Perivascular adipose tissue and coronary vascular disease

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Abstract

Coronary perivascular adipose tissue (PVAT) is a naturally occurring adipose tissue depot that normally surrounds the major coronary arteries on the surface of the heart. While originally thought to promote vascular health and integrity, there is a growing body of evidence to support that coronary PVAT displays a distinct phenotype relative to other adipose depots and is capable of producing local factors with the potential to augment coronary vascular tone, inflammation, and the initiation and progression of coronary artery disease. The purpose of the present review is outline previous findings regarding the cardiovascular effects of coronary PVAT and the potential mechanisms by which adipose-derived factors may influence coronary vascular function and the progression of atherogenesis.

Introduction

Coronary perivascular adipose tissue (PVAT) is a visceral adipose tissue of mesothelial origin that normally surrounds the major coronary arteries on the surface of the heart[1, 2]. Coronary PVAT is functionally distinct from the adipose tissue found on the surface of the myocardium, which is defined as myocardial (epicardial) adipose tissue (mEAT)[3, 4]. In addition to adipocytes and pre-adipocytes, coronary PVAT contains fibroblasts, macrophages, leukocytes, as well as blood vessels and autonomic nerves. With no fascia separating PVAT from the coronary circulation and myocardium, these essential components of the heart share the same microcirculation[1]. Originally perceived as a relatively ubiquitous and benign tissue that largely provides structural support and insulation[5, 6], it is becoming clear that factors derived from PVAT (adipokines) are capable of influencing a variety of key (patho)physiologic parameters. In particular, recent data support that cardiac adiposity expands with obesity[7], that atherosclerotic plaques occur predominately in coronary arteries that are encased in PVAT[7-10], and that coronary PVAT volume is positively associated with underlying plaque burden[11]. Patients with high mEAT volume have also been shown to have a higher incidence of atrial fibrillation, independent of

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left atrium enlargement[12-14]. As such, cardiac adiposity has been identified as an independent risk factor for coronary artery disease[8, 15, 16] and a predictor of future coronary events[17]. While specific adipokines can serve to promote vascular health and integrity[5, 18, 19], evidence is mounting in support of marked up-regulation of pro-atherogenic mRNA and protein expression profiles in coronary PVAT and mEAT in the setting of obesity[20-25]. This aberrant regulation of coronary PVAT also correlates with underlying vascular dysfunction and disease in obesity[23, 26-30]. Thus, there is growing evidence to support the hypothesis that local alterations in PVAT-derived factors contribute to the initiation, progression and expansion of coronary disease[24], independent of changes in visceral adipose tissue and/or systemic adipokine levels that may occur in the setting of obesity[31]. The purpose of the present review is to outline current data regarding the cardiovascular effects of coronary PVAT and the potential mechanisms by which adipose-derived factors may influence coronary endothelial and smooth muscle function and the progression of atherogenesis.

Vascular Effects of Peripheral vs. Coronary PVAT

Initial studies in to the vascular effects of peripheral (non-cardiac) PVAT demonstrated significant reductions in contractile responses to a variety of agonists in aorta[32-35], mesenteric[36-38], and human internal thoracic arteries[39, 40]. This "anti-contractile" (or ADRF) vasodilator effect has been attributed to PVAT-derived adiponectin[41], hydrogen sulfide (H_2S)[37], hydrogen peroxide (H_2O_2)[33], and Ang1-7[42] mediated vasodilation via the opening of voltage-dependent K_V7 channels[37], BK_{Ca} channels[40, 43] and/or Kir channels[33]. In contrast, the presence of peripheral PVAT has also been shown to potentiate contraction of mesenteric arteries to electrical field stimulation via increased production of angiotensin II and superoxide[44, 45]. Recent data from Watts *et al.* implicate chemerin as a PVAT-derived constricting factor in aortic and mesenteric vascular beds[46]. Thus, non-cardiac PVAT is capable of producing factors that illicit both vasodilation and vasoconstriction.

