


REVIEW ARTICLE

Role of PVAT in coronary atherosclerosis and vein graft patency: friend or foe?

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Perivascular adipose tissue (PVAT) releases numerous factors and adipokines with paracrine effects on both vascular structure and function. These effects are variable as they depend on regional differences in PVAT among blood vessels and vary with changes in adiposity. There is considerable evidence demonstrating an association between coronary PVAT and the development and progression of coronary artery disease, which is associated with inflammation, oxidative stress, angiogenesis, vascular remodelling and blood clotting. However, PVAT also has a protective role in vascular grafts, especially the no-touch saphenous vein, in patients undergoing coronary artery bypass. This beneficial influence of PVAT involves factors such as adipocyte-derived relaxing factor, nitric oxide (NO), leptin, adiponectin, prostanoids, hydrogen sulphide and neurotransmitters, as well as mechanical protection. This article aims to highlight and compare the dual role of PVAT in the development and progression of coronary atherosclerosis, as well as in increased graft patency. Different deleterious and protective mechanisms of PVAT are also discussed and the inside-outside signalling paradigm of atherosclerosis development re-evaluated. The bidirectional communication between the arterial and venous wall and their surrounding PVAT, where signals originating from the vascular wall or lumen can affect PVAT phenotype, has been shown to be very complex. Moreover, signals from PVAT also influence the structure and function of the vascular wall in a paracrine manner.

LINKED ARTICLES

This article is part of a themed section on Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets? To view the other articles in this section visit <http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.20/issuetoc>

Abbreviations

ADRF, adipocyte-derived relaxing factor; AT, adipose tissue; BH₄, tetrahydrobiopterin; CABG, coronary artery bypass graft; IL, interleukin; ITA, internal thoracic artery; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; PCAT, pericoronary adipose tissue; PPAR, peroxisome proliferator-activated receptors; PVAT, perivascular adipose tissue; SV, saphenous vein; TNF, tumor necrosis factor; 4-HNE, 4-hydroxy nonenal; VSMC, vascular smooth muscle cells

Tables of Links

TARGETS	
Voltage-gated ion channels^a	Enzymes^c
Calcium-activated potassium channels	Akt (PKB)
Ca _v 1.2 channel	eNOS
Nuclear hormone receptors^b	
PPAR- γ	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (^{a,b,c}Alexander *et al.*, 2015a,b,c).

Perivascular adipose tissue (PVAT) is a local adipose tissue (AT) depot surrounding blood vessels. It was previously thought to act only as a passive structural support for the vasculature and was routinely removed in experiments on isolated blood vessel function and bypass graft preparation (Fernández-Alfonso, 2004). There is now a large body of evidence suggesting that PVAT is phenotypically different in adipocytes from different origin, morphology or stage of differentiation, as well as in cell composition from other AT depots, such as subcutaneous or visceral AT (Gil-Ortega *et al.*, 2015). It releases an important number of vasoactive factors that elicit a paracrine signalling effect on the vascular wall, influencing structure and function. This paracrine effect is an additional, distinctive, feature compared to the endocrine signalling associated with subcutaneous and visceral AT. There are regional phenotypic differences among PVATs, depending on the specific vascular bed, which differentially affect both the physiology of the blood vessel wall as well as the pathogenesis of vascular disease (Gil-Ortega *et al.*, 2015). Moreover, the influence of PVAT differs with changes in adiposity (Gálvez-Prieto *et al.*, 2012; Fernández-Alfonso *et al.*, 2013). Therefore, PVAT exhibits either a deleterious or a protective role depending on the vascular bed location, its magnitude and on the physiological or pathophysiological situation.

PVAT has been suggested to be associated with the development of atherosclerosis in the aorta (Fitzgibbons *et al.*, 2011; Chang *et al.*, 2012; Kawahito *et al.*, 2013; Shields *et al.*, 2013). However, most evidence, covered previously in several excellent recent reviews (Fitzgibbons and Czech, 2014; Iacobellis, 2015; Mazurek and Opolski, 2015), also demonstrates an association between pericoronary AT and the development of coronary artery disease. Coronary artery disease, due to atherosclerosis and/or coronary vasospasm, is a leading cause of mortality worldwide (World Health Organization factsheet, 2016). A mainstay in the treatment of symptomatic coronary artery disease patients, which reduces ischaemia to a greater extent than medical treatment, is revascularization. Coronary artery bypass grafting (CABG) is the most commonly performed revascularization procedure alongside percutaneous coronary intervention (Farooq and Serruys, 2015). The preservation of PVAT in blood vessel segments used for CABG, mainly saphenous vein (SV), significantly increases graft patency (Souza *et al.*, 2002; 2006; Samano *et al.*, 2015).

LIGANDS		
4-HNE	BH4	NO
5-HT	IL-1 β	Noradrenaline
Adiponectin	IL-6	TNF α
Angiotensin II	Leptin	

This article aims to highlight and compare the dual role of PVAT in the development and progression of coronary atherosclerosis, as well as on increased graft patency. It also discusses different deleterious and protective mechanisms of PVAT, and re-evaluates the inside-outside signalling paradigm of atherosclerosis development.

