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Original Paper

# IMPACT OF BODY MASS INDEX ON PARAMETERS OF THE LEFT ATRIUM: CARDIAC COMPUTED TOMOGRAPHY STUDY

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Increased Body Mass Index (BMI) is often used as a predictor for cardiovascular diseases, and it is also known to be associated with left atrial enlargement, potentially affecting anatomic structures of the left atrium. The aim of the study was to determine the association between BMI and parameters of the left atrium, including characteristics of the pulmonary veins (PVs), found in cardiac computed tomography (CT) scan. The retrospective study included 140 patients with a mean age of 66.9 years (SD = 7.8). There were statistically significant correlations between BMI and volume changes of the left atrium during the cardiac cycle:  $V_{max}$  ( $r_s = 0.199$ , p = 0.023),  $V_{min}$  ( $r_s =$ 0.177, p = 0.043),  $V_{mean}$  ( $r_s = 0.190$ , p = 0.029), which supports previously known data. The study also revealed unique associations regarding the impact of BMI on PV structures. There was a significant correlation between BMI and PV orifice size in the left inferior PV ( $r_s = 0.216$ , p = 0.032) and the right accessory PV ( $r_s = -0.629$ , p = 0.012). The right PV angle was positively correlated with BMI (p = 0.436). The results support previously known associations between increased BMI and left atrial enlargement and show a statistically significant effect of increased BMI on the characteristics of pulmonary veins.

Keywords: obesity, anatomy of the left atrium, pulmonary vein orifice size, pulmonary vein angle.

# INTRODUCTION

Obesity is a disease with a complex multifactorial pathogenetic mechanism (Powell-Wiley *et al.*, 2021) and, paradoxically alongside under-nutrition, has spread to a level of epidemic proportions (World Health Organization, 2019). There are studies supporting the theory of changes in the human phenotype from predominantly normal weight and underweight to overweight and obese by changes in the food system, automation of jobs, and motorisation of transportation (Swinburn *et. al.*, 2011). Despite the warnings and the broad spectrum of informational campaigns worldwide, the obesity problem has tripled since 1975 (World Health Organization, 2019) and only continues to spread.

To estimate body fat, the body mass index (BMI) is used internationally, calculated by dividing the weight of a person in kilograms divided by their height in metres squared. Following the World Health Organization criteria (World Health Organization, 2019), overweightness is defined by BMI  $\ge 25$  and < 30 kg/m<sup>2</sup>, and obesity by BMI  $\ge 30$  kg/m<sup>2</sup>. BMI strongly correlates with body fat percentage at the population level; however, the ability to describe and evaluate body fat in an individual can be affected (Romero-Corral et al., 2008) by potential alterations of age, sex, and ethnicity (Loos et al., 2012). Use of the BMI is also criticised for its inability to differentiate between lean body mass and fat, and for ignoring the significant role fat distribution in the body plays for the pathogenesis of cardiovascular complications (Rothman, 2008). Nevertheless, BMI is still used because of its simplicity and its cost and time effectiveness, not only for clinical practice, but also for scientific purposes.

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Increased body weight in many pathways links to the development of cardiovascular diseases (CVD) directly and often by amplifying the risk factors, including arterial hypertension, type 2 diabetes, dyslipidemia (Powell-Wiley et al., 2021). The possible mechanisms of how excess body fat leads to CVD and increases the CVD mortality rate are impressively heterogeneous (Powell-Wiley et al., 2021). For example, studies in the early 2000s found that adipose tissue is an active organ with endocrinal ability to produce a wide range of bioactive substances called adipokines, which may affect angiogenesis, vascular homeostasis, insulin sensitivity, and glucose and lipid metabolic processes (Kershaw et al., 2004). Furthermore, obesity tends to make changes in haemodynamics, causing adverse modifications in the cardiovascular system. The parts of the maladaptive cascade are expansion in intravascular volume because of sodium retention, increased cardiac output (CO) due to increased heart rate (HR) and stroke volume (SV) as a result from sympathetic nervous activation and sympathetic overactivity, and increase in systemic vascular resistance (SVR) caused by inflammatory reactions (Loos, 2012). As follows, an increase in volumes and filling pressures predisposes to abnormal remodelling and geometry changes of the left ventriculum (LV) and, sooner or later, the left atrium (LA) (Loos, 2012). The LA enlargement is mainly caused by pathologic LV diastolic filling (Chakko, 1991), enhancing the risk for atrial fibrillation (AF) development, the most common type of heart rhythm disorder (Kornej et al., 2020).