Experiments to elucidate the vascular effects of coronary PVAT are rather limited and somewhat conflicting. Studies in isolated coronary arteries from lean or hypercholesterolemic swine show little to no effect of coronary PVAT on endothelial-dependent vasodilation or coronary contractile responses to endothelin-1, angiotensin II, or the thromboxane A2 mimetic U46619[47-49]. Alternatively, coronary PVAT has been found to diminish endothelial-dependent dilation in dogs[29, 50] and to significantly exacerbate underlying coronary endothelial dysfunction in obese swine[48]. Further studies in "clean" (PVAT free) conduit coronary arteries revealed that the addition of coronary PVAT from lean swine augments contractile responses to KCl-induced depolarization and to prostaglandin F2α in proportion to the amount of PVAT added to the bath[23]. Interestingly, this effect was also observed in response to mesenteric PVAT, but not subcutaneous PVAT. Furthermore, the constricting effect of coronary PVAT was markedly exaggerated in endothelium intact and denuded coronary arteries from obese swine. Additional findings support that these enhanced effects are associated with substantial alterations in the protein expression of obese coronary PVAT[23, 24] and with inherent differences in the phenotype of obese smooth muscle cells[51, 52]. Taken together, these findings indicate that factors derived from coronary PVAT can act to impair endothelial-dependent dilation and potentiate

contractions of coronary vascular smooth muscle, especially in the setting of obesity. Potential mediators and mechanisms of these influences are discussed below.

In summary, the findings to date indicate that the vascular effects of PVAT are highly dependent upon anatomical location of the artery/adipose tissue depot, the species being studied, the pharmacologic agonist(s) used, and the underlying phenotype of the endothelium and smooth muscle in relation to the overall health status of the studied model[23, 53]. Generally, PVAT from peripheral beds exerts vasodilator "anti-contractile" influences whereas coronary PVAT tends to induce vasoconstrictor effects, which includes attenuation of endothelial-dependent dilation. It is important to recognize that the experimental evidence thus far derives from *in vitro* examination of isolated arteries. Thus, the functional (physiologic) relevance of these vascular influences on the regulation of blood pressure, organ blood flow, and/or progression of disease remains a critical and experimentally difficult question to address moving forward. In addition, more careful examination of the precise cell types and mediators responsible for these effects is also warranted.

Expression Profiles in Coronary PVAT

Recent evidence supports that there are substantial differences in gene and protein expression in different adipose tissue depots (e.g. subcutaneous vs. coronary) and that these profiles are significantly altered in the setting of disease. Examination of PVAT surrounding the major coronary arteries suggests that this adipose depot is phenotypically consistent with both white and brown adipose tissue[54, 55]. Data from the Weintraub laboratory indicate that adipocytes from human coronary PVAT exhibit a reduced state of adipogenic differentiation compared to adipocytes from other depots from the same subjects (e.g. subcutaneous or perirenal-visceral)[56] and that expression of pro-inflammatory genes and secretion of cytokines such as IL-6, IL-8, and monocyte chemoattractant protein (MCP-1) is markedly elevated in coronary PVAT vs. other adipose tissue depots and/or in the presence of coronary artery disease[20, 56] (see Table). Furthermore, recent findings from our laboratory as well as others support that this heightened pro-inflammatory environment of coronary PVAT is markedly exacerbated by obesity and/or with the progression of coronary artery disease[21-23, 26, 31, 48, 57-59]. In particular, increased expression of "pro-atherogenic" factors including leptin, resistin, tumor necrosis factor-α, IL-6, chemerin and calpastatin have been documented to date[9, 23, 26, 46, 48, 57, 60-64]. Diminished expression of potentially "vasculoprotective" proteins such as adiponectin, which has been associated with improvements in endothelial function[65], has also been demonstrated in human coronary PVAT in the setting of obesity and coronary artery disease[26, 31, 58, 66, 67, 68] (see Figure). Interestingly, augmented expression of the osteogenic factors osteoprotegerin[20] and osteoglycin[23] were also recently identified in coronary PVAT. These factors have been previously linked with atherosclerosis and the severity of coronary artery disease[69, 70]. Accordingly, strong and growing evidence supports that coronary PVAT displays a distinct phenotype relative to other adipose tissue depots and is capable of locally producing factors with the potential to influence the initiation and progression of coronary vascular dysfunction and disease.

