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EDITORIAL

Biological plausibility and implications of obesity associated valvular heart diseases

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Abstract

Obesity contributes to the development and progression of cardiovascular risk factors and diseases, but so far not much attention has been given to obesity and valvular heart disease. Several observational and mendelian randomization studies have reported an association between body mass index with aortic valve stenosis, but also with secondary functional mitral regurgitation and tricuspid regurgitation in a more indirect manner. Several mechanisms can lead to the link between obesity and valvular heart diseases: left ventricular dilation, as obesity directly contributes to ischemic heart disease and ventricular remodeling, atrial myopathy as well as atrial remodeing and arrhythmias, such as atrial fibrillation, that predispose to valvular regurgitation, but also pulmonary hypertension, which could be the consequence of obesity-related inflammation, insulin resistance, and oxidative stress, valvular calcification which is often associated with adiposity and as a direct effect of increased epicardial adipose tissue and pericardial restraint. Individuals with obesity associated valvular heart disease may experience worse symptoms, quality-of-life, exercise capacity, and risk for adverse outcomes. The effect of and the mechanism for various vavular heart diseases in relation to obesity has not been investigated in depth. Recently, incretin-based drugs and sodium-glucose cotransporter-2 inhibitors have been shown to reduce adiposity, and improve HF outcomes; however, the implications of these drugs on valvular heart diseases have not been evaluated. With innovations in therapies for obesity, several questions merit discussion. Considering the prevalence of obesity and its association with valvular heart diseases, not studying these common comorbid conditions represents a significant missed opportunity.

Key words: obesity, valvular heart disease, aortic stenosis, mitral regurgitation, tricuspid regurgitation.

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Introduction

The prevalence of obesity is increasing globally. Obesity contributes to the development and progression of cardiovascular risk factors, including dyslipidemia, type-2 diabetes, and hypertension; cardiovascular disease (CVD), including stroke, myocardial infarction, atrial fibrillation (AF), and heart failure (HF); and cardiovascular death. Over two-thirds of deaths in individuals with obesity are attributable to CVD. While the association between obesity and CVD is known, not much attention has been given to obesity and valvular heart disease (VHD).

Epidemiologic association

Several observational studies have reported an association between body mass index (BMI) with aortic valve stenosis. Among 71,817 individuals free of CVD, compared with BMI of 18.5-22.5 kg/m^2, the hazard for developing aortic stenosis was 1.24 (1.05-1.48) for BMI 25.0-29.9 kg/m^2 and 1.81 (1.47-2.23) for ≥30 kg/m^2.[1] Obesity is associated with secondary functional mitral regurgitation (FMR) and tricuspid regurgitation (FTR) in a more indirect manner as obesity contributes to ischemic heart disease and ventricular remodeling, as well as atrial remodeing and arrhythmias, that predispose to valvular regurgitation. In patients with HF and preserved ejection fraction (HFpEF) and with AF, the prevalence of moderate-severe TR in ~40%.[2] FTR is related with right ventricular remodeling that occurs in obese individuals regardless of HF.[3] In trials of FMR and FTR interventions, the average BMI was 27 kg/m^2, indicating over half of the patients were overweight or obese.

Mendelian randomization association

Observational studies are susceptible to confounding and reverse causation bias. Larsson *et al.* applied the Mendelian randomization (MER) design to evaluate BMI and CVD among 367,703 United Kingdom Biobank participants.[4] MER is an epidemiologic method based on genetic variants associated with the modifiable risk factor as proxy indicators to infer causality, since alleles are randomly assorted at conception. In this study, genetically predicted BMI was associated with 8 of 14 CVD, with the strongest association with aortic stenosis. The association was driven by fat mass index, with no association with fat-free mass index. An association between genetically predicted BMI and AF was also reported, which is of interest since AF in related to secondary FMR and FTR.

Mechanisms of obesity associated valvular heart disease

Several mechanisms can lead to the link between obesity and VHD (Figure 1).

