13889

Accepted Manuscript

Visceral Adiposity and Left Ventricular Mass and Function in Patients with Aortic Stenosis: The PROGRESSA Study

Romain Capoulade, MSc Éric Larose, DVM, MD, FRCPC, FAHA Patrick Mathieu, MD, FRCSC Marie-Annick Clavel, DVM, PhD Abdellaziz Dahou, MD Marie Arsenault, MD Élisabeth Bédard, MD Samuel Larue-Grondin, Florent Le Ven, MD Jean G. Dumesnil, MD, FRCPC, FACC Jean-Pierre Després, PhD, FAHA Philippe Pibarot, DVM, PhD, FACC, FAHA, FESC, FASE

Please cite this article as: Capoulade R, Larose É, Mathieu P, Clavel M-A, Dahou A, Arsenault M, Bédard É, Larue-Grondin S, Le Ven F, Dumesnil JG, Després J-P, Pibarot P, Visceral Adiposity and Left Ventricular Mass and Function in Patients with Aortic Stenosis: The PROGRESSA Study, *Canadian Journal of Cardiology* (2014), doi: 10.1016/j.cjca.2014.02.007.

Visceral Adiposity and Left Ventricular Mass and Function in Patients with Aortic Stenosis: The PROGRESSA Study

Romain Capoulade, MSc, Éric Larose, DVM, MD, FRCPC, FAHA, Patrick Mathieu, MD, FRCSC, Marie-Annick Clavel, DVM, PhD, Abdellaziz Dahou, MD, Marie Arsenault, MD, Élisabeth Bédard, MD, Samuel Larue-Grondin, Florent Le Ven, MD, Jean G. Dumesnil, MD, FRCPC, FACC, Jean-Pierre Després, PhD, FAHA, Philippe Pibarot, DVM, PhD, FACC, FAHA, FESC, FASE.

Institut Universitaire de Cardiologie et de Pneumologie de Québec / Québec Heart & Lung Institute, Laval University, Québec city, Québec, Canada.

Address for correspondence: Dr Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec city, Québec, Canada, G1V-4G5.

Telephone number: 418-656-8711 (ext. 5938)   Fax number: 418-656-4602

E-mail address: philippe.pibarot@med.ulaval.ca

Short title: Visceral Obesity and Left Ventricle in Aortic Stenosis

Word count: 4748

Brief Summary

The purpose of this study was to examine the association between amount and distribution of body fat and LV hypertrophy and systolic dysfunction in aortic stenosis (AS) patients. The increased total adiposity as well as a high proportion of visceral adipose tissue (VAT) are both associated with LV hypertrophy, independent of AS severity and hypertension. The excess VAT and a high proportion of VAT relative to total adipose tissue are independently associated with impaired LV systolic function in AS.

ABSTRACT

Background: Recent studies have reported that obesity, metabolic syndrome, and diabetes are associated with LV hypertrophy (LVH) and dysfunction in aortic stenosis (AS) patients. The purpose of this study was to examine the association between amount and distribution of body fat and LVH and systolic dysfunction in AS patients.

Methods: 124 patients with AS were prospectively recruited in the PROGRESSA study and underwent Doppler-echocardiography and computed tomography (CT). Presence and severity of LVH was assessed by LV mass indexed for height$^{2.7}$ (LVMi) and LV dysfunction by global longitudinal strain (GLS). CT was used to quantify abdominal visceral (VAT) and subcutaneous (SAT) adipose tissue, and total adipose tissue (TAT).

Results: Body mass index (BMI) correlated strongly with TAT (r=0.85), moderately with VAT (r=0.70), and SAT (r=0.69), and weakly with the proportion of VAT (VAT/TAT ratio: r=0.19). In univariate analysis, higher BMI, TAT, VAT, SAT, and VAT/TAT were associated with increased LVMi whereas higher VAT and VAT/TAT ratio were associated with reduced GLS. Multivariate analysis revealed that larger BMI (p<0.0001) and higher VAT/TAT ratio (p=0.01) were independently associated with greater LVH, whereas only the VAT/TAT ratio (p=0.03) was independently associated with reduced GLS.

Conclusion: This study suggests that both total and visceral adiposity are independently associated with LVH in AS patients. Furthermore, impairment of LV systolic function does not appear to be influenced by total obesity but is rather related to excess visceral adiposity. These findings provide impetus for elaboration of interventional studies aiming at visceral adiposity in AS population.

Key words: Aortic stenosis, Visceral obesity, Doppler Echocardiography, LV hypertrophy, LV dysfunction

INTRODUCTION

The pressure overload associated with aortic stenosis (AS) and/or systemic arterial hypertension leads to the development of left ventricular hypertrophy (LVH). LV hypertrophy has been linked to occurrence of LV diastolic and systolic dysfunction,[1] increased risk of cardiac events,[2-4] higher operative risk for aortic valve replacement (AVR) and worse long-term outcomes[5] in the AS population.

In the SEAS trial (Simvastatin Ezetimibe in Aortic Stenosis), larger body mass index, a crude marker of total adiposity, was associated with LV hypertrophy in patients with asymptomatic AS, independent of AS severity and presence of concomitant hypertension.[6] In the ASTRONOMER trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin), we reported that metabolic syndrome and insulin resistance were associated with higher prevalence of concentric LVH and more pronounced impairment of LV systolic function at baseline as well as with faster progression of LVH during follow-up.[7, 8] Lindman et al. also reported an association between type 2 diabetes and LV hypertrophy and dysfunction in patients with severe AS.[9]

Because of its strong link with insulin resistance and type 2 diabetes, we hypothesized that excess visceral adiposity could be one of the key factors underlying the clinical association between obesity, metabolic syndrome, or diabetes and the development of LV hypertrophy and dysfunction in the AS population. The respective contributions of total versus visceral adiposity to variation in LV geometry and function among AS patients remain unknown. The objective of this prospective study was thus to examine the association between the content and distribution of body fat and the presence of LV hypertrophy and systolic dysfunction in patients with AS.

METHODS

Patients with AS recruited in the PROGRESSA study (Clinical Trial register: NCT01679431) underwent comprehensive Doppler-echocardiography to assess aortic valve morphology and function, LV geometry and function, and global LV hemodynamic load. Moreover, the amount and distribution of body fat were evaluated by body mass index (BMI) and waist circumference, as well as by computed tomography (CT) with the analyses of cross-sectional images of the abdomen at the L4-L5 intervertebral space. Detailed description of the methods is available in the Online Supplementary Materials.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation. The continuous variables were tested for normality of distribution and homogeneity of variances with the Shapiro-Wilk and Levene tests, respectively. These variables were then compared with unpaired Student t-test or two-way ANOVA followed by a Tukey's post hoc test when appropriate. Categorical data were expressed as percentage and compared with the Chi-square or Fischer's exact tests when appropriate. Correlations between anthropometric (i.e. BMI or waist circumference) and CT parameters (i.e. total adipose tissue [TAT], subcutaneous adipose tissue [SAT], visceral adipose tissue [VAT] and VAT/TAT ratio) of adiposity were determined using Pearsons's product-moment correlations. Multivariate linear regression analyses were performed to identify the impact of each anthropometric or CT parameters of adiposity on the study end-points (i.e. LV mass index [LVMi], LV ejection fraction [LVEF], and global longitudinal strain [GLS]). The following relevant variables were entered simultaneously in the multivariable models: age, gender, hypertension, systolic blood pressure, diabetes (LVMi only), coronary artery disease,

5

creatinin level (LVMi only), peak aortic jet velocity, and valvulo-arterial impedance. Standardized regression coefficients were presented as mean ± standard error (βeta coeff ± SE). Given the high level of correlations between parameters of adiposity, multivariate models were inspected for multicollinearity by calculating the Variance Inflation Factor. A p value < 0.05 was considered statistically significant for all statistical analyses.

RESULTS

Population Characteristics

Among the 124 patients included in this study, mean age was 67±13 years, 73% were men and 71% had systemic arterial hypertension, 40% presented coronary artery disease, 67% hyperlipidemia, 33% metabolic syndrome, and 20% diabetes. LDL cholesterol was 2.33±0.83 mmol.l^{-1}, HDL cholesterol was 1.41±0.43 mmol.l^{-1}, triglycerides was 1.41±0.76 mmol.l^{-1} and creatinin level was 84 ±21 umol.l^{-1}. The average peak aortic jet velocity was 2.9±0.6 m.s^{-1}, peak and mean transvalvular gradient were 34±13 mmHg and 19±8 mmHg respectively, whereas aortic valve area was 1.25±0.31 cm^2. 31 (25%) patients presented severe AS. Mean systolic and diastolic blood pressures were 138±18 mmHg and 77±9 mmHg, and mean Z_{va} was 3.6±0.8 mmHg.ml^{-1}.m^2. The LVMi was 49.6±10.2 g.m$^{-2.7}$ and the RWT was 0.52±0.08. The mean LVEF was 66±6% and mean GLS was 20.6±3.1|%| (Table S1 in Online Supplementary Materials).