The link between LA enlargement and abnormal changes in electrophysiology can be explained by remodeling at structural, and even electrical, levels (Abed, 2013) with signs of increased myocardial fibrosis (Shuai, 2019) and inflammation following slowing and vectoral alternations in electrical impulse conduction (Abed, 2013). The study by Mynger et al. (2012) showed a slowing of conduction in the PV ostia and a shortening of the effective refractory period in the PVs and LA, which was described as the key to electrophysiological alternation's association with the enlargement, impaired stretching, and contraction of the LA (Pouwels, 2019). Despite the fact that the isolation of ectopic foci in PVs gave a fresh start in the treatment of AF (Haïssaguerre, 1998), there is still lack of data explaining the connection between increased BMI and changes in the PV ostia size and anatomy characteristics.

The aim of the study was to determine the associations between BMI and the parameters of the left atrium, including characteristics of the pulmonary veins (PV), in a cardiac computed tomography (CT) scan.

### MATERIALS AND METHODS

The retrospective study included 140 patients aged 18 years and older, with no previously known cardiac pathology. All patients were evaluated by the following criteria — age, sex, weight, and height and underwent a multi-slice cardiac computed tomography (CT) scan. To ensure the accuracy of the data, anthropometric measurements were recorded at the hospital just before the CT procedure.

The BMI was calculated by dividing the weight of the person in kilograms divided by height in metres squared, following the World Health Organization recommendations (World Health Organization, 2019).

The next step was to conduct a cardiac CT scan in supine position followed by an evaluation of the left atrium, performed by making five three-dimensional reconstruction models of the heart during the cardiac cycle. The cardiac cycle stages were evaluated according to a electrocardiogram (ECG) registered during the CT scan.

Using 3D reconstruction models of the LA, the following measurements were made: the maximal volume of the LA  $(V_{max}, ml)$ , the minimal volume of the LA  $(V_{min}, ml)$ , the mean volume of the LA during the cardiac cycle  $(V_{mean}, ml)$ , and the mean volume of the LA appendage during the cardiac cycle (ml). The following PV characteristics were evaluated: number of PV ostiae on each side (left and right), diameter of PV ostiae (mm), and angle between PV on each side (left and right, °).

Statistical analysis of the collected data was performed using the IBM SPSS Statistics 27 software, with the value of the statistical significance as p < 0.05. Before the study, approval by the Medical Ethics Committee was received, and all scientific investigations were made in accordance with the Declaration of Helsinki.

# RESULTS

A total of 140 patients with no previously known cardiac pathology were enrolled in the study. The mean age of the patient group was 66.9 years (SD = 7.8), 75% (105) were male and 25% (35) were female. Their mean height was 1.72 m (SD = 8.2), mean weight 76.10 kg (SD = 13.6), and mean BMI 25.5 (SD = 3.8).

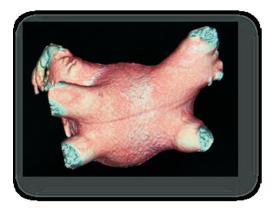
The left atrial volume was evaluated at three stages: maximum filling, minimum filling, and mean volume during the cardiac cycle. The mean maximal volume was 138.6 ml (SD = 35.7), the mean minimal volume was 93.6 ml (SD = 29.9), and mean volume during the cardiac cycle was 116.2 ml (SD = 31.8). The mean volume of the left atrial appendage was 12.1 ml (SD = 4.8) (Table 1).