Pericoronary adipose tissue and coronary atherosclerosis development and progression

The AT of the heart, known as pericardial AT, consists of paracardial and epicardial fat. Both depots are different in embryological origin, anatomy and function (Sacks and Fain, 2007; Iacobellis, 2014). Paracardial fat is located within the mediastinum on the external surface of the parietal pericardium. Epicardial AT is contained beneath the visceral layer of the serous pericardium, mainly concentrated in the atrio-ventricular and interventricular grooves, covering the major branches of the coronary arteries [pericoronary adipose tissue (PCAT)] and to a lesser extent, the atria, the right ventricle and the apex of the left ventricle (myocardial AT) (Sacks and Fain, 2007; Iacobellis, 2014). Since PCAT constitutes part of the epicardial AT with no distinct anatomical barrier, there has been some confusion and both terms have been treated synonymously (Iacobellis, 2015).

PCAT volume increases with age, is higher in men than in women (Rabkin, 2007) and correlates with coronary artery disease risk factors (Fitzgibbons and Czech, 2014). Even though epicardial AT shows a strong correlation with anthropometric and imaging measurements of visceral AT with increasing body mass index (Iacobellis *et al.*, 2003), the amount by which the PCAT is increased is not necessarily related to obesity and seems to be mostly regulated locally, and is independent of increases in systemic AT (Ohyama *et al.*, 2016). Greater volumes of epicardial AT are not only associated with the severity of coronary artery stenosis in patients with known coronary artery disease (Jeong *et al.*, 2007) but also with high-risk plaques independently of risk factors, coronary artery calcification score and obstructive coronary artery disease (Lu *et al.*, 2016). In addition, atherosclerotic plaques and regions of coronary artery calcification colocalize with PCAT (Prati *et al.*, 2003; Mahabadi *et al.*, 2013),

whereas they are absent in segments underneath myocardial bridges (Ishii *et al.*, 1998; Ishikawa *et al.*, 2006) (Figure 1A). However, this is not always the case. PCAT and coronary artery calcification are not always present together, and plaques are not completely absent in myocardial bridges, suggesting that other factors, such as differences in haemodynamic parameters might contribute to these effects.

Following the original proposal of Russell Ross (1999), the development of atherosclerotic lesions is initiated by signalling originating from the vessel lumen or at the endothelial/intimal interface. However, due to its close contact with the coronary arteries, PCAT might also play a role in the development and progression of coronary artery disease. Several observations support the local paracrine influence of PCAT on the development of coronary artery disease; PCAT-derived adipokines and cytokines diffuse through the adventitia and media (Iacobellis, 2015) or pass through the *vasa vasorum* (Yudkin *et al.*, 2005) to reach the coronary endothelium and lumen (Figure 1).

Pathophysiological mechanisms involved in plaque development and progression are inflammation, oxidative stress, angiogenesis, vascular remodelling and blood clotting. Inflammation plays a central role in atherosclerosis (Ross, 1999; Libby *et al.*, 2002). Patients with coronary artery disease exhibit an increased expression of inflammatory genes in epicardial AT compared to subcutaneous AT independently of several clinical variables (Mazurek *et al.*, 2003). Gene expression analysis of *in vitro* differentiated pericoronary adipocytes

shows an increased expression of genes associated with inflammation (Chatterjee *et al.*, 2013). In addition, pericoronary adipocytes exhibit a pro-inflammatory phenotype (high levels of MCP-1, IL-6, IL-8 and pro-angiogenic mediators and reduced adiponectin) thus playing a key role in both the recruitment of inflammatory cells and the development of vascular disease (for review, Omar *et al.*, 2014). Moreover, inflammatory cells involved in the atherosclerotic process, in particular activated monocytes, macrophages and T-lymphocytes, are also resident in epicardial AT and PCAT (Mazurek *et al.*, 2003; Iacobellis, 2015). Oxidized LDL (oxLDL) is stored in PCAT and conveyed by CD68(+)-macrophages into the coronary intima (Uchida *et al.*, 2016). Oxidative stress is higher in epicardial AT than in subcutaneous AT from coronary artery disease patients with lower catalase levels (Salgado-Somoza *et al.*, 2010).

Another consequence of PCAT-derived inflammation is the stimulation of an angiogenic response and the development of a collateral circulation in patients with coronary artery disease (Okamoto *et al.*, 2001). Plaque neovascularization is composed of a network of capillaries that arise from the adventitial *vasa vasorum* and extend into the intimal layer of atherosclerotic lesions. These plaque capillaries have been proposed to be important regulators of plaque growth and lesion instability and may thus play an important role in modulating the disease process (Okamoto *et al.*, 2001). In this context, *in vitro* differentiated pericoronary adipocytes exhibit an increased expression of angiogenesis-related genes

