INDIRECT ULTRASOUND EVALUATION OF LEFT VENTRICULAR OUTFLOW TRACT DIAMETER IMPLICATIONS FOR HEART FAILURE AND AORTIC STENOSIS SEVERITY ASSESSMENT.

Gabriele Pestelli[1], Andrea Fiorencis[2], Valeria Pergola[3], Giovanni Luisi[4], Vittorio Smarrazzo[5], Filippo Trevisan[2], and Donato Mele[6]

[1]Morgagni-Pierantoni Hospital
[2]Azienda Ospedaliero Universitaria di Ferrara Arcispedale Sant'Anna
[3]Università degli Studi di Padova Dipartimento di Scienze Cardiologiche Toraciche e Vascolari
[4]Azienda Ospedaliero Universitaria di Ferrara Arcispedale Sant'Anna
[5]Affiliation not available
[6]University of Ferrara

November 23, 2020

Abstract

Background. Whereas dependency of left ventricular outflow tract diameter (LVOTD) from body surface area (BSA) has been established and a BSA-based LVOTD formula has been derived, the relationship between LVOTD and aortic root and LV dimensions has never been explored. This may have implications for evaluation of LV output in heart failure (HF) and aortic stenosis (AS) severity. Methods. A cohort of 540 HF patients who underwent transthoracic echocardiography was divided in a derivation and validation subgroup. In the derivation subgroup (N=340) independent determinants of LVOTD were analyzed to derive a regression equation, which was used for predicting LVOTD in the validation subgroup (N=200) and compared with the BSA-derived formula. Results. LVOTD determinants in the derivation subgroup were sinuses of Valsalva diameter (SVD, beta=0.392, P<0.001), BSA (beta=0.229, P<0.001), LV end-diastolic diameter (LVEDD, beta=0.145, P=0.001), and height (beta=0.125, P=0.037). The regression equation for predicting LVOTD with the aforementioned variables (LVOTD=6.209+[0.201xSVD]+[1.802xBSA]+[0.03xLVEDD]+[0.025xHeight]) did not differ from (P=0.937) and was highly correlated with measured LVOTD (R=0.739, P<0.001) in the validation group. Repeated analysis with LV end-diastolic volume instead of LVEDD and/or accounting for gender showed similar results, whereas BSA-derived LVOTD values were different from measured LVOTD (P<0.001). Conclusion. Aortic root and LV dimensions affect LVOTD independently from anthropometric data and are included in a new comprehensive equation for predicting LVOTD. This should improve evaluation of LV output in HF and severity of AS, avoiding use of LVOT velocity-time integral alone, which can be misleading, especially when LV cavity and aortic root dimensions are abnormal.

1

Vittorio Smarrazzo[6], MD, Filippo Trevisan[3], MD, and Donato Mele[3], MD

[1]Cardiology Unit, Morgagni-Pierantoni Hospital, Forlì;[2]Cardiovascular Research Unit, Fondazione Sacco, Forlì; [3]Cardiology Unit, University Hospital of Ferrara, Ferrara; [4]Cardiology Unit, University Hospital of Padova, Padova; [5]Cardiology Unit, Infermi Hospital, Faenza; [6]Cardiology Unit, Umberto I Hospital, Lugo, Italy.

Word count: 4692 (text + reference + figure legends)

Address for correspondence

Donato Mele, MD

Cardiology Unit

University Hospital of Ferrara

Viale Aldo Moro 8

44024 Cona, Ferrara

Tel: 0532-239062

e-mail: *donatomele@libero.it*

ABSTRACT

Background. Whereas dependency of left ventricular outflow tract diameter (LVOTD) from body surface area (BSA) has been established and a BSA-based LVOTD formula has been derived, the relationship between LVOTD and aortic root and LV dimensions has never been explored. This may have implications for evaluation of LV output in heart failure (HF) and aortic stenosis (AS) severity.

Methods. A cohort of 540 HF patients who underwent transthoracic echocardiography was divided in a derivation and validation subgroup. In the derivation subgroup (N=340) independent determinants of LVOTD were analyzed to derive a regression equation, which was used for predicting LVOTD in the validation subgroup (N=200) and compared with the BSA-derived formula.

Results. LVOTD determinants in the derivation subgroup were sinuses of Valsalva diameter (SVD, beta=0.392, P<0.001), BSA (beta=0.229, P<0.001), LV end-diastolic diameter (LVEDD, beta=0.145, P=0.001), and height (beta=0.125, P=0.037). The regression equation for predicting LVOTD with the aforementioned variables (LVOTD=6.209+[0.201xSVD]+[1.802xBSA]+[0.03xLVEDD]+[0.025xHeight]) did not differ from (P=0.937) and was highly correlated with measured LVOTD (R=0.739, P<0.001) in the validation group. Repeated analysis with LV end-diastolic volume instead of LVEDD and/or accounting for gender showed similar results, whereas BSA-derived LVOTD values were different from measured LVOTD (P<0.001).

Conclusion. Aortic root and LV dimensions affect LVOTD independently from anthropometric data and are included in a new comprehensive equation for predicting LVOTD. This should improve evaluation of LV output in HF and severity of AS, avoiding use of LVOT velocity-time integral alone, which can be misleading, especially when LV cavity and aortic root dimensions are abnormal.