The most common variation was with two PVs connecting to the posterior wall of the left atrium on each side (Fig. 1). On the right side, two PV orifices occurred in 85.7% of the cases (120), but on the left side, two PVs were connecting to the left atrium in 78.6% (110) of the cases. On the right side there were 12.2% (17) cases with only one accessory PV, 1.4% (2) with two accessory PVs and only one case (0.7%) was with one common right PV. On the left side, one common PV connecting to the left atrium was seen in 21.4% (30) of cases (Fig. 2, Table 2).

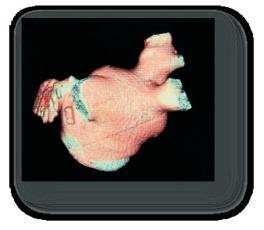
Table 1. Volumetric parameters of the left atrium

Parameters	Value, ml		
LA volume			
V <sub>max</sub>	138.6 (SD = 35.7)		
V <sub>min</sub>	93.6 (SD = 29.9)		
V <sub>mean</sub>	116.2 (SD = 31.8)		
T A A 1	121 (CD 4.9)		
LAA volume	12.1 (SD = 4.8)		

LA, left atrium; LAA, left atrial appendage;  $V_{max}$ , maximal volume of the left atrium;  $V_{min}$ , minimal volume of the left atrium;  $V_{mean}$ , mean volume of the left atrium during the cardiac cycle



*Fig. 1.* Cardiac CT 3D reconstruction model of the left atrium. Posterior view – two pulmonary vein orifices on each side (Verhovceva, 2021).



*Fig.* 2. Cardiac CT 3D reconstruction of the left atrium. Posterolateral view – one common pulmonary vein on the left side (Verhovceva, 2021).

Table 2. Number of pulmonary vein orifices

Number of PV orifices	Frequency, % (n)	
Right side		
2 PV orifices	85.7 (120)	
3 PV orifices	12.2 (17)	
4 PV orifices	1.4 (2)	
1 PV orifice	0.7 (1)	
Left side		
2 PV orifices	78.6 (110)	
1 PV orifice	21.4 (30)	

PV, pulmonary vein

As the size of the PV orifice changes during the systole and diastole, the diameter of the orifices was measured at the maximal PV orifice opening. Two diameter measurements were recorded — the longest and the shortest — and, to ensure accuracy of results, the multiplication of both measurements of diameter was calculated. The measurements of the right pulmonary veins were: superior mean<sub>max</sub> 18.5 mm (SD = 2.8) and mean<sub>min</sub> 13.4 mm (SD = 3.2); inferior mean<sub>max</sub> 16.2 mm (SD = 2.7) and mean<sub>min</sub> 12.6 mm (SD = 2.5); and accessory mean<sub>max</sub> 10.1 mm (SD = 2.1) and mean<sub>min</sub> 7.1 mm (SD = 1.8). The measurements of the left pulmonary veins were superior mean<sub>max</sub> 18.4 mm (SD = 3.1) and mean<sub>min</sub> 12.6 mm (SD = 2.7); inferior mean<sub>max</sub> 16.2 mm (SD = 2.2) and mean<sub>min</sub> 10.5 mm (SD = 2.5); and common PV truncus mean<sub>max</sub> 29.9 mm (SD = 4.1) and mean<sub>min</sub> 13.1 mm (SD = 2.7) (Table 3). The angle between PVs was evaluated at maximal filling of the left atrium, with mean measurement 50.16° (SD = 14.68) on the right side and mean 48.5° (SD = 13.5) between left pulmonary veins (Table 4).

There was a statistically significant correlation between BMI and left atrial volume (Table 5). BMI was positively correlated with maximal volume of the left atrium ( $r_s = 0.199$ , p = 0.023), minimal volume of the left atrium ( $r_s = 0.177$ , p = 0.043) and with mean volume of the left atrium during the cardiac cycle ( $r_s = 0.190$ , p = 0.029). The volume of the left atrial appendage did not show any statistically significant correlation with BMI (p = 0.354).

The statistics of PV ostial diameter also showed statistically significant associations with BMI. The BMI positively correlated with the diameter of left inferior pulmonary vein orifice ( $r_s = 0.216$ , p = 0.032); however, the diameter of left superior pulmonary vein orifice did not show any significant correlation with BMI (p = 0.189). The diameter of right PV orifice showed a statistically significant correlation with BMI only in the accessory PVs ( $r_s = -0.629$ , p = 0.012).