Body Fat Content and Distribution

In the overall sample, BMI was 28.3±4.4 kg.m^{-2} and waist circumference was 100±13 cm. The CT-derived adiposity variables were: TAT: 482±169 cm^2, SAT: 273±103 cm^2, VAT: 209±104 cm^2 and VAT/TAT ratio: 0.42±0.11 (Table S1 in Online Supplementary Materials).

Figure 1 shows the correlation between the clinical and CT parameters of adiposity. The TAT was strongly correlated with BMI (r=0.85, p<0.0001; Figure 1, Panel A) and waist circumference (r=0.84, p<0.0001; Figure 1, Panel B). There was a moderate correlation between SAT and BMI (r=0.69, p<0.0001; Figure 1, Panel C) or waist circumference (r=0.59, p<0.0001; Figure 1, Panel D). VAT appeared to correlate better with waist circumference (r=0.79, p<0.0001; Figure 1, Panel F) than with BMI (r=0.70, p<0.0001; Figure 1, Panel E). The VAT/TAT ratio correlated weakly with BMI (r=0.19, p=0.03, Figure 1, Panel G) and waist circumference (r=0.33, p<0.0001; Figure 1, Panel H).

Association between Adiposity Parameters and LV Hypertrophy

In univariate analysis, higher values of BMI (p<0.0001), waist circumference (p=0.0002), TAT (p=0.002), VAT (p<0.0001), and VAT/TAT ratio (p=0.0003) were significantly associated with larger LVMi whereas SAT was not (p=0.33) (Table S2 in Online Supplementary Materials).

After adjustment for clinical and echocardiographic data, BMI, waist circumference, TAT, VAT, and VAT/TAT ratio remained associated with larger LVMi (Table S2 in Online Supplementary Materials). In a second multivariate model including the clinical and echocardiographic factors as well as the adiposity parameters that were significant in the first model (i.e. BMI, waist circumference, VAT, and VAT/TAT ratio), only BMI (p<0.00001) and VAT/TAT ratio (p=0.01) remained significantly associated with larger LVMi (Table S2 in Online Supplementary Materials; model R^2 = 0.35). In the latter model, TAT was not included as the preferred index of total adiposity due to its strong collinearity with BMI. Further adjustment for bicuspid valve phenotype provided similar results. The Variance Inflation Factor was <10 thus confirming that the level of multicollinearity in these multivariate models is acceptable.

7

After dichotomisation (median value) of the two indices of adiposity independently associated with LVMi in multivariate analysis, patients with the combination of high BMI and high VAT/TAT ratio had significantly higher LVMi (Figure 2, Panel A) and also showed a greater prevalence of LVH (Figure 2, Panel B) compared to the 3 others groups. The subgroup that had the lowest LVMi and prevalence of LVH also had both low BMI and low VAT/TAT ratio values. There was no significant interaction between BMI and VAT/TAT ratio and these 2 parameters thus had additive but not synergistic effects on LVMi.

Association between Adiposity Parameters and LV systolic dysfunction

In univariate analysis, BMI (p=0.25) was not associated with reduced LVEF and waist circumference was of borderline significance (p=0.05). VAT (p=0.04) and VAT/TAT ratio (p=0.03) were the only adiposity parameters associated with reduced LVEF (Table S3 in Online Supplementary Materials). After adjustment for clinical and echocardiographic data, VAT and VAT/TAT ratio remained associated with lower LVEF (Table S3 in Online Supplementary Materials). However, after including both indices in the multivariate model, none of them reached statistical significance (Table S3 in Online Supplementary Materials; model R^2 = 0.14).

In univariate analysis, VAT/TAT ratio (p=0.009) was significantly associated with reduced GLS and there was a trend for association with VAT (p=0.07). After adjustment for clinical and echocardiographic data, both VAT and VAT/TAT ratio were associated with lower GLS. When both parameters were included in the multivariate model, only VAT/TAT ratio remained independently associated with impaired GLS (Table S4 in Online Supplementary Materials; model R^2 = 0.16). Further adjustment for bicuspid valve phenotype provided similar results. The Variance Inflation Factor was <10 for all multivariate models presented in Tables S3 and S4 (Online Supplementary Materials).

8

After dichotomisation (median value) of VAT and VAT/TAT ratio, the patients with both high VAT and high VAT/TAT ratio had significantly lower GLS compared to those with high VAT but low VAT/TAT ratio as well as those with low VAT and low VAT/TAT ratio (Figure 2, Panel C). In addition, patients with low VAT and high VAT/TAT ratio also had lower GLS compared to those with high VAT and low VAT/TAT ratio. There was no significant interaction between VAT and VAT/TAT ratio with regards to impact on GLS and the effects of these 2 adiposity parameters were solely additive.

DISCUSSION

The main findings of this study are: *(1)* Increased total adiposity as well as a high proportion of visceral adipose tissue are both associated with LVH, independent of AS severity and hypertension; *(2)* Excess VAT and a high proportion of VAT relative to TAT are independently associated with impaired LV systolic function in AS, whereas excess total adiposity is not; (3) SAT is not associated with LV hypertrophy or dysfunction.

Amount and distribution of body fat versus LV hypertrophy

In patients with AS, LVH compensates for pressure overload. However, the magnitude of LVH is highly variable from one patient to another and may often become inappropriately high for the level of stroke work. Hence, severe LVH has been linked to worse outcomes in patients with AS.[1, 3-5, 10]

In the SEAS study after correction for stenosis severity and hypertension, a greater BMI was associated with the presence of LVH.[6] The present findings endorse and extend these previous findings. Larger BMI was indeed the most powerful predictor of higher LV mass even after

adjustment for other clinical and echocardiographic parameters. BMI is the anthropometric variable most frequently used in clinical practice to assess total adiposity and to diagnose obesity. Obesity produces an increment in total blood volume and cardiac output that is caused in part by the increased metabolic demand induced by excess body weight. Thus, at any given level of activity, the cardiac workload is augmented in obese subjects. In the Strong Heart Study, the cardiac output was 20 to 40 % higher in obese individuals compared to lean individuals of the same height.[11] In the context of AS, this increase in stroke volume associated with obesity may result in a substantial increase in gradient and thus in pressure overload, given that the gradient is a squared function of flow. In addition, in obese patients, the Frank-Starling curve is shifted to the left because of incremental increases in left ventricular filling pressure and volume, which over time may produce chamber dilation and LVH. The findings of the present study show that total adiposity is the most important metabolic determinant of LVH in patients with AS. Furthermore, these findings also demonstrate that besides the total amount of body fat, the regional distribution of adipose tissue also plays an additive role in the development of LVH. Indeed, in the present study, a greater proportion of VAT relative to TAT was associated with LVH independently of BMI.

Visceral obesity has been linked to insulin resistance and to a cluster of metabolic abnormalities often referred as the metabolic syndrome.[12] In the ASTRONOMER study, we reported that metabolic syndrome and insulin resistance were associated with higher prevalence of LV concentric hypertrophy at baseline and faster progression of LVH during follow-up in patients with mild to moderate AS.[7, 8] In a cross-sectional study of patients with severe AS undergoing valve replacement, Lindman et al. showed that type 2 diabetes is associated with more pronounced LV hypertrophy and worse systolic function.[9] Visceral obesity, metabolic syndrome, and diabetes are associated with hypertension and, in turn, hypertension may contribute to

10

LVH.[13] However, in the present study, VAT and VAT/TAT ratio remained associated with increased LVMi, independently of the diagnosis of hypertension, the systolic blood pressure, and the valvulo-arterial impedance, suggesting that other factors related to visceral obesity and ensuing insulin-resistance may be involved in the development of LVH in AS. To this effect, it should be emphasized that insulin resistance is one of the predominant metabolic abnormalities associated with visceral obesity and insulin resistance may promote myocardial hypertrophy and fibrosis through several signaling pathways including Akt, TGF-β, and PPAR.[14] Moreover, a recent study in a large US population reported an association between plasma concentration of free fatty acid, which is typically elevated in patients with visceral obesity, and the incidence of heart failure.[15]

The findings of this study thus suggest that development of LV hypertrophy in AS patients is not solely determined by the magnitude of LV pressure overload, but is also, in large part, related to the total amount as well as the regional distribution of body fat.

