunction and an increase in the vascular tone of the vasa vasorum may be enhanced in these states due to the enhanced

inflammation and the reduction in the bioavailability of nitric oxide, secondary to the increase in endogenous oxidative stress. Eventually, these alterations in the balance of vasoreactive factors and endothelial cell function may lead to the functional reduction in blood flow to the vascular wall and local hypoxia potentially resulting in vasa vasorum neovascularization to meet the perfusion needs of the arterial wall. The imbalance between vascular nutrient supply and demand might even be worsened by an enhanced metabolism and/or size of the vascular wall upon exposure to a cardiovascular risk factor. This relates to the hypoxia or anoxemia theory of atherosclerosis [84]. Indeed, recent studies in hypertensive rats demonstrated increase in hypoxia-inducible factor 1 alpha (HIF-1α) and VEGF expression in the aorta, which was subsequently followed by increase in vasa vasorum density around the aorta [23]. A similar increase in HIF-1α and VEGF has been demonstrated in coronary arteries in hypercholesterolemic pigs [85]. This study also indicated that the reversibility of endothelial dysfunction at the early stages of atherosclerosis was associated with a parallel reduction in the coronary vasa vasorum spatial density (neovascularization). Vasa vasorum neovascularization has also been shown to precede the development of atherosclerotic lesion and even the impairment of endothelium-dependent vaso-relaxation, a hallmark of early atherosclerosis [17]. Hence, there seems to be an interaction between the pathophysiologic state of the vessel and the vasa vasorum spatial density, which is a dynamic, not a static, process.

The reduction in vascular wall hypoxia coincides with the decrease in the expression of pro-angiogenic factors in the coronary arterial wall [18,19,86]. Thus, preservation of endothelial function of the vasa vasorum and thereby preservation of adventitial blood supply might be a common mechanism of the neovascularization in different vascular beds.

Elevated plasma lipid concentration [87] and coronary artery luminal endothelium damage have been shown to be major factors in the initiation and progression of atherogenesis [88, 89]. However, it is plausible that the coronary artery vasa vasorum have an aggregate endothelial surface area that is comparable in size to the host vessel's luminal endothelium, especially in early stages of atherosclerosis, when there is increased density of vasa vasorum [90,91]. Hence, disparity between the luminal and vasa vasorum endothelial surfaces areas may be an important factor. In addition, it seems possible that vasa vasorum blood flow may be selectively reduced by increased smooth muscle tone in proximal vasa vasorum due to reduced endothelial transduction function, infection, inflammation or thrombosis. This would result in hypoxia and reduced removal of substances from the media, which must now accumulate. Despite this possible inequality in anatomic endothelial surface areas it is not clear if the functional surface areas and endothelial permeabilities (i.e., permeability surface area products) at the two sites are comparable and equally susceptible to damage or loss of function. Such mismatch of endothelial function would seem plausible [92]. Importantly, however, the "host artery" endothelium has a high pressure driving substances into the intima whereas the lower luminal pressure in the vasa vasorum (due to the small diameter of these vessels which causes a pressure drop as described by Poiseuille's Law) creates a pressure gradient which favors solute transport from host artery lumen towards the adventitia as described by Darcy's Law. Indeed, that it is more likely that substances diffuse into the vasa from the media, rather than the opposite, has been shown by the clearance of radiolabeled molecules [75,93,94].

One of the possible consequences of infiltration of lipids into the subintima or media is that vasa proliferate due to the angiogenic stimulus they generate via the concomitant oxidative stress [95]. Specific angiogenic factors have been shown to play a role in the proliferation of vasa vasorum [93,96-98]. However, the angiogenesis may just not be enough to meet the need for increased endothelial surface area product of the vasa vasorum.

3.4 Role of Vasa Vasorum as a Portal for Cellular Invasion of the Arterial Wall

Neovascularization of the vasa vasorum could conceivably function as a conduit for entry of macrophages and inflammatory factors that may potentially promote the progression of the disease and angiogenesis [79]. Moreover, as increased endothelial permeability and fragility are cardinal features of pathological neovascularization [99] pro-atherogenic cellular and soluble plasma components may enter the vessel wall more easily through ruptured and/or leaky vasa vasorum thereby further enhancing the progression of atherosclerosis [100]. Indeed, there is an increased influx to, as well as a decreased drainage from, the coronary vessel wall in the porcine model of hypercholesterolemia [101]. Pathological and experimental studies are consistent with the contention that vasa vasorum hemorrhage may be a key factor in the development of unstable atherosclerotic lesions [102,103].