1. **Left ventricular dilation:** Left ventricular (LV) dilatation in obesity may be caused by higher blood volume and cardiac output accompanying obesity or due to myocardial ischemia as obesity is associated with coronary disease. Dyslipidemia is common in obesity and is associated with risk of coronary disease, acute coronary syndromes, and HF, increasing the risk for FMR and FTR. Coronary disease can lead to remodeling, causing FMR and FTR related to papillary muscle architecture distortion.
2. **Atrial myopathy:** Obesity is related with fat accumulation and fibrosis, and development of LV hypertrophy. Obesity is associated with concentric remodeling, increasing stiffness, and diastolic dysfunction. Persistent increases in LV pressures lead to atrial hypertension, enlargement, and failure, leading to atrial FMR and FTR.
3. **Atrial fibrillation:** Obesity is associated with increased risk of AF. Epicardial adipose tissue is proarrhythmic and is associated with atrial remodeling and AF. Obesity is a shared risk factor for AF and HFpEF. Biatrial myopathy is common in HFpEF,[5] and is associated with atrial FMR and FTR characterized by dilation of mitral and tricuspid annuli.
4. **Pulmonary hypertension:** Obesity related inflammation, insulin resistance, and oxidative stress may exacerbate vascu-

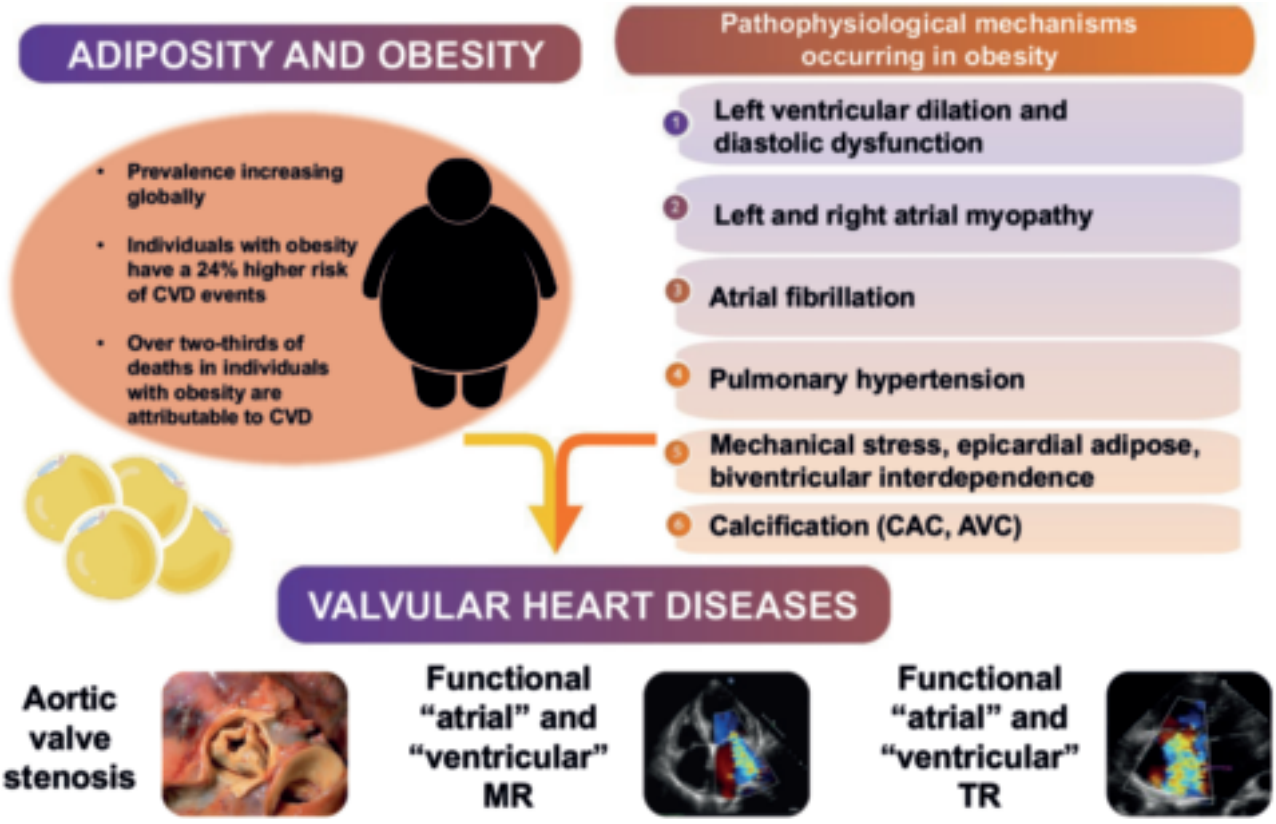

Figure 1. Obesity is one of the global burden of developed countries, with a prevalence in the USA now exceeding 40%. This condition is strictly related to cardiovascular diseases and events, due to many pathophysiological mechanisms. At least six of them could explain the biological plausibility of those "obesity-related" valvular heart diseases, which clinical implications could be useful for diagnostic and therapeutic management of these patients. AVC, aortic valve calcification; CAC, coronary artery calcification; CVD, cardiovascular dsisease; MR, mitral regurgitation; TR, tricuspid regurgitation.

lar remodeling in pulmonary hypertension. It is also associated with pulmonary hypertension due to left heart disease.[6] Pulmonary capillary wedge pressure and intra-vascular volume correlate with BMI. FTR may occur with left heart disease and pulmonary hypertension and as a consequence of right ventricular dilatation.

5. **Direct effect:** Patients with obesity have more pericardial fat and restraint resulting in changes in ventricular interdependence, increasing LV pressures and risk for FMR.
6. **Calcification:** Obesity is associated with higher coronary artery calcium score, which is associated with calcification and atherosclerosis at other sites also. Calcification in either the aortic or/and mitral valves are associated valvular stenosis. There is also an association between obesity, dyslipidemia and aortic stenosis. Genome-wide meta-analysis show that dyslipidemia, inflammation, calcification, and adiposity play important roles in aortic stenosis.[7]

Thus, various mechanisms may account for the development of primary (calcific stenosis) and secondary (FMR and FTR) VHD. It is less clear if obesity is related to primary MR or TR.

Clinical and research implications

Individuals with obesity associated VHD may experience worse symptoms, quality-of-life, exercise capacity, and risk for adverse outcomes. The effect of and the mechanism for various VHD in relation to obesity has not been investigated in depth. Recently, incretin-based drugs and sodium-glucose cotransporter-2 inhibitors have been shown to reduce adiposity, and improve HF outcomes; however, the implications of these drugs on VHD have not been evaluated. With innovations in therapies for obesity, several questions merit discussion. Should obesity be treated prior to valvular interventions? Can treatment of obesity slow progression of mild or moderate aortic stenosis? Would optimal treatment of obesity impact on mediators of FMR and FTR, e.g. HF with reduced ejection fraction, AF, and hypertension, change natural history of VHD? Similar to medical optimization prior to mitral transcatheter edge-to-edge procedures as it may favorably impact LV remodeling, could obesity targeting therapies could have a similar effect? Could this reduce or delay the need for interventions? Which VHD and at what stage should one intervene with respect to obesity? Even if an intervention is needed, would concomitant management of obesity lead to better outcomes from valvular interventions? Should VHD development and progression be an outcome in trials of obesity therapy? Considering the prevalence of obesity and its association with VHD, not studying these common comorbid conditions represents a significant missed opportunity.

Contributions

FF, drafting of the manuscript, creating central figure, critically revising the manuscript, final approval of the manuscript submitted; BRL,critically revising the manuscript for important intellectual content, final approval of the manuscript submitted; JB, conception and design of the manuscript, critically revising the manuscript for important intellectual content, final approval of the manuscript submitted.

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