Amount and distribution of adiposity versus LV systolic dysfunction

In the ACC/AHA-ESC guidelines for the management of AS, LV systolic dysfunction is defined solely by the LVEF. However, LVEF is also influenced by LV geometry and it underestimates the extent of myocardial systolic dysfunction in presence of LV concentric hypertrophy, as is often the case in patients with AS. Accordingly, several studies report that up to one third of asymptomatic patients with preserved LVEF have a significant impairment of intrinsic myocardial systolic function as documented by parameters of LV longitudinal function.[16-18] Furthermore, these parameters have been shown to be superior to LVEF to predict adverse outcomes in AS.[16-20] From a pathophysiological standpoint, these data are consistent with the concept that the increase in wall stress and intra-myocardial pressure as well as the reduction in

myocardial blood flow in AS occur mainly in the subendocardium, where the myocardial fibers are oriented longitudinally. To overcome these inherent limitations of the LVEF, we also used the global longitudinal strain to assess LV systolic function.

As opposed to what was observed for LVH, total adiposity does not appear to be significantly associated with the LV systolic dysfunction in AS. In fact, the VAT and VAT/TAT were found to be the main adiposity parameters associated with reduced LVEF and GLS in this study. The effect of these parameters appears to be additive but not synergistic. These associations persisted after adjustment for stenosis severity, hypertension, and global hemodynamic load.

Chronic LV pressure overload induces a shift in myocardial substrate oxidation from free-fatty acids (FFA) towards carbohydrates.[21, 22] In a myocardium already confronted to reduced FFA oxidation because of pressure overload, insulin resistance linked to visceral obesity may further enhance FFA supply, and thereby aggravate the accumulation of triglycerides within the myocytes.[21] This inappropriate accumulation of lipids in the hypertrophied myocardium may result in contractile dysfunction and eventually cell apoptosis (i.e. lipotoxicity phenomenon).[23] To this effect, Mahmod et al. reported that pronounced myocardial steatosis is present in patients with severe aortic stenosis and is independently associated with reduced LV systolic function.[22] Marfella et al. also found that among patients with severe AS, those with metabolic syndrome have more pronounced myocardial steatosis and this was associated with lower LV ejection fraction.[24]

The other mechanisms that could explain the independent association between visceral obesity and LV systolic dysfunction in AS include the following: i) Excessive epicardial fat may secrete locally acting cytokines and/or adipokines that may alter myocardial function;[25] ii) Visceral obesity and metabolic syndrome associated with impaired coronary microvascular function, which may, in turn, negatively impact myocardial perfusion and function.

Clinical Implications

The present findings highlight that AS patients with larger BMI are prone to develop pronounced LVH. Furthermore, besides total adiposity, preferential lipid deposition in the visceral adipose tissue compartment predisposes to LVH and systolic dysfunction. BMI and waist circumference are largely parameters of total obesity, which are easily measurable in the clinical setting but cannot distinguish visceral from subcutaneous adiposity. As proposed by Lemieux et al., excess visceral adiposity may, however, be identified by the simultaneous presence of an elevated waist circumference combined with fasting hypertriglyceridemia (i.e. hypertriglyceridemic waist).[26] The use of imaging techniques such as CT and magnetic resonance imaging have improved our ability to precisely and reliably quantify individual differences in body fat distribution and to selectively distinguish subcutaneous adiposity from visceral abdominal adipose tissue.[27]

The results of this study therefore suggest that excess visceral adipose tissue distribution may represent an early index of dangerous ectopic lipid deposition linked to altered myocardial lipid metabolism and eventually to impaired ventricular geometry and function. Other studies reported that the metabolic abnormalities linked to visceral obesity (i.e. metabolic syndrome and type-2 diabetes) are associated with increased prevalence of aortic valve calcification,[28, 29] faster progression of AS,[30] and faster degeneration of aortic bioprosthetic valves.[31] As lifestyle modification programs including regular physical activity have been shown to mobilize visceral adipose tissue and ectopic fat depots,[27] it is suggested that lifestyle modification interventions may represent interesting early options to halt or slow disease progression at both the valvular and ventricular levels in patients with AS. Considering the limited therapeutic options for AS, randomized trials may be conducted to test the added value of prevention program targeting excess visceral/ectopic adiposity for the reduction of disease progression rate and cardiovascular events.

Study Limitations

The design of the study was cross-sectional and our observations do not imply causality. Longitudinal studies will be needed to examine the impact of the amount and distribution of body fat on the evolution of LV hypertrophy and function and on patients' outcomes. Given the relatively small sample size, some of the models may be slightly overfitted. Furthermore, in future studies, it would be interesting to include a control group of patients with similar levels and distribution of adiposity but no aortic stenosis.

The data of GLS was not available in all patients due to poor quality images or inadequate frame rate, which could introduce a selection bias in the analysis of this end-point. Nonetheless, the characteristics, and in particular the adiposity parameters, of the patients with or without GLS data were similar. In this study, we analyzed the association between the amount and distribution of fat on the most commonly used Doppler-echocardiographic parameters of LV geometry and function (i.e. LVMi, LVEF, and GLS). Further studies are needed to examine the relationship between adiposity parameters and: i) regional LV wall thickness and strain; ii) LV rotation.

CONCLUSION

The results of this study suggest that obesity (reflected by larger BMI) as well as excess visceral adiposity (reflected by higher VAT/TAT ratio) are independently associated with LV hypertrophy in AS patients. On the other hand, impairment of LV systolic function does not appear to be influenced by total adiposity per se but rather by excess visceral adiposity. These findings provide impetus for the elaboration of lifestyle modification programs aiming at the reduction of adiposity, and in particular of visceral adiposity.

Disclosures:

Dr. Després has served as a speaker for Abbott Laboratories, AstraZeneca, Solvay Pharma, GlaxoSmithKline, and Pfizer Canada, Inc.; has received research funding from Eli Lilly Canada; and has served on the advisory boards of Novartis, Theratechnologies, Torrent Pharmaceuticals Ltd., and Sanofi-Aventis. The other authors have reported no relationships relevant to the contents of this paper to disclose.

Reference List

1. Dumesnil JG, Shoucri RM. Effect of the geometry of the left ventricle on the calculation of ejection fraction. Circulation 1982; 65:91-8.

2. Greve AM, Boman K, Gohlke-Baerwolf C, et al. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. Circulation 2012; 125:346-53.

3. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic value of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart 2011; 97:301-7.

4. Holme I, Pedersen TR, Boman K, et al. A risk score for predicting mortality in patients with asymptomatic mild to moderate aortic stenosis. Heart 2012; 98:377-83.

5. Duncan AI, Lowe BS, Garcia MJ, et al. Influence of concentric left ventricular remodeling on early mortality after aortic valve replacement. Ann Thorac Surg 2008; 85:2030-9.

6. Lund BP, Gohlke-Barwolf C, Cramariuc D, Rossebo AB, Rieck AE, Gerdts E. Effect of obesity on left ventricular mass and systolic function in patients with asymptomatic aortic stenosis (a Simvastatin Ezetimibe in Aortic Stenosis [SEAS] substudy). Am J Cardiol 2010; 105:1456-60.

7. Pagé A, Dumesnil JG, Clavel MA, et al. Metabolic syndrome is associated with more pronounced impairment of LV geometry and function in patients with calcific aortic stenosis: A substudy of the ASTRONOMER trial. (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin). J Am Coll Cardiol 2010; 55:1867-74.

8. Capoulade R, Clavel MA, Dumesnil JG, et al. Insulin resistance and LVH progression in patients with calcific aortic stenosis: A substudy of the ASTRONOMER trial. J Am Coll Cardiol Img 2013; 6:165-74.

9. Lindman BR, Arnold SV, Madrazo JA, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. Circ Heart Fail 2011; 4:286-92.

10. Aurigemma GP, Silver KH, McLaughlin M, Mauser J, Gaasch WH. Impact of chamber geometry and gender on left ventricular systolic function in patients over 60 years of age with aortic stenosis. Am J Cardiol 1994; 74:794-8.

11. Collis T, Devereux RB, Roman MJ, et al. Relations of stroke volume and cardiac output to body composition. The strong heart study. Circulation 2001; 103:820-5.

