

Commentary Article

# FACTORS CONTRIBUTING TO DIFFERENCES IN THE ANTICONTRACTILE FUNCTION OF THORACIC AND ABDOMINAL PERIVASCULAR ADIPOSE TISSUE

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## About the Study

Perivascular Adipose Tissue (PVAT) is a unique ectopic fat depot that attaches to the majority of blood vessels. Initially, it is regarded solely as a structural supportive tissue that provides physical protection for blood vessels [1]. However, PVAT is noted for maintaining vascular homeostasis because of its proximity to and direct contact with the adventitia which is considered as its foremost function [2,3]. This specialized tissue secretes adipokines with vasodilatory functions and regulates vascular function via paracrine and endocrine mechanisms [4-6]. Interestingly, PVAT exhibits phenotypic differences depending on its anatomical location. Specifically, thoracic PVAT consists of Brown Adipose Tissue (BAT), whereas abdominal PVAT comprises a combination of both BAT and White Adipose Tissue (WAT) [7,8]. PVATs in different regions exhibit significant variations not only in phenotype, but also in the number and size of adipocytes, the degree of immune cell infiltration, the response to various agonists, the ability to release specific adipokines, Norepinephrine (NE) concentrations and innervation. The considerable heterogeneity between thoracic and abdominal PVAT may lead to regional variations in anticontractile function.

Previous studies have demonstrated that the number and size of abdominal adipocytes are significantly greater than those of thoracic adipocytes and the levels of inflammatory genes and immune cell infiltration markers in abdominal PVAT are greater than those in thoracic PVAT. The pro-inflammatory and proatherosclerotic characteristics

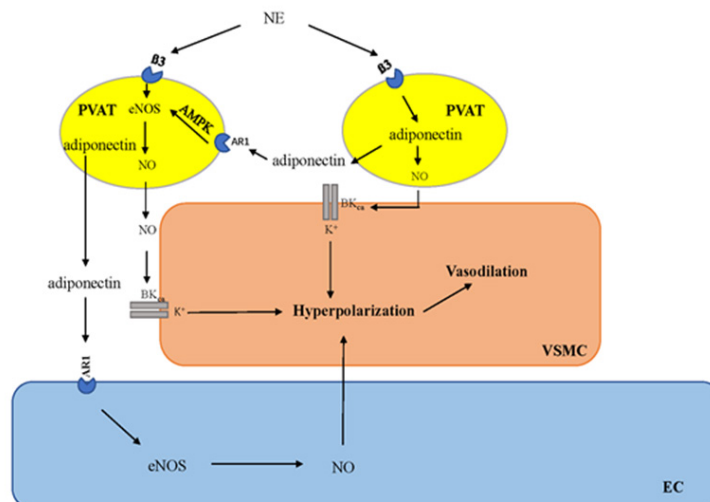
of abdominal PVAT are more pronounced than those of thoracic PVAT, potentially accounting for the heightened susceptibility of the abdominal aortic region to the disease [9]. The differences in histology and the immune cell response of thoracic and abdominal PVAT may be associated with regional differences in PVAT-mediated vascular function. In the rat aorta it was observed that PVAT diminishes the contractile response to NE, this is the major role of PVAT in vascular function [10]. However, the heterogeneity of PVAT across various aortic regions results in regional differences in the modulation of vascular function. The anticontractile function was found to be impaired in the abdominal PVAT group compared with the thoracic aorta group. Victorio et al., conducted an analysis of the mechanisms responsible for regional differences in the anticontractile function of PVAT by comparing Nitric Oxide (NO) synthesis and availability. Reactive Oxygen Species (ROS) production and lipid peroxidation were found to be comparable between the abdominal and thoracic aorta as well as between abdominal and thoracic PVAT, whereas the expression of endothelial Nitric Oxide Synthase (eNOS) and NO utilization in the abdominal PVAT are notably lower compared to those in thoracic PVAT, with no significant changes observed in the vasculature [11]. Hence, regional disparities in NO production derived from eNOS in PVAT adipocytes might contribute to the variations in their anticontractile function. However, a previous study demonstrated that the inhibition of NOS does not block the anticontractile function of aortic PVAT. Therefore, it can potentially be deduced that the relaxation factor derived from PVAT is not NO [12]. When PVAT is stimulated, it releases a transferable anticontractile

tile factor known as adiponectin, it is evident from the experiments with organ bath solution transfer. NO enhances the opening of large-conductance calcium- and voltage-activated  $K^+$  channels BKCa in Vascular Smooth Muscle Cells (VSMCs) derived by adipocyte resulting in membrane hyperpolarization and subsequent vasodilation. The release of the vasodilator adiponectin from PVAT is initiated by the activation of the  $\beta_3$ -adrenergic receptor. This mechanism is mediated by the sympathetic neurotransmitter NE, a sympathetic neurotransmitter as shown in [5,13-16].

Interestingly, similar regional disparities in the concentration of NE within adipose tissue have been observed. Ahmad et al., conducted an analysis of the content of NE in thoracic PVAT, superior mesenteric PVAT, mesenteric PVAT and retroperitoneal fat and reported that thoracic PVAT, which contains more brown adipocytes, had a greater content of NE; that mesenteric PVAT, which contains more white adipocytes, had a lower content of NE. The NE content in thoracic PVAT was approximately 7-fold higher than that in mesenteric PVAT. Furthermore, the NE content in superior mesenteric PVAT was intermediate between the levels observed in thoracic and mesenteric PVA. The variations in NE content between different tissues may be associated with differences in the adipose tissue phenotype [17]. Thus, the abdominal PVAT, which comprises a mixture of brown and white tissue, may have lower levels of NE than

the thoracic PVAT dose [9]. Additionally, NE is a sympathetic neurotransmitter and because it stimulates the anticontractile function of PVAT, there is substantial evidence that PVAT is innervated by sympathetic nerves [10,13,18-20]. Similarly, the nerve density in adipose tissue varies regionally. Contreras et al., elucidated the major role of nerve density in facilitating the development of the brown adipocyte phenotype. Compared with WAT, BAT contains a greater number of sympathetic fibers [21-23]. Analysis of the innervation density of aortic PVAT, mesenteric PVAT and WAT revealed that aortic PVAT, which contains brown adipocytes, is densely innervated by sympathetic nerves, whereas mPVAT, which consists of white adipocytes and WAT are less densely innervated.

Therefore, the innervation density of brown-like thoracic PVAT depots are found to be more than that of abdominal PVAT depots, comprising of a mixture of brown and white tissues. It could be a complex phenomenon associated with the elevated NE content in thoracic PVAT. NE concentrations and Sympathetic innervation were found to reveal regional variations within PVAT and the release of anticontractile factors from PVAT is driven by processes downstream of the NE-mediated stimulation of adipocytes [16]. Variations in NE content between thoracic and abdominal PVAT may influence regional disparities in anticontractile function by affecting the activity of the  $\beta_3$ -adiponectin-eNOS pathway.



**Figure 1.**  $\beta_3$ -adrenoceptor is activated by Norepinephrine (NE) derived from sympathetic nerves, which leads to the stimulation of adiponectin secretion from adipocytes in PVAT and the regulation of vascular tone through downstream signaling pathways. Note: AMPK: Adenosine Monophosphate-Activated Proteinkinase; eNOS: Endothelial Nitric Oxide Synthesis; NO: Nitric Oxide; ARI: Adiponectin Receptor 1, PVAT: Perivascular Adipose Tissue; VSMC: Vascular Smooth Muscle Cells; EC: Endothelial Cells

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