SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The implication of 3D echocardiography derived left atrial anatomy and volumetric analysis in clinical routine

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The PhD Defense takes as an online meeting on 30th May 2022, 2:00 pm.

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Abbreviations

2D - two-dimensional

2DE - two-dimensional echocardiography

3D - three dimensional

3DE - three-dimensional echocardiography

ABPs - systolic blood pressure

ABPd - diastolic blood pressure

AF - atrial fibrillation

AUC- Area under the curve

BSA - body surface area

CB - cryoballon

CBA - cryoballon ablation

CI - confidence interval

CT - computed tomography

CTEPH - chronic thromboembolic pulmonary hypertension

HR - heart rate

IQR - interquartile range

LA - left atrium

LAA - left atrial appendage

LAV min - left atrial minimum volume

LAV max - left atrial maximal volume

LAVi max - left atrial maximal volume indexed to body surface area

LAVi min - left atrial minimum volume indexed to body surface area

LV - left ventricle

LV EDV - left ventricular enddiastolic volume

LV ESV - left ventricular endsystolic volume

LV EDVi - left ventricular enddiastolic volume indexed to body surface area

LV ESVi - left ventricular endsystolic volume indexed to body surface area

LV EF - left ventricular ejection fraction

MRi - magnetic resonance imaging

PH - pulmonary hypertension

PV - pulmonary vein

PVI - pulmonary vein isolation

PAPm - mean pulmonary artery pressure

PAWP - pulmonary capillary wedge pressure

PVR - pulmonary vascular resistance

RAPm - right atrial pressure

RAV min - right atrial minimum volume

RAV max - right atrial maximum volume

RAVi max - right atrial maximal volume indexed to body surface area

RAVi min - the value of the right atrial minimum volume indexed to the body surface

RF - radiofrequency ablation

RV - right ventricle

RV EDVi - body surface index indexed for right ventricular enddiastolic volume

RV ESVi - right ventricular endsystolic volume indexed to body surface area

RV EF - right ventricular ejection fraction

SD - standard deviation

TEE - transoesophageal echocardiography

1. Introduction

1.1. Limitations of two-dimensional (2D) echocardiography

Three-dimensional (3D) imaging has been a major advancement in the development of echocardiography. Thus, due to the complex spatial anatomy and continuous movement of the heart, traditional 2D echocardiography can provide only limited information about the spatial relationships of cardiac structures and their changes during the cardiac cycle. Based on the images displayed by 2D echocardiography, the interpretation of spatial information is very difficult in many cases even for an experienced examiner. Understanding 2D images are further complicated by the fact that anatomical landmarks are often not clearly identifiable. In three-dimensional echocardiography (3DE), the examined structure is imaged together with its surroundings, thus facilitating the interpretation of the anatomical situation.

The advantage of the 3D technique can also be seen in the increased accuracy of the measurements. While the reconstructed images provided by 3DE allow for real measurement of each parameter, traditional 2D echocardiography uses mathematical calculations based on geometric assumptions to determine the dimensions of each structure. The assumptions can result in a different rate of inaccuracy depending on the structure being studied.

1.2. The importance of the anatomical features of pulmonary veins

The inflow pattern of the pulmonary veins (PV) into the left atrium is widely varied, the unusual pattern exists in 56.5% of the population (1). Knowledge of the anatomical inflow pattern of PVs may be particularly important especially if pulmonary vein isolation (PVI) is planning, which is the most common and effective interventional treatment for atrial fibrillation today (2 - 4). Radiofrequency (RF) catheter ablation is considered as a standard method for PVs isolation. More recently, the cryoballon ablation (CA) technique based on tissue freezing has become more popular. This method is simpler and learning the CA needs less time than RF ablation (5, 6), however, both have the same efficiency and safety profile (7). The rate of procedural PV occlusion by the cryoballoon and the continuous circumferential extension of tissue injury in the PV ostium determines the permanent success of PVI after CA. One of the main determinants of PV occlusion success is the anatomy of pulmonary veins. Recently computed tomography (CT) and cardiac magnetic resonance imaging (MRI) studies have identified several parameters specific to pulmonary veins that may have prognostic value in predicting the early and late success of CA. These include inflow pattern variations of PVs (left common PV, supra-numerical PVs) (8–10), as well as parameters describing the size of the ostiums and the surroundings of the veins (8, 11–18). However, conventional 2D echocardiography is not suitable for displaying or measuring most of these parameters. 3D TEE can be an alternative tool to CT or MRI to visualize PVs, even if the reconstruction of PVs is technically more complicated. Another important advantage of 3D TEE performed before PV isolation is the capability for exclusion the presence of thrombus in the left atrial appendage. That is the important reason why TEE can be considered a routine examination before left atrial interventions. However, the CT has a limited capability for displaying the thrombus inside the appendage due to its less resolution. The advantage of TEE is more because it requires less time compared to CT or MRI scans, the cost is significantly lower, and the TEE does not expose the patient and medical staff to radiation. Currently, the available 3D TEE protocols for displaying PVs are primarily aimed to help and control the catheter manipulation during CA, while the data on how the TEE can display the PVs themselves are rather conflicting (18 - 20). In the studies, the authors also pointed at the patient's supine position among the 3DE limitations may be an important factor influencing the visual display of PVs. However, it has not been investigated whether changing the patient's position can improve the assessment of PVs and the accuracy of the measurements.