12. Despres JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008; 28:1039-49.

13. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension 2009; 53:577-84.

14. Sharma N, Okere IC, Duda MK, Chess DJ, O'Shea KM, Stanley WC. Potential impact of carbohydrate and fat intake on pathological left ventricular hypertrophy. Cardiovasc Res 2007; 73:257-68.

15. Djousse L, Benkeser D, Arnold A, et al. Plasma Free Fatty Acids and Risk of Heart Failure: The Cardiovascular Health Study. Circ Heart Fail 2013; 6:964-9.

16. Dumesnil JG, Shoucri RM, Laurenceau JL, Turcot J. A mathematical model of the dynamic geometry of the intact left ventricle and its application to clinical data. Circulation 1979; 59:1024-34.

17. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010; 96:1364-71.

18. Ng AC, Delgado V, Bertini M, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J 2011; 32:1542-50.

19. Cramariuc D, Gerdts E, Davidsen ES, Segadal L, Matre K. Myocardial deformation in aortic valve stenosis - relation to left ventricular geometry. Heart 2009; 96:106-12.

20. Lafitte S, Perlant M, Reant P, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. Eur J Echocardiogr 2009; 10:414-9.

21. Zhang L, Jaswal JS, Ussher JR, et al. Cardiac Insulin Resistance and Decrease Mitochondrial Energy Production Precede the Development of Systolic Heart Failure Following Pressure Overload Hypertrophy. Circ Heart Fail. 2013.
Ref Type: In Press

22. Mahmod F, Bull S, Suttie JJ, et al. Myocardial Steatosis anf Left Ventricular Contractile Dysfunction in Patients with Severe Aortic Stenosis. Circ Cardiovasc Imaging . 2013.
Ref Type: In Press

23. Mathieu P, Pibarot P, Larose E, Poirier P, Marette A, Despres JP. Visceral obesity and the heart. Int J Biochem Cell Biol 2008; 40:821-36.

24. Marfella R, Di Filippo C, Portoghese M, et al. Myocardial lipid accumulation in patients with pressure-overloaded heart and metabolic syndrome. J Lipid Res 2009; 50:2314-23.

25. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006; 113:898-918.

26. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? Circulation 2000; 102:179-84.

27. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation 2012; 126:1301-13.

28. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation 2006; 113:2113-9.

29. Katz R, Budoff MJ, Takasu J, et al. Relationship of metabolic syndrome to incident aortic valve calcium and aortic valve calcium progression: the multi-ethnic study of atherosclerosis. Diabetes 2009.

30. Capoulade R, Clavel MA, Dumesnil JG, et al. Impact of metabolic syndrome on progression of aortic stenosis: Influence of age and statin therapy. J Am Coll Cardiol 2012; 60:216-23.

31. Briand M, Pibarot P, Despres JP, et al. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. Circulation 2006; 114:I512-I517.

FIGURE LEGENDS

FIGURE 1: Association between Anthropometric Parameters and Computed Tomography Parameters of Adiposity.

Legend: Correlation between *(1)* body mass index or waist circumference and *(2)* abdominal total adiposity (Panels A and B), subcutaneous adiposity (Panels C and D), visceral adiposity (Panels E and F), VAT/TAT ratio (Panels G and H).

VAT: visceral adipose tissue; TAT: total adipose tissue.

FIGURE 2: Left Ventricular Mass and Longitudinal Strain according to Adiposity Parameters.

Legend: Panels A and B show the comparison of LV mass index and prevalence of LV hypertrophy after dichotomization by median values of body mass index and VAT/TAT ratio. Panel C shows the comparison of global LV longitudinal strain after dichotomization by median values of VAT and VAT/TAT ratio

VAT: visceral adipose tissue; TAT: total adipose tissue. *$p<0.05$ versus BMI<28-Ratio<0.42 group; §$p<0.05$ versus BMI<28-Ratio>0.42 group; †$p<0.05$ ver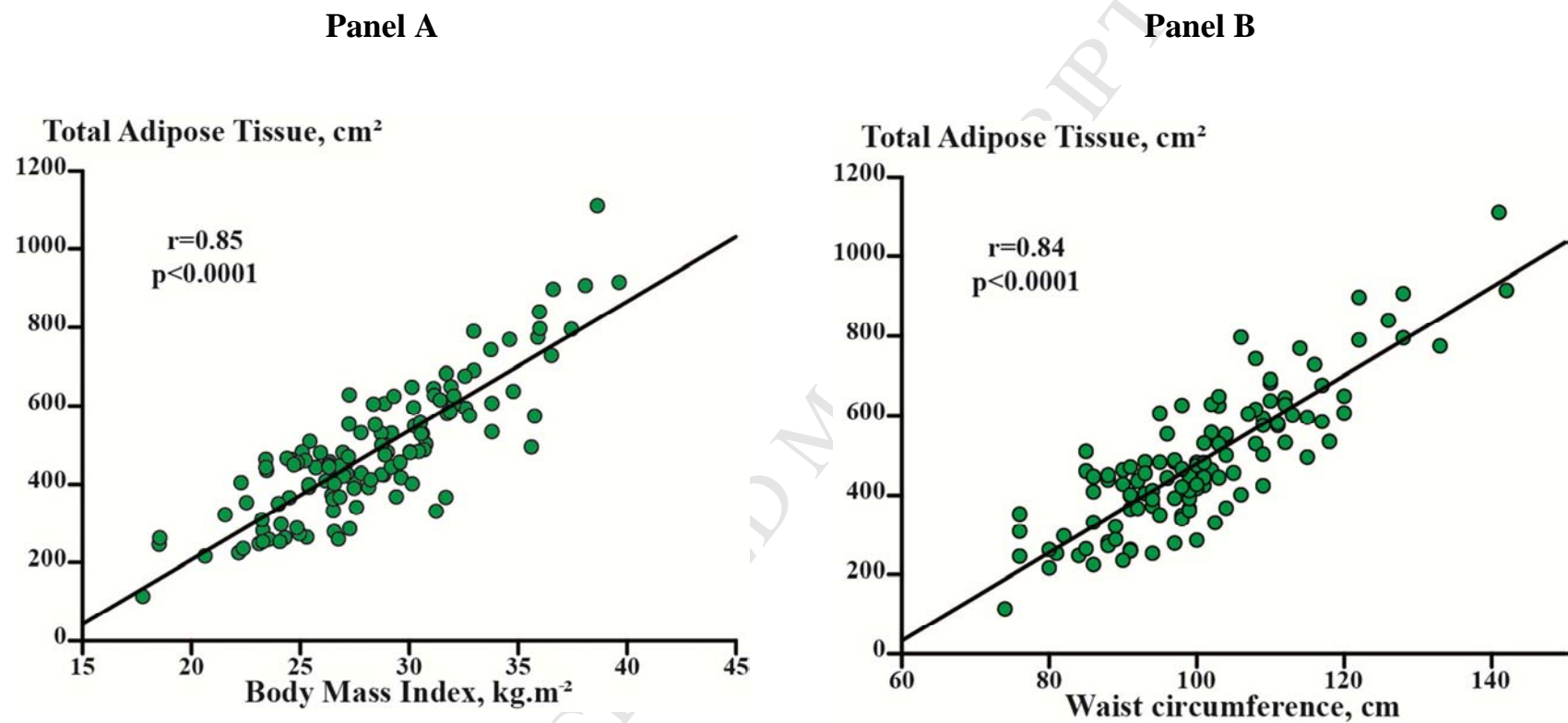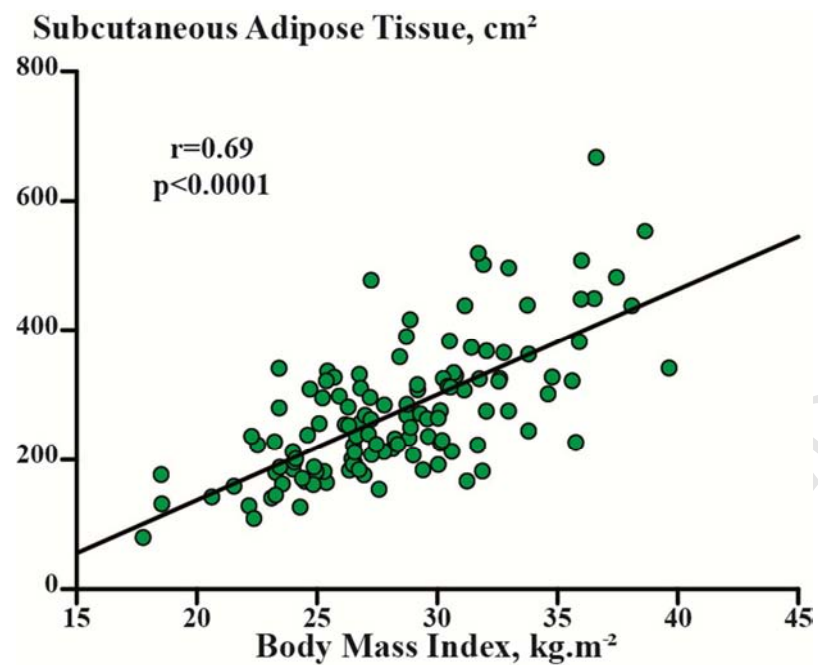sus BMI≥28-Ratio<0.42 group; ¶$p<0.05$ versus VAT≥181-Ratio>0.42 group; ‡$p<0.05$ VAT<181-Ratio>0.42 group. Error bars represent the SEM.
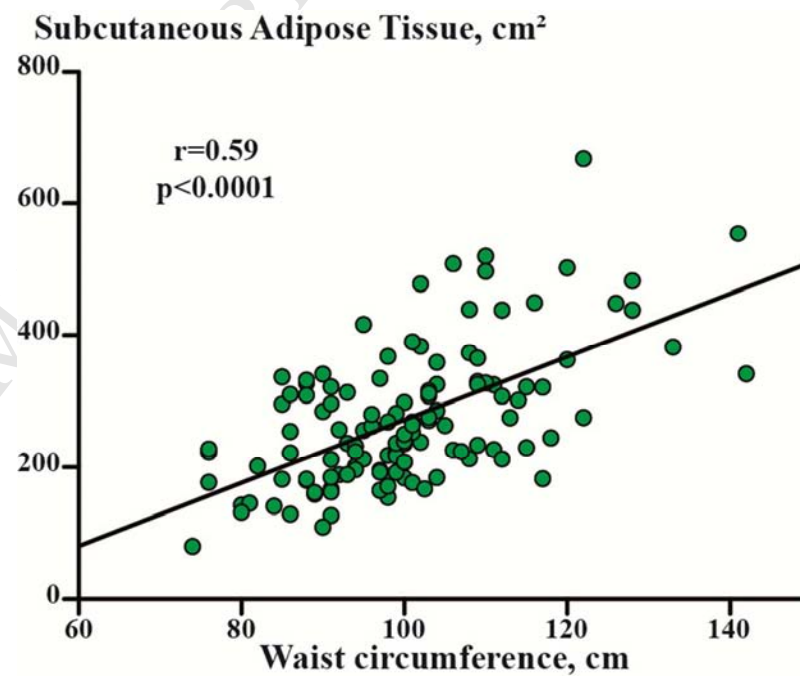
FIGURE 1