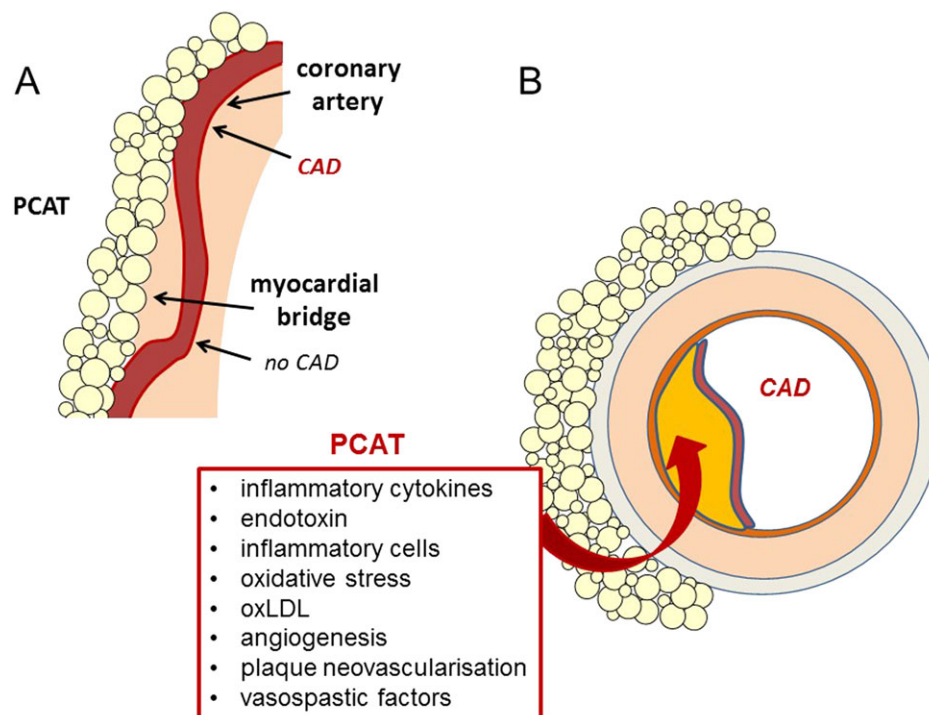


Figure 1

Influence of PCAT on the development and progression of coronary artery disease (CAD). (A) Coronary artery segments in contact with PCAT often exhibit atherosclerotic plaques, whereas coronary artery segments under myocardial bridges do usually not develop CAD. (B) Paracrine mechanisms through which PCAT influences the development of CAD. PCAT-derived adipokines, cytokines, reactive oxygen species and inflammatory cells diffuse through the adventitia and media or enter through the *vasa vasorum* to reach the coronary endothelium and contribute to atherosclerotic plaque development and progression.

(Chatterjee *et al.*, 2013). In addition, pericoronary adipocytes also show an increased expression of genes related to vascular remodelling and blood clotting (Chatterjee *et al.*, 2013).

Whereas inflammation is most often associated with atherosclerosis, vasospastic angina is a more rare condition. The underlying causes of coronary artery spasm are endothelial dysfunction, primary vascular smooth muscle cell hyperreactivity to a variety of vasoconstrictors and adventitial abnormalities (for review see Lanza *et al.*, 2011). In fact, the degree of adventitial coronary stimulation is associated with inflammatory cytokine-induced spasmogenic changes of vascular smooth muscle cells in animal models (Shimokawa *et al.*, 1996). More recently, a role for PCAT in coronary artery spasm has also been suggested. In Ossabaw swine, PCAT releases factors that initiate and/or potentiate contraction of coronary arteries independently of their effects on the coronary endothelium. The augmented contractile effects of PCAT from obese individuals are related to alterations in calpastatin, rho-dependent signalling, increased functional expression of Cav1.2 channels or altered activity of potassium channels in coronary arteries (Owen *et al.*, 2013). These signalling pathways may contribute to the initiation or progression of coronary artery disease in obesity (Noblet *et al.*, 2015)

Vasa vasorum formation is also enhanced at the spastic coronary segment in patients with vasospastic angina, which correlates with the extent of the coronary contractions (Nishimiya *et al.*, 2016). Moreover, PCAT volume is increased at the spastic segments, suggesting it contributes to coronary spasm (Nishimiya *et al.*, 2016). Interestingly, these are patients with normal weight (BMI < 25 kg·m⁻²) suggesting that the increased volume of PCAT is not necessarily related to obesity (Ohyama *et al.*, 2016).

Altogether, these observations led to the outside-to-inside signalling paradigm, in which changes in the adventitia and/or PCAT could also induce changes in the inner layer of the intima thus having a deleterious influence on the development and progression of coronary artery disease (Figure 1). Indeed, periadventitial application of endotoxin, MCP-1, IL-1 β or oxLDL induces an influx of inflammatory cells into the arterial wall, coronary vasospasm or intimal lesions, suggesting that bioactive molecules from the pericoronary tissues may alter arterial homeostasis (Prescott *et al.*, 1989; Shimokawa *et al.*, 1996; Miyata *et al.*, 2000).

The protective role of PVAT in vessels used for CABG

There is evidence that PVAT has a protective role in blood vessels commonly used as grafts in patients undergoing CABG. The first CABG performed was connecting the right internal thoracic artery (ITA) to the atherosclerotic coronary artery, an operation carried out at the Bronx Municipal Hospital Centre in New York by Robert H. Goetz in 1960 (Konstantinov, 2000). Within a decade, Favaloro (1969) introduced the use of the SV as a conduit in patients undergoing CABG. Over subsequent years, a variety of other blood vessels have been used as bypass grafts, including the radial artery and the right gastroepiploic artery. At present the ITA, the radial artery and the SV are the three most commonly

used vessels in patients undergoing CABG (Lytle *et al.*, 1985; Mehta *et al.*, 1997).

