Obesity, Systemic Hypertension, and Pulmonary Hypertension: A Tale of Three Diseases

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Abstract: Cardiovascular disease (CVD), especially ischemic heart disease and stroke, is the major cause of death worldwide, accounting for more than one-third of all deaths annually. Hypertension is the most prevalent and modifiable risk factor of CVD-related deaths. The same is true for obesity, which is currently being recognized as a major global epidemic. The prevalence of obesity in the United States has increased dramatically, from 13.4% in 1960 to 36.5% in 2014, with as much as 70.7% of the American adult population being overweight or obese (CDC). Epidemiological studies have shown that obesity predisposes to hypertension and CVD – with the relationship between markers of obesity and blood pressure being almost linear across different populations. In this

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review, we discuss systemic and pulmonary hypertension in the context of obesity. (Curr Probl Cardiol 2021;46:100599.)

Introduction

Cardiovascular disease (CVD), especially ischemic heart disease and stroke, is the major cause of death worldwide, accounting for more than one-third of all deaths annually.[1] Hypertension is the most prevalent and modifiable risk factor of CVD-related deaths. Globally, it represents an enormous public health burden. Hypertension is known to be associated with many familiar cardiac sequelae, including coronary artery disease, cerebrovascular disease, renal insufficiency, atherosclerosis, left ventricular hypertrophy, atrial fibrillation, and congestive heart failure.[2] Epidemiological studies have shown that obesity predisposes to hypertension and CVD − with the relationship between markers of obesity and blood pressure being almost linear across different populations.[3] Obesity is currently recognized as a major global epidemic. The prevalence of obesity in the United States has increased dramatically, from 13.4% in 1960 to 36.5% in 2014, with as much as 70.7% of the American adult population being overweight or obese Centers for Disease Control and Prevention (CDC). In this review, we discuss systemic and pulmonary hypertension (PH) in the context of obesity and their clinical implications in obese patients.

Obesity and Systemic Hypertension

The new 2017 American College of Cardiology and American Heart Association Guidelines for high blood pressure in adults lowered the recognizable limit of hypertension, categorizing patients as having either elevated (120-129 mm Hg systolic and less than 80 mm Hg diastolic) or Stage I hypertension (130-139 mm Hg systolic or 80-89 mm Hg diastolic) as compared to previous guidelines which used 140 mm Hg systolic and 90 mm Hg diastolic as the start of Stage 1 hypertension. New guidelines were intended to increase awareness of complications which can occur at even lower blood pressure levels. and encourage early intervention including lifestyle modifications. This new definition has resulted in nearly half of the U.S. adult population (45%) being labelled with hypertension.[4] Since the new guidelines propose more aggressive thresholds for the treatment and prevention of hypertension, the main challenge we

presently face is how to control modifiable risk factors to help attain normal blood pressure limits.

Obesity-related hypertension predisposes to multiple cardiac sequelae and has thus become one of the more important risk factors for CVD. Collectively, epidemiological, cross-sectional, and prospective studies have linked obesity to hypertension.[5] The Framingham Study was one of the most notable, and found that hypertension is about twice as prevalent in the obese when compared to their nonobese counterparts.[6,7] Additionally, Stamler et. al. reported an odds ratio for hypertension of obese, relative to nonobese (body mass index [BMI] < 25 kg/m^2), to be as high as 2.42 for younger adults and 1.54 for older ones.[8] Moreover, when the Framingham cohort was divided into BMI quintiles, those in the highest BMI quintile had 16 mm Hg higher systolic and 9 mm Hg higher diastolic blood pressures than those in the lowest quintile.[9]

Interestingly, studies have shown that cardiometabolic sequelae observed in obese patients are different from the ones observed in lean patients with hypertension. The obesity paradox, however, is a recent controversial idea which states that while obese individuals are more likely to develop cardiovascular structural abnormalities, they may have a reduced age-adjusted all-cause mortality and ischemic heart disease mortality than lean individuals with hypertension.[10] While some evidence suggest that the obesity paradox may exist in hypertension, it likely has a neural mechanism through persistent activation of the sympathetic nervous system – explaining why obese individuals with hypertension have an increased risk of renal insufficiency. Moreover, the structural changes in the kidney secondary to obesity are significant. with the pressure of peri-renal fat, coupled with increased abdominal pressure secondary to central obesity, contributing to altered renal sodium reabsorption.