1.3. Measurement of left atrial volumes by echocardiographic methods

The left atrial volume characterizes best the size of the left atrium, as the change in atrial volume considers the real geometrical change of the atrium. Changes in the left atrial volume are known to have prognostic value in many diseases (21 - 31). The most recommended 2DE method for measuring left atrial volume is the Simpson's method (a disc summation method in two orthogonal views) which is regularly used to determine left ventricular volume (32, 33). The limitations of 2DE left atrial volumetric measurement are the same as it is known according to left ventricular measurements. Moreover, the shape of the left atrium is more complex than the left ventricle's, so the error resulting from the geometric assumption is more prominent. 2DE underestimates the actual left atrial volume. In contrast, left atrial volume measured with 3DE correlated well with MRI measurements (34, 35). Using spatial information, the left atrial data are more accurate and reproducible than those calculated from 2DE data (36).

1.4. Importance of left atrial volume determination

In pulmonary hypertension (PH) the accurate determination of atrial volume may have an important clinical implication. PH is defined as the right pulmonary arterial pressure is 25 mmHg or higher measured by right side catheterization (Swan-Ganz). Many diseases can contribute to the development of PH, which includes not only lung disease but also heart disease. The disease is classified into 5 groups based on its clinical appearance.

Classification based on a diverse clinical presentation can be simplified by the hemodynamic approach of PH. According to the latest recommendations, PH can be divided into two main subtypes: precapillary (mainly due to pulmonary vascular disease or secondary lung disease) or postcapillary (secondary form due to left-sided heart disease) pulmonary hypertension.

The two subtypes require different therapeutic strategies. To classify patients into the different subtypes, the current PH guideline recommends measuring pulmonary arterial wedge pressure (PAWP) by right heart catheterization. Postcapillary PH is characterized if the PAWP is above 15 mm Hg.

1.5. Correlation between left ventricular filling pressure and atrial volumes

Left atrial (LA) size is known to be a marker of left ventricular filling pressure and it is closely related to pulmonary arterial wedge pressure (PAWP) (37). In left-sided heart disease, PAWP correlates more strongly with LA pressure than left ventricular end-diastolic pressure (38). In addition, several studies have shown an association between right atrial pressure and left ventricular filling pressure in patients with heart failure, both in preserved (HFpEF) and in reduced ejection fraction (HFrEF) (39, 40). LA size can be used as a marker of left ventricular filling pressure, while the right atrial size can also be used as a marker of right atrial pressure (36). These results suggest that right atrial size may also be useful in identifying patients with pulmonary hypertension due to left heart disease, however, the relationship between PAWP and right atrial pressure and right atrial size is unclear. While volumetric measurements determined by 2DE often underestimate the actual volume of the atrium, while the volumes measured with 3DE are closely correlated with those value which is measured by MRI (41, 42).

2. Aims

In the present study, we aimed to develop a protocol based on three-dimensional echocardiography dedicated to the imaging of pulmonary veins, which is suitable for the detailed examination of pulmonary veins and the characterization of their spatial relationship. The images acquired with the dedicated protocol should be able to determine the parameters characteristic of pulmonary veins accurately. We hypothesize that the success of cryoablation in isolating the pulmonary veins can be increased with the knowledge of pulmonary veins anatomy.