Table 3. Diameter of pulmonary vein orifices

Diameter of PV orifices	Mean maximal value, mm	Mean minimal value, mm	Mean multiplied value, mm	
Right side				
Superior	18.5 (SD = 2.8)	13.4 (SD = 3.2)	253.4 (SD = 91.2)	
Inferior	16.2 (SD = 2.7)	12.6 (SD = 2.5)	209.5 (SD = 70.4)	
Accessory	10.1 (SD = 2.1)	7.1 (SD = 1.8)	75.0 (SD = 32.0)	
Left side				
Superior	18.4 (SD = 3.1)	12.6 (SD = 2.7)	236.1 (SD = 76.1)	
Inferior	16.2 (SD = 2.2)	10.5 (SD = 2.5)	173.4 (SD = 52.6)	
Common truncus	29.9 (SD = 4.1)	13.1 (SD = 2.7)	388.7 (SD = 87.4)	
PV, pulmonary vein				

Table 4. Pulmonary vein angle

PV angle	Value, °
Right side	50.16 (SD = 14.68)
Left side	48.50 (SD = 13.5)

PV, pulmonary vein

Parameters	r <sub>s</sub>	р
LA volume, mL		
V <sub>max</sub>	0.199	0.023
V <sub>min</sub>	0.177	0.043
V <sub>mean</sub>	0.190	0.029
LAA volume, mL	0.082	0.354
Diameter of the PV orifice, mm		
Right side		
Superior	-0.060	0.500
Inferior	0.089	0.313
Accessory	-0.629	0.012
Left side		
Superior	-0.133	0.189
Inferior	0.216	0.032
Common truncus	0.004	0.983
PV angle, °		
Right	0.178	0.044
Left	-0.073	0.436

*Table 5.* Body Mass Index correlation with parameters of the left atrium (Spearman's rank-order correlation test)

LA, left atrium; LAA, left atrial appendage;  $V_{max}$ , maximal volume of the left atrium;  $V_{min}$ , minimal volume of the left atrium;  $V_{mean}$ , mean volume of the left atrium during the cardiac cycle; PV, pulmonary vein

BMI had a significant positive correlation with the right PV angle ( $r_s = 0.178$ , p = 0.044), but the angle between left PVs did not show any correlation with BMI (p = 0.436).

#### DISCUSSION

This study demonstrated a statistically significant association between an increase of the Body Mass Index (BMI) and parameters of the left atrium (LA) at anatomic and volumetric dimensions. As the noteworthy associations can be considered positive BMI correlation with the LA volumetric data through the cardiac cycle ( $V_{max} - r_s = 0.199$ , p = 0.023,  $V_{min} - r_s = 0.177$ , p = 0.043, and  $V_{mean} - r_s =$ 0.190, p = 0.029). Obesity-related LA enlargement has been discussed in several studies (Norman, 2019), and our study proves the accuracy of the collected data.

Regarding the pulmonary vein (PV) statistics, the strongest correlation was found in BMI and the diameter of the right accessory PV ostia ( $r_s = -0.629$ , p = 0.012). This means that an increase in BMI can potentially affect haemodynamics through the accessory PVs by increasing the pressure in periostial segments of the PVs. The second strongest correlation was seen with BMI and the diameter of the left inferior PV orifice ( $r_s = 0.216$ , p = 0.032), meaning that elevation in BMI scores is associated with an increase in the left inferior PV ostial size, potentially impacting LA inflow volume during the filling phase. Finally, the BMI scores demonstrated a positive correlation with right PV angle ( $r_s = 0.178$ , p = 0.044).

No other associations in BMI and PV ostial size on PV angle were found. While other structures showed statistically significant correlations, the field of PV anatomic variations should be examined further, for instance, with a larger subject group or by changing the measurement method from manual to an automated algorithm. While the found relations may not be classified as strong, the results are still statistically significant and can play a role in a cascade of significant scientific findings, giving fresh insight on a common disease (according to the Centres for Disease Control and Prevention statistical analysis, AF is the most common type of treated heart arrythmia (CDC, 2021) or potentially build a substrate for new scientific studies. The found statistics can be used as a base for further studies, as the quality of imaging diagnostics has grown since the last wave of anatomic and volumetric cardiac research in the beginning of the 2000s.

#### CONCLUSIONS

The aim of the study, to find out associations between BMI and parameters of the left atrium, including characteristics of the pulmonary veins (PVs), was accomplished and revealed unique relations, with potentially impact on electrophysiologic changes in patients with a phenotype of overweight and obese.

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The authors declare the absence of conflict of interest.

#### REFERENCES

- Abed, H. S., Samuel, C. S., Lau, D.H., Kelly, D. J., Royce, S. G., Alasady, M., Mahajan, R., Kuklik, P., Zhang, Y., Brooks, A. G., *et al.* (2013). Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation. *Heart Rhythm*, **10**, 90–100. DOI: 10.1016/j.hrthm.2012.08.043.
- Abed, H. S., Wittert, G. A., Leong, D. P., Shirazi, M. G., Bahrami, B., Middeldorp, M. E., Lorimer, M. F., Lau, D. H., Antic, N. A., Brooks, A. G. *et al.* (2013). Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: A randomized clinical trial. *J. Amer. Med. Assoc.*, **310** (19), 2050–2060. DOI: 10.1001/jama.2013.280521.
- Aiad, N. N., Hearon, C., Hieda, M., Dias, K., Levine, B. D., Sarma, S. (2019). Mechanisms of left atrial enlargement in obesity. *Amer. J. Cardiol.*, **124** (3), 442–447. https://doi.org/10.1016/j.amjcard.2019.04.043.
- Chakko, S., Mayor, M., Allison, M. D., Kessler, K. M., Materson, B. J., Myerburg, R. J. (1991). Abnormal left ventricular diastolic filling in eccentric left ventricular hypertrophy of obesity. *Amer. J. Cardiol.*, 68, 95–98. DOI: 10.1016/0002-9149(91)90718-z.
- Haïssaguerre, M., Jaïs, P., Shah, D. C., Takahashi, A., Hocini, M., Quiniou, G., Garrigue, S., Mouroux, A. L., Métayer, P. L., Clémenty, J. (1998). Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *New Engl. J. Med.*, **339**, 659–666. DOI: 10.1056/NEJM199809033391003.
- Kershaw, E. E., Flier, J. S. (2004). Adipose tissue as an endocrine organ. J. Clin. Endocrinol. Metab., 89 (6), 2548–2556. https://doi.org/10.1210/jc.2004-0395.
- Kornej, J., Börschel, C. S., Benjamin, E. J., Schnabel, R. B. (2020). Epidemiology of atrial fibrillation in the 21<sup>st</sup> century. *Circul. Res.*, **127**, 4–20. https://doi.org/10.1161/CIRCRESAHA.120.316340.

- Loos, R. J. F. (2012). Genetic determinants of common obesity and their value in prediction. *Best Practice Res. Clin. Endocrinol. Metab.*, **26** (2), 211–226. https://doi.org/10.1016/j.beem.2011.11.003.
- Munger, T. M., Dong, Y., Masaki, M., Oh, J. K., Mankad, S. V., Borlaug, B. A., Asirvatham, S. J., Shen, W. K., Lee, H. C., Bielinski, S. J., *et al.* (2012). Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. *J. Amer. College Cardiol.*, **60** (9), 851–860. DOI: 10.1016/j.jacc.2012.03.042.
- Pouwels, S., Topal, B., Knook, M. T., Celik, A., Sundbom, M., Ribeiro, R., Parmar, C., Ugale, S. (2019). Interaction of obesity and atrial fibrillation: An overview of pathophysiology and clinical management. *Expert Rev. Cardiovasc. Ther.*, **17** (3), 209–223. DOI: 10.1080/14779072.2019.1581064.
- Powell-Wiley, T. M., Poirier, P., Burke, L. E., Després, J. P., Gordon-Larsen, P., Lavie, C., Lear, S. A., Ndumele Ch. E., Neeland, I. J., Sanders, P. *et al.* (2021). Obesity and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation*, **143** (21), 984–1010. https://doi.org/10.1161/CIR.000000000000973.

