Review

The implication of vasa vasorum in surgical diseases of the aorta

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Summary

Vasa vasorum (VV) are microscopic vases that perfuse the vessel’s wall; arteries and veins. Many recent researches support the opinion that VV have a significant role in aortic pathology. The VV, or ‘the vessels of the vessels’, form a network of microvessels that lie in the adventitia and penetrate the outer media of the host vessel wall. Although the importance of the VV in providing nutritional support is not well known, obstruction of blood flow through these vessels has been implicated in the pathogenesis of many cardiovascular diseases such as aortic intramural hematoma, aortic aneurysm, and acute or chronic aortic dissection. Although the proliferation of VV due to atherogenic stimuli is controversial, experimental and clinical studies strongly suggest the potential of VV in vascular proliferative disorders. It seems that the rupture of VV is implicated in intramural hematoma, which can develop in acute aortic dissection. In this review article, we would like to stress the anatomy and mainly the pathophysiology, and the implication of VV in the acute and chronic aortic pathologies.

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1. Introduction

The aortic wall consists of three layers: the inner layer of intima, the middle layer of media, and the outer layer of adventitia [1]. Within the wall of the host blood vessel, a network of microvessels is formed, the vasa vasorum. Despite lying predominantly in the adventitia, in certain large arteries, veins, and atherosclerotic arteries, these microvessels also penetrate the media [2—4]. They constitute nutrient vases within the wall of most arteries, including the aorta and coronary arteries, carotids, and femoral arteries [5,6], as well as within some intracerebral arteries and the vena cava [7,8]. A network of capillaries/venules is then laid down around the outer media, and the vasa vasorum veins empty into the veins in close proximity to the arteries [9]. Interest in the vasa vasorum has lasted for more than a century [10], first because of their attribute to supply blood to the walls of host vessels, and, second, because of their possible participation in certain cardiovascular diseases, such as atherosclerosis [7,11–16], coronary interventions [17–19], diet-induced hypercholesterolemia [20–23], and hypertension [24–26]. It is remarkable that removal of periaortic fat containing the vasa vasorum [27] or occlusion of the vasa vasorum surrounding the abdominal aorta of dogs [11] causes extensive medial necrosis and changes aortic reactivity in vivo.

2. Classification

Two anatomically distinct types of vasa exist: first-order vasa run longitudinally to the lumen of the vessel, while second-order vasa are arranged circumferentially around the host vessel [28]. The origination of vasa vasorum differs a lot, as vasa in the ascending aorta originate from coronary and brachiocephalic arteries, while vasa in the descending thoracic aorta arise from the intercostal arteries; further, vasa in the abdominal aorta may originate from the lumbar and mesenteric arteries and from the lumen of the aorta itself [7,29]. Large veins are also supplied by vasa, the ‘vasa venarum’, lying in the adventitia and penetrating the media [30]. The venules of the vasa venarum seem to emerge from the adventitia and drain into adjacent veins rather than into the lumen of the parent vessel [31]. Arterial vasa are easily
distinguishable from venous vasa, as they have a straight course, whereas the course of venous vasa is more tortuous [3]. In addition, arterial vasa are less numerous with fewer branches and have a smaller lumen than the small veins [7]. As regards their location, vasa vasorum divide into three categories. Arterial vasa vasorum may lie in the host vessel’s main lumen (internal vasa vasorum) or in nearby major branches (external vasa vasorum), while venous vasa vasorum drain into concomitant veins. Finally, coronary vasa vasorum are functionally end-arteries with deduced hemodynamic characteristics similar to the vasculature in general [9,32].