Within the context of coronary PVAT expression profiles it is important to consider how factors produced in the coronary adventitia are able to traverse the arterial wall to influence the endothelium and/or vascular smooth muscle. The current hypothesis is that the vasa vasorum, a network of small vessels that supply blood to the walls of large blood vessels, is interspersed within the PVAT and thus is capable of delivering adventitial-derived factors to conduit coronary arteries[71-73]. This hypothesis is supported by prior studies which have demonstrated that neovascularization of the coronary vasa vasorum precedes the development of overt endothelial dysfunction in swine fed a high cholesterol diet[72] and by experiments which found increases in blood flow through the vasa vasorum to the intima of atherosclerotic coronary arteries of monkeys[74]. Neovascularization originating from the adventitia has also been associated with the extent of inflammation and coronary disease in humans[75]. Although the temporal association between expansion of the coronary vasa vasorum and the development endothelial dysfunction and atherosclerosis is intriguing, further studies to directly examine this hypothesis for the transit of PVAT-derived factors across the coronary wall are needed.

Pathways Influenced by Coronary PVAT

As outlined above, initial studies regarding the vascular effects of coronary PVAT have shown that factors produced by this depot can impair endothelial-dependent vasodilation and augment coronary smooth muscle constriction, especially in the setting of obesity[23, 24]. At present we are far from understanding the precise factors and signaling pathways responsible for the vascular effects of coronary PVAT. However, there are recent investigations which provide insight regarding potential mechanisms of PVAT-induced coronary vascular dysfunction.

Data from our laboratory support that coronary PVAT significantly attenuates endothelial dependent dilation of isolated coronary arteries in the setting of obesity[48]. This endothelial dysfunction was associated with elevated expression of the adipokine leptin, which we have demonstrated induces significant reductions in coronary endothelial nitric oxide production via a PKC-β dependent phosphorylation of eNOS at the Thr^{495} inhibitory site[48, 50, 62]. This hypothesis is supported by additional studies that found that the endothelial effects of obese coronary PVAT are abrogated by the inhibition of leptin receptors with a recombinant, pegylated leptin antagonist or by the inhibition of PKC-β with ruboxistaurin[48]. These findings are corroborated by data from other laboratories which have documented increased activation of PKC-β in obesity[76-79]. Prior studies have also implicated leptin in other key aspects of atherogenesis, including: 1) monocyte chemattraction[80]; 2) promotion of cholesterol ester accumulation in foam cells[81]; 3) reduction of plasma high density lipoprotein cholesterol and apolipoprotein A-I concentrations[82, 83]; 4) activation of acute phase reactants[84, 85]; 5) elevation of oxidative stress and modification of plasma lipoproteins[86]; 6) augmented DNA-binding activity of proinflammatory transcription factors[87].

Alternatively, reductions in adiponectin expression in obese coronary PVAT could facilitate inflammation, endothelial dysfunction, and atherogenesis as recent data from Karastergiou *et al.* indicate that administration of recombinant adiponectin successfully reversed PVAT-

mediated increases in endothelial adhesion molecule expression (ICAM-1) and adhesion of monocytic cells to human coronary artery endothelial cells[61]. PVAT-derived adiponectin has also been shown to improve the bioavailability of nitric oxide in gluteal arteries obtained from healthy, but not obese humans[41]. Prior studies also demonstrate that adiponectin administration diminishes oxidative stress, inflammation, and improves endothelial function via adenosine monophosphate-activated protein kinase (AMPK)-induced phosphorylation of eNOS at Thr[176][65, 88, 89]. Taken together, these findings suggest that an imbalance between pro-atherogenic vs. anti-atherogenic PVAT-derived adipokines could serve to activate a number of key regulatory pathways to promote obesity-induced coronary artery disease at a local level. Alterations in these pathways, along with other adipokines such as resistin and tumor necrosis factor-α that are known to negatively impact endothelial function and vascular remodeling[90-95] should be further explored.