Regarding the methods of harvesting these vessels, the ITA is used as an *in situ* graft that remains connected at its proximal end, whereas both the SV and radial artery are excised and harvested as free grafts. It is noteworthy that both arteries are generally harvested with the surrounding pedicle of PVAT intact, whereas this pedicle is removed from the SV, following the original harvesting technique described by Favaloro (1969), 'Care must be taken to dissect only the vein, avoiding as much as possible the adventitia that surrounds it'. Thus the surrounding PVAT was routinely removed. One reason for SV graft stripping is that it is easier to detect side branches, which need to be carefully ligated to prevent bleeding or a tamponade and death in the worst case scenario (Sabik, 2011). However, stripping vessels of their outer layers leads to considerable vascular damage and structural changes in the graft (Tsui and Dashwood, 2002; 2013). In using the term 'conduit' (a 'pipe' or 'channel'), it seems that when preparing the vessel by established methods the vascular damage caused may produce a graft of poor quality that may require early replacement.

The ITA is accepted as the 'gold standard' for CABG since the patency rate at 10 years for this vessel is reported to be 95% compared with ~60% for the SV (Mehta *et al.*, 1997). Nevertheless, the SV is most commonly used as a graft because: (i) it is technically easy to use due to its relatively large diameter and wall characteristics; (ii) it is long and can be used to perform multiple grafts and reach any coronary artery; and (iii) it is easily harvested (Sabik, 2011). However, the performance of SV grafts is poor compared with the ITA; thrombotic occlusion being the main cause of early SV graft failure (for review see de Vries and Quax, 2016). Certainly, there are publications suggesting that the SV is inferior to the ITA (Izzat *et al.*, 1994; George *et al.*, 2006) and perhaps also the radial artery (Habib *et al.*, 2013). However, most, if not all reviews and multi-centre studies, are based on data from patients receiving SV grafts that are damaged due to using the harvesting technique originally described by Favaloro (1969).

An atraumatic, no-touch, technique of harvesting the SV with surrounding PVAT intact was introduced 20 years ago by Souza (1996) (Figure 2). This technique provides a superior graft to those prepared conventionally, with a patency superior to the radial artery (Dreifaldt *et al.*, 2013) and comparable to the ITA both in the short- (Souza *et al.*, 2002) and long-term (Souza *et al.*, 2006; Samano *et al.*, 2015). Could the cushion of surrounding PVAT, that remains intact in no-touch SV grafts, play a role in its improved performance? The most likely answer to this question is affirmative, as this distinct outermost layer of fat may 'protect' the SV in a number of ways once it has been implanted as a bypass graft in patients undergoing coronary revascularization.

Mechanical protection of PVAT

Firstly, there is evidence that PVAT has mechanical properties that protect other vascular structures from the various traumatic conditions inflicted on the vein during harvesting. For example, a high proportion of veins go into spasm while being harvested due to their manipulation by surgical instruments, a condition that can be overcome using high-pressure

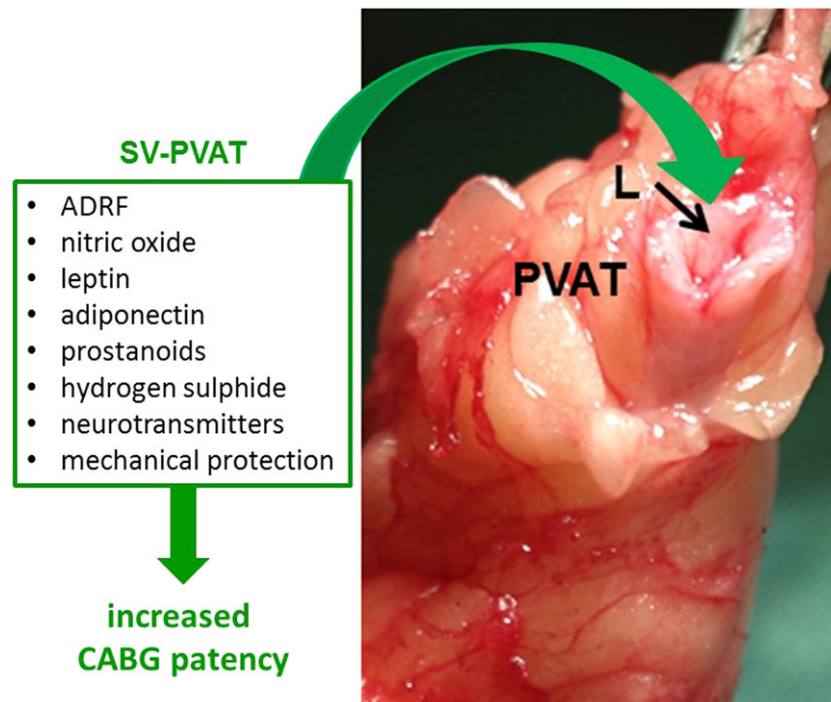


Figure 2

No-touch saphenous vein (SV) used as coronary artery bypass graft (CABG). The SV is surrounded by a cushion of PVAT. The vein lumen (L) represents a site where several of the protective PVAT-derived factors listed may confer beneficial effects that contribute to the superior performance of SV grafts in patients undergoing CABG.

intraluminal distension (Baron *et al.*, 2010). Since no-touch SV are handled via their surrounding tissue (Figure 2), spasm does not occur and the need for distension and resulting tissue damage is obviated. The cushion of surrounding fat also protects against pressure-induced disruption of the luminal endothelium and the harmful consequences of reduced local NO levels, including vasospasm, increased platelet activation and neointimal hyperplasia (Tsui and Dashwood, 2002; Baron *et al.*, 2010; Dashwood and Tsui, 2013). Once implanted, the surrounding fat acts as a buffer against arterial haemodynamics and prevents grafts of excessive length from kinking, a situation that reduces myocardial blood supply with serious consequences for the patient (Souza *et al.*, 2008).