Panel A

Panel B

FIGURE 1

Panel C   **Panel D**

FIGURE 1

Panel E
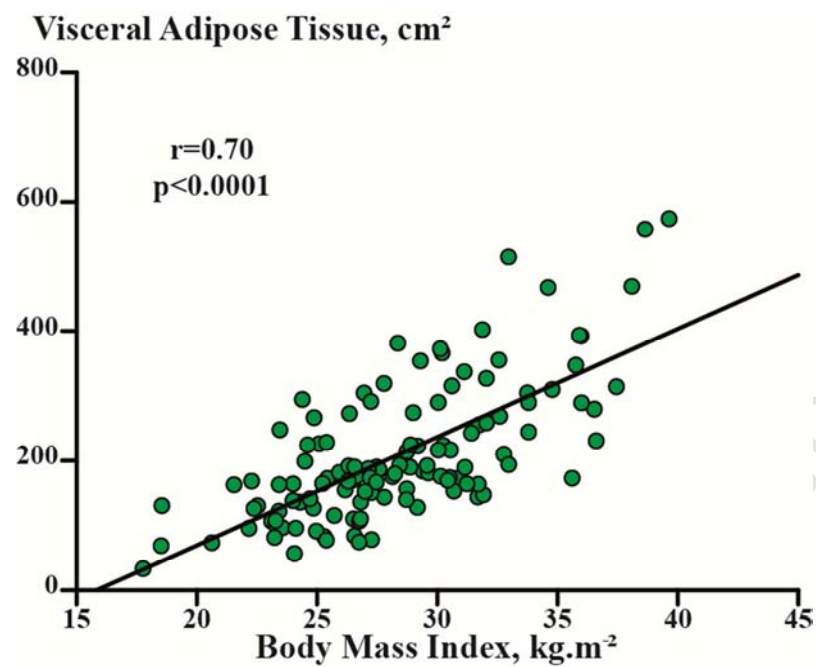
Panel F
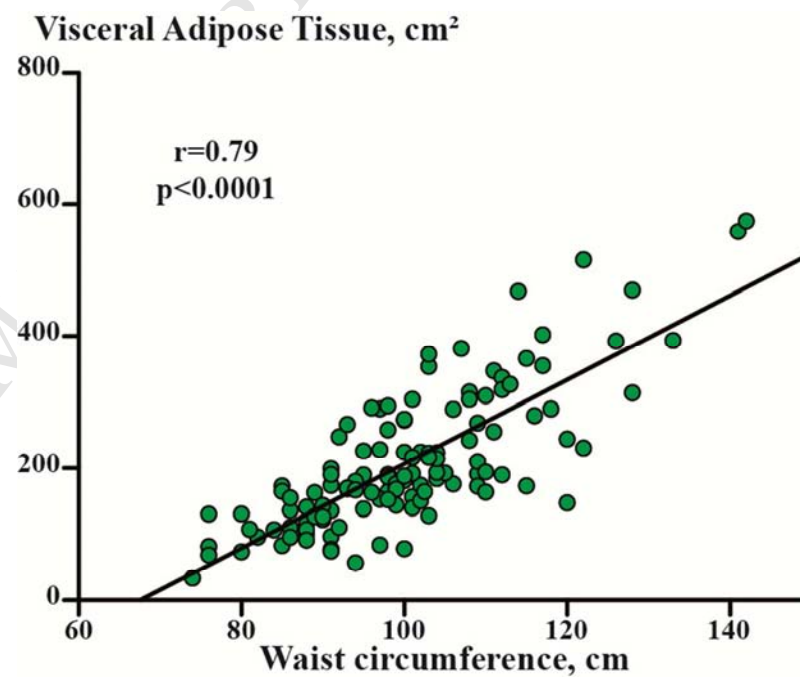
FIGURE 1

Panel G
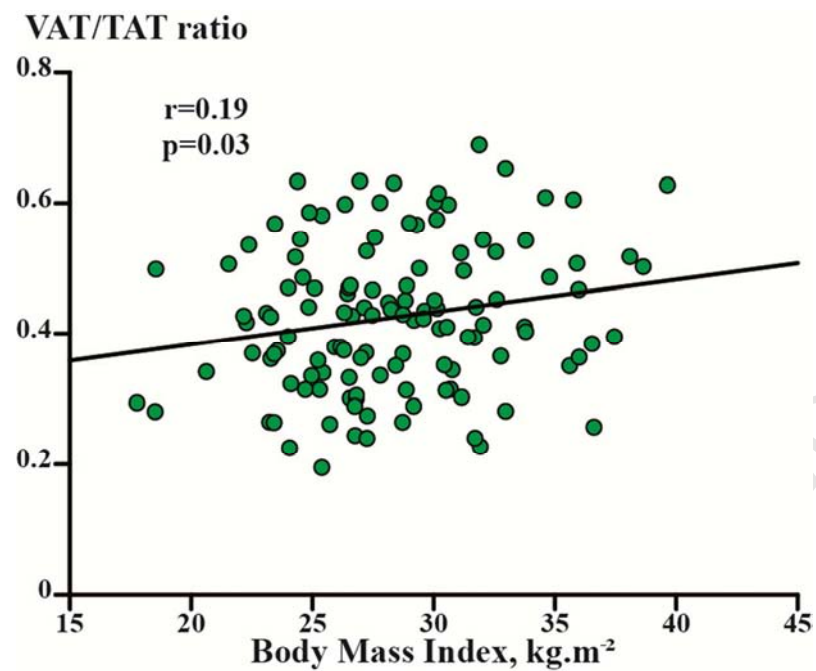
Panel H
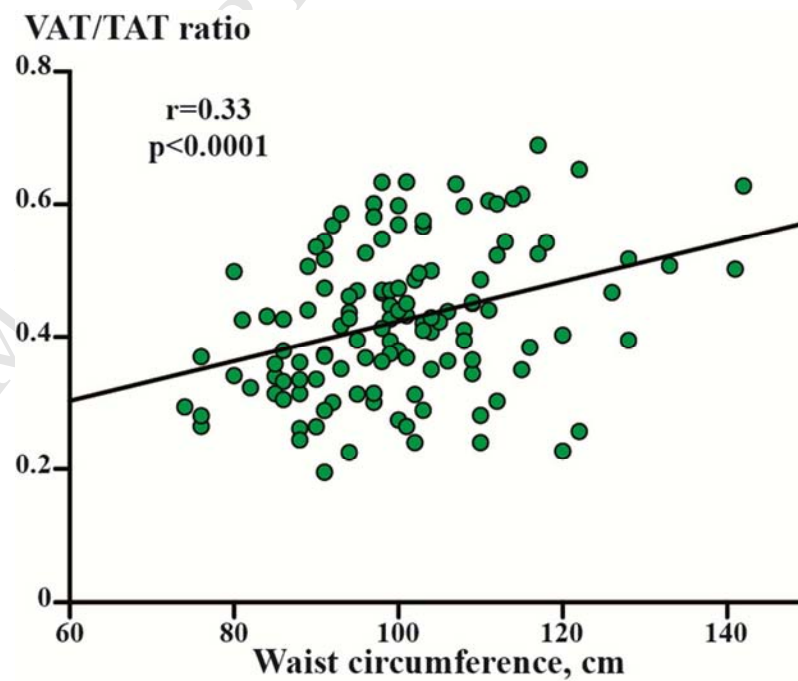
FIGURE 2

Panel A
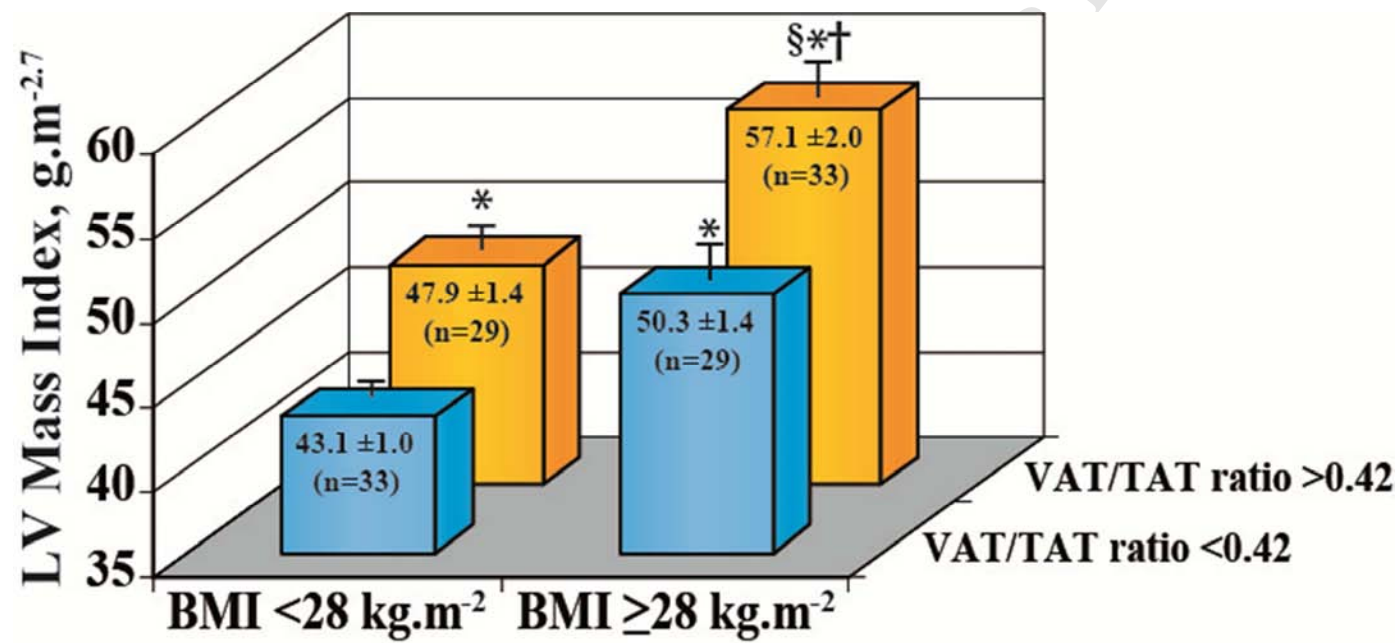
FIGURE 2

Panel B
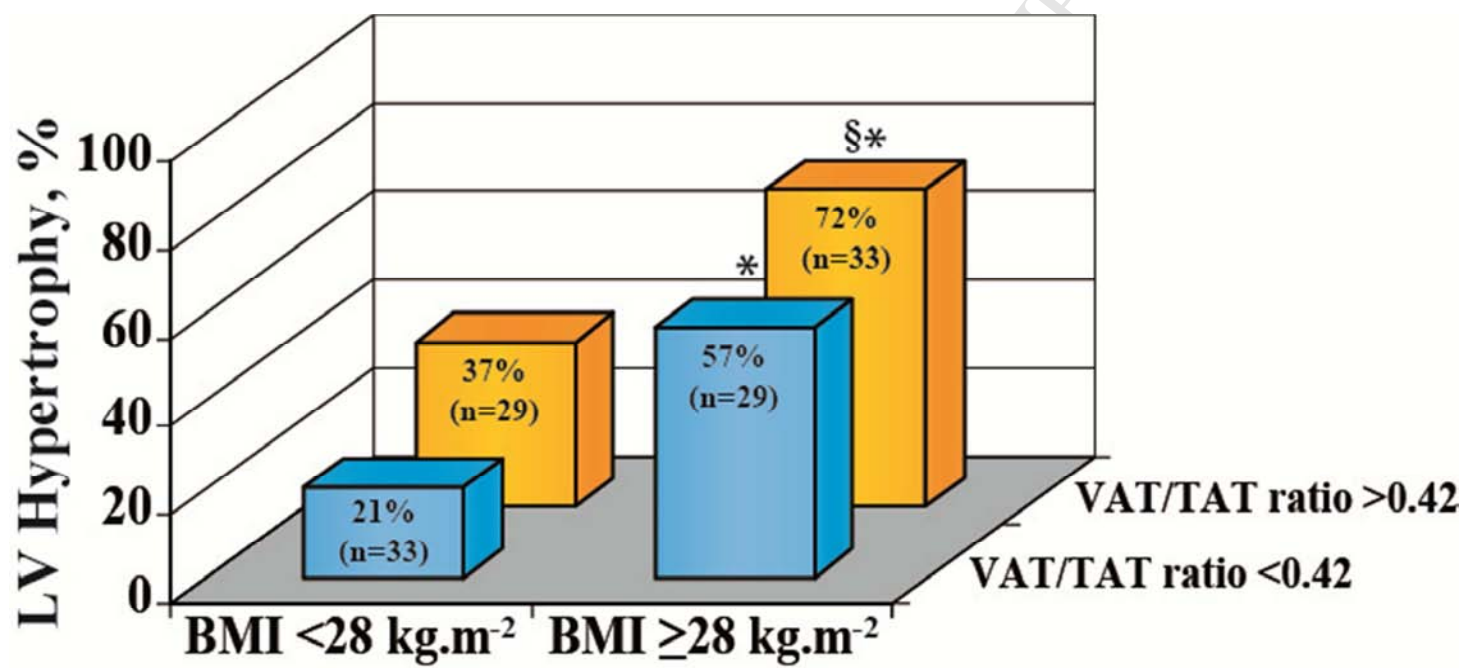
FIGURE 2

Panel C
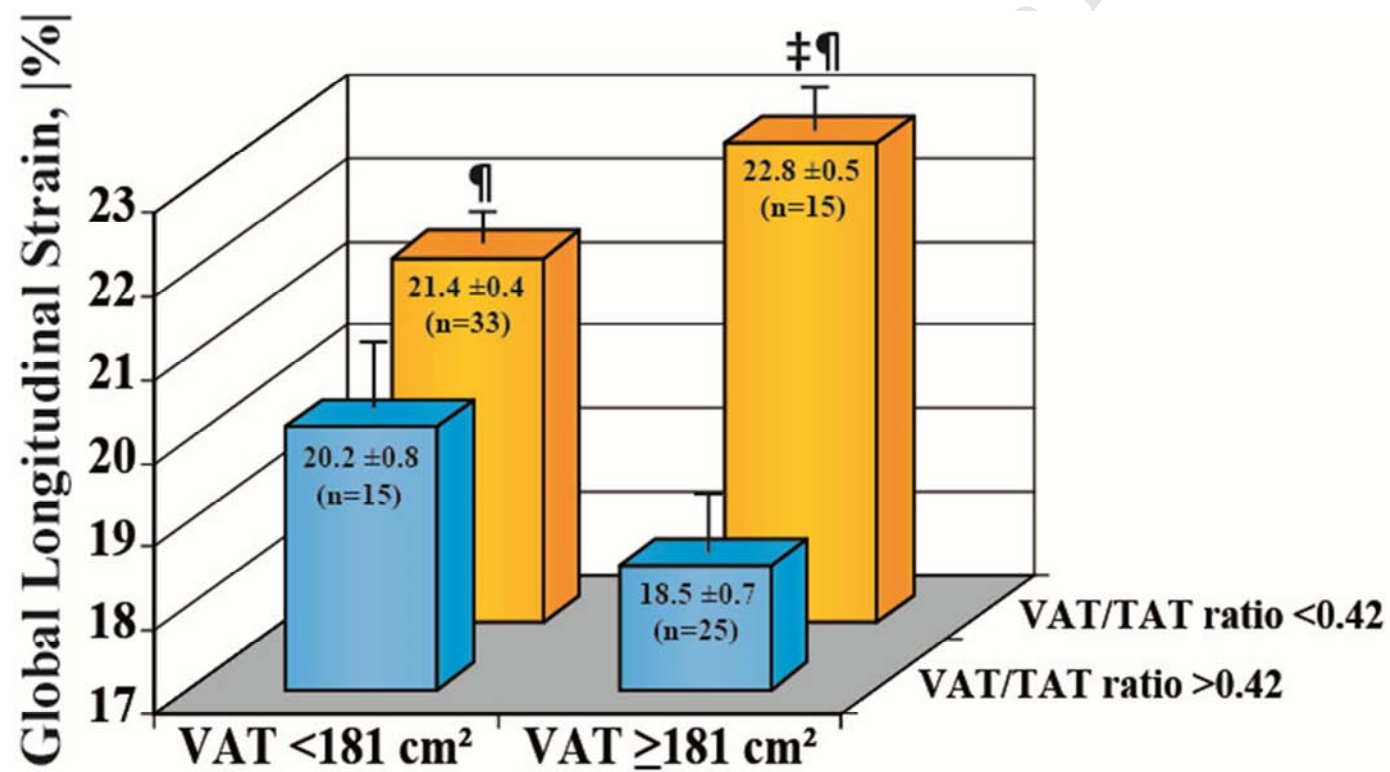
Online Supplementary Materials

TITLE: Visceral Adiposity and Left Ventricular Mass and Function in Patients

with Aortic Stenosis: The PROGRESSA Study

AUTHORS: Romain Capoulade, MSc, Éric Larose, DVM, MD, FRCPC, FAHA, Patrick Mathieu, MD, FRCSC, Marie-Annick Clavel, DVM, PhD, Abdellaziz Dahou, MD, Marie Arsenault, MD, Élisabeth Bédard, MD, Samuel Larue-Grondin, Florent Le Ven, MD, Jean G. Dumesnil, MD, FRCPC, FACC, Jean-Pierre Després, PhD, FAHA, Philippe Pibarot, DVM, PhD, FACC, FAHA, FESC, FASE.

METHODS

Patient Population

Patients with AS recruited in the PROGRESSA study (Clinical Trial register: NCT01679431) underwent Doppler-echocardiography and computed tomography (CT) within one month. Inclusion criteria were age >21 years old and peak aortic jet velocity >2.5 m.s^{-1}. Patients were excluded if they had symptomatic AS, moderate to severe aortic regurgitation or mitral valve disease (mitral stenosis or regurgitation), LVEF <50%, and if they were pregnant or lactating. The study was approved by the Ethics Committee of the Quebec Heart and Lung Institute, and patients signed a written informed consent at the time of inclusion.

Clinical data

Clinical data included age, gender, weight, height, body mass index (BMI), waist circumference, systolic and diastolic blood pressures, documented diagnoses of hypertension (patients receiving antihypertensive medications or having known but untreated hypertension [blood pressure $\geq$ 140/90 mmHg]), diabetes (patients receiving oral hypoglycemic or insulin medications, or, in the absence of such medications, having a fasting glucose $\geq$ 7 mmol/l), hyperlipidemia (patients receiving cholesterol-lowering medication or, in the absence of such medication, having a total plasma cholesterol level > 6.2 mmol/l), and coronary artery disease (history of myocardial infarction or coronary artery stenosis [i.e. >50%] on coronary angiography). The clinical identification of patients with the features of the metabolic syndrome was based on the modified criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[1]

Doppler Echocardiographic Data

Aortic valve morphology and function: LV stroke volume (SV) was calculated with the use of pulsed-wave Doppler in the LV outflow tract. The Doppler-echocardiographic indices of AS severity included peak aortic jet velocity (V_{peak}), peak and mean transvalvular pressure gradients (MG) obtained with the use of the modified Bernoulli equation, and the aortic valve area (AVA) calculated by the standard continuity equation. The degree of aortic valve calcification was scored according to the criteria proposed by Rosenhek et al.[2] Severe AS was defined according the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (i.e. $V_{peak} > 4$ m.s^{-1}, MG >40mmHg or AVA <1cm²).[3]