Recently, Owen *et al.* documented that coronary PVAT is capable of releasing factors that initiate and/or potentiate coronary contraction via activation of voltage-dependent ion channels (i.e. $Ca_V1.2$ channels)[23]. This effect of PVAT was substantially augmented in tissues obtained from obese relative to lean swine, thus suggesting that obesity increases production of "adipose-derived constricting factors" from coronary PVAT. A global proteomic assessment of coronary PVAT supernatant from lean and obese swine revealed substantial alterations in key regulatory pathways, including cellular growth and proliferation (51 molecules) and cellular movement (39 molecules). Of particular interest were increases in RhoA (2.9-fold) and calpastatin (1.6-fold) which are directly linked to smooth muscle contraction, Ca^{2+} sensitization, and the progression of hypertension[96, 97]. Further studies to examine the effects of calpastatin, a known endogenous calpain inhibitor[97, 98] revealed that this protein dose-dependently augments contractions of isolated coronary arteries similarly to that of coronary PVAT. Interestingly, interrogation of the Rho-kinase pathway revealed that coronary contractions to lean PVAT are largely mediated via a Rho-dependent pathway, whereas enhanced coronary contractions to obese coronary PVAT occurred independent of Rhokinase signaling (was unaffected by the inhibition of Rho-kinase). These data, along with concurrent evidence that PVAT-derived factors significantly impair coronary vasodilation of H_2O_2-sensitive K^+ channels[23], indicate that the effects of coronary PVAT are related not only to inherent alterations in coronary PVAT expression profiles but also to underlying mechanistic differences in obese coronary artery smooth muscle cells. This hypothesis is supported by earlier studies from our laboratory and others which have demonstrated that obesity decreases the functional expression of coronary K^+ channels[99-103] and increases coronary $Ca_V1.2$ channel current, expression, and contraction[51, 52, 104].

Implications and Conclusions

Taken together, there is a growing body of evidence to support that changes in the phenotypic expression patterns in coronary PVAT occur concomitantly with mechanistic alterations in endothelium and vascular smooth muscle. These changes appear to be dependent on the unique characteristics of the cell types involved and the underlying environment/milieu in which they reside. However, the extent to which PVAT-derived factors "causally" contribute to changes in vascular expression of K^+ channels, Ca^{2+}

channels, Rho-signaling, macrophage/foam cell formation, and/or regional heterogeneity of smooth muscle differentiation/proliferation and atheroma progression has not been determined. Future research to delineate the involvement of specific adipose tissue cell types, how adipose tissue-derived factors are delivered to the vascular wall and possibly systemic circulation (i.e. vasa vasorum), identity of precise mediators, as well as signaling pathways and end-effector mechanisms influenced by coronary perivascular and epicardial adipose tissue beds remain central questions moving forward.

Acknowledgments

Abbreviations

ADRF	adipose derived relaxing factor
AMPK	adenosine monophosphate-activated protein kinase
H_2O_2	hydrogen peroxide
H_2S	hydrogen sulfide
mEAT	myocardial epicardial adipose tissue
MCP-1	monocyte chemoattractant protein-1
PKC	protein kinase C
PVAT	perivascular adipose tissue

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Significance

There is a growing body of evidence to support that changes in the phenotypic expression patterns in coronary perivascular adipose tissue (PVAT) occur concomitantly with mechanistic alterations in endothelium and vascular smooth muscle in the setting of cardiovascular disease. These changes appear to be dependent on the unique characteristics of the cell types involved and the underlying environment/milieu in which they reside. This review summarizes current findings regarding the cardiovascular effects of coronary PVAT and outlines potential mechanisms by which adipose-derived factors may influence coronary disease.
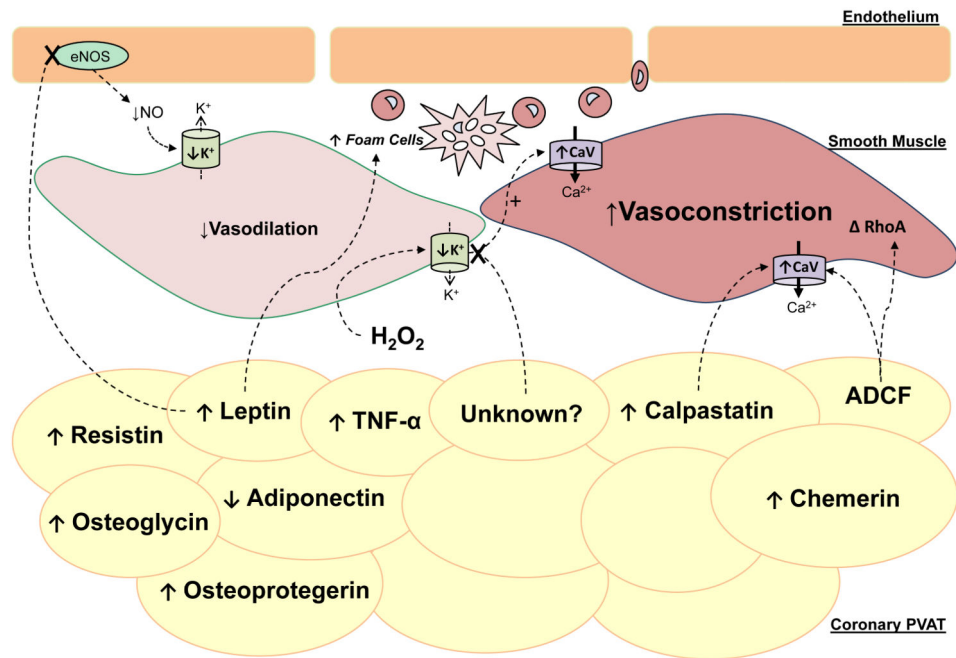
Figure 1.
Schematic diagram outlining known alterations in coronary PVAT-derived adipokines and potential downstream effector mechanisms in endothelium and vascular smooth muscle. Leptin released from coronary PVAT diminishes eNOS activity, preventing nitric oxide mediated dilation of vascular smooth muscle via activation of K^+ channels and contributes to the recruitment of macrophages and retention of foam cells in the extravascular space. Calpastatin and an unknown adipose-derived constricting factor(s) (ADCF) increase vasoconstriction via $Ca_V1.2$ channels and may function to increase RhoA activity in healthy coronary smooth muscle. Other adipokines implicated in other vascular beds may also play a role in promoting coronary vascular endothelial and smooth muscle dysfunction, including, but not limited to: increases in resistin, chemerin, osteoglycin, osteoprotegerin, and decreases in adiponectin production.

Table

Comparison of coronary perivascular and subcutaneous adipose tissue adipokine expression.

Adipokine	Condition	Coronary PVAT Expression Relative to Subcutaneous	References
Leptin	NCAD	↓ mRNA	60
	CAD	↓ mRNA	57
Adiponectin	NCAD	↓ mRNA, ↓ protein secretion	60
	CAD	↑ protein secretion	26
TNF-α	NCAD+CAD	↑ mRNA	64
	CAD	↑ mRNA, ↑ protein secretion	63
		↓ protein secretion	26
IL-6	NCAD	↑ mRNA	60, 20
	NCAD+CAD	↑ mRNA	64
	CAD	↓ mRNA	57
		↑ protein secretion	63
IL-1β	NCAD+CAD	↑ mRNA	64
	CAD	↑ mRNA, ↑ protein secretion	63
MCP-1	NCAD	↑ protein secretion	60
	NCAD+CAD	↑ mRNA	64
	CAD	↑ mRNA, ↑ protein secretion	63
PAI-1	CAD	↓ mRNA	57

NCAD, no coronary artery disease; CAD, coronary artery disease; NCAD+CAD, grouped population of NCAD and CAD; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1.