Histologically, no-touch SVs have a dramatically different appearance to those prepared by conventional surgery. The no-touch technique minimizes trauma and damage, with the SV maintaining its normal architecture and, in so doing, provides useful control samples for comparative studies (Dashwood *et al.*, 2009). Since the introduction of this technique, a number of studies have described the considerable damage that occurs to a variety of important vascular structures likely to affect vein graft patency. At the vein's innermost layer, the endothelium, regions of denudation and ultrastructural shape changes in conventionally compared with no-touch SVs have been described (Tsui *et al.*, 2001, Tsui and Dashwood, 2002, Ahmed *et al.*, 2004, Vasilakis *et al.*, 2004, Dashwood *et al.*, 2009). Within the media, ultrastructural changes in vascular smooth muscle cells occur in conventional versus no-touch veins where dramatic shape changes and signs of nuclear mitotic activity are observed

using transmission electron microscopy (Vasilakis *et al.*, 2004). Stripping of the outer layers of the SV damages the adventitia and the *vasa vasorum* (Ahmed *et al.*, 2004; Vasilakis *et al.*, 2004; Dreifaldt *et al.*, 2011). Disruption of the *vasa vasorum* is most likely to have a detrimental effect on veins, since these microvessels are more pronounced than in arteries where circulating blood is oxygenated. In addition, there is experimental evidence that removal of the adventitia or occlusion of the *vasa vasorum* by surrounding them with a close fitting collar reduces transmural blood supply and promotes neointimal and atheroma formation, events involved in graft occlusion (Barker *et al.*, 1993; 1994).

Protective role of PVAT-derived vasoactive factors

A number of factors have been identified in the PVAT of human vessels that may play a role in their performance as bypass conduits (Figure 2). In a recent review Szasz and colleagues, discuss adipocytes and stromal cells contained within PVAT as a source of molecules affecting the underlying smooth muscle and endothelial cells that possess 'anti-contractile' rather than 'relaxant properties' (Szasz *et al.*, 2013). This terminology may be important when considering the beneficial role of PVAT-derived factors.

Adipocyte-derived relaxing factor. The first functional studies on PVAT surrounding human ITA showed that it elicits an anti-contractile effect due to the release of a transferable factor named adipocyte-derived relaxing factor (ADRF) (Gao

et al., 2005). This finding suggests that PVAT may play a role in the superior patency rate reported for this vessel when used as a conduit in patients undergoing CABG (Lytle *et al.*, 1985; Mehta *et al.*, 1997). The earlier evidence that PVAT affected the human ITA (Gao *et al.*, 2005) is supported by other groups. *In vitro* studies using segments of both animal and human vessels indicate that the effects of PVAT are mediated via ADRF (Aghamohammadzadeh *et al.*, 2012; Gollasch, 2012). For example, Malinowski *et al.* (2013) used isolated rings of human ITA *in vitro* to examine the possibility that potassium channels may be involved in the action of ADRF. Segments of ITA were precontracted with 5-HT and relaxed by adding PVAT to the tissue bath, first without and then in the presence of an appropriate potassium channel blocker. It was finally concluded that PVAT of human ITA releases relaxing factor(s) and that Ca²⁺-dependent potassium channels are involved in this relaxant effect. In a previous study, these authors reported data relating to the use of 'skeletonized' ITA. By comparing 5-HT-induced contractions of human ITA with and without pedicle intact in the presence of various potassium channel blockers, it was concluded that PVAT of human ITA releases a relaxing factor that appears to act through Ca²⁺-dependent potassium channels (Malinowski *et al.*, 2008). Although, to date, ADRF has not been identified several candidates have been suggested including adiponectin, hydrogen sulphide and palmitic acid methyl ester (Tano *et al.*, 2014).

NO. Endothelial NOS (eNOS), the main enzyme responsible for the conversion of L-arginine to NO, is present within the PVAT of no-touch SV and also localized to the endothelial cells lining the main vessel lumen, *vasa vasorum* and capillaries. High protein levels of eNOS protein were found in tissue extracts of PVAT and NO production was shown to occur using the citrulline assay (Dashwood *et al.*, 2007). Given that NO is a potent relaxant, these results suggest that PVAT-derived NO may play an important role in the improved patency of no-touch SVs via a local action on the vessel's outermost surface.

Leptin and adiponectin. Using similar *in vitro* methodology, the adipokine, leptin, was demonstrated to have a relaxant effect that was neither NO nor endothelial-dependent (Momin *et al.*, 2006). High protein expression of leptin was detected in PVAT surrounding no-touch SV grafts using immunohistochemistry and western blot analysis (Dashwood *et al.*, 2011). Also, the leptin levels assessed by ELISA were within the active range in *in vitro* blood vessel preparations (Momin *et al.*, 2006).

More recently, adiponectin, an adipokine known to be anti-inflammatory, that promotes insulin sensitivity and provides cardiometabolic protection has also been identified in PVAT of bypass vessels (Shen *et al.*, 2016), a finding of potential importance. Interestingly, in this study, positive adiponectin immunostaining was identified that was associated, not only with the endothelium of the main vessel lumen but also with the *vasa vasorum* and capillary network within the PVAT (Shen *et al.*, 2016).