Left ventricular geometry: LV minor axis internal dimension (LVID), posterior wall thickness (PWT), and inter-ventricular septal thickness (IVST) were measured at end-diastole according to the recommendations of the American Society of Echocardiography.[4] The relative wall thickness (RWT) was calculated by dividing the sum of the LV posterior wall and inter-ventricular septal thicknesses by the LV internal dimension (RWT = [PWT+IVST]/LVID). Left ventricular mass was calculated with the corrected formula of the American Society of Echocardiography and was indexed to a 2.7 power of height, as previously validated.[5-7] The LVH was defined as an indexed LV mass (LVMi) >49 g.m$^{-2.7}$ in men and >47 g.m$^{-2.7}$ in women.[5-7]

Left ventricular function: LV ejection fraction was measured with the use of biplane Simpson method. The LV longitudinal strain was measured by speckle-tracking with dedicated commercial software (2D Cardiac Performance Analysis, TomTec Imaging Systems, Munich, Germany). The global longitudinal strain (GLS) was calculated as the average of longitudinal strain of the 2-chamber, 3-chamber, and 4-chamber apical views. The GLS data were expressed in absolute value (|%|). GLS was available in 88 (71%) of the 124 patients included in this study.

The measurement of GLS was not feasible in the remaining patients due to poor image quality and/or insufficient frame rate. However, patients with GLS data available had similar characteristics, and particularly adiposity parameters, compared to those with missing GLS data. Intra- and inter- observer variability were 6% and 7.5%, respectively.

Global LV hemodynamic load: As a measure of global LV hemodynamic load, we calculated the valvulo-arterial impedance: $Z_{va}=(SBP+\Delta P_{mean})/SVi$ where SBP is the systolic blood pressure, ΔP_{mean} the mean transvalvular gradient, and SVi is the stroke volume indexed to body surface area.[6, 8, 9]

Computed Tomography Data

Cross-sectional images of the abdomen were obtained by dual-source multi-detector CT (Somatom Definition, Siemens) at the L4-L5 intervertebral space using standardized procedures,[10] and state-of-the-art dose reduction strategies. Image analysis was performed off-line in a standardized core laboratory using dedicated software (sliceOmatic, Tomovision, Montreal, Québec, Canada) by trained technicians blinded to clinical and Doppler-echocardiographic data. Cross-sectional areas of visceral (VAT) and subcutaneous (SAT) adipose tissue were quantified using an attenuation range of -190 to -30 Hounsfield units (HU). Total adipose tissue area was determined as the sum of visceral and subcutaneous adipose tissue areas (TAT=VAT+SAT). The VAT/TAT ratio was calculated as an index of the proportion of total abdominal adipose tissue located in the visceral compartment.

Study End-Points

The study end-points were LV hypertrophy assessed by LVMi and LV systolic dysfunction assessed by LVEF and GLS.