Recently, studies on obesity indicate that excess weight gain is not necessarily a determinant for the development of obesity-related diseases, but rather abnormal body fat distribution is a more important factor in terms of morbidity and decreased quality of life.[11,12] According to the Dallas Heart Study, the distribution, rather than the quantity, of body fat was found to be implicated with hypertension. BMI was shown to be associated with incident hypertension, with a relative risk of 1.24 (95%CI 1.12-1.36, $P < 0.0001$) per standard deviation increase. However, once visceral adiposity and subcutaneous fat were included in the model, only visceral adipose tissue remained significant, with a relative risk of 1.22 (95%CI 1.07-1.39, $P = 0.004$) for each standard deviation increase.[13] The study noted that the most significant association between visceral

adiposity and hypertension was observed with retroperitoneal fat, bringing to light the local effects of fat surrounding the kidneys.

Furthermore, emerging evidence shows that visceral adipose tissue, relative to subcutaneous adipose tissue, is more sensitive to lipolysis and secretes higher amounts of inflammatory cytokines – playing a larger role in the CVD spectrum.[14] Visceral adipose tissue is associated with increased proinflammatory cytokines, such as Tumor Necrosis Factor (TNF-alpha) and inteleukin-6, but less adiponectin. These cytokines induce insulin resistance, further contributing to endothelial dysfunction and the subsequent development of atherosclerosis.[15,16] Moreover, visceral adipose tissue generates greater activation of the sympathetic nervous system than its subcutaneous counterpart[17] (Table).

Weight loss and Hypertension

Strict blood pressure control, according to the newly laid down guidelines, have a significant impact on CVD mortality. However, accomplishing this goal seems to be the primary challenge which clinicians will face in the future. Many antihypertensive treatments significantly reduce blood pressure levels and thereby reduce the incidence of stroke, myocardial infarction, and heart failure to between 20% and 50%.[18] A population wide reduction of 5.5 mm Hg systolic or 3.0 mm Hg diastolic would roughly translate to a 15% and 27% decline in incident coronary heart disease and stroke, respectively.[18,19] Growing evidence shows that the health effects associated with obesity can be reversed with weight loss.[20] Many clinical studies in humans have also examined the relationship between weight loss and blood pressure change. The landmark trial of hypertension prevention, one of the largest of these studies, found that a 2-kg loss in weight over a 6-month period resulted in a decline of 3.7 mm Hg in systolic and 2.7 mm Hg in diastolic blood pressures.[21] The mechanisms by which weight loss contributes to reduction in blood pressure invoke a myriad of pathways including changes in insulin resistance, changes in vascular structure and function, ion transport, and activation of the sympathetic nervous system, as well as changes in levels of natriuretic peptide.[18,22] Yet, the effects of weight loss in this context over longer periods of time are less clear. From a study examining 8 years of follow-up in a group of obese patients who received gastric bypass surgery to induce weight loss, their initial weight loss of 18% of presurgical body weight was associated with a reduction in blood pressure of about 12 mm Hg systolic and 8 mm Hg diastolic. Over a 6- to 8-year period, there was an overall very slight gain of weight; however, blood pressure