Other PVAT-derived factors that influence the reactivity of human vessels used as grafts include prostanoids (Ozen *et al.*, 2013) and hydrogen sulphide (Beltowski, 2013).

Role of perivascular nerves

Sympathetic control of 'body fat' is well established, with noradrenaline being the predominant neurotransmitter involved. However, the interaction between the vascular nerves and PVAT is not well documented. Certainly, given the distribution of perivascular nerves within, or in close proximity to PVAT, the activity of adipokines may be influenced via vascular nerve activity or they may affect transmitter action, uptake or stability (Dashwood and Loesch, 2011; Bulloch and Daly, 2014). Apart from their transmitter action, many neurotransmitters possess mitogenic activity and, in this way, may play a role in the vascular remodelling associated with graft failure. This possibility was corroborated using a porcine vein graft model, where dramatic neural reorganization was demonstrated. Here, in the short-term, there was an almost complete depletion of perivascular nerves located in the media whereas, in the long-term, there was an obvious appearance of large paravascular nerve bundles and a marked increase in small paravascular nerves in the neoadventitia, changes that are associated with the VSMC proliferation and neointimal thickening that occurs in graft failure (Dashwood *et al.*, 2000; 2002). Data regarding 'nerve/fat' interactions are sparse; however, using rat mesenteric arteries, there is evidence for an interaction between adipocyte-derived angiotensin II and contractile responses mediated by neuronal excitation (Lu *et al.*, 2010).

Differences in patency between arteries and veins used for CABG

A number of groups remove the pedicle when preparing the ITA as a graft, a technique termed 'skeletonization' (Gaudiani *et al.*, 1988). This method is mainly used for practical purposes whereby 'elongation of the internal mammary artery during balloon calibration aids in the performance of sequential grafts' (Gaudiani *et al.*, 1988). There are, however, conflicting reports regarding the patency of pedicled versus skeletonized ITA (Del Campo, 2003) and some concerns regarding the use of skeletonization. Recent studies (Benedetto *et al.*, 2016) have shown no increased risk for skeletonized single ITAs, not even in diabetic patients. Skeletonization of the radial artery has also been used, although not often (Hirose *et al.*, 2003).

Therefore, the preservation of PVAT on arteries may not play as important a role as in the veins used in bypass procedures. There also appears to be regional differences between arterial and venous PVAT. In fact, adipocytes in PVAT surrounding the ITA are smaller than those in the PVAT of the SV and, apart from adipocytes, the artery is encapsulated in connective tissue, muscle and brown AT (Shen *et al.*, 2016). From studies cited in this review, it seems that many of the factors derived from PVAT have similar anti-contractile activity and have been identified in both arteries and veins. However, there might be differences in the expression pattern and relative amount of these factors leading to variations in the protective effects of PVAT in arterial and venous grafts.

Moreover, differences in the anatomical site, rather than between arteries and veins should not be excluded. Further studies need to be performed to elucidate these possibilities.

Vasa vasorum and transmural blood flow

Apart from a local, adventitial, effect, there is the potential for PVAT-derived factors to be transported from the outermost to the innermost layers of the SV (Fernandez-Alfonso *et al.*, 2016). The *in vivo* blood supply of the vasa vasorum of human SV (Figure 3) is via the external iliac artery (Lescalié *et al.*, 1986), and this route may convey a variety of factors that act on the outer vein layers and the media. However, retrograde transport of blood through the vasa vasorum from the lumen to the adventitia in no-touch SVs has been observed after removal of vascular clamps in CABG patients (Souza *et al.*, 2006), and this is supported by results from studies

where the adventitial vasa vasorum have been filled with blood perfused *in vitro* via the lumen of isolated human SV segments (Souza *et al.*, 2008; Dreifaldt *et al.*, 2011). This microvessel network extends further than the adventitial surface, since India ink staining appears not only in medial and adventitial vasa vasorum, but also in capillaries within the PVAT of no-touch SV segments perfused *in vitro*. These observations are taken as evidence for a novel system of transporting factors from outer to inner layers of the vessel, as well as to the lumen. In this way, ADRFs may play a role in maintaining a healthy graft after bypass surgery by preserving transmural flow through the vasa vasorum (Fernandez-Alfonso *et al.*, 2016). This may be of particular relevance to the SV, as this microvascular network is more pronounced and penetrates deeper into the media than in the ITA or the radial artery (Dreifaldt *et al.*, 2011).

Although this 'transmural transport system' has only been shown experimentally, and in isolated SV segments, it is possible that under certain conditions, pathological factors