In our further studies, we sought to answer the question of whether atrial volumes measured with 3DE may be suitable for distinguishing between precapillary and postcapillary pulmonary hypertension.

3. Patient population and methods

3.1. Visualization of pulmonary veins by three-dimensional echocardiography

We developed our own protocol for the imaging of PVs with 3D TEE. Eighty consecutive patients with atrial fibrillation followed by Electrophysiological Outpatient Clinic of the Department of Cardiology and Cardiac Surgery, University of Debrecen, between 2018 and 2020 were selected. The patients were scheduled for pulmonary vein isolation (PVI) with cryoballon ablation (CBA) and TEE examination before CBA. The indication for the TEE study was the exclusion of the intracardiac thrombus prior to PVI. All the patients read and signed the informed consent before the examination, as approved by the local ethics committee (OGYÉI / 12743/2018). 3D TEE was acquired using an Epiq 7C (Philips Medical Systems, Andover, MA) equipped with an X8-2t transducer or a GE Vivid E95 (GE Vingmed Ultrasound, Norway) equipped with a 6VT-D transducer. 3D datasets were analyzed with a dedicated commercial software (4D Cardio-view 3, Tomtec Imaging GmbH, Unterschleissheim, Germany).

3.1.1. Description of the 3D TEE method

Patient preparation and placement prior to the study was modified from the well-known routine only to prepare the possibility of the change of the patient's position.

Using the image acquisition protocol, the first step was to visualize the left atrial appendage (LAA) using 2D acquisition. The probe was in the upper (or mid) transoesophageal position at 20-45°. The image showed the LAA. The left lateral ridge and the left upper PV were displayed at 60-80°, then the 3D dataset was acquired and confirmed by cropping the dataset in order to visualize the LAA and the left lateral ridge with the left upper PV ostium. If the dataset did not encompass the whole structure of the LAA and the left lateral ridge, the image acquisition was repeated while changing the probe angulation, flexion or changing the patient position.

The next step was to visualize the left PVs. The probe angulation was changed to at around 120° in order to centralize the image to the LAA, then the probe was turned slightly counterclockwise while moving the probe head to anteflexion. When the left PV ostium was visible, Color Doppler was used to confirm that both the upper and lower PV was visible (figure 5). Then the 3D dataset was acquired and confirmed by cropping the image to left upper and lower PV ostia with the intervenous ridge. If the dataset did not encompass the whole structure of the left PV ostium, image acquisition should be repeated while changing the probe angulation, flexion or changing the patient position.

The next step was the visualization of the right PVs. The probe angulation was changed to approximately 45° in order to centralize the image to the LAA, then the probe was turned slightly clockwise while moving the probe head to anteflexion. When the right PV ostium was visible, Color Doppler-coded imaging was used to confirm that both the upper and lower PV was clearly visible. Then the 3D dataset was acquired and confirmed by cropping the image to the right upper and lower PV ostia with the intervenous ridge. If the dataset did not encompass the whole structure of the right PVs ostia, image acquisition should be repeated while changing the probe angulation, flexion or changing the patient position.

The next step was to prepare the 3D dataset offline and perform the measurements. The selected 3D dataset was opened in a dedicated platform-specific or a vendor-independent software for multiplanar reconstruction of the 3D images. First, one should select a frame timed to the T wave, then two perpendicular planes are positioned to the PV ostia. The 3rd plane represents the *en face* view of the ostium, which is suitable to measure dimensions (distances, area). If the two perpendicular planes are fitted to the ridge, the widths of the ridges can be measured.

3.2. Implication of 3DE derived left atrial volume analysis

Eighty-eight consecutive patients with pulmonary hypertension followed by the Pulmonary Hypertension Outpatient Clinic of the Department of Cardiology and Cardiac Surgery, University of Debrecen, between December 2018 and January 2020 were included. The patients were scheduled for an echocardiographic examination and right heart catheterization to verify the diagnosis and to plan a treatment strategy. All of the patients read and signed the informed consent before the examination, as approved by the local ethics committee (No: 5893-2/2018/EKU). This investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177).