Word count: 250

KEYWORDS: Left ventricular outflow tract; heart failure; aortic stenosis; echocardiography; stroke volume; stroke distance.

INTRODUCTION

Left ventricular outflow tract diameter (LVOTD) is a key measure in echocardiographic practice because it allows the non-invasive estimation of LV output and specifically of stroke volume and stroke volume index (SVI). These measures are relevant in multiple clinical settings, including risk-stratification in heart failure

(1-4), decision to operate atrial and ventricular septal defects (5) and for diagnosis, risk-stratification and treatment of aortic stenosis (6-8). LVOTD is routinely measured with transthoracic echocardiography (7). However, a precise measurement of the LVOTD can be challenging in some patients and measurement errors can lead to misevaluation of LV output and aortic stenosis severity (9-13).

Previously, Leye et al. showed that a moderate linear correlation exists between LVOTD and body surface area (BSA), thus they derived an equation for estimating LVOTD from BSA (LVOTD$_{BSA}$), which was proposed as a safeguard when direct LVOTD measurement is difficult or not possible (14). Due to the LVOTD correlation with BSA, some authors have suggested the LVOT velocity-time integral (or stroke distance) to be a SVI analog with simpler calculation and proposed it for prognostic assessment (15). Analogously, a dimensionless index has been proposed in addition to aortic valve area calculation to avoid LVOTD measurement for aortic stenosis grading (7). However, we have recently observed a better prognostic capability of SVI over stroke distance in heart failure (16), suggesting a more active role of LVOTD in determining LV output. We hypothesized that the variability of LVOTD over BSA was due to the size of the anatomical structures close to the LVOT, such as the aortic root and LV cavity, that have never been taken into account previously (14,15).

In this study we decided to: 1) explore the relationship among LVOTD, LV and aortic root dimension beyond BSA, in order to derive a more comprehensive equation for predicting LVOTD size; and, 2) validate this equation in a different cohort of patients, comparing its performance with the previously published equation based on BSA only (14). We preliminary compared LVOTD measurements obtained during transthoracic echocardiography (TTE) with those performed during transesophageal echocardiography (TEE) to verify the accuracy of the TTE LVOTD measurements.

METHODS

Study patients. Three different groups of patients who underwent echocardiography at the University Hospital of Ferrara were retrospectively examined and enrolled in the present study.

TEE group . In 53 consecutive patients referred for clinically indicated TEE from January to April 2018, we measured the LVOTD during both TTE and TEE. Both measurements were performed blindly one from the other. TEE indications were: assessment of aortic and or mitral valve disease severity (N=25), exclusion of left atrial appendage thrombi or cardiac masses (N=13), evaluation for patent foramen ovale (N=8), and suspected endocarditis (N=7). There was no exclusion criterion except unmeasurable LVOTD during TTE.

Derivation group . This group was used to derive a regression equation for predicting LVOTD using its independent determinants. It included 340 consecutive patients with heart failure who underwent echocardiography from January to August 2018.

Validation group . This group was used to validate the derived regression equation and compare it with the previously published one based on BSA (14). It included 200 consecutive patients with heart failure who underwent echocardiography from September to December 2018.

For both the derivation and validation groups, exclusion criteria were history of aortic valve or aortic root surgical or transcatheter intervention (N=17, derivation group; N=14, validation group), and poor echogenicity that could affect aortic root, LVOT, LV end-diastolic diameter (LVEDD) and LV volume measurement (N=39, derivation group; N=18 derivation group). Aortic stenosis (aortic valve area [?]1.5 cm^2) was not considered an exclusion criterion. Demographic and clinical patients' characteristics were collected.

TTE examination . A comprehensive two-dimensional echocardiographic, Doppler and color Doppler examination was performed using a GE Vivid 7 or E9 echo scanner (GE Health Care, Milwaukee, US) equipped with a 3.5 MHz transducer. Echocardiographic images were stored in digital format and analyzed using the EchoPAC software v. 201 (GE Health Care, Milwaukee, US). One trained physician did all the echocardiographic measures, according with the American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines (17). LV end-diastolic and end-systolic volumes were calculated from orthogonal apical views using the biplane Simpson method. LV ejection fraction was derived from the standard

3

equation (17). Two-dimensional linear internal measurements of the LV were acquired in the parasternal long-axis view carefully obtained perpendicular to the LV long-axis, and measured at the level of the mitral valve leaflet tips (17). Electronic calipers were positioned at the interface between myocardial wall and cavity and the interface between wall and pericardium (17). The diameter at the level of the sinuses of Valsalva (SVD) was measured at end-diastole, in a strictly perpendicular plane to that of the long-axis of the aorta using the leading-edge-to-leading-edge convention (17). Aortic root dilatation was defined as SVD indexed to BSA (SVDI) ≥21mm/m^2, according with previous adult normal reference studies (17-19). LVOTD was measured using the zoom mode at the insertion of the leaflets (at the annulus level) in midsystole with the inner-edge-to-inner-edge approach from the parasternal long-axis view (7,17). LVOT$_{BSA}$ was calculated with the equation LVOTD$_{BSA}$=12.1+5.7xBSA (14), with BSA calculated with the Mosteller formula (14,20). For intraobserver variability, measurements were repeated by the same physician one week later; for interobserver variability, measurements were performed by a second physician who used the same criteria and was blind to the results of the first observer (17).