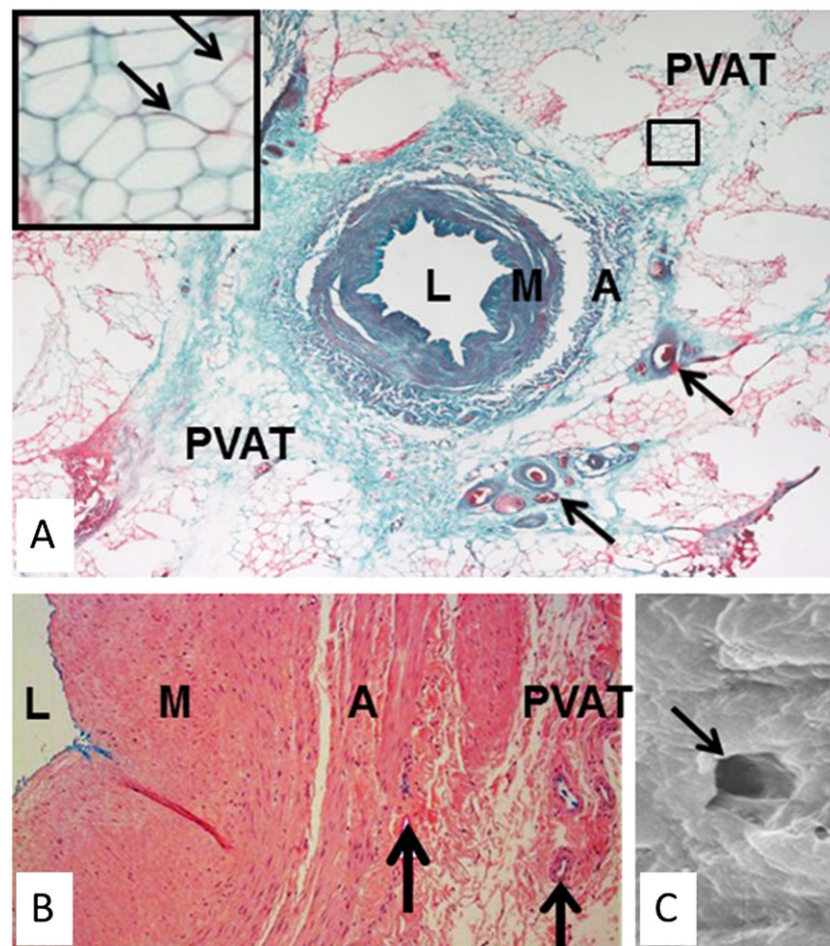


Figure 3

Inside-out/outside-in connections in human no-touch saphenous vein (SV). (A) Transverse section of a no-touch SV. Arrows indicate vasa vasorum. Inset, higher magnification of area in (B) showing adipocytes with embedded capillaries (arrows). (B) Part of a transverse section of no-touch SV perfused with Indian ink (blue stain). There is staining of the lumen and vasa vasorum within the adventitia and PVAT. (C) Scanning electron micrograph of the endothelial surface of the lumen of a no-touch SV showing the termination of a vasa vasorum (arrow). L, lumen; M, media; A, adventitia. Stained section in (B) provided by Dr Craig Daly (www.cardiovascular.org). Indian ink perfused vein in (C) is from Dr Mats Dreifaldt (unpublished). Scanning electron micrograph in (C) is from Vasilakis *et al.*, 2004.

circulating in the vessel lumen or released in the vessel wall may undergo retrograde transport to affect medial cells or cells within PVAT that are involved in inflammatory or other processes associated with coronary artery disease. Interestingly, a 'corrupted feedback hypothesis' has been suggested for noradrenaline, which, although conventionally classified as a vasoconstrictor, dilates the SV when it diffuses from the vein's *vasa venarum* into the media from the vessel lumen (Crotty, 2003). *In vitro*, this process is involved in the retrograde blood flow from the lumen of the canine SV to its *vasa vasorum* (Crotty, 1989). Such a process might occur in no-touch SV grafts and, if so, these inside-to-outside connections are possibly involved in the superior results obtained using this technique.

Bidirectional crosstalk between the vascular wall and PVAT

Based on the preceding data, the inside-to-outside signalling paradigm of Russel Ross might be re-evaluated and improved. An attractive hypothesis is that PVAT dysfunction might originate in the lumen and at the endothelial/luminal surface, starting a vicious cycle of bidirectional crosstalk between the vessel wall and PVAT (Figure 4). There is increasing evidence for this in several scenarios.

Uchida *et al.* (2016) have suggested that macrophages from the systemic circulation enter the myocardium and the PCAT through neovascularized *vasa vasorum*, obtain oxLDL from the PCAT and transport it to the intima. After

endothelial denudation of mice femoral and rat iliac arteries there is a significant down-regulation in adiponectin and an up-regulated expression of pro-inflammatory cytokines in PVAT (Takaoka *et al.*, 2009). This is followed by PPAR- γ -mediated phenotypic changes and the infiltration of inflammatory cells into PVAT that is dependent on vascular TNF- α expression, which influences neointimal formation following vascular injury (Takaoka *et al.*, 2010). This suggests that PVAT may protect against neointimal formation after angioplasty under physiological conditions and that inflammatory changes in the PVAT may have a direct role in the pathogenesis of vascular disease (Takaoka *et al.*, 2009).