3. 2. 1. Right heart catheterization

RHC examination was performed by an independent cardiologist who was blinded to the results of the echocardiographic examination and data. The initial access site was the superior vena cava via the jugular vein, and a 7-F Swan-Ganz catheter (B. Braun Melsungen AG, Melsungen, Germany) was introduced. The methods used for the right heart catheterization and the measurement of the hemodynamic parameters were performed as previously described (43). A triple-lumen, balloon-tipped thermodilution catheter was used for the measurement of intracardiac pressures, pulmonary artery wedge pressure (at end-expiration) and cardiac output (CO). A blood sample was drawn to evaluate the pulmonary artery oxygen saturation. CO was calculated with a minimum of 3 (in atrial fibrillation or frequently occurring premature contractions, a minimum of 5) consecutive measurements that should not differ by > 10%. Pulmonary vascular resistance (PVR) was calculated based on the in- and outflow pressure values, and CO was measured by thermodilution. The variables that were collected included pulmonary artery pressure (PAP, systolic, diastolic and mean), mean PAWP, mean right arterial pressure, PVR, CO and CI. None of the patients had interatrial or interventricular shunts. Pressure values were expressed as mmHg, and PVR was expressed as dyne•s^{-1}•cm^{-5}. PH was defined as a mean pulmonary arterial pressure (PAPm) $\geq$ 25 mmHg at rest (48) by direct pressure measurements during right heart catheterization. Seventy-five patients fulfilled the PAPm criteria. Precapillary PH was defined if the PAWP was 15 mmHg or lower, and postcapillary PH was defined if the pulmonary capillary wedge pressure was higher than 15 mmHg (44).

3.2.2. Echocardiography

Echocardiography examinations were performed in all 75 patients within 24 hours of right heart catheterization according to the local protocol. 3DE was acquired using an Epiq 7C (Philips Medical Systems, Andover, MA) equipped with an X5-1 transducer. Patients were scanned in the left lateral decubitus position on an examination bed with a dedicated left-sided cutout, which allows optimal probe access for apical RV-focused acquisitions. Full-volume acquisitions of the RV, including the RA, were performed from the RV-focused apical view during a single breath-hold using second-harmonic imaging, and the full-volume acquisitions of the LA were performed from the LA-focused apical view. The image acquisition method was the same as that used for recording the RV images. The gain settings were optimized before the data acquisition. The temporal resolution was maximized by optimizing the sector width and minimizing the depth. The image optimization maneuvers were implemented as previously described (45). Whenever possible, imaging included 6-beat 3D full-volume datasets focused on the desired chamber in one single breath hold. The average frame rate was 32±9 volumes/s for RV, 32±17 volumes/s for RA, and 42±24 volumes/s for the LA datasets. All 3D datasets were digitally stored and analyzed offline.

3.2.2.1. 3D measurements

3DE datasets of the RV were analyzed offline to measure the end-diastolic and end-systolic volumes and the ejection fraction of the right ventricle using a commercial software package (4D RV-Function 2.0, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The software was previously validated against cMRI (46, 47). Left ventricular volumes (left ventricular end-diastolic volume index - LV EDVi; left ventricular end-systolic volume index - LV ESVi); and ejection fraction (left ventricular ejection fraction - LV EF) were also measured using validated, commercially available vendor-independent software (4D LV-Function, TomTec Imaging Systems GmbH, Unterschleissheim, Germany) (59). Commercial software was used to analyze the 3DE datasets of the LA and RA, where the maximum and minimum atrial volumes were analyzed (4D Cardio-view 3, Tomtec Imaging Systems GmbH, Unterschleissheim, Germany). The end-systolic and the end-diastolic frame chosen by the software were checked and adjusted manually to the timing of the AV valve movement, if necessary. All of the volumetric analyses were performed by an experienced cardiologist who was blinded to the RHC-derived data. The atrial volume ratio was calculated from the ratio of the RA volume to the LA volume.