TEE examination . The examination was performed using a GE Vivid E9 echo scanner equipped with a 5 MHz transducer. Echocardiographic images were stored in digital format and analyzed using the EchoPAC software v. 201. The LVOTD was measured using the zoom mode, as described for TTE, on images acquired in the aortic long-axis view at the mid-esophageal position using an image plane with about 120deg rotation (21). Measurements were performed by an independent operator who was blind to the measurements performed on the TTE images.

Statistical analysis and study endpoints. Normal distribution was tested with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean and standard deviation or median values with 25th and 75th percentiles if normally or non-normally distributed, respectively. Categorical variables were reported as counts and percentages. For continuous normal and non-normal variables, Student's t-test and Mann-Whitney U test were respectively used for comparisons between two unpaired groups. Categorical variables were compared by the chi-square test. Pearson correlation was used for normally distributed variables, whereas Spearman correlation was used if at least one variable had non-parametric distribution. Comparison of LVOTD measured during both TTE and TEE was performed using a paired Student's t test. To assess for error and bias, the Bland-Altman method was used. The correlation between LVOTD, anthropometrics data (patient BSA and height), LVEDD, SVD and age were studied with univariate linear regression analysis in the derivation group. For the primary endpoint of the derivation study, the covariates that were found to be statistically correlated with LVOTD were included in the multivariate linear regression model (Model 1) in order to derive a regression equation for predicting LVOTD (LVOTD$_{RE1}$). LVEDD and SVD were included as non-indexed values for this analysis to facilitate the utilization of the derived formula. The independent covariates from Model 1 were included as indexed values in a secondary multivariate linear regression analysis with the difference between measured LVOTD (LVOTD$_M$) and LVOTD$_{BSA}$ as endpoint, to corroborate the results of Model 1. Secondary endpoints for the derivation group were: 1) an analogous multivariate linear regression model (Model 2) including LV end-diastolic volume (LVEDV) instead of LVEDD as covariate; 2) a repeated multivariate linear regression analysis with the addition of gender (Model 3, with LVEDD; Model 4, with LVEDV). A regression equation was derived for each secondary multivariate model (LVOTD$_{RE2}$, LVOTD$_{RE3}$, LVOTD$_{RE4}$). For the primary endpoint of the validation study, the Student's t-test for paired samples was used to compare LVOTD$_{RE1}$ and LVOTD$_{BSA}$ (14) with LVOTD$_M$ in the validation group. As a secondary endpoint, the other regression equations (including LVEDV and/or gender) were also tested. Multicollinearity between the variables in all the multivariate models was assessed by calculation of the variance inflation factor, with a value ≥5 indicating significant collinearity. The intra- and interobserver variability for SVD, LVEDD, LVEDV, LVOTD$_M$, LVOTD$_{RE1}$, LVOTD$_{RE2}$ and their derived LVOT areas were assessed in a random sample of 25 patients. Observer variability was determined as the standard deviation of the mean error and expressed as percentage of the first measure for each variable. Data were analyzed using the IBM SPSS Statistics software, v. 24. Differences were considered statistically significant for P<0.05. The study was approved by the local Ethics Committee.

RESULTS

TTE and TEE measurements of LVOTD . The 53 patients in whom LVOTD was measured during TTE and TEE had a mean age of 64 +- 16 years (40 males and 13 females). Mean LVOTD was 21.2 +- 2.2 mm at TTE and 21.2 +- 2.1 mm at TEE (P=0.774). Correlation between the TTE and TEE techniques was excellent (r=0.921, P<0.001) (Supplementary Figure 1). The Bland-Altman method showed no trend for under- or over-estimation using TTE (Supplementary Figure 1).

Derivation and validation group patients . Characteristics of the derivation and validation group patients are reported in Table 1. No significant difference was found for age, gender, anthropometric data, LV volumes and EF, SVD, LVOTD and LVEDD between the derivation and validation groups. Prevalence of coronary artery disease and chronic obstructed pulmonary disease were higher in the derivation group (Table 1).

Determinants of LVOTD in the derivation study . Spearman correlations between LVOTD and pre-specified covariates for the derivation group are reported in Table 2. Patient height, BSA, SVD, LVEDD and LVEDV significantly correlated with LVOTD (Table 2, Figure 1). SVD showed the highest correlation (R=0.568, P<0.001), followed by anthropometric variables (BSA R=0.532, height R=0.525; all P values <0.001) and LV measures (LVEDD R=0.357, LVEDV R=0.363; all P values <0.001). All correlations were confirmed by univariate linear regression analysis (Table 2). On multivariate linear regression analysis for the primary endpoint in the derivation study, SVD (beta=0.392, P<0.001), BSA (beta=0.229, P<0.001), LVEDD (beta=0.145, P=0.001) and height (beta=0.125, P=0.037) were independently associated with LVOTD (Model 1, Table 3). No significant multicollinearity was found (all variance inflation factors <0.3). An analogous linear regression model including SVD and LVEDD as indexed values was performed, showing independent correlation of SVDI (beta=0.448, P<0.001) and LVEDD index (beta=0.138, P=0.002) with LVOTD. A regression equation was derived from linear regression analysis including SVD, BSA, LVEDD and height for predicting LVOTD dimension (LVOTD$_{RE1}$, Table 4).