Table. Landmark studies and derived inferences

Serial	Study	Inference
1	Savale L, Tu L, Rideau D, Izziki M, Maitre B, Adnot S, Eddahibi S. Impact of interleukin-6 on hypoxia-induced pulmonary hypertension and lung inflammation in mice. Respiratory research. 2009 Dec;10 (1):6.	Interleukin-6 receptors are expressed on inflammatory and vessel wall cells and it can affect both lung inflammation and vascular remodeling. Study showed that hypoxic IL-6-/- mice had a decrease in infiltration of inflammatory cells and lung vessel wall remodeling.
2	Izikki M, Guignabert C, Fadel E, Humbert M, Tu L, Zadigue P, Dartevelle P, Simonneau G, Adnot S, Maitre B, Raffestin B. Endothelial-derived FGF2 contributes to the progression of pulmonary hypertension in humans and rodents. The Journal of clinical investigation. 2009 Mar 2;119 (3):512-23.	Dysregulation of Fibroblast growth factor 2 (FGF2) signaling plays a role in pulmonary vascular remodeling and progression of pulmonary hypertension. Excessive production of FGF2 by pulmonary endothelial cells promotes pulmonary artery smooth muscle cells growth and this effect was found to be stronger in patients with idiopathic pulmonary hypertension as compared to controls.
3	Ketonen J, Shi J, Martonen E, Mervaala E. Periadventitial adipose tissue promotes endothelial dysfunction via oxidative stress in diet-induced obese C57Bl/6 mice. Circulation Journal. 2010;74 (7):1479-87.	Diet induced obesity in the mice leads to increased formation of reactive oxygen species, NADPH oxidase expression and recruitment of pro-inflammatory markers in the perivascular adipose tissue. These changes are associated with endothelial dysfunction via decrease in the anti-contractile effect of perivascular adipose tissue and endothelial dysfunction.
4	Xia N, Horke S, Habermeier A, Closs EI, Reifenberg G, Gericke A, Mikhed Y, Münzel T, Daiber A, Förstermann U, Li H. Uncoupling of endothelial nitric oxide synthase in perivascular adipose tissue of diet-induced obese mice. Arteriosclerosis, thrombosis, and vascular biology. 2016 Jan;36(1):78-85.	Study showed that induction of obesity in mice via high fat diet leads to uncoupling of perivascular adipose tissue endothelial nitric oxide synthase and vascular dysfunction. This occurs due to induction of arginase and deficiency of l-arginine. Such effects were not observed in mice with normal control diet.
6	Caglayan E, Trappiel M, Behringer A, Berghausen EM, Odenthal M, Wellnhofer E, Kappert K. Pulmonary arterial remodelling by deficiency of peroxisome proliferator-activated receptor-γ in murine vascular smooth muscle cells occurs independently of obesity-related pulmonary hypertension. Respiratory research. 2019 Dec;20 (1):42.	Study done on Wild Type and Vascular smooth muscle cell- specific peroxisome proliferator-activated receptor-γ knockout mice that were fed low fat diet or high fat diet for 24 weeks. It showed that insulin resistance correlated with the increase in right ventricular pressure. Vascular smooth muscle cell- specific peroxisome proliferator-activated receptor-γ deficiency lead to pulmonary vascular muscularization independently of the diet-induced rise in right ventricle systolic pressure

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Serial	Study	Inference
6	Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, Sydykov A, Lai YJ, Weissmann N, Seeger W, Grimminger F. Reversal of experimental pulmonary hypertension by PDGF inhibition. The Journal of clinical investigation. 2005 Oct 3;115(10):2811-21.	Monocrotaline/hypoxia induced severe pulmonary hypertension in rats reversed by use of platelet derived growth factor receptor antagonist STI571 (imatinib).
7	Zamanian RT, Hansmann G, Snook S, Lilienfeld D, Rappaport KM, Reaven GM, Rabinovitch M, Doyle RL. Insulin resistance in pulmonary arterial hypertension. European respiratory journal. 2009 Feb 1;33 (2):318-24.	A case control study in female patients with pulmonary arterial hypertension insulin resistance is more prevalent than in general female population. In study it was noted that age and degree of obesity influenced insulin resistance prevalence in general female population but not in the pulmonary arterial hypertension cohort.
8	Hansmann, G., et al., Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. Circulation, 2007. 115(10): p. 1275-84	Study showed that high fat diet fed apoE -/- mice developed insulin resistance, had lower plasma adiponectin, and had elevated right ventricular systolic pressure with associated right ventricle hypertrophy and elevated peripheral pulmonary artery muscularization. These changes were reversed by a peroxisome proliferator−activated receptor-γ agonist (rosiglitazone)
9	Almeneessier AS, Nashwan SZ, Al-Shamiri MQ, Pandi-Perumal SR, BaHammam AS. The prevalence of pulmonary hypertension in patients with obesity hypoventilation syndrome: a prospective observational study. Journal of thoracic disease. 2017 Mar;9 (3):779.	Prospective observational study assessed the prevalence of pulmonary hypertension by echocardiography among obesity hypoventilation syndrome patients. Study showed that pulmonary hypertension was prevalent in 71.4% of women and 61.9% of men with obesity hypoventilation syndrome.
10	Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. Annals of surgery. 1988 May;207 (5):604.	Morbidly obese patients undergoing gastric surgery were assessed for prevalence of obesity hypoventilation syndrome (OHS) and associated clinically significant pulmonary hypertension and cardiac dysfunction. Patients with OHS had significantly higher mean pulmonary artery pressure and pulmonary artery occlusion pressures. Follow up in 3-9 months showed significant drop in pulmonary artery and pulmonary artery occlusion pressure after the weight loss.