3.3. Statistical analysis

Statistical analyses were performed with SPSS 24.0 for Windows (Statistical Product and Service Solutions, version 24, SPSS Inc., Chicago, IL, USA). Normality was assessed with a normal probability (Q-Q) plot and with a Shapiro-Wilk test. All continuous variables are reported as the mean ± standard deviation. The analyses for continuous data were performed with independent t-test. Non-normally distributed values are expressed as the median (interquartile range) and were compared using the Mann-Whitney U test. The correlations were checked using Spearman's correlations. Univariate logistic regression analysis was performed to determine factors associated with postcapillary PH. Continuous variables with significant correlations >0.70 or <−0.70 were considered to have collinearity. Clinical relevance determined which variables were to be included in the multivariate regression models. Significant associations from the univariate analysis then were analyzed with a multivariate logistic regression model with forward selection depending upon likelihood ratio statistics to identify the independent predictors of postcapillary PH. Odds ratio and 95% CIs were calculated at each independent continuous variable. Mathematical calculations regarding the variables without normal distribution were performed before the logistic regression analysis. ROC analysis was used to compare the distinction performance of the independent parameters and to determine the cutoff value. Agreement between 2DE and 3DE left atrial volumes were analyzed using Bland-Altman method. To assess the reproducibility in left atrial volumes, ten randomly selected patients were remeasured by the observer who initially analyzed the selected images (intraobserver variability) and by an independent observer who was blinded to the initial observer's results (interobserver variability). Intra- and interobserver variability was expressed in percent variability, defined as the absolute differences between pairs of repeated measurements divided by their mean. A value of $p<0.05$ was accepted as indicative of statistical significance, and all P values were two-sided.

4. Results

4.1. Visualization of pulmonary veins by three-dimensional echocardiography

The enrollment was performed consecutively all of the screened eighty patients were enrolled. Using our specific protocol to visualize the PVs, all pulmonary veins could be visualized. Analyzing the reconstructed images obtained with 3DE, the image quality was excellent for the upper pulmonary veins. The upper left pulmonary vein was displayed completely and in good quality in 96% of the cases (Grade 1), in 1.5% of the cases the 1/3 portion of the vein's wall was not clearly visible (Grade 2), and in 3% of all left upper PV the half of the vein's wall was not visualizable (Grade 3). In opposite, all of the right upper PVs could be detectable in excellent quality (100% Grade 1). The lower pulmonary veins were more difficult to visualize (left lower PV: 84% Grade 1, 1.6% Grade 2, and 10% Grade 3; right lower PV 93% Grade 1, 3% Grade 2, and 4% Grade 3). The classification was performed as follows: Grade 1: the 3D reconstruction image shows the entire cross-section of the pulmonary vein in good quality. Grade 2: 1/3 of the vein wall is not clearly visible in the reconstructive cross-sectional view of the PV. Grade 3: half of the vein is not clearly visible in the reconstructive cross-sectional view of the PV.

4.2. Implication of atrial volumes in pulmonary hypertension

4.2.1. Patient characteristics

Thirty-eight patients had precapillary PH, while 37 patients had postcapillary PH. There were more male patients in the postcapillary PH group, and their body surface area (BSA) was significantly higher. Systemic blood pressure and heart rate did not differ between the groups. According to the NICE classification (44, 49), patients with postcapillary PH predominantly belonged to group 2, while most of the patients with precapillary PH could be classified into group 1, 3 and 4.

4.2.2. Right heart catheterization parameters

Although their pulmonary artery pressure values were similar, the pulmonary vascular resistance was higher in the precapillary PH group than in the postcapillary PH group (571 (IQR 279, 942) dyne•s^{-1}•cm^{-5} vs 370 (IQR 253, 452) dyne•s^{-1}•cm^{-5}; p=0.017). The mean right atrial pressure was found to be significantly higher in the postcapillary group (13$\pm$6 mmHg vs 8$\pm$5 mmHg; p=0.001), as was the PAWP (12 (IQR 9, 13) mmHg vs 22 (IQR 17, 26) mmHg; p<0.0001).

4.2.3. Echocardiographic parameters

Right ventricular systolic function was impaired in both groups (the RV EF was 34$\pm$12% in precapillary PH vs 29$\pm$8% in postcapillary PH; p=0.06). The right ventricular indexed end-systolic volume was higher in the postcapillary PH group (precapillary PH: (69 (IQR 45, 93) ml/m^2 vs 81 (IQR 65, 101) ml/m^2; p=0.032). Both the maximum and minimum indexed left atrial volumes were larger in the postcapillary PH group (LAVi max: 41±25 ml/m^2, LAVi min: 26±24 ml/m^2 in the precapillary PH vs the LAVi max: 64±32 ml/m^2, LAVi min: 50±22 ml/m^2 in the postcapillary PH; $p<0.0001$), even though only the indexed minimum volume of the right atrium was significantly lower in the precapillary PH group (RAVI min: 38±26 ml/m^2 in the precapillary PH vs 51±27 ml/m^2 in the postcapillary PH; $p=0.02$). The atrial volume ratios were similar in the two patient groups (1.66±1.1 in the precapillary PH vs 1.1±0.59 in the postcapillary PH; $p=0.02$). The left ventricular volumes were significantly larger, while LVEF was lower in the postcapillary PH group.