TABLE S1: Patients Characteristics (n=124)

Clinical data

Age, years	67 ±13
Male gender, %	73%
Height, cm	167 ±9
Weight, kg	79 ±15
Body surface area, m^2	1.9 ±0.2
Body mass index, $kg.m^{-2}$	28.3 ±4.4
Waist circumference, cm	100 ±13
History of hypertension, %	71%
Systolic blood pressure, mm Hg	138 ±18
Diastolic blood pressure, mm Hg	77 ±9
History of smoking, %	73%
Coronary artery disease, %	40%
Hyperlipidemia, %	67%
Metabolic Syndrome, %	33%
Diabetes, %	20%
LDL cholesterol, $mmol.l^{-1}$	2.33 ±0.83
HDL cholesterol, $mmol.l^{-1}$	1.41 ±0.43
Triglycerides, $mmol.l^{-1}$	1.41 ±0.76
Creatinin, $umol.l^{-1}$	84 ±21

Doppler-echocardiographic data

Bicuspid aortic valve, %	19%
Aortic valve calcification score	2.5 ±0.6
Peak aortic jet velocity, $m.s^{-1}$	2.9 ±0.6
Peak transvalvular gradient, mm Hg	34 ±13
Mean transvalvular gradient, mm Hg	19 ±8
Aortic valve area, cm^2	1.25 ±0.31
Severe aortic stenosis, %	25%
Valvulo-arterial impedance, $mm\ Hg.ml^{-1}.m^2$	3.6 ±0.8
LV end-diastolic diameter, mm	46 ±5
Inter-ventricular septum thickness, mm	12 ±2
Posterior wall thickness, mm	11 ±2
Relative wall thickness ratio	0.52 ±0.08
LV mass index, $g.m^{-2.7}$	49.6 ±10.2
LV ejection fraction, %	66 ±6%
Global longitudinal strain, |%| (n=88)	20.6 ±3.1

Computed tomography data

Visceral abdominal tissue, cm²	209 ±104
Subcutaneous abdominal tissue, cm²	273 ±103
Total abdominal tissue, cm²	482 ±169
VAT/TAT ratio	0.42 ±0.11

Legend: LV: left ventricle; VAT: visceral adipose tissue; TAT: total adipose tissue. Values are mean ±SD unless otherwise indicated.

TABLE S2: Association between Adiposity Parameters and LV Mass index

Adiposity parameters	Univariate		Adjusted for clinical and echocardiographic factors*		Adjusted for clinical, echocardiographic and adiposity factors¶	
	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value
Anthropometry						
Body mass index, kg.m^{-2}	0.43 ± 0.19	<0.0001	**0.40 ± 0.21**	**<0.0001**	**0.40 ± 0.20**	**<0.0001**
Waist circumference, cm	0.33 ± 0.07	0.0002	**0.32 ± 0.08**	**0.001**	0.20 ± 0.19	0.41
Computed tomography						
Total adipose tissue, cm^2	0.28 ± 0.005	0.002	**0.29 ± 0.006**	**0.002**	_	_
Visceral dipose tissue, cm^2	0.37 ± 0.008	<0.0001	**0.35 ± 0.01**	**0.0004**	0.32 ± 0.03	0.22
Subcutaneous adipose tissue, cm^2	0.09 ± 0.009	0.33	0.17 ± 0.009	0.07	_	_
VAT/TAT ratio	0.33 ± 7.98	0.0003	**0.25 ± 10.10**	**0.03**	**0.25 ± 9.40**	**0.01**

Legend: VAT: visceral adipose tissue; TAT: total adipose tissue; βeta coeff. is the standardized regression coefficient ±SE.

*: Association between each individual adiposity parameter and LV mass index with adjustment for clinical and echocardiographic data: i.e. age, gender, hypertension, systolic blood pressure, diabetes, coronary artery disease, creatinin level, peak aortic jet velocity, and valvulo-arterial impedance.

¶: Association between adiposity parameters and LV mass index with adjustment for clinical and echocardiographic data as well as other adiposity parameters. The adiposity parameters entered in this model were those with a p value<0.05 after adjustment for clinical and echocardiographic factors except TAT that was excluded due to very strong collinearity with body mass index.

TABLE S3: Association between Adiposity Parameters and LV Ejection Fraction

Adiposity parameters	Univariate		Adjusted for clinical and echocardiographic factors*		Adjusted for clinical, echocardiographic and adiposity factors¶	
	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value
Anthropometry						
Body mass ndex, $kg.m^{-2}$	-0.11 ± 0.12	0.25	-0.09 ± 0.13	0.35	–	–
Waist circumference, cm	-0.18 ± 0.04	0.05	-0.14 ± 0.05	0.16	–	–
Computed tomography						
Total adipose tissue, cm^2	-0.11 ± 0.003	0.24	-0.14 ± 0.003	0.13	–	–
Visceral adipose tissue, cm^2	-0.19 ± 0.005	0.04	**-0.22 ± 0.006**	**0.03**	-0.15 ± 0.007	0.26
Subcutaneous adipose tissue, cm^2	0.01 ± 0.005	0.88	-0.05 ± 0.005	0.60	–	–
VAT/TAT ratio	-0.20 ± 4.65	0.03	**-0.23 ± 5.77**	**0.04**	-0.13 ± 7.29	0.36

Legend: VAT: visceral adipose tissue; TAT: total adipose tissue; βeta coeff. is the standardized regression coefficient ±SE.

*: Association between each individual adiposity parameter and LV ejection fraction with adjustment for clinical and echocardiographic data : i.e. age, gender, hypertension, systolic blood pressure, coronary artery disease, peak aortic jet velocity, and valvulo-arterial impedance.

¶: Association between adiposity parameters and LV ejection fraction with adjustment for clinical and echocardiographic data as well as other significant adiposity parameters. The adiposity parameters entered in this model were those with a p value<0.05 after adjustment for clinical and echocardiographic factors.

TABLE S4: Association between Adiposity Parameters and LV Global Longitudinal Strain

Adiposity parameters	Univariate		Adjusted for clinical and echocardiographic factors*		Adjusted for clinical, echocardiographic and adiposity factors ¶	
	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value	βeta coeff. ±SE	p value
Anthropometry						
Body mass index, $kg.m^{-2}$	-0.04 ± 0.08	0.75	-0.04 ± 0.09	0.72	_	_
Waist circumference, cm	-0.07 ± 0.03	0.55	-0.02 ± 0.03	0.86	_	_
Computed tomography						
Total adipose tissue, cm^2	-0.04 ± 0.002	0.72	-0.04 ± 0.002	0.74	_	_
Visceral adipose tissue, cm^2	-0.20 ± 0.003	0.07	**-0.27 ± 0.004**	**0.05**	0.005 ± 0.005	0.97
Subcutaneous adipose tissue, cm^2	0.11 ± 0.003	0.31	0.11 ± 0.003	0.35	_	_
VAT/TAT ratio	-0.29 ± 2.98	0.009	**-0.37 ± 3.74**	**0.005**	**-0.37 ± 4.88**	**0.03**

Legend: VAT: visceral adipose tissue; TAT: total adipose tissue; βeta coeff. is the standardized regression coefficient ±SE.

*: Association between each individual adiposity parameter and LV global longitudinal strain with adjustment for clinical and echocardiographic data: i.e. age, gender, hypertension, systolic blood pressure, coronary artery disease, peak aortic jet velocity, and valvulo-arterial impedance.

¶: Association between adiposity parameters and LV global longitudinal strain with adjustment for clinical and echocardiographic data as well as other significant adiposity parameters. The adiposity parameters entered in this model were those with a p value<0.05 after adjustment for clinical and echocardiographic factors.

REFERENCES

1. Expert panel. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adults treatment panel III). JAMA 2001; 285:2486-92.

2. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000; 343:611-7.

3. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006; 114:e84-231.

4. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18:1440-63.

5. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995; 25:1056-62.

6. Pagé A, Dumesnil JG, Clavel MA, et al. Metabolic syndrome is associated with more pronounced impairment of LV geometry and function in patients with calcific aortic stenosis: A substudy of the ASTRONOMER trial. (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin). J Am Coll Cardiol 2010; 55:1867-74.

7. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992; 20:1251-60.

8. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol 2009; 54:1003-11.

9. Briand M, Dumesnil JG, Kadem L, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: Implications for diagnosis and treatment. J Am Coll Cardiol 2005; 46:291-8.

10. Ferland M, Despres JP, Tremblay A, et al. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. Br J Nutr 1989; 61:139-48.