Moreno et al., [104] demonstrated that neovascularization, as manifested by the localized appearance of microvessels, is increased in ruptured plaques in the human aorta. Furthermore, they could demonstrate that microvessel density is increased in lesions with inflammation, with intraplaque hemorrhage, and in thin-cap fibroatheromas. A recent study by Langheinrich et al., [76] demonstrates the association among different advanced atherosclerotic lesions, adventitial vasa vasorum neovascularization and adventitial inflammation in apoE$^{-/-}$/LDL$^{-/-}$ double knockout mice.

4. Summary

The role of vasa vasorum in maintaining the integrity of the walls of vessels more than 0.5 mm in diameter is not fully understood, although they clearly are present when the wall is thicker than can be maintained viable by diffusion of solutes from the lumen alone. There is clearly a strong association between the density of vasa vasorum in an arterial vessel wall and severity of plaque formation, but it is still not clear whether the vasa vasorum play a causative or merely reactive role. The latter possibility is complicated by the possibility that the development of new vasa vasorum is too late and/or that the new vasa vasorum serve as conduit which facilitates cellular invasion of the vessel wall and thereby impact on the type of plaque formed. Table 1 summarizes literature references that address the possible roles of vasa vasorum in atherosclerosis.

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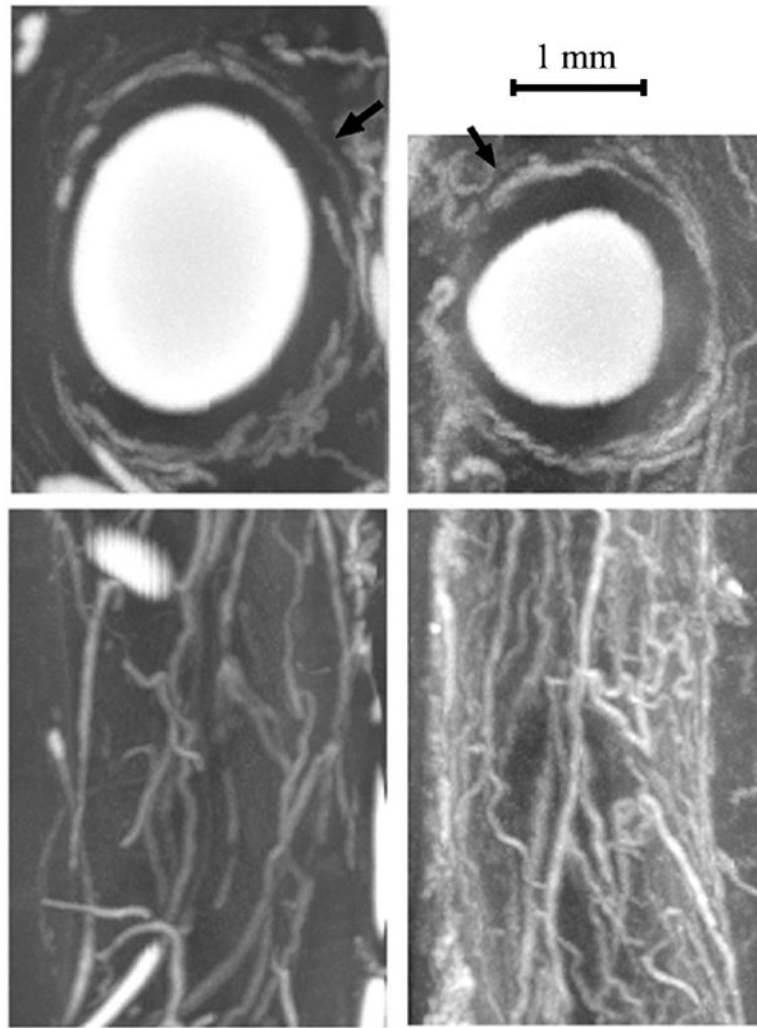
Figure 1.
Top two panels are micro-CT transaxial images through a porcine coronary artery. The white regions are a radiopaque silicon-based polymer injected into the vascular lumen. In the left panel the polymer was injected into the coronary artery lumen at 100 mmHg pressure and in the right panel it was injected into the concomitant vein's lumen at 100 mmHg pressure. The arrows point to opacified vasa vasorum around the main lumen. These conditions result in the larger coronary arterial lumen due to the higher intracoronary intralumenal pressure in the left upper panel and the increased number of vasa vasorum due to the reduced arterial lumen pressure resulting in a proportional decrease in the intramural pressure in the right panels. The lower panels are the corresponding axial projections of those arteries after the contrast in the main lumens was "removed" by image manipulation.
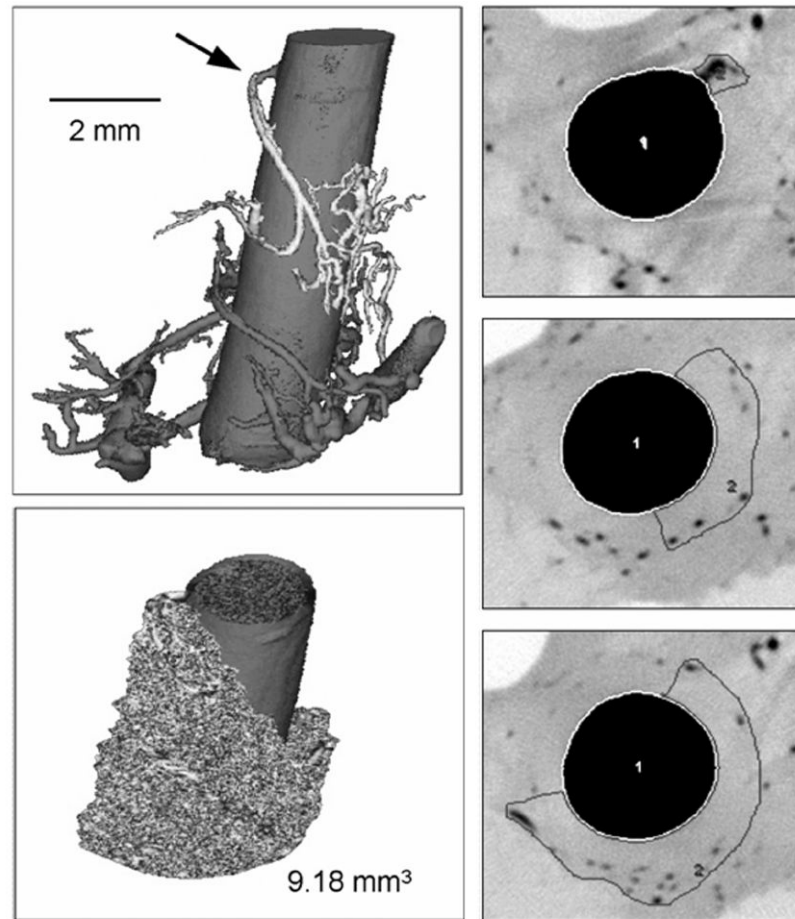
Figure 2.
Upper left panel: Volume-rendered micro-CT image of a porcine right coronary artery (20 μm cubic voxel size). The origin of the vasa vasorum interna from the main coronary artery lumen is indicated by the arrow. Right panels: grayscale-inverted μ-CT cross-sections with areas of perfusion. These areas of perfusion enclose the vasa vasorum branches that belong to the tree in the upper left panel. After adding the areas of perfusion in all contiguous cross-section images, the volume of vessel wall perfused can be assessed (lower left panel). [With permission from Gössl M et al., Ref. 29].

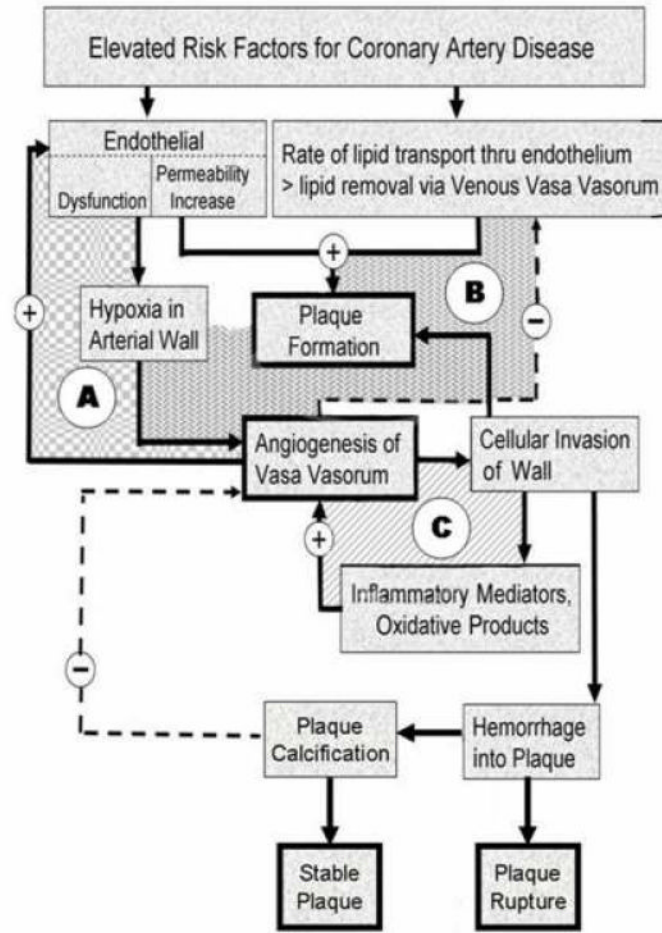## Possible Roles of Vasa Vasorum in Coronary Atherosclerosis

Figure 3.
This is a flow chart of the proposed cascade of events triggered by increased risk factors (such as elevated plasma lipids) and altered endothelial function. There are positive feedback loops (e.g., A, C) which result in progressive plaque formation and ultimately plaque rupture or plaque calcification. The negative feedback loops (e.g., B) involve the salutary effect of new vasa vasorum formation and the anti-angiogenesis association of plaque stabilization with calcification. The relative magnitude and time of onset of these various reactions to the initial stimuli determine the specific course followed (i.e., relentless progression vs. self limiting) in any one individual case. (See text for more detailed discussion).
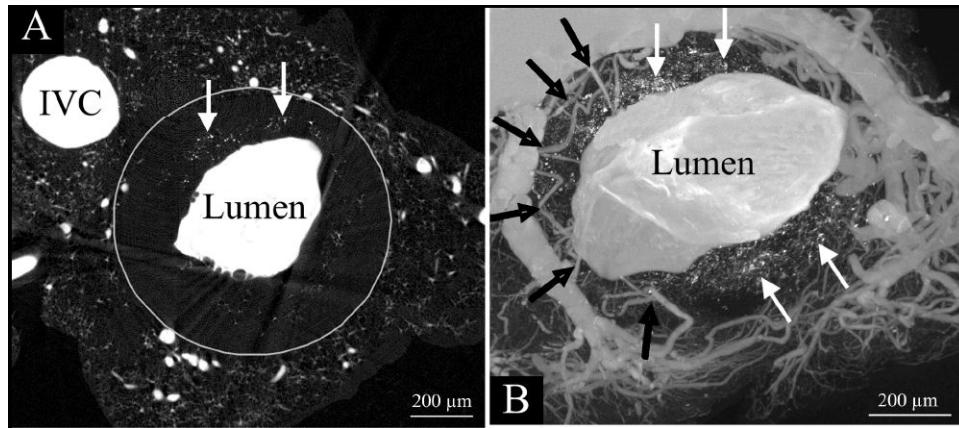
Figure 4.
Micro-CT transaxial images of a double knockout mouse (LDL$^{-/-}$, apoE$^{-/-}$) aorta after it was injected with a radiopaque silicon polymer. The aortic lumen (large white area) is irregular rather than round because of the atherosclerotic plaques encroaching into the lumen. The small vessels around the lumen are vasa vasorum. Note that unlike the "clear" zone between the vasa vasorum and the main lumen in the normal artery (upper panels of Fig. 1), the black arrows in this image show vasa vasorum entering the plaque area close to the main lumen surface. These are the newly formed vasa vasorum in response to the plaque formation process. Also, the white arrows point to isolated punctate opacities in the region of the plaques. These were shown to be small accumulations of iron and calcium, presumably the remains of red blood cells. [Abridged version of Figure 3 with permission from Langheinrich AC et al., Ref. 109].

Table 1

Evidence Suggesting the Role of the Vasa Vasorum in Atherosclerosis	References
Distribution	
Higher vasa vasorum density in vascular beds more prone for developing atherosclerosis.	51,105
Higher density of vasa vasorum in the proximal segments of the vessels than in the distal segments.	106
Heterogeneous distribution of atherosclerotic plaques.	29
Relationship to coronary artery disease risk factor and reversibility	
Induction: Increase in vasa vasorum density in models of atherosclerosis and vascular injury.	14,16 17,78
Reversibility: Inhibition of vasa vasorum angiogenesis attenuates the progression of atherosclerosis.	18,56,57, 78,79,82
Relationship with cardiovascular events	
Vasa vasorum neovascularization and hemorrhage contributing to plaque rupture and cardiovascular events.	107,108, 102,104