Determinants of discrepancy between LVOTD$_M$ and LVOTD$_{BSA}$. The difference between LVOTD$_M$ and LVOTD$_{BSA}$ was correlated at multivariate linear regression analysis with SVD and LVEDD as indexed values and height in the derivation group, with the aim to corroborate primary findings (Model 1, Table 5; Figure 2). SVDI (beta=0.499, P<0.001), LVEDD index (beta=0.151, P=0.002) and height (beta=0.2, P<0.001) were all confirmed as independent determinants of the discrepancy between LVOTD$_M$ and LVOTD$_{BSA}$ (Table 5).

Validation of the regression equation for predicting LVOTD . The regression equation for predicting LVOTD (LVOTD$_{RE1}$) and LVOTD$_{BSA}$ were tested in the validation group (Table 6). The LVOTD$_{RE1}$ showed a high correlation (R=0.739, P<0.001) and the lowest mean difference with LVOTD$_M$ (0.02+- 1.57 mm), whereas LVOTD$_{BSA}$ showed a moderate correlation with LVOTD$_M$ (R=0.531, P<0.001) and the highest mean difference (-0.51+- 1.95 mm) (Table 6). Paired Student's t-test revealed that LVOTD$_{RE1}$ did not differ from LVOTD$_M$, whereas LVOTD$_{BSA}$ was statistically different from LVOTD$_M$ (P<0.001, Table 6). Figure 3 shows the distribution of differences between LVOTD$_M$ and LVOTD$_{BSA}$ (left panel) and LVOTD$_{RE1}$ (right panel). The use of our regression equation allowed to predict LVOTD$_M$ with less than+- 2 mm of error in 84% of cases, whereas it was 65.5% with the BSA-based formula (Figure 3).

Results with LVEDV instead of LVEDD. Similar results were obtained using LVEDV instead of LVEDD for all the analyses in the derivation group (univariate analysis, Table 2; multivariate model 2, Table 3; LVOTD$_{RE2}$, Table 4; multivariate model 2 for discrepancy between LVOTD$_M$ and LVOTD$_{BSA}$, Table 5) and in the validation group (LVOTD$_{RE2}$, Table 6), respectively. LVOTD$_{RE2}$ had just a slightly lower absolute correlation than LVOTD$_{RE1}$ with LVOTD$_M$ (Table 6).

Effects of gender . When gender was added to multivariate analysis in the derivation group, SVD was confirmed as the main determinant of LVOTD (beta=0.351, P<0.001), followed by BSA (beta=0.258, P<0.001), female sex (beta=-0.175, P<0.001) and LVEDD (beta=0.134, P=0.003) or LVEDV (beta=0.122, P=0.001), whereas height was not associated with LVOTD (model 3 and 4, Table 3). The regression equations (Table 4) derived from the models with gender, BSA, SVD and LVEDD (LVOTD$_{RE3}$) or LVEDV (LVOTD$_{RE4}$)

5

maintained high correlation and no significant difference with $LVOTD_M$ in the validation study, but showed a slightly lower absolute correlation than $LVOTD_{RE1}$ with $LVOTD_M$ (Table 6).

Intra-observer and inter-observer variability. Intra-observer and inter-observer variabilities are reported in Table 7. While similar good percentage variability was observed between SVD, LVEDD, LVEDV and $LVOTD_M$, variability of LVOT area derived from regression equations was lower than that of the measured LVOT area.

DISCUSSION

In this study we documented for the first time that both SVD and LVEDD (or LVEDV) were significantly correlated with LVOTD in addition to patient BSA and height (or gender) in patients undergoing echocardiography. SVD had the strongest association with LVOTD. On the basis of these observations, we derived a comprehensive equation including SVD, LVEDD and patient BSA and height, which showed a high correlation with $LVOTD_M$ and better performance than $LVOTD_{BSA}$ in a validation patient cohort. Alternative equations including LVEDV instead of LVEDD with/without gender were also obtained but did not improve the results of the primary analysis.

Limits of anthropometric variables in determining chamber and aortic root dimensions in adults. Aortic root normal-reference studies have notoriously shown low correlation between anthropometric variables (mainly BSA and height) and SVD in adults (18,19). For example, in the EACVI NORRE aortic root study, linear models considering age, gender, and body size barely explained around one-quarter of the total variance in determining aortic root dimension in adults (19). This is why regression equations for prediction of aortic size (and derived nomograms) based only on these parameters should be interpreted with caution, taking into account this limitation (19). In our derivation study, BSA showed moderate correlation with LVOTD and low correlation with SVD. Even in our validation study, $LVOTD_{BSA}$ had moderate correlation with $LVOTD_M$, reflecting moderate correlation between BSA and LVOTD. These observations are in line with previously reported correlations (14,18,19). All these findings indicate that the wide biological variability in aortic and LVOT dimension is not entirely explained by simple demographic and anthropometric variables (19).

In our study, a regression equation including anthropometric and biologic (LV and aortic root) dimensions had high correlation with $LVOTD_M$ in the validation group. These results may be explained by a proximity anatomical effect in distorting the LVOT independently from BSA. To our knowledge, this correlation has never been explored before. Interestingly, both intra-and inter-observer variability of LVOT area derived from regression equations were lower than those related to the measured LVOT, which were similar to previous findings (22). This may be due to the well-known amplification of the error derived from squaring the LVOTD measurement when calculating the LVOT area.

Clinical implications and perspectives . There are two main clinical messages from this study: 1) measures of LV output and aortic stenosis severity that avoid use of LVOTD measurement may be misleading in particular anatomical conditions, namely abnormal LV and aortic root dimensions; 2) a well-performing formula for predicting LVOTD is now available accounting not only for anthropometric data but also for LV and aortic root dimensions.

Regarding the first message, it should be underlined that, while LVOT is a BSA-dependent measure (14,15), LVOT velocity-time integral (or stroke distance) has been hypothesized to be independent on BSA and to represent, therefore, a SVI analog (15). However, two issues limit this assumption. Firstly, the BSA independency was originally supposed in normal individuals (15): in these subjects a minor role of LV cavity and aortic root dimension is expected. However, in patients with aortic root enlargement, normal BSA and reduced stroke distance suggesting a low flow status, a relatively high LVOTD assures a normal SVI. For example, with a BSA of 1.8 m^2, a stroke distance of 12 cm and a LVOTD of 27 mm, SVI is 38 ml/m^2. Secondly, the accuracy of stroke distance has never been compared for assessing LV output with invasive measurement, whereas SV (or other LVOTD-including measures such as cardiac output) has shown high correlation with the invasive measurement in several studies (22-31). In addition, comparing the usefulness

of SVI and stroke distance as prognostic markers, a better stratification capability of SVI was shown in one study (16).

The LVOTD measurement is also avoided in the aortic dimensionless index, which has been proposed in addition to aortic valve area calculation for aortic stenosis grading (7). Although the dimensionless index has shown prognostic value in asymptomatic and minimally symptomatic patients with aortic stenosis with preserved LV ejection fraction and without significant valve regurgitation (32), it was not better than other markers of aortic stenosis severity, including aortic valve area, for grading aortic valve stenosis in another study (33).

Our findings evidence pathophysiological reasons to encourage calculation of SVI and aortic valve area over stroke distance and dimensionless index whenever possible in the assessment of LV output and aortic stenosis severity grading. In particular, the interpretation of LVOTD-free indexes should be taken with caution in cases of abnormal LV and aortic root dimensions.

Previous studies tried to overcome the limits of LVOTD measurement by using alternative techniques, such as three-dimensional echocardiography (34) and multidetector computed tomography (35) for the assessment of aortic stenosis severity. However, it should be noticed that different techniques could imply different cut-off values to refer to for prognostic assessment: for example, an aortic valve area cut-off value of 1.2 cm^2 should be used for assessing aortic stenosis severity with a hybrid multidetector computed tomography-Doppler approach rather than the established 1 cm^2 obtained with the standard ultrasound method (7,35). Thus, in current clinical echocardiographic practice measuring LVOTD remains an almost inevitable, although sometimes difficult task.

Study limitations. 1) We recognize that our formula uses four different variables (BSA, height, SVD and LVEDD), thus it might seem too complicated for clinical practice. However, those measures are commonly obtained in standard echocardiography and the equation could be easily integrated in the echocardiograph to give an automatic response once all the measurements are performed, without additional time consume. In addition, many reporting software can provide derived calculations (such as the aortic valve area) automatically and could therefore integrate our formula as an assistance tool for cases in which LVOTD is scarcely or incorrectly visualized. 2) Our formula includes both BSA and height. Although height is one of the variables used for the calculation of BSA, there was no significant multicollinearity in the regression model (variance inflation factor for height and BSA were 2.2 and 2.1, respectively), thus both variables were included in the formula. 3) Multidetector computed tomography was not performed in this study as an external reference for TTE LVOTD evaluation. However, we documented that in our patients the LVOTD measurements at TTE and TEE were similar, thus indicating accuracy of TTE measurements. Our data are in line with those of Leye et al., who showed a very high correlation between TTE and TEE for measuring the LVOTD (R=0.95, P<0.001; P=0.26 for difference between techniques) (14). 4) LVEDD was chosen as LV dimension parameter for the primary endpoint rather than LVEDV because of the proximity between LVEDD and LVOTD measurement sites (the basal LV and the LVOT, respectively). Whether three-dimensional echocardiography would have given a higher correlation between LV volumes and LVOTD is unknown. However, the regression equation including LVEDD had the highest correlation with LVOTD$_M$. 5) In the present study LVOTD was measured at the level of the annulus, which is considered the preferred site by current guidelines on aortic stenosis assessment (7), even though there is lack of general consensus and some laboratories use a more proximal site (up to 1 cm apical to the annulus) for this measure. Our findings may not be applied to predicting LVOTD at different levels of the LVOT. Evidences in support of the measurement at the level of the aortic annulus have been recently reviewed (36), in addition to a very recent phase-contrast cardiovascular magnetic resonance comparative study (37).

Conclusions . We documented that aortic root and LV dimensions affect LVOTD independently from anthropometric data in an adult heart failure patient cohort. On this ground, it is evident that bypassing LVOTD measurement with surrogate markers of LV output (stroke distance) and dimensionless indexes in aortic stenosis severity grading may be misleading, especially in presence of abnormal LV cavity and aortic root dimensions. A comprehensive equation for predicting LVOTD, including aortic root and LV dimensions,

was derived and validated in the present study to help the physician in the calculation of LVOTD when it is difficult to calculate. Further multicenter investigations are needed to support a more extensive application of our formula in routine echocardiographic clinical practice.

Conflicts of Interest: Nothing to disclose.

REFERENCES

1. De Marco M, Gerdts E, Mancusi C, et al. Influence of Left Ventricular Stroke Volume on Incident Heart Failure in a Population With Preserved Ejection Fraction (from the Strong Heart Study). Am J Cardiol 2017;119:1047–1052.
2. Kamperidis V, van Wijngaarden SE, van Rosendael PJ, et al. Restrictive Mitral Valve Annuloplasty: Prognostic Implications of Left Ventricular Forward Flow. Ann Thorac Surg 2017;104:1464–1470.
3. Mele D, Pestelli G, Molin DD, et al. Echocardiographic Evaluation of Left Ventricular Output in Patients with Heart Failure: A Per-Beat or Per-Minute Approach? J Am Soc Echocardiogr 2020;33:135-47.
4. Mele D, Pestelli G, Dini FL, et al. Novel echocardiographic approach to hemodynamic phenotypes predicts outcome of patients hospitalized with heart failure. Circ Cardiovasc Imaging 2020;13:e009939.
5. Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31:2915–2957.
6. Rusinaru D, Bohbot Y, Ringle A, et al. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Eur Heart J 2018;39:1992-1999.
7. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:372-392.
8. Falk V, Baumgartner H, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg 2017;52:616-664.
9. Lewis JF, Kuo LC, Nelson JG, et al. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984;70:425-31.
10. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J Am Coll Cardiol 1989;13:545-50.
11. Zoghbi WA, Farmer KL, Soto JG, et al. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. Circulation 1986;73:452-9.
12. Myreng Y, Molstad P, Endresen K, et al. Reproducibility of echocardiographic estimates of the area of stenosed aortic valves using the continuity equation. Int J Cardiol 1990;26:349-59.
13. Raggi P, Vasavada BC, Rodney E, et al. Doppler echocardiographic methods to estimate severity of aortic stenosis. Am J Cardiol 1995;76:615-8.
14. Leye M, Brochet E, Lepage L, et al. Size-Adjusted Left Ventricular Outflow Tract Diameter Reference Values: A Safeguard for the Evaluation of the Severity of Aortic Stenosis. J Am Soc Echocardiogr 2009;22:445–451.
15. Goldman JH, Schiller NB, Lim DC, et al. Usefulness of stroke distance by echocardiography as a surrogate marker of cardiac output that is independent of gender and size in a normal population. Am J Cardiol 2001;87:499–502.
16. Mele D, Pestelli G, Smarrazzo V, et al. Left Ventricular Output Indices In Hospitalized Heart Failure: When "Simpler" May Not Mean "Better". Int J Cardiovasc Imaging 2020; https://doi.org/10.1007/s10554-020-01946-x.
17. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28:1-39.
18. Roman MJ, Devereux RB, Kramer-Fox R, et al. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507–512.
19. Saura D, Dulgheru R, Caballero L, et al. Two-dimensional transthoracic echocardiographic normal

reference ranges for proximal aorta dimensions: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging 2017;18:167–179.

20. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.

21. Flachskampf FA, Wouters PF, Edvardsen T, et al. Recommendations for transoesophageal echocardiography: EACVI update 2014. Eur Heart J Cardiovasc Imaging 2014;15:353-365.

22. Lewis JF, Kuo LC, Nelson JG, et al. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984;70:425–431

23. Labovitz AJ, Buckingham TA, Habermehl K, et al. The effects of sampling site on the twodimensional echo-Doppler determination of cardiac output. Am Heart J 1985;109:327–332.

24. Dittmann H, Voelker W, Karsch KR, et al. Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography. J Am Coll Cardiol 1987;10:818–823.

25. Dericbourg C, Tribouilloy C, Kugener H, et al. Noninvasive measurement of cardiac output by pulsed Doppler echocardiography. Correlation with thermodilution. Arch Mal Coeur Vaiss 1990;83:237–244.

26. Gola A, Pozzoli M, Capomolla S, et al. Comparison of Doppler echocardiography with thermodilution for assessing cardiac output in advanced congestive heart failure. Am J Cardiol 1996;78:708–712.

27. Stein JH, Neumann A, Preston LM, et al. Echocardiography for hemodynamic assessment of patients with advanced heart failure and potential heart transplant recipients. J Am Coll Cardiol 1997;30:1765–1772.

28. Temporelli PL, Scapellato F, Eleuteri E, et al. Doppler echocardiography in advanced systolic heart failure. A noninvasive alternative to Swan-Ganz catheter. Circ Heart Fail 2010;3:387–394.

29. Nagueh SF, Bhatt R, Vivo RP, et al. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. Circ Cardiovasc Imaging 2011;4:220–227.

30. Reddy YNV, Melenovsky V, Redfield MM, et al. High-output heart failure: a 15-year experience. J Am Coll Cardiol 2016;68:473–482.

31. Mele D, Andrade A, Bettencourt P, et al. From left ventricular ejection fraction to cardiac hemodynamics: role of echocardiography in evaluating patients with heart failure. Heart Fail Rev 2020;25:217–230.

32. Rusinaru D, Malaquin D, Marechaux S, et al. Relation of Dimensionless Index to Long-Term Outcome in Aortic Stenosis With Preserved LVEF. JACC Cardiovasc Imaging 2015;8:766–775.

33. Whitener GB, Shanahan PC, Wolf BJ, et al. Grading Aortic Valve Stenosis With Dimensionless Index During Pre-cardiopulmonary Bypass Transesophageal Echocardiography: A Comparison With Transthoracic Echocardiography. J Cardiothorac Vasc Anesth 2019;33:2376–2384.

34. Liu S, Churchill J, Hua L, et al. Direct Planimetry of Left Ventricular Outflow Tract Area by Simultaneous Biplane Imaging: Challenging the Need for a Circular Assumption of the Left Ventricular Outflow Tract in the Assessment of Aortic Stenosis. J Am Soc Echocardiogr 2020;33:461–468.

35. Clavel MA, Malouf J, Messika-Zeitoun D, et al. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. JACC Cardiovasc Imaging 2015;8:248-57.

36. Delgado V, Clavel M-A, Hahn RT, et al. How Do We Reconcile Echocardiography, Computed Tomography, and Hybrid Imaging in Assessing Discordant Grading of Aortic Stenosis Severity? JACC Cardiovasc Imaging 2019;12:267–282.

37. Guzzetti E, Capoulade R, Tastet L, et al. Estimation of Stroke Volume and Aortic Valve Area in Patients with Aortic Stenosis: A Comparison of Echocardiography versus Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2020;33:953-963.

FIGURES AND FIGURE LEGENDS

Figure 1. Correlations between the left ventricular outflow tract (LVOT) diameter and Body Surface Area, Sinuses of Valsalva diameter, LV end-diastolic diameter and volume in the derivation group (N=340). Spearmen R and P values are reported.

Figure 2. Correlations of the discrepancy between measured left ventricular outflow tract diameter (LVOTD$_M$) and BSA-derived LVOTD (LVOTD$_{BSA}$) with Sinuses of Valsalva diameter and LV end-diastolic diameter as indexed values in the derivation group (N=340). Spearmen R and P values are reported.

9

Figure 3. Distribution of differences between measured left ventricular outflow tract diameter ($LVOTD_M$) and predicted LVOTD according with BSA-derived formula ($LVOTD_{BSA}$) (14) and our regression equation formula ($LVOTD_{RE1}$, Table 4). SD, standard deviation.

TABLES

Table 1 – Characteristics of the study population

	Total N=540	Derivation Group N=340	Validation Group N=200	P
Age (years)	79 (71-86)	79 (71-86)	80 (73-85)	0.319
Male	285 (53%)	172 (51%)	113 (57%)	0.184
Height (cm)	165 (160-172)	165 (160-172)	165 (160-173)	0.734
Weight (kg)	75 (65-85)	75 (65-85)	75 (65-87)	0.574
BMI (kg/m^2)	26.9 (23.9-30.4)	27 (23.9-29.8)	26.7 (23.7-30.9)	0.641
BSA Mosteller (m^2)	1.86 (1.7-2)	1.86 (1.7-2)	1.87 (1.7-2)	0.617
History of HF	146 (27%)	98 (29%)	48 (24%)	0.223
History of AF	228 (42%)	133 (39%)	95 (48%)	0.057
Hypertension	396 (73%)	250 (74%)	146 (73%)	0.893
Diabetes	155 (29%)	99 (29%)	56 (28%)	0.782
CKD	174 (32%)	106 (31%)	68 (34%)	0.782
CAD	202 (37%)	141 (42%)	61 (31%)	0.011
COPD	96 (18%)	70 (21%)	26 (13%)	0.031
Aortic stenosis	57 (11%)	41 (12%)	16 (8%)	0.138
LVEDV (ml)	110 (85-144)	113 (88-145)	108 (82-141)	0.271
LVESV (ml)	55 (35-91)	55 (36-96)	53 (35-83)	0.262
LVEF (%)	50 (35-59)	49 (33-58)	50 (37-59)	0.278
$LVOTD_M$ (mm)	22.14 ± 2.04	22.08 ± 1.88	22.23 ± 2.29	0.425
$LVOTD_{BSA}$ (mm)	22.71 ± 1.41	22.69 ± 1.4	22.75 ± 1.44	0.623
LVEDD (mm)	51 (46-57)	51 (46-57)	51 (45-57)	0.264
LVEDDI (mm/m^2)	28 (25-31)	28 (25-31)	27 (24-30)	0.07
SVD (mm)	34 (32-37)	34 (32-37)	35 (32-38)	0.252
SVDI (mm/m^2)	19 (17-20)	18 (17-20)	19 (17-20)	0.671
Aortic root dilatation	89 (17%)	50 (15%)	39 (20%)	0.179