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Serial	Study	Inference
11	Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax. 2000 Nov 1;55(11):934-9.	Pulmonary hypertension was significantly prevalent in a population of sleep apnea syndrome without chronic obstructive pulmonary disease. Pulmonary hypertension was also found to be related to severity of obesity and its effects on the respiratory mechanics.
12	Sheu EG, Channick R, Gee DW. Improvement in severe pulmonary hypertension in obese patients after laparoscopic gastric bypass or sleeve gastrectomy. Surgical endoscopy. 2016 Feb 1;30(2):633-7.	A retrospective chart review of the morbidly obese patients with pulmonary hypertension who underwent bariatric surgery showed improved pulmonary artery pressure, decreased need for pulmonary hypertension medications and supplemental oxygen, and improved exercise capacity.

rebounded to the point where, near the end of the study, a similar or even higher level of BP was observed as compared to the untreated controls.[23] The probable reasons, as the authors suggest, are that the remaining obesity in the surgically treated patients causes reoccurrence of hypertension and that the insulin is not the only mediator of hypertension or sympathetic nervous system hyperactivity in obese subjects.[23] Although evidence highlighting the role of obesity in systemic hypertension is mounting, studies exploring the implications of obesity in PH is limited and needs further insight and research.

Obesity and Pulmonary Hypertension

PH is defined as resting mean pulmonary artery pressure greater than 20 mm Hg on right heart catheterization.[24,25] The World Health Organization has classified PH into 5 categories based on underlying etiology.[25] It is reported that 5% of obese, otherwise healthy, individuals have PH of moderate or severe degree based on pulmonary artery systolic pressure >50 mm Hg on echocardiogram.[26] Favorable changes in pulmonary artery pressure and right ventricle systolic pressure have been reported in obese patients after bariatric surgeries.[27] Obesity leads to significant structural and hemodynamic changes through its effects on the cardiovascular system and is linked to group 1 PH (pulmonary arterial hypertension[PAH]), group 2 PH (due to left heart disease) and group 3 PH (due to lung diseases and/or hypoxia) by multiple pathophysiologic mechanisms.[28,29]

Perivascular Adipose Tissue and Vascular Dysfunction

Perivascular adipose tissue (PVAT) surrounds most of the body's blood vessels, other than the vasculature in the brain. In contrast to large vessels where PVAT is separated by an anatomical barrier, in small vessels PVAT is an integral part of the vessel wall.[30] PVAT is a functionally specialized type of adipose tissue, as compared to adipocytes in visceral or subcutaneous fat depots, and possesses a distinct phenotype and function based on its location.[31] Adipocytes in PVAT are smaller in size and less differentiated, with properties to release proinflammatory markers and growth factors.[32] In addition to providing mechanistic support to vasculature, PVAT has endocrine and paracrine functions which include the secretion of chemokines/cytokines (eg, tumor necrosis factor α, interleukin 6), adipokines (eg, leptin, adiponectin, resistin), and vasoactive factors.[33] These factors reach the medial and endothelial layers either by direct diffusion or through the vasa vasorum. In response to vascular injury, perivascular tissue is also involved in the inflammatory response which suggests bi-directional communication between PVAT and vascular cells.[30] Healthy PVAT protects the vasculature by its vasodilator and/or anticontractile, anti-inflammatory, and antiproliferative effects.[30,31,34] In case of PVAT dysfunction as in obesity, adipocytes de-differentiate, become metabolically active, and start producing pro-inflammatory cytokines and chemokines. These pro-inflammatory markers trigger inflammatory cell infiltration, precipitating inflammation which plays a significant role in the pathogenesis of obesity-associated CVD and other chronic conditions[33,35,36] (Fig).