4.2.4. Regression analysis

Linear regression analysis revealed a significant correlation between the LA minimum and maximum volumes and the PAWP ($r^2=0.38$ ($p<0,0001$) for LA minimum volume and $r^2=0.24$ ($p<0,0001$) for LA maximum volume). Both RA minimum and maximum volumes correlated with the mean right atrial pressure and the PAWP; however, the relationship between the PAWP and the RA minimum volume was stronger ($r^2=0.1$ ($p=0,005$) for RA minimum volume vs PAWP; $r^2=0.05$ ($p=0,04$) for RA maximum volume vs PAWP). The RA volumes showed a stronger correlation with the mean right atrial pressure, and the RA minimum volume correlated better with the

RAPm than the RA maximum volume (r^2=0.29 (p<0,0001) vs r^2=0.22 (p<0,0001), respectively). According to the relevant LV parameters, the BSA indexed LV end-diastolic volume correlated with the PAWP (r^2= 0.37; p<0,0001), and it was stronger than the correlation of LV EF with the PAWP (r^2= -0.27; p<0,0001).

Logistic regression analysis was used to determine which of these parameters can be used to distinguish between precapillary and postcapillary PH. The univariate logistic regression analysis demonstrated that the PVR, mean right atrial pressure, RAVi min, indexed left atrial maximum and minimum volume, LV EDVi and LV EF were correlated with postcapillary PH. When association between the parameters were tested, significant correlations (Spearman rank correlation < -0.70 and > 0.70) were observed between LV EF and end-diastolic volume, and LAVi maximum and minimum volume. We opted to include the highly correlated parameters in those pairs. The following parameters were chosen as inputs for multivariate logistic regression model: PVR, mean RAP, LV EDVi, right atrial and left atrial minimum volume. The model showed three significant variables: mean RAP (OR: 1.39; CI, 1.13-1.72; p=0.002), LV EDVi (OR: 1.05; CI, 1.02-1.08; p=0.001) and LAVi minimum (OR: 1.09; CI, 1.02-1.16; p=0.011), which were identified as the strongest independent predictors detecting postcapillary PH. Regarding the ROC curves of the parameters for predicting postcapillary PH, the AUCs for mean RAP, LV EDVi and LAVi min were 0.71 (95% CI, 0.59-0.82), 0.80 (95% CI, 0.71-0.9) and 0.86 (0.76-0.95), respectively. Concerning the performance of the atrial volume ratio and the LAVI max for differentiating postcapillary PH, the AUC's were much lower [AUC of atrial volume ratio: 0.66 (95% CI, 0.53-0.78) and AUC of LAVi max: 0.78 (95% CI, 0.67-0.89)]. The ROC analysis indicated a possible cutoff value of 27.7 ml/m2 for LAVi min (AUC=0.86; sensitivity=86%, specificity=76%) and 59 ml/m2 for LV EDVi (AUC=0.80; sensitivity=72%, specificity=71%) to predict postcapillary PH. Combining the LV EDVi and LAVI min, the differentiation capability of the volumetric measurement could increase the performance (AUC=0.89 (95% CI, 0.82-0.96); sensitivity=83%, specificity=82%) which underlines the additive value of LAVI minimum over the LV EDVi for predicting postcapillary PH. Because of the correlation of the mean RAP and the RAVI min, we tested the performance of RAVI min, which was low, as expected (AUC=0.66; 95% CI, (0.53-0.78).

4.2.5. Testing the reproducibility

Intra- and interobserver variability for LAVi min was good, as reflected by percent variability of 2% at 2DE and 1% at the 3DE measurements. As expected, the bias between the 2DE and the 3DE measured volume was larger in postcapillary PH group (9 ml (IQR 3, 15) in precapillary and 20 ml (IQR 6, 31) in postcapillary, p=0.006) where the atrial volumes were significantly larger causing less accuracy regarding probably the geometrical assumption.