Continuous non-parametric variables are expressed as median (25th and 75th percentiles), parametric variables as mean ± standard deviation and categorical variables as counts (frequency). AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic diameter index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; $LVOTD_M$, measured left ventricular outflow tract diameter; $LVOTD_{BSA}$, LVOTD expected from BSA; SVD, Sinuses of Valsalva diameter; SVDI, Sinuses of Valsalva diameter index.

Table 2 - Correlation and univariate linear regression analysis with $LVOTD_M$ in the derivation group

	R	P	Univariate (beta)	P
BSA	0.532	**<0.001**	0.549	**<0.001**

Height	0.525	**<0.001**	0.531	**<0.001**
SVD	0.568	**<0.001**	0.578	**<0.001**
LVEDD	0.357	**<0.001**	0.371	**<0.001**
LVEDV	0.363	**<0.001**	0.361	**<0.001**
Age		0.367		0.306

Abbreviations as in Table 1.

Table 3 - Multivariate linear regression analysis with LVOTD$_M$ in the derivation group

	Multivariate Model 1 (beta)	P	Multivariate Model 2 (beta)	P	Multivariate Mod
BSA	0.229	**<0.001**	0.318	**<0.001**	0.258
Height	0.125	**0.037**		0.054	
SVD	0.392	**<0.001**	0.411	**<0.001**	0.351
LVEDD	0.145	**0.001**	Not tested		0.134
LVEDV	Not tested		0.155	**<0.001**	Not tested
Female	Not tested		Not tested		-0.175

Abbreviations as in Table 1.

Table 4 – Regression equations for prediction of LVOTD$_M$ from the derivation group

LVOTD$_{RE1}$	LVOTD = 6.209 + (0.201×SVD) + (1.802×BSA) + (0.03×LVEDD) + (0.025×Height)
LVOTD$_{RE2}$	LVOTD = 9.698 + (0.21×SVD) + (2.442×BSA) + (0.005×LVEDV)
LVOTD$_{RE3}$	LVOTD = 11.097 + (0.18×SVD) + (1.985×BSA) + (0.028×LVEDD) [- 0.655 (if Female)]
LVOTD$_{RE4}$	LVOTD = 11.876 + (0.177×SVD) + (2.128×BSA) + (0.004×LVEDV) [- 0.647 (if Female)]

LVOTD$_{RE1, RE2, RE3, RE4}$, regression equation number 1,2,3,4 for predicting LVOTD$_M$, respectively. Other abbreviations as in Table 1.

Table 5 - Correlation with difference between LVOTD$_M$ and LVOTD$_{BSA}$ in the derivation group

	Multivariate Model 1 (beta)	P	Multivariate Model 2 (beta)	P
SVDI	0.499	**<0.001**	0.522	**<0.001**
LVEDDI	0.151	**0.002**	Not tested	
Height	0.2	**<0.001**	0.156	**0.002**
LVEDVI	Not tested		0.148	**0.002**

Abbreviations as in Table 1.

Table 6 – Comparison of different formulas for predicted LVOTD$_M$ in the validation group

	Mean ± SD
LVOTD$_{BSA}$ (14)	22.75 ± 1.44
LVOTD$_{RE1}$	22.21 ± 1.41
LVOTD$_{RE2}$	22.12 ± 1.36
LVOTD$_{RE3}$	22.2 ± 1.39
LVOTD$_{RE4}$	22.17 ± 1.38

11

*Difference = (LVOTD$_M$ – Predicted LVOTD). SD, standard deviation. Other abbreviations as in Table 1 and 4.

Table 7 – Intra-observer and inter-observer variability.

	Intra-observer variability	Inter-observer variability
SVD	1.3 mm (3.8%)	1.6 cm (4.7%)
LVEDD	1.4 mm (2.8%)	2.0 mm (4.1%)
LVEDV	5.6 ml (5.6%)	6.2 ml (6.1%)
LVOTD$_M$	0.8 mm (3.4%)	1.0 mm (4.7%)
LVOTD$_{RE1}$	0.3 mm (1.2%)	0.3 mm (1.5%)
LVOTD$_{RE2}$	0.3 mm (1.3%)	0.4 mm (1.6%)
LVOT$_M$ area	0.28 cm^2 (6.9%)	0.38 cm^2 (9.3%)
LVOT$_{RE1}$ area	0.09 cm^2 (2.4%)	0.11 cm^2 (2.9%)
LVOT$_{RE2}$ area	0.1 cm^2 (2.6%)	0.12 cm^2 (3.1%)

Abbreviations as in Table 1 and 4.