Two studies by Antonopoulos *et al.* (2015, 2016) further support bidirectional signalling in human vessels surrounded by PVAT. In SV and ITA, peroxidation products produced in the vascular wall [4-hydroxynonenal (4-HNE)] up-regulate adiponectin gene expression in PVAT via PPAR- γ . PVAT-derived adiponectin improves NO production and reduces superoxide anions through a combined effect on eNOS activation (via PI3/Akt phosphorylation) and coupling (by increasing BH4 bioavailability) (Margaritis *et al.*, 2013). Moreover, these authors showed that an increased level of NADPH oxidase-derived superoxide anion in the arterial wall is correlated with increased adiponectin gene (ADIPOQ) expression in the PVAT surrounding it. Activation of NADPH oxidase in the ITA wall leads to the local production of oxidation products, that is, 4-HNE up-regulates PPAR- γ -mediated ADIPOQ expression in the neighbouring PVAT (Antonopoulos *et al.*, 2015). These findings indicate that oxidation products released from the arterial wall may represent

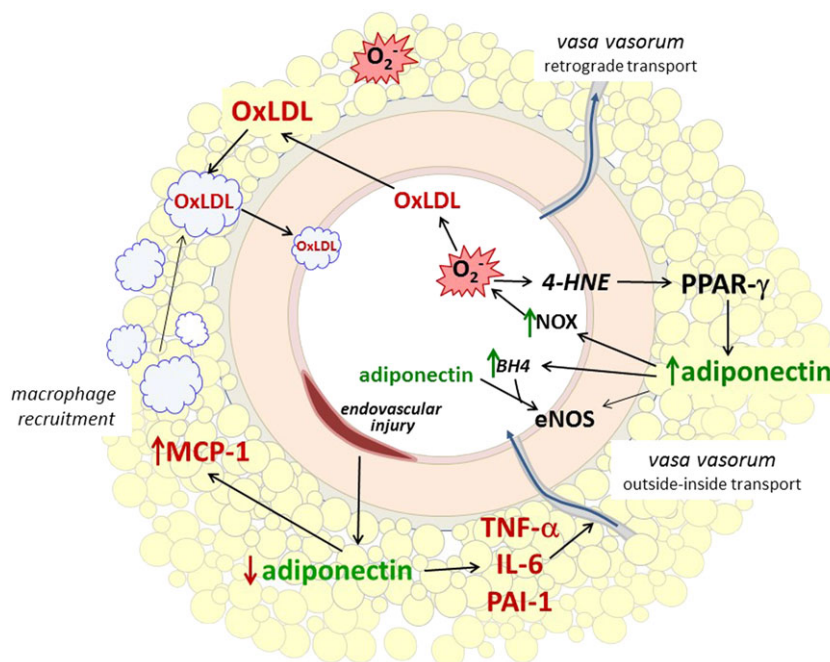


Figure 4

Bidirectional paradigm. Signals from the lumen and from the endothelial/luminal surface modulate PVAT function/dysfunction by the inside-outside paradigm described by Russel Ross. Alterations in PVAT then have a paracrine beneficial/deleterious influence on the endothelium. 4-HNE, 4-hydroxynonenal; BH4, tetrahydrobiopterin; MCP-1, monocyte chemoattractant protein; NOX, NADPH oxidase; O₂⁻, superoxide anion; PAI-1, plasminogen activator inhibitor type 1.

'rescue signals' towards PVAT to increase the expression of adiponectin as a local mechanism for controlling vascular NADPH oxidase activity.

In summary, there appears to be a more complex bidirectional communication between the arterial and venous wall and their surrounding PVAT than first realized. Signals originating from the vascular wall or lumen can affect PVAT structure and function, whereas signals from PVAT also influence structure and function of the vascular wall in a paracrine manner.

Conclusions and future perspectives

Taken together, the data presented in this review suggest that PVAT has a dual role depending on the blood vessel it surrounds and on the physiological/pathophysiological situation. Coronary PVAT has a deleterious influence in the development and progression of coronary artery disease, associated with inflammation, oxidative stress, angiogenesis, vascular remodelling and blood clotting. However, a protective role of PVAT is observed in vascular grafts, especially the no-touch SV, increasing graft patency in patients undergoing CABG. These influences involve a complex bidirectional communication between the vascular wall and its surrounding PVAT, observations that require further analysis in different vessels and physiological/pathophysiological situations.

The characterization of deleterious PVAT-derived factors and mechanisms associated with vascular disease development and progression provides a list of potential therapeutic targets (i.e. inflammatory cytokines and oxidant molecules) for designing novel therapeutic strategies. The most logical approach might be to shift the local imbalance of PVAT-derived factors towards an increase in protective factors, such as ADRF, leptin and adiponectin, thus reducing oxidative stress and inflammation. However, the finding that oxidation products from the vascular wall may be 'rescue signals' targeted towards PVAT to increase adiponectin as a control mechanism of vascular NADPH oxidase (Antonopoulos *et al.*, 2015) suggests any such treatment may be more complex. Indeed, in certain cases antioxidant therapy has been ineffective (Myung *et al.*, 2013) or, in some situations, even detrimental (Gale *et al.*, 1995).

It should be noted that most of these findings show an association between PVAT and both beneficial and deleterious influences on the vascular wall, although there is no current proof of causality. Therefore, there is no doubt that further experimental research is needed to mechanistically link PCAT as a cause of coronary artery disease, as well as further evidence that preservation of PVAT plays an important role in increased graft patency.

Without doubt, many questions regarding the bidirectional pathways and PVAT-vascular wall interactions in health and disease remain unanswered. A deeper understanding of the pathological and physiological conditions is required in order to confirm whether these fat depots confer beneficial or detrimental effects on the vessel in question and whether therapeutic targeting should be luminal or abluminal.

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Author contributions

M.G.-O., I.A. and B.S. wrote the PCAT section and contributed to Figures 1 and 4. D.S. and M.D. wrote the SV section and contributed to Figures 2 and 3. M.S.F.-A. and M.R.D. organized and supervised text and figures; wrote the final version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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