5. Discussion

5.1. Visualization of pulmonary veins by three-dimensional echocardiography

In the present work, we were the first to present a special method for three-dimensional transoesophageal imaging of pulmonary veins capable of producing high-quality 3D images of all pulmonary veins. Using this specific protocol, the visibility of all pulmonary veins was 100%, and in 93% of the acquired images had high quality. One key element of the method is the changing the patient's position during the study in case the visibility of each PV is inadequate. The latter step of the method contributes mainly to the proper 3D TEE mapping of PVs. The greatest challenge in examining pulmonary veins with TEE is the imaging of the lower pulmonary veins. Adequate image quality of pulmonary veins is suitable for reconstruction, thereby making more accurate measurements.

Detailed visualization of pulmonary veins and accurate knowledge of their anatomical features are especially important during pulmonary vein isolation, mainly in planning and performing cryoballon ablation. Cryoballon ablation is an alternative technique to radiofrequency ablation in isolating the pulmonary veins in atrial fibrillation. The success of the procedure depends mainly on the adequacy of the tissue damage at the ostium of the pulmonary veins. Several anatomical parameters of the pulmonary vein have recently been identified that may be important in predicting the short- and long-term success of cryoballon ablation (8 - 13). CT is the gold standard for examining the pulmonary veins. However the CT scan alone is not suitable to rule out the presence of left atrial thrombus (50, 51). For this purpose, transesophageal echocardiography is the preferred examination method prior to pulmonary vein isolation, which is a two-dimensional method in general (52). In some cases, the intracardiac echocardiography (ICE) is the alternative technique for TEE with the main advantage that it does not require sedation, but the image quality is not comparable to the TEE's. In addition, ICE is not suitable for planning the intervention due to its more invasive nature (53).

In general, the 2D technique is not suitable for imaging all of the pulmonary veins or measuring their specific parameters. Based on the results of studies using the 2D TEE to investigate the anatomical features of the pulmonary veins, only 94% of all pulmonary veins can be imaged, especially the visualization of the lower ones is challenging (54, 55).

Early studies with 3DE were also unclear about the benefit of using the 3D method. Ottaviano et al., using the 3D TEE method to guide cryoablation, reported that it is suitable for visualizing all of the PVs in all patients, visualizing the ostium of the veins, and visualizing the surrounding anatomical structures (18).

In contrast, Faletra and colleagues pointed out that using the same 3DE method as described by Ottaviano, they could not reproduce the full visualizability of all pulmonary veins. Of the 22 patients who underwent 3D TEE-controlled cryoablation, only in 4 patients, visualization of all PVs was possible, and 3 of 4 PVs were visualized in 11 patients, while in 2 patients, no PV could be visualized. Visualization was considered optimal in 63% of the left upper pulmonary vein and in 77% of the right upper PVs. 50% of the right lower PV and 47% of the left lower PV cases could not be seen (56).

Among the potentially complicating factors for complete imaging of pulmonary veins, the authors identified the posterior localization of the lower pulmonary veins as the most important. In addition, the patient's supine position affected more the visibility of the veins, as the supine position leads to antero-posterior compression of the atrium. The authors also hypothesized that the rigid endotracheal tube may also reduce the free movement of the transoesophageal tube in the esophagus (56).

Mita et al., examined the effect of patient position during TEE. They confirmed that the patient's body position during the TEE study significantly affects the visibility of individual structures of the heart (57).

In the present study, changing the patient's position was an important element of imaging pulmonary veins with 3D TEE, which improved the image quality and the visibility of PVs. Using this modified protocol, we were able to visualize all four pulmonary veins of the 80 patients included in the study (100% visualization). The image quality was optimal in 93%.

5.1.2. Limitations of visualization of pulmonary veins by 3D TEE

The study was a single-centre study with a relatively small sample size. In the present study the rate of patents with atrial fibrillation at the time of imaging was only 22%, however, the arrhythmia did not affect the 3D image quality.

5.2. Implications of measuring atrial volumes with 3DE

This part of the study revealed that the BSA-indexed left atrial minimum volume (LAVi min) is a useful (sensitive and quite specific) parameