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The Role of Adipose Tissue in the Regulation and Dysregulation of Blood Pressure: A Conceptual Narrative Review

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Abstract

Adipose tissue is a metabolically active tissue with its amount and functionality known to affect cardiometabolic status of individuals including blood pressure. The aim of this review is to summarize the interactions of adipose with skeletal muscle and liver in the regulation and dysregulation of blood pressure. Online searches of Google Scholar, PubMed, and Scopus were conducted. Increased metabolic demands from tissues such as adipose tissue, skeletal muscle and gut causes local vasodilation and simultaneous widespread sympathetic activation to prevent fall in cardiac output and divert blood away from metabolically less active tissue at the moment. Both local vasodilatation and the systemic vasoconstriction are triggered by the same local factors such as ATP, ADP and bradykinin with the vasoconstriction effects mediated through afferent reflexes. This can cause blood pressure to either rise or fall depending on the balance between the local vasodilatory and systemic vasoconstrictor effects essentially making local metabolic activity a central factor in determining systemic blood pressure. Increased metabolic activity of skeletal muscle is synonymous with increased physical activity whereas increased metabolic activity of the gut is synonymous with feeding. In both cases, there is increased adipose tissue metabolic activity for opposing reasons; lipolysis in the former and fat storage in the latter. Increased lean body mass inevitably happens in the context of increased physical activity and skeletal muscle mass and with reduction of both fat mass and adipose tissue afferent reflex, hence reduction in blood pressure. Obesity happens under exactly opposite context; decreased physical activity and an increase in both fat mass and adipose tissue afferent reflex and thus high blood pressure.

Keywords: Adipose tissue, Blood pressure, Hypertension, Obesity

INTRODUCTION

Blood pressure is a function of the cardiac output and total peripheral resistance. The relationship is expressed in the equation:

Blood Pressure = cardiac output × total peripheral resistance (Hall & Hall, 2020).

The total peripheral resistance is dependent on the degrees of vasoconstriction of arterioles (resistance vessels) cardiac output is in turn dependent on the stroke volume (amount of blood pumped by heart during each beat) and heart rate. The stroke volume is dependent on force of heart contractility as well as end-diastolic volume; the latter is dependent on venous return

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to the heart (determined by constriction of veins, capacitance vessels) and total blood volume (Ghosh & Pandit, 2019; Hall & Hall, 2020)

The adipose tissue is a metabolically active endocrine organ which also serves as a 'sink' for lipids (Frayn & Karpe, 2014). Fat is known to be toxic to cells (lipotoxicity) and adipose tissue is known for its exceptional ability to store large amounts of fat without the effects of lipotoxicity. Consequently, adipose tissue was known to serve as lipid 'sink.' Absence of fat, known as lipodystrophy, is known to be associated with ectopic fat accumulation and insulin resistance with diabetes. Excess fat also leads to 'overflow' from the adipose tissue 'sink' and ectopic fat accumulation, insulin resistance and diabetes. Thus excess and absence of fat are both dangerous as they lead to ectopic fat accumulation and impaired homeostasis (Sotornik *et al*., 2012; Frayn & Karpe, 2014).

The most popular conception of blood pressure control is the one describing the roles of brain (through reflexes such as baroreceptor reflex) (Ghosh & Pandit, 2019; Hall & Hall, 2020) and the kidneys (through pressure diuresis/natriuresis and renin-angiotensin aldosterone axis) (Baek & Kim, 2021; Prieto *et al*., 2021) in the short term and long term control of blood pressure. Both the neurocentric and renocentric barostats have sensors (such as arterial baroreceptors located in carotid sinuses and aortic arch for the neurocentic barostat and juxtaglomerular cells of affarent arterioles for the renocentric barostat) which detect blood pressure through wall stretch and control blood pressure through a negative feedback reflex mechanism (Ghosh & Pandit, 2019; Hall & Hall, 2020; Baek & Kim, 2021; Prieto *et al*., 2021).

Clinical and epidemiological studies have consistently revealed a strong association between increased adiposity/obesity and high blood pressure (Zhang *et al*., 2008; Ataie-Jafari *et al*., 2018; Saneei *et al*., 2019; Mirzababaei *et al*., 2019). It is not immediately obvious how the role of adipose tissue fits into the neurocentric and renocentric barostatic model of blood pressure control. The aim of this review is to present an extended model of blood pressure control referred to as barokinetic model which emphasizes multiple blood pressure set-points rather than a single one.

SINGLE OR MULTIPLE BLOOD PRESSURE SET-POINT(S); ARGUMENTS AGAINST BAROSTASIS

The first step in extending the barostatic model is recognizing its limitations. Joyner & Limberg (2014) and Raven & Chapleau (2014) raised the question if the blood pressure was indeed a regulated variable. They pointed instances of marked variability of blood pressure which include: marked intra-individual diurnal variation in blood pressure which can be as high as 30%, equally marked inter-individual variation in blood pressure among normotensive individuals, high blood pressures during exercise which can be extremely high during heavy lifting and the phenomenon of post-exercise hypotension, which can last for hours.

Under these physiological conditions, the baroreceptor reflex was found to reset and function normally to regulate the new blood pressure set-point (Hall & Hall, 2020; Joyner & Limberg, 2014; Raven & Chapleau, 2014; Fadel & Raven, 2012). Even the renal barostat resets in chronic hypertension to function at an abnormally high pressure set-point (Ghosh & Pandit, 2019; Hall & Hall, 2020).

It thus appears that blood pressure is regulated at various set points determined by the physiological demands; this has been termed homeokinesis to differentiate it from the notion

of a fixed blood pressure set-point (homeostasis). The barostats can be reset to regulate any blood pressure set-point determined by barokinetic mechanisms (Raven & Chapleau, 2014).

INTEGRATION OF LOCAL TISSUE BLOOD FLOW WITH BAROKINESIS

If there are various blood pressure set-points depending on the particular physiological condition, then it is important to elucidate the underlying barokinetic mechanisms. Joyner & Limberg (2014) noted that tissue blood flow is one of the most important variable affecting blood pressure; higher blood pressures are needed for increased tissue perfusion in situations of increased metabolic need. With decreased metabolic need and thus decreased tissue perfusion, a lower blood pressure is required. Thus a fundamental driver for barokinesis might be local tissue blood flow. Figure 1 shows the distribution, at rest, of cardiac output among different organs in the human body. The major takers of cardiac output (kidneys, splanchnic circulation and skeletal muscle) can increase their local blood flow several fold under increased metabolic demand; this happens through increased vasodilation of local arterioles. This amounts to massive decrease in total peripheral resistance and will lead to hypotension and impaired tissue perfusion if cardiac output increase is not high enough. This is how local tissue blood flow becomes integrated with blood pressure regulation.

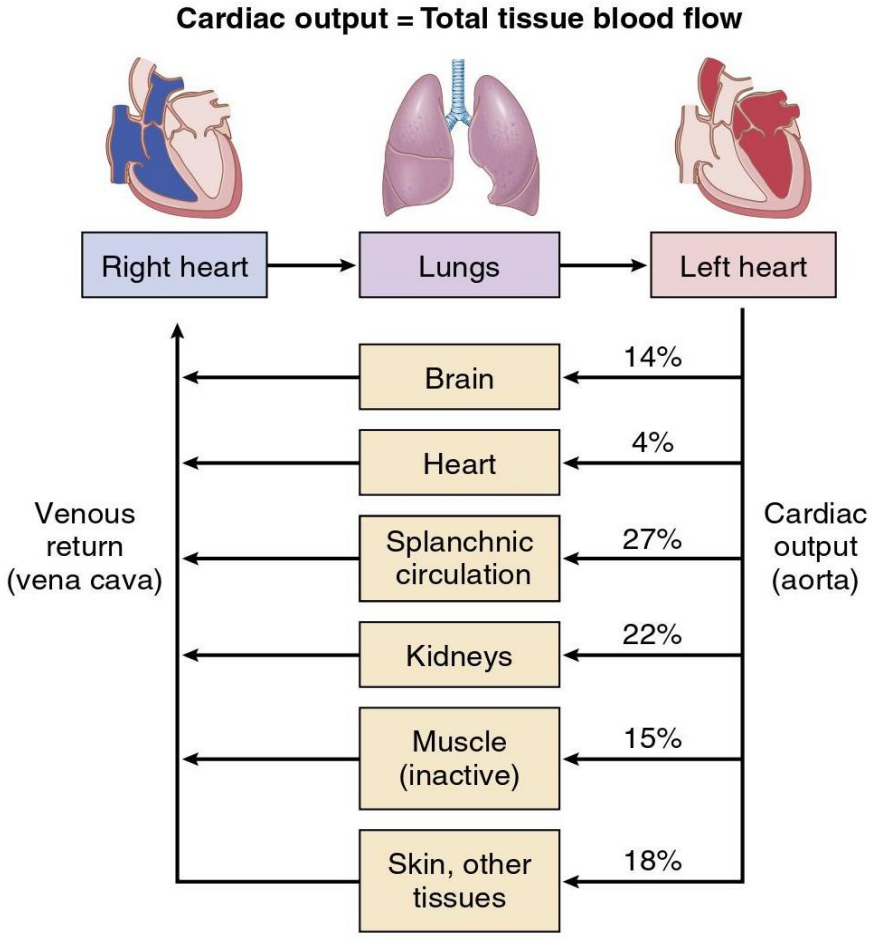

Figure 1: The Distribution of Cardiac Output among Body Organs.
(Source: Hall and Hall (2020))

ADIPOSE TISSUE-SKELETAL AXIS OF BLOOD PRESSURE CONTROL

The adipose tissue is a metabolically active endocrine organ which also serves as a 'sink' for lipids. In the basal fasting state, the blood flow (maintained by Nitric Oxide) to the white adipose tissue (which forms 85% of adipose tissue mass) is about 3mls per minute per 100g of

tissue (Frayn & Karpe, 2014); this is twice the blood flow in resting skeletal muscle (measured as mls per min per 100g of tissue) (Frayn & Karpe, 2014; Sotornik *et al*., 2012). Basal blood flow is increased acutely with both feeding (about 2 to 3 fold increase) (Sotornik *et al*., 2012) and exercise(Frayn & Karpe, 2014) for opposing reasons; increased transport of triglycerides and (and less importantly glucose) to the adipose tissue for storage during feeding and for transport of free fatty acids out of the adipose tissue to the contracting skeletal muscle during exercise.

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The skeletal muscle accounts for 31% and 38% of body weight in females and males respectively (Janssen *et al*., 2000) and receives about 15% of cardiac output in the resting state(Hall & Hall, 2020). This flow per weight might not appear much compared to flow to kidneys or brain which account for just 0.4% and 2% of body weight respectively but receive 22% and 14% of cardiac output (Figure 2). However, during intense physical activity muscle blood blow can increase 25-50 fold far exceeding the capacity of the heart to supply this increased demand while maintaining the normal supply to other organs (Hall & Hall, 2020).

The link between local regulation of skeletal muscle blood flow and systemic barokinetic effects exists through the following steps (Figure 2):

i. A somatic nerve stimulated contraction of skeletal muscle leads to increased metabolic demand and triggers both autoregulatory mechanisms as well as stimulation of affarent (type III and type IV) nerve endings. The latter initiates the so-called ergoreflex (a combination of an exercise metaboreflex and pressor reflex) which leads to increased sympathetic outflow from the brain (Aimo *et al*., 2021; Ichinose *et al*., 2014).
ii. Increased sympathetic outflow triggers a widespread vasoconstriction in splanchnic, renal and skin vascular beds. The rise in total peripheral resistance leads to a rise in blood pressure and thus increasing skeletal muscle perfusion pressure to increase skeletal muscle blood flow Aimo *et al*., 2021; Ichinose *et al*., 2014).
iii. The skeletal muscle has to protect itself from the widespread vasoconstrictor response it triggers. This 'sympatholyis' is mediated by myogenic autoregulation, locally produced autacoids including endothelial-derived nitric oxide and prostaglandins (PGE2 & PGI2) as well as rise in local extracellular potassium and hydrogen ion concentrations (Hong & Kim, 2017; Mortensen & Saltin, 2014). The overall effects are increased total peripheral resistance in all tissues with the exception of the contracting skeletal muscle leading to not only rise in systemic arterial blood pressure but diversion of blood from other tissues to the contracting skeletal muscle. The local skeletal muscle blood flow regulatory mechanisms are thus linked with systemic arterial blood pressure in what is referred to as 'barokinesis.' Finally, it is important to mention that sympatholysis is more pronounced in distal arterioles of skeletal muscles and less pronounced in proximal arterioles and feeder arteries; this has been suggested to mean the distal arterioles dilate

and increase blood flow to meet the metabolic demands of the contracting skeletal muscle while the proximal arterioles maintain their vasoconstriction to sustain systemic arterial blood pressure (Thomas, 2015)

iv.

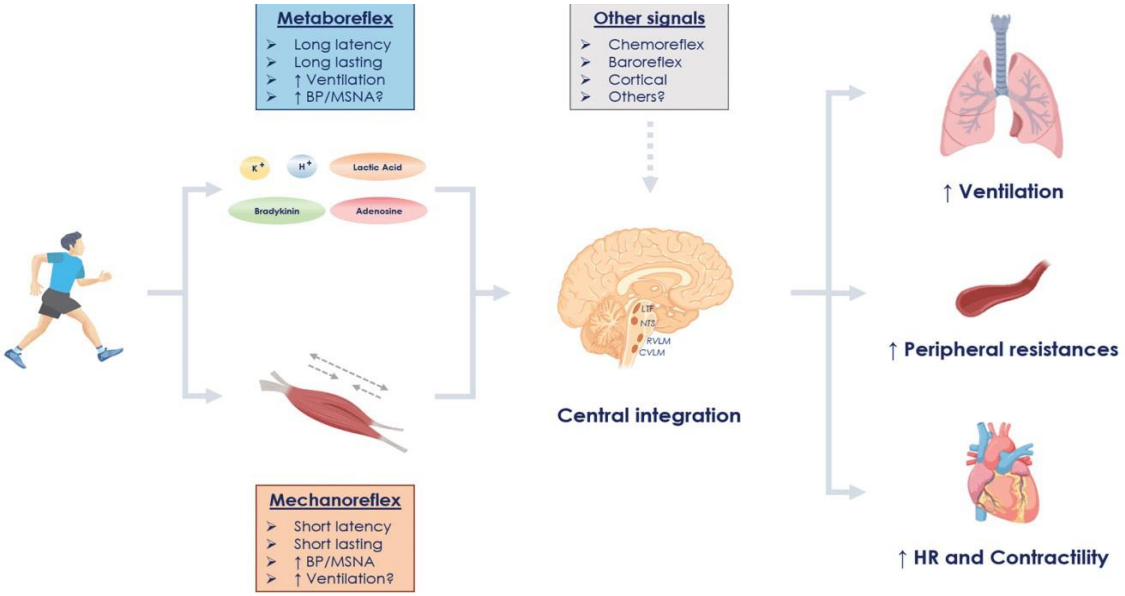

Figure 2: Skeletal Muscle and Barokinesis.
(Source: Aimo et al., (2021))

ADIPOSE TISSUE-LIVER AXIS OF BLOOD PRESSURE CONTROL

As mentioned earlier, basal blood flow to adipose tissue is increased acutely with feeding (about 2 to 3 fold increase) (Sotornik et al., 2012) for increased transport of triglycerides and (and less importantly glucose) to the adipose tissue for storage.

The liver is about 2% of the body weight but receives 27% of cardiac output (6% through the hepatic artery and 21% through the portal vein). The splanchnic circulation is designed in such a way that all the blood to the spleen, pancreas and gut wall drains to the liver through the portal vein. The combined flow from the portal vein and hepatic artery pass through liver capillary bed (sinusoids) before draining to the inferior vena cava through via the hepatic veins (Figure 3) (Hall & Hall, 2020)

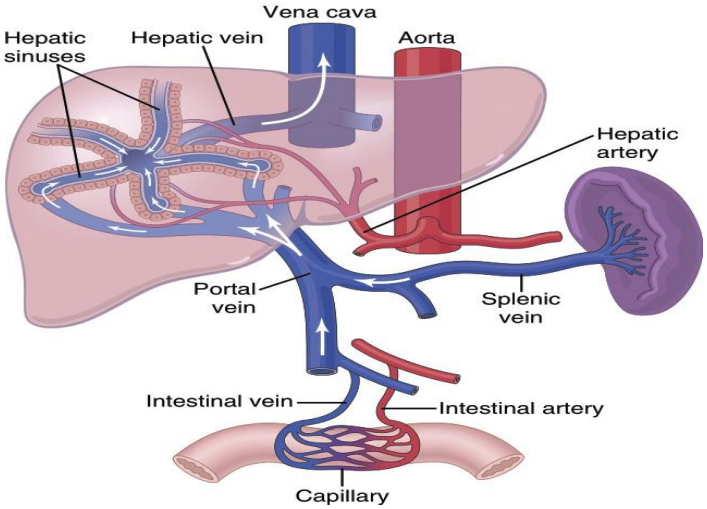

Figure 3: The Splanchnic Circulation.
(Source: Hall and Hall (2020))

As in the kidneys, brain and skeletal muscle, the link between local regulation of portal blood flow and systemic barokinetic effects exists through the following steps:

i. A reduction of hepatic blood flow or reduced oxygen concentration in hepatic circulation will lead to increased production and accumulation of adenosine in the hepatic interstitium. Increased adenosine leads to increased stimulation of vagal affarent nerve endings. The latter initiates the so-called hepatorenal reflex which leads to increased sympathetic outflow from the brain (Lautt, 2007). This adds to meal-induced sympathetic activation probably mediated by insulin secretion (van Baak, 2008; Wider, 2016).
ii. Increased sympathetic outflow triggers a widespread vasoconstriction in renal and skin vascular beds. The rise in total peripheral resistance leads to a rise in blood pressure and thus increasing liver perfusion pressure to increase hepatic blood flow rate (Wider, 2016; Lautt, 2007).
iii. The Liver has to protect itself from the widespread vasoconstrictor response it triggers. This local 'sympatholyis' is mediated by the so-called hepatic artery buffer response (HABR). HABR is initiated by the same stimulus that initiates hepatorenal reflex i.e. adenosine. Adenosine acts on the hepatic smooth muscle cells to cause vasodilation and increases hepatic artery blood flow thereby countering any sympathetic-mediated constriction of the hepatic artery (Eipel, 2010; Lautt, 2007). The overall effects of reduced hepatic blood flow are increased total peripheral resistance from vasoconstriction, which liver escapes from through the HABR (Lautt, 2007). This leads to not only rise in systemic arterial blood pressure but diversion of blood from other tissues to the metabolically active liver. The local hepatic blood flow regulatory mechanisms are thus linked with systemic arterial blood pressure in what is referred to as 'barokinesis.'

INTEGRATION OF BLOOD PRESSURE REGULATION

During exercise, as explained earlier, there is increased sympathetic outflow in response to skeletal muscle contraction. The skeletal muscle will need free fatty acids from adipose tissue for aerobic metabolism (Frayn & Karpe, 2014). Similarly, during feeding, as explained under the section of liver barokinesis, there is increased sympathetic outflow in response to meal (probably mediated by insulin action) (Emanuel *et al*., 2017); but there will be a need to deliver absorbed dietary fat to the adipose tissue for storage. This delivery of lipids to and from the adipose tissue can happen only when adipose tissue is able to 'escape' from the systemic vasoconstriction triggered by meal- or exercise-induced sympathoexcitation. This escape happens because of the expression of beta-2 adrenergic receptors in the walls of adipose tissue vasculature. Sympathetic activation of beta-2 receptors leads to vasodilatation. Consequently, beta-2 blockers were found to inhibit both meal- (Sotornik *et al*., 2012; Frayn & Karpe, 2014) and exercise-induced increased adipose tissue blood flow (ATBF); and beta-adrenergic agonists augment ATBF (Sotornik *et al*., 2012).

The vasodilation in adipose tissue adds to the vasodilation of skeletal muscle during exercise and to the vasodilation of splanchnic circulation during feeding (Sotornik et al., 2012). The combined vasodilation predisposes to hypotension during exercise and feeding respectively. To counter hypotension, adipose tissue increased metabolism leads to stimulation of affarent sympathetic nerve endings and trigger the so-called sympatho-excitatory adipose affarent reflex (AAR) (Xiong et al., 2014; Dalmasso et al., 2020). Local stimulants of AAR include adenosine, leptin and bradykinin (Figure 2.25); these are also known local vasodilators. Affarent impulses are carried to the hypothalamus paraventricular neurons (PN) from which projections reach the rostral ventrolateral medulla (RVLM) and intermediolateral column (IML). The sympathetic outflow leads to potent widespread vasoconstriction to raise the blood

pressure and counter the hypotensive effects of vasodilation in the adipose tissue, splanchnic (during feeding) and skeletal muscle (during exercise) vascular beds (Xiong et al., 2014; Dalmasso et al., 2020). This way, local mechanisms regulating ATBF are linked to systemic arterial blood pressure regulation in what is referred to as barokinesis.

CONCLUSION

Understanding the role of adipose tissue in the regulation and dysregulation of blood pressure requires an extension of the conventional barostatic model of blood pressure control to include the role of metabolic activity and blood flow to local tissues and the fact that there are multiple blood pressure set-points rather than a single one.

Adipose tissue works closely with muscle and gastrointestinal tract in controlling blood pressure; increased adipose tissue blood is associated with either increased splanchnic blood flow (during feeding to deposit absorbed lipids) or increased skeletal muscle flow (during exercise to release fatty acids for skeletal muscle oxidation). Increased blood flow to these three tissues (fat, skeletal muscle and gastrointestinal tract) triggers systemic sympathetic system activation; blood pressure at any given point is a balance between the local vasodilatation and the triggered systemic vasoconstriction. Obesity is by definition, increased fat mass without the corresponding increase in lean body (skeletal muscle) mass. Although the relatively low skeletal muscle mass means less metabolic demand on the adipose tissue, the increased fat mass and thus increased adipose tissue innervation in obesity means an increase, in absolute terms, of adipose tissue afferent reflex (AAR) stimulation of the sympathetic nervous system; the increased sympathetic stimulation would in turn leads to higher adipose tissue metabolic activity (lipolysis) and thus an even more AAR stimulation of sympathetic nervous system; without a corresponding increase in skeletal muscle mass and vasodilation, this sympathetic overstimulation leads to abnormally high blood pressure.

REFERENCES

Aimo, A., Saccaro, L. F., Borrelli, C., Fabiani, I., Gentile, F., Passino, C., Emdin, M., Piepoli, M. F., Coats, A. J. S., & Giannoni, A. (2021). The ergoreflex: how the skeletal muscle modulates ventilation and cardiovascular function in health and disease. *European Journal of Heart Failure*, ~~*23*(9), 1458–1467.~~ https://doi.org/10.1002/ejhf.2298

Baek, E. J., & Kim, S. (2021). Current Understanding of Pressure Natriuresis. *Electrolytes & Blood Pressure*, *19*(2), 38. https://doi.org/10.5049/EBP.2021.19.2.38

Dalmasso, C., Leachman, J. R., Osborn, J. L., & Loria, A. S. (2020). Sensory signals mediating high blood pressure via sympathetic activation: role of adipose afferent reflex. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *318*(2), R379–R389. https://doi.org/10.1152/ajpregu.00079.2019

Eipel, C. (2010). Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. *World Journal of Gastroenterology*, *16*(48), 6046. https://doi.org/10.3748/wjg.v16.i48.6046

Emanuel, A. L., Meijer, R. I., Muskiet, M. H. A., van Raalte, D. H., Eringa, E. C., & Serné, E. H. (2017). Role of Insulin-Stimulated Adipose Tissue Perfusion in the Development of Whole-Body Insulin Resistance. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *37*(3), 411–418. https://doi.org/10.1161/ATVBAHA.116.308670

Fadel, P. J., & Raven, P. B. (2012). Human investigations into the arterial and cardiopulmonary baroreflexes during exercise. *Experimental Physiology*, *97*(1), 39–50. https://doi.org/10.1113/expphysiol.2011.057554

Frayn, K. N., & Karpe, F. (2014). Regulation of human subcutaneous adipose tissue blood flow. *International Journal of Obesity*, *38*(8), 1019–1026. https://doi.org/10.1038/ijo.2013.200

Ghosh, S. K., & Pandit, J. J. (2019). Neurological and humoral control of blood pressure. *Anaesthesia & Intensive Care Medicine*, *20*(5), 301–305. https://doi.org/10.1016/j.mpaic.2019.02.007

Hall, J. E., & Hall, M. E. (2020). *Guyton and Hall Textbook of Medical Physiology* (14th editi). Elsevier.

Hong, K.-S., & Kim, K. (2017). Skeletal muscle contraction-induced vasodilation in the microcirculation. *Journal of Exercise Rehabilitation*, *13*(5), 502–507. https://doi.org/10.12965/jer.1735114.557

Ichinose, M., Maeda, S., Kondo, N., & Nishiyasu, T. (2014). Blood pressure regulation II: what happens when one system must serve two masters—oxygen delivery and pressure regulation? *European Journal of Applied Physiology*, *114*(3), 451–465. https://doi.org/10.1007/s00421-013-2691-y

Janssen, I., Heymsfield, S. B., Wang, Z., & Ross, R. (2000). Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *Journal of Applied Physiology*, *89*(1), 81–88. https://doi.org/10.1152/jappl.2000.89.1.81

Joyner, M. J., & Limberg, J. K. (2014). Blood pressure regulation: every adaptation is an integration? *European Journal of Applied Physiology*, *114*(3), 445–450. https://doi.org/10.1007/s00421-013-2636-5

Lapidus, L., Bengtsson, C., Larsson, B., Pennert, K., Rybo, E., & Sjöström, L. (1984). Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *British Medical Journal (Clinical Research Ed.)*, *289*(6454), 1257–1261. https://doi.org/10.1136/bmj.289.6454.1257

Lautt, W. W. (2007). Regulatory processes interacting to maintain hepatic blood flow constancy: Vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. *Hepatology Research*, *37*(11), 891–903. https://doi.org/10.1111/j.1872-034X.2007.00148.x

Mortensen, S. P., & Saltin, B. (2014). Regulation of the skeletal muscle blood flow in humans. *Experimental Physiology*, *99*(12), 1552–1558. https://doi.org/10.1113/expphysiol.2014.081620

Ohlson, L. O., Larsson, B., Svärdsudd, K., Welin, L., Eriksson, H., Wilhelmsen, L., Björntorp, P., & Tibblin, G. (1985). The Influence of Body Fat Distribution on the Incidence of Diabetes Mellitus: 13.5 Years of Follow-up of the Participants in the Study of Men Born in 1913. *Diabetes*, *34*(10), 1055–1058. https://doi.org/10.2337/diab.34.10.1055

Raven, P. B., & Chapleau, M. W. (2014). Blood pressure regulation XI: overview and future research directions. *European Journal of Applied Physiology*, *114*(3), 579–586. https://doi.org/10.1007/s00421-014-2823-z

Sotornik, R., Brassard, P., Martin, E., Yale, P., Carpentier, A. C., & Ardilouze, J.-L. (2012). Update on adipose tissue blood flow regulation. *American Journal of Physiology-Endocrinology and Metabolism*, *302*(10), E1157–E1170. https://doi.org/10.1152/ajpendo.00351.2011

Thomas, G. D. (2015). Functional sympatholysis in hypertension. *Autonomic Neuroscience*, *188*, 64–68. https://doi.org/10.1016/j.autneu.2014.10.019

van Baak, M. A. (2008). Meal-induced activation of the sympathetic nervous system and its cardiovascular and thermogenic effects in man. *Physiology & Behavior*, *94*(2), 178–186. https://doi.org/10.1016/j.physbeh.2007.12.020

Wider, M. (2016). Metabolic syndrome and the hepatorenal reflex. *Surgical Neurology International*, *7*(1), 99. https://doi.org/10.4103/2152-7806.194147

Xiong, X.-Q., Chen, W.-W., & Zhu, G.-Q. (2014). Adipose afferent reflex: sympathetic activation and obesity hypertension. *Acta Physiologica*, *210*(3), 468–478.

https://doi.org/10.1111/apha.12182

Zhang, C., Rexrode, K. M., van Dam, R. M., Li, T. Y., & Hu, F. B. (2008). Abdominal Obesity and the Risk of All-Cause, Cardiovascular, and Cancer Mortality. *Circulation*, *117*(13), 1658–1667. https://doi.org/10.1161/CIRCULATIONAHA.107.739714