Obesity, Perivascular Adipose Tissue, and Pulmonary Arterial Hypertension

Accumulating evidence has shown the existence of localized inflammation in adipose tissue which promotes low-grade systemic inflammation and adds to the complications associated with obesity such as insulin resistance, nonalcoholic fatty liver disease, PH and obesity-related cardiomyopathy.[37] Obesity induces structural and functional changes in the PVAT. These alterations in the PVAT lead to increased secretion of vasoconstrictors and pro-inflammatory factors.[31] In obese patients, adipocytes hypertrophy and PVAT mass increases. The hypertrophy, along with reduced angiogenesis and decreased capillary density, lead to PVAT hypoxia which promotes inflammation by secretion of inflammatory cytokines and chemokines.[38-40] Release of chemokines such as monocyte

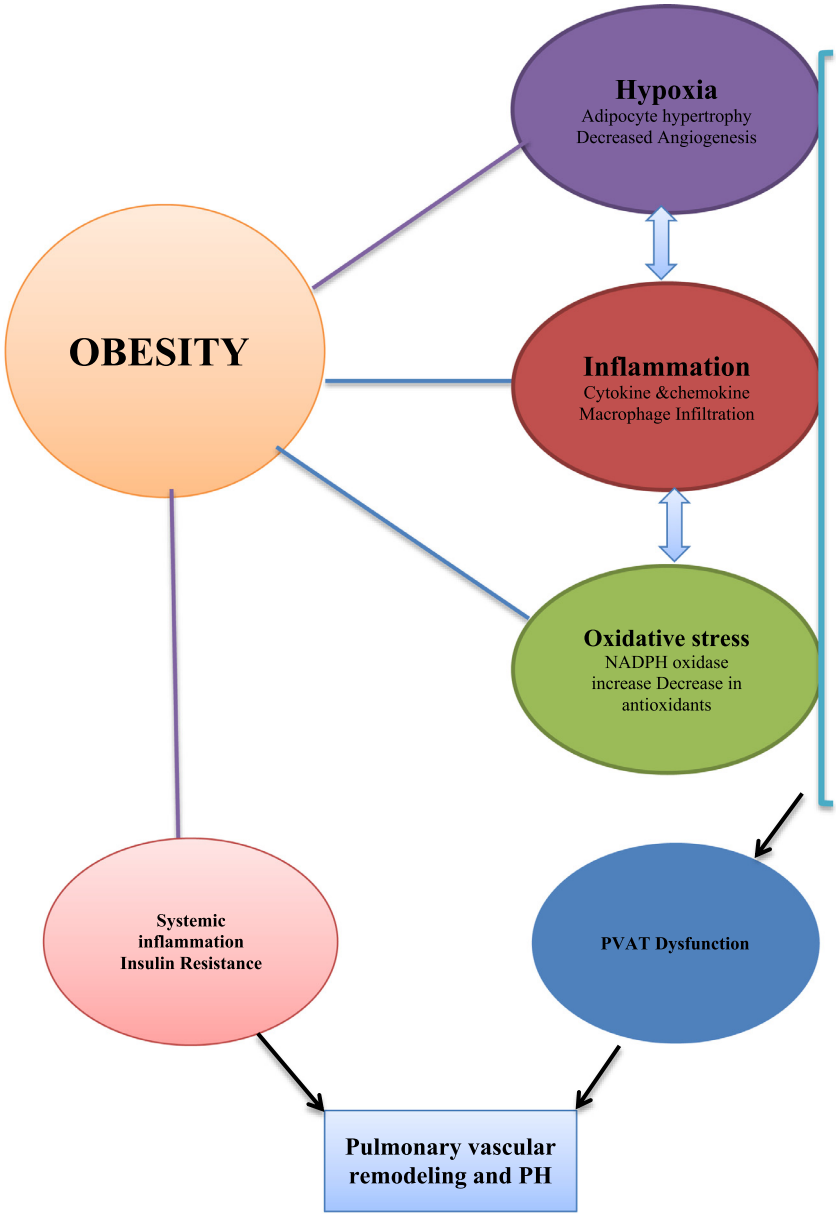

FIG. Obesity leads to perivascular adipose tissue (PVAT) dysfunction via adipose tissue hypoxia, PVAT inflammation and oxidative stress. Obesity induced systemic inflammation, insulin resistance and PVAT dysfunction lead to pulmonary vascular remodeling and pulmonary hypertension (PH).

chemoattractant protein-1 (MCP=1) triggers infiltration of macrophages which drive PVAT inflammation and oxidative stress.[40,41] Studies have shown that diet-induced obesity in animal models upregulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and downregulates antioxidants (eg, glutathione, superoxide dismutase), promoting oxidative stress.[42,43] This is accompanied by a decrease in endothelial nitric oxide synthase, impairing tonic release of nitric oxide in obesity.[43] The obesity-induced PVAT dysfunction promotes inflammation within PVAT, increases oxidative stress, and leads to the loss of the anticontractile effect of PVAT in the small arteries, inhibiting vasodilator responses to acetylcholine.[31,33,40]