3. Pathophysiologic characteristics and its function

It has been observed that vasa are present in the media of the aorta of those animals in which the aortic wall thickness is more than 0.5 mm [33], or as redefined by Wolinsky and Glagov [34], when aortic wall exceeds 29 lamellae. Indeed, when the aorta has less than 29 lamellae, the vasa vasorum are absent from the media, whereas in the aorta of large animals, only the outer lamellae are supplied by the vasa vasorum in contrast to the inner 29 lamellae, which are avascular. For example, the media of human abdominal aorta, which is avascular, has 28 lamellae. Interestingly, the avascular regions of the abdominal aorta are prone to atherosclerosis [34], showing that the blood supply provided by the vasa vasorum may be protective. Hence, it is possible that decreases in blood flow through these microvessels contribute to atherosclerosis. Coronary arteries constitute an exception to the above definitions, as the critical wall thickness is less in coronary arteries (0.35 mm) than in the aorta [33]. Low luminal oxygen tension is the reason why large veins, despite having thin walls, are supplied by a dense network of vasa, and vasa vasorum of the canine aorta dilate in response to acute systemic hypoxia [35]. Similar to veins, the pulmonary artery, which also has low luminal oxygen tension, has a more extensive supply of vasa vasorum in the adventitia and outer media than systemic arteries [36]. Therefore, both oxygen tension and wall thickness are important determinants of the presence of vasa; and diseases that cause increases in wall thickness or hypoxia may result in important implications for the host vessel [7]. Moreover, it is clear that in certain cardiovascular diseases, including atherosclerosis, the number and density of vasa alter, which is in close relation to changes in blood supply to the conduit vessel wall [7]. Like other small-resistance arteries, arterial vasa are neuronally innervated. Despite the neural innervation of vasa being mainly sympathetic [37], other nerve types are also present in some vasa vasorum. For example, human saphenous vein [37] and rat carotid arteries [38] have calcitonin gene-related peptide- (CGRP) and substance P (SP)-containing nerves around their vasa vasorum. The endothelial surface area of the vasa vasorum has been estimated to be similar in size to that of the host vessel. The larger vasa vasorum display a regularly layered vascular structure of endothelial cells, vascular smooth muscle cells, and surrounding connective tissue [9] implying not only that the vasa vasorum may actively regulate their own tone rather than serving as a passive channel for blood flow [7] and vascular perfusion but also that the vascular adventitia, and, to a lesser extent, the media, are exposed to the same blood cells and components that are in the main lumen. Moreover, the media is exposed to the blood products from both directions, the main arterial lumen and the adventitial vasa vasorum, as it is ‘sandwiched’ between them [9]. However, the general drift of blood products tends to be from the main lumen toward the adventitia because of the higher blood pressure within the main arterial lumen [9]. Ohhira and Ohhashi [39] removed sections of the vasa vasorum attached to the canine thoracic aorta and proved that they are sensitive to a range of constrictor agents [7,39]:

5-hydroxytryptamine (5-HT) ≫ noradrenaline (NA) ≫ adrenaline ≫ dopamine

Scotland et al. [40] showed that isolated porcine vasa contract in response to a range of constrictors. Interestingly, the profile of vasoconstrictor reactivity of the isolated vasa is quite different from other small arteries, in that, whereas endothelin-1 (ET-1) produced concentration-dependent contractions, the vasa appear to be relatively insensitive to NA, thromboxane A2 (TXA2), mimetics, and angiotensin II (AngII) [7]. Just to mention that, circulating plasma levels of ET-1 are elevated in several diseases including atherosclerosis, hypertension, congestive heart failure asthma, and diabetes [41]. These data show clearly that the vasa vasorum can respond to vasoconstrictors, and support the hypothesis that these vessels regulate their own tone independently of the host vessel [7]. The vasa vasorum are also sensitive to several vasodilators. Perfusion pressure through the vasa vasorum is depressed by acetylcholine, histamine, isoprenaline, adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine or sodium nitroprusside [39]. Moreover, precontracted isolated vasa relax in response to the vasodilators bradykinin (BK), SP, and CGRP [40]. Vasa vasorum are able to maintain a dilated state and, thereby a satisfying blood flow to the vessel wall due to their increased sensitivity to vasodilators compared with vasoconstrictors [7]. Finally, the vasa vasorum in blood vessels are likely to be related to nutritional needs [7].

4. Role of the vasa vasorum in aortic diseases

Pathological neo-vascularization of the vessel wall constitutes a consistent feature in the formation of atherosclerotic plaque and progression of the disease [6,13,42]. Moreover, microvessels play a role in plaque hemorrhage linked with the development of symptoms in cerebrovascular disease [43,44]. In addition, coronary lesions from patients with acute myocardial infarction are characterized by an increase in the number of microvessels, proving a potential role of microvessels in plaque rupture and instability [6,14,16,45]. Furthermore, atherosclerotic changes of the vasa vasorum seem to be related to the formation of aneurysms [46]. Atherosclerosis results in thickening of the vasa’s intima layer. Hence, the distance between the endothelial layer and the media increases, compromising the nutrient and oxygen supply, while small intramural vasa vasorum may be obstructed by adventitial fibrosis. Reduced
nutrient and oxygen supply to the media leads to media thinning, and a necrosis is subsequent because of the necrosis of the smooth muscle cells [47]. Gore [48] suggested that rupture of aortic vasa vasorum may result in dissection, after having caused disintegration of the aortic wall. Moreover, a hematoma without a tear may occur if there is a rupture of the vasa vasorum of the media layer [6,43,47].

4.1. Role of vasa vasorum in atherosclerosis

Atherosclerosis is a progressive inflammatory disease affecting the entire vascular wall of large arteries [49]. Despite endothelial dysfunction, which constitutes the first step in the development of atherosclerosis, the vasa vasorum in the adventitia of large arteries seem to have a decisive role in the pathogenesis of this disease [7]. It is the interaction between the vasa vasorum and the endothelial function of the host vessel that results in impaired endothelial function such as occurs in early atherosclerosis [9]. Vasa vasorum can proliferate in response to acute arterial injury although their number—under normal conditions—remains constant throughout life [7]. Moreover, the combination of the presence of vasa and high intravascular blood pressure appears to be crucial for development of atherosclerosis [50]. According to the American Heart Association, atherosclerosis affects different vascular beds to a different extent [51,52]. The aorta and proximal coronary circulation, as well as the femoral, renal, and carotid arteries, are frequently affected by atherosclerotic lesions [9]. In addition, elevation of ET-1 levels plays a role in atherosclerosis [41,53], and it is subsequent that arterial vasa might constrict in response to this ET-1, so that a reduction in nutrient blood flow to the vessel wall occurs [7]. Several studies [11,13,15,16,27,53–55] suggest that impairment of nutrient blood flow through the vasa vasorum may be a factor in vessel wall hypoxia and that it is able to cause atherosclerosis or other degenerative conditions of the host vessel. The structure and function of the vasa vasorum indicate the sensitivity of the vascular wall to hypoxia, which is also highly dependent on the distribution and the density of the vasa vasorum [9]. Increased transport of low-density lipoprotein (LDL) across the endothelium seems to be involved in the very earliest stages of atherogenesis. Delivery of LDL, and probably oxidized products, may occur at a rate greater than can be accommodated by vasa vasorum despite angiogenesis, as they do not function properly, preceding cellular infiltration/proliferation in arterial wall [56–59]. Apart from the increased delivery (or impaired removal) of LDL from the arterial wall by the vasa vasorum [60], oxygen delivery through vasa vasorum also constitutes a remarkable factor causing atherogenesis [61–63]. Low oxygen tension has been proven to accelerate atherogenesis and interfere with LDL transport [64]. As regards sensitivity to oxygen tension, vasa vasorum in arteries occluded by atheromatous plaques may proliferate because of the diminution in oxygen tension in the vessel wall [7]. Furthermore, Williams et al. [65] suggest that the smooth muscle of vasa vasorum of atherosclerotic arteries is more sensitive to vasoconstrictors; thus decrease in blood flow to the vessel wall results in further vessel wall hypoxia and contributes to the progression of atherosclerosis. Moreover, atherosclerotic lesion formation is preceded by neo-vascularization of the vasa vasorum [32,66]. In normal arteries, the adventitia are not inflamed, but once atherogenesis takes place, adventitial inflammation increases with the extent and severity of atherosclerotic plaque formation [49,67]. This inflammatory reaction is associated with increased vasa vasorum. As these newly formed vessels are connected to the main vessel, the neo-vascularization of the vasa vasorum may also serve as an entry for macrophages and inflammatory factors that may contribute to the progression of the disease as also angiogenesis [68,69]. In addition, pathological neo-vascularization is characterized by increased endothelial permeability and fragility [70]. The active role of vasa vasorum is strongly supported by Moulton et al. [68,71], who demonstrated a reduced lesion progression in apoE-deficient mice after inhibiting vasa vasorum neo-vascularization. On the other hand, microvessels that grow into the media and intima may nourish and stabilize the growing plaque by delivering growth factors and hormones [72], and they may also maintain nutrient blood flow to the thickened vessel wall, thus restricting the progression of the lesion [7]. Independently of the cause, occlusion of vasa leads to weakening of the arterial wall, necrosis of sections of the media, and subintimal lipid accumulation, even if plasma cholesterol levels are low [73].

4.2. Role of vasa vasorum in atherosclerotic plaque rupture

Atherosclerotic plaque rupture is the critical, final event leading to unstable angina and myocardial infarction. Injuries due to shear stress or turbulence, rupture of the vasa vasorum, vasospasm, and increased circumferential stress have been proposed as precursors of plaque rupture [74]. Increase of vessel-wall and plaque microvessels in ruptured atherosclerotic plaques shows that there is an association between microvessels and plaque instability [75], as the inhibition of plaque angiogenesis is beneficial for plaque stability [68,71]. Moreover, several studies have suggested that vasa vasorum hemorrhage may be a definite factor in the formation of unstable atherosclerotic lesions [76]. Moreno et al. [75] observed that total neovessel density was higher in ruptured plaques when compared with non-ruptured plaques. Moreover, total neovessel density was decreased in fibrocalcific plaques when compared with lipid-rich and ruptured plaques. Lesions with mild inflammation were present in combination with the lowest total neovessel density, lesions with moderate inflammation with moderate total neovessel density, and lesions with severe inflammation with the highest one [75].

4.3. Role of vasa vasorum in aortic aneurysms

Extensive changes in the vasa vasorum of canine aorta were observed in a study [4] examining their morphology after massive overdilation with angioplasty balloon catheters. The dilated aortic segment contained fewer vasa vasorum, some of which were disrupted and stretched as well. In addition, after 4–8 weeks, there was remarkable revascularization by the vasa vasorum. A dense network of tortuous vasa vasorum with irregular caliper was formed [4].
Hyperplasia and proliferation of all three wall layers result in increased oxygen demand, which is why the vasa vasorum proliferate. However, even severe damage of the adventitia with total local disruption of the vasa vasorum does not lead to medial necrosis or progressive aneurysm formation, as long as the lumbar arteries are untouched [4].

4.4. Role of vasa vasorum in aortic dissection

Hypertension-related spontaneous rupture of the aortic vasa vasorum might result in intramural hematoma, and, subsequently, in intimal tear. Hemorrhage of the vasa vasorum weakens the media, and, the arterial pressure from blood flow in the aortic lumen subsequently favors the entrance of blood from the lumen into the aortic media [1,77]. Decreased vasa vasorum flow, occurring in arterial hypertension, may increase the stiffness of the outer ischemic media of the aorta, contributing to the formation of aortic dissection [1].

4.5. Role of vasa vasorum in intramural hematoma

Intramural hematoma belongs to the category of ‘acute aortic syndromes’. According the recent international bibliography, Intramural hematoma (IMH) and penetrating atherosclerotic ulcer (PAU) may lead to acute aortic dissection [6,27,78—81]. It is also estimated as an independent determinant of progression to aortic aneurysm formation and aortic rupture [82,83]. Intramural hematoma is a localized separation of the aortic wall layers by partially or totally clotted blood without an intimal tear. Rupture of the vasa vasorum in the media is the presumable reason why intramural hematoma occurs [84—87]. Intramural hematoma can first appear in hypertensive and atherosclerotic patients after a hemorrhage from vasa vasorum rupture into the media either spontaneously, or, more rarely, as a result of penetrating atherosclerotic ulcer [6]. Although a blunt chest trauma with aortic wall injury rarely leads to intramural hematoma [88,89], a thoracic trauma is also a possible cause for the development of intramural hematoma [1]. The international bibliography [79,82,83] suggests that the intramural hematoma unfolds to relapse, progression to classic aortic dissection, or formation of an aneurysm within 30 days of hospital admission. Atherosclerotic lesions of the thoracic aorta may ulcerate and penetrate the internal elastic lamina of the aortic wall [78]. This can result in separation of the layers of the media and in the formation of intramural hematoma [90,91], as blood leaks into the media from the aortic lumen due to arterial pressure [48]. It originates from ruptured vasa vasorum in medial wall layers and results in an aortic wall infarct that may cause a secondary tear, causing, eventually, in some cases, an aortic dissection [92,93]. The initial hematoma of the aortic wall may be augmented and may further influence the media layer of the aorta [6,47,94]. Consequently, intramural hematoma weakens the aorta and may evolve to either outward aortic rupture or inward disruption of the intima leading to aortic dissection [77,78,94,95].

4.6. Role of vasa vasorum in restenosis

When vessels are occluded with atheromatous plaques, transluminal angioplasty with balloon is the current method of restoring blood flow [7]. This procedure is associated with stretching and splitting of the intima/media as well as the adventitia of the vessel [96]. However, restenosis often occurs within 6 months, as vessel size often returns to preangioplasty dimensions. According to a recent three-dimensional study of the anatomy of normal and balloon-injured porcine coronary arteries, a decrease in the ratio of first-order to second-order vasa 28 days after balloon injury is observed [7]. Moreover, the severity of stenosis is tightly associated with the density of vasa [18]. In addition, endothelial damage of the large vessel after angioplasty is proven by several studies. It is interesting that these procedures may also harm the endothelium of the vasa vasorum, resulting in impaired endothelium-dependent control of blood flow to the vessel wall and following vessel wall hypoxia, which is a stimulus for the induction of several growth factors and cytokines, may facilitate luminal narrowing [7].

4.7. Role of vasa vasorum in hypertension

Power-Doppler imaging of blood flow through the vasa vasorum of normal human carotid arteries shows that perfusion of vasa vasorum occurs after the main flow velocity in the lumen of the carotid artery [97]. This means that the vasa vasorum fill during diastole like it happens in the coronary circulation. Hence, an increase in arterial pressure in the host vessel results in a reduction in perfusion of the vasa vasorum [7]. In addition, elevation of blood pressure and, therefore, compression of the aortic wall is associated with a noticeable reduction in blood flow through the vasa vasorum [98]. Therefore, in a situation such as hypertension, it is conceivable that increases in sensitivity to constrictors are possible. Such decreases in blood flow of the vasa vasorum would be able to cause vessel wall hypoxia, a stimulus for remodeling [7].

4.8. Role of vasa vasorum in deep-vein thrombosis and vein bypasses

The most important source of nutrition for the walls of large veins are the vasa venarum. Damage to endothelial cells is obviously the forerunner for thrombus formation. Therefore, disruption of blood flow through microvessels nourishing large veins may participate in endothelial damage and subsequent thrombosis [7]. Similarly, disruption of vasa venarum blood flow during venous bypasses may have implications for the viability of the bypass. Vasa are sensitive to oxygen tension, and, therefore, if vasa venarum are exposed to arterial oxygen tension, their number and distribution may also change [7]. However, although acute changes in distribution of vasa venarum take place, there is little evidence that these alterations have an impact on the health of the grafted vein [99].

5. Conclusions

The vasa vasorum, or ‘the vessels of the vessels’ constitute an important nutrient support to the vessel’s wall. Deficient nutrient and oxygen supply of the media lead to
media thinning and necrosis. Rupture of aortic vasa vasorum may result in intramural hematoma or acute aortic dissection after having caused disintegration of the aortic wall.

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