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- Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., Allison, T. G., Batsis, J. A., Sert-Kuniyoshi, F. H., Lopez-Jimenez, F. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. *Int. J. Obesity*, **32**, 959–966. https://doi.org/10.1038/ijo.2008.11.
- Rothman, K. J. (2008). BMI-related errors in the measurement of obesity. *Int. J. Obesity*, **32**, 56–59. https://doi-org.db.rsu.lv/10.1038/ijo.2008.87.
- Shuai, W., Kong, B., Fu, H., Shen, C., Jiang, X., Huang, H. (2019). MD1 deficiency pro-motes inflammatory atrial remodelling induced by high-fat diets. *Canad. J. Cardiol.*, **35**, 208–216. DOI: 10.1016/j.cjca.2018.11.02.
- Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., Gortmaker, S. L. (2011). The global obesity pandemic: Shaped by global drivers and local environments. *Lancet*, **378**, 804–814. DOI: 10.1016/S0140-6736(11)60813-1.
- World Health Organization (2019). Obesity and overweight fact sheet. WHO Media Cent.

https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 20.03.2022).

# ĶERMEŅA MASAS INDEKSA IETEKME UZ SIRDS KREISĀ PRIEKŠKAMBARA PARAMETRIEM DATORTOMOGRĀFIJAS AINĀ

Paaugstināts ķermeņa masas indekss (ĶMI) tiek uzskatīts par kardiovaskulāro saslimšanu riska faktoru. Zināms, ka ĶMI pieaugums saistīts ar sirds kreisā priekškambara (KP) palielinājumu, kas, savukārt, iespējams ietekmē KP anatomiskās struktūras. Pētījuma mērķis bija retrospektīvi izpētīt iespējamās asociācijas starp ĶMI un KP parametriem, tostarp pulmonālo vēnu (PV) anatomiskajām variācijām datortomogrāfijas ainā. Pētījuma izlases grupā tika iekļauti 140 pacienti vecumā virs 18 gadiem, bez iepriekš zināmas kardiālas patoloģijas. Vidējais pētījuma dalībnieku vecums 66,9 gadi (SD = 7,8). Datu analīzes rezultātā tika atrastas statistiski nozīmīgas korelācijas starp ĶMI un KP tilpuma mērījumiem sirds cikla laikā:  $V_{max}$  ( $r_s = 0,199$ , p = 0,023),  $V_{min}$  ( $r_s = 0,177$ , p = 0,043),  $V_{vidējais}$  ( $r_s = 0,190$ , p = 0,029), kas atbilst iepriekš zināmajiem datiem par aptaukošanās saistību ar sirds kreisās daļas kameru tilpuma palielināšanos. Tika reģistrēta iepriekš neaprakstīta ĶMI ietekme uz PV struktūrām — statistiski nozīmīga pozitīva korelācija starp ĶMI un kreisās apakšējās PV ietekas diametru ( $r_s = 0,216$ , p = 0,032) un negatīva korelācija ar labo papildus PV ietekas diametru ( $r_s = -0,629$ , p = 0,012). Labās puses PV leņķis uzrādīja pozitīvu korelāciju ar ĶMI ( $r_s = 0,178$ , p = 0,044), taču kreisās puses PV leņķa ietekme netika novērota (p = 0,436). Pētījuma ietvaros tika apstiprināti iepriekš zināmi asociācijas modeļi ķermeņa masas pieauguma ietekmes uz kreisā priekškambara tilpuma izmaiņu aspektā, kā arī tika novērotas statistiski nozīmīgas ķermeņa masas indeksa iezīmes uz pulmonālo vēnu parametriem. Iegūtās korelācijas nevar tikt klasificētas kā stipras, taču novērotajām saistībām ir potenciāls efekts nākotnes pētījumu īstenošanai.