PAH develops due to progressive remodeling of small to midsize pulmonary arteries. Perivascular and systemic inflammation, such as those occurring in patients with autoimmune diseases, are considered to play an important role in the pathogenesis of PAH.[44] Various inflammatory cells (eg, T & B cells, macrophages, dendritic cells) and markers (eg, IL-1, IL-6, MCP-1, tumor necrosis factor-α) contribute to the pathogenesis of PAH.[45,46] Evidence from animal studies has shown that among the cytokines, IL-6 has the most prominent role in the pathogenesis of PAH, especially hypoxia-induced PAH.[47,48] Interleukin-6 and fibroblast growth factor-2, induced by IL-1, are considered to promote the proliferation of smooth muscle-like cells and fibroblasts of the pulmonary vasculature, as seen in PAH.[49,50] TNF-α and IL-1β increase extracellular matrix proteins in the vascular lesions of PAH.[51] Several of the cytokines (eg, TNF-α) and interleukins (eg, IL-1β, -2, -8) correlate with outcomes and serve as prognostic markers of PAH.[52,53] Obesity-induced local PVAT and systemic inflammation continue to affect remodeling of pulmonary vasculature in PAH.[38,39]

Insulin Resistance and Pulmonary Arterial Hypertension

Obesity is associated with low-grade local and systemic inflammation which has a significant role in the pathogenesis of several chronic diseases. Obesity-associated inflammation promotes insulin resistance, not only by its effects on the local adipose tissue, but also on hepatocytes.[54] Inflammation in these sites leads to insulin resistance by inhibition of insulin-receptor and insulin-receptor substrate 1 in the insulin signaling pathway, inhibition of peroxisome proliferator-activated receptor gamma (PPAR-γ) and by the increase of plasma free fatty acids by lipolysis. TNF-α mediates the inhibition of insulin-receptor substrate 1 and PPAR-γ.[55-57] Plasma free

fatty acids and glucose stimulate pancreatic β cells and increase insulin production leading to hyperinsulinemia, which in turn, worsens insulin resistance.[58,59] The platelet derived growth factor-BB (PDGF-BB)/mitogen-activated protein kinase signaling pathway plays a key role in pulmonary vascular disease by causing smooth muscle cell (SMC) proliferation and migration.[60,61] PPAR-γ inhibits PDGF-BB-induced SMC proliferation via apolipoprotein E (apoE) and adiponectin.[62] Insulin resistance is associated with reduced levels of apoE and adiponectin with pronounced PDGF-BB signaling, leading to arterial vessel wall thickening. Studies in diabetic apoE-deficient mice have shown heightened PDGF-BB signaling in association with insulin resistance, which leads to neointimal thickening of arterial walls and PAH.[62,63] Thiazolidinediones, PPAR-γ agonists, play an important role in the differentiation of adipocytes, improve insulin sensitivity and inhibit PDGF-BB-induced SMC proliferation.[62,64,65]

Oxidative Stress and Pulmonary Arterial Hypertension

Oxidative stress is an imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms. In lung parenchyma, endothelial cells, neutrophils, macrophages in the alveoli and PVAT, alveolar epithelial cells and eosinophils are the sources of ROS.[66] Superoxide (O_2^-) and hydrogen peroxide (H_2O_2) are the main ROS involved in the signaling pathways, with O_2^- playing a significant role in vascular remodeling.[67,68] NADPH, uncoupled nitric oxide synthase, xanthine oxidase, and dysfunctional mitochondria are involved in increased ROS production in PH.[68] The NADPH oxidase family is considered the most important source of ROS. Triggers for increased generation of ROS include hypoxia, inflammation and shear stress on the pulmonary vasculature. Increased levels of ROS lead to increased pulmonary vascular resistance and vessel wall thickening which contribute to PH.[66]

Obesity-induced inflammatory responses in the PVAT is associated with infiltration of macrophages due to high concentration of MCP-1.[40,41] Macrophages upregulate NADPH oxidase and increase generation of O_2^- and H_2O_2. High concentrations of these ROS induce pulmonary vascular constriction due to decreased production of nitric oxide and increased release of vasoactive mediators via endothelial dysfunction.[42,43] ROS increase the gene expression and secretion of endothelin-1 which increases vasoconstriction, with levels of endothelin-1 correlating with degree of pulmonary vascular resistance.[69] Oxidative stress also leads to an imbalance between thromboxane A2, a vasoconstrictor and mediator of PH, and prostacyclin which promotes vascular

remodeling.[66,70] ROS also promote smooth muscle contraction by increasing the intracellular free calcium concentration.[71] In the acute setting, these factors increase vascular tone but chronically will lead to SMC hypertrophy and vascular remodeling, contributing to PAH. ROS induce the expression of several growth factors, such as PDGF, vascular endothelial growth factor, fibroblast growth factor-2, and modulate pulmonary vascular remodeling.[66,72]

Cardiopulmonary Conditions in Obesity and Pulmonary Hypertension

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is defined by daytime alveolar hypoventilation with partial arterial pressure of carbon dioxide ($PaC0_2$) $\geq$ 45 mm Hg in an individual with BMI $>$ 30 kg/m^2, after exclusion of alternate causes of hypoventilation.[73,74] Individuals with OHS have sleep-disordered breathing and diurnal hypoxemia as well. OHS is not only associated with respiratory impairments, but also with cardiovascular derangements and has a significant impact on pulmonary artery pressure and right ventricular systolic function.[75,76] PH has been reported in more than 50% of patients of OHS.[76,77] Hypercapnia with associated acidosis, hypoxemia, and restrictive lung disease associated with severe obesity and wide intrathoracic pressure during the respiratory cycle, are mediators of PH in patients with OHS.[29] Noninvasive positive pressure ventilation is a mainstay treatment. It is effective in ameliorating hypoxemia and hypercapnia, with its use being inversely related to pulmonary artery pressure.[73,75,78]

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is common in obese patients and its prevalence is increasing with the worldwide epidemic of obesity. Increasing BMI is associated with worsening degree of OSA.[79] Chronic hypoxia due to chronic pulmonary diseases such as chronic obstructive pulmonary disease or respiratory muscle weakness is the major cause of PH in such diseases. Chronic hypoxia leads to pulmonary vasoconstriction and vascular smooth muscle hypertrophy that can result in PH.[80,81] It has been reported that 10% of adult males and 5% of adult females experience >15 episodes of apnea or hypopnea for every 1 hour of sleep, with those with severe OSA suffering from upwards of several hundred episodes of

hypoxia.[82,83] Pulmonary hypertension prevalence varies widely from 17% to nearly 50% in patients with OSA ([82,84,85]) Pulmonary hypertension affects right ventricular function, leading to right ventricular hypertrophy and dysfunction, with severe OSA linked to these changes (28). OSA itself causes a small degree of increase in pulmonary artery pressure in the absence of other causes of hypoxia or obesity related hemodynamic changes (28, 82). Treatment of OSA with continuous positive airway pressure (CPAP), which relieves upper airway obstruction and hypoxemia, can lead to a decrease in the incidence of pulmonary hypertension (29, 87).[84]

Chronic Pulmonary Thrombo-embolism

Chronic thromboembolism is a well-known cause of PH. Obesity, insulin resistance, and a sedentary lifestyle increase the risk of deep venous thrombosis and pulmonary embolism.[29] Chronic pulmonary embolism can lead to smooth muscle hypertrophy and fixed pulmonary vascular resistance.

Conclusions

Obesity-related hypertension is a chronic, yet fast-growing epidemic. As the prevalence of obesity increases, its cost burden rises in tandem and represents a heavy toll on our healthcare system. Recent estimates indicate that obesity-related health problems accounts for nearly 20% of health care costs in the United States. As a major modifiable risk factor in the development and progression of hypertension and CVD, the management of obesity should receive greater attention and support from the federal government and health institutions. Although more data is needed to fully elucidate the association between obesity and PH, there is increasing evidence that obesity plays a significant role in its development not only via local and systemic inflammation, but also through obesity-related cardiopulmonary conditions. PH in obese patients can be due to any number of underlying etiologies and such patients should undergo thorough evaluation and treatment. Weight loss, through healthy dietary habits or surgical intervention, and noninvasive ventilation in patients with OSA and OHS lead to significant improvements in cardiopulmonary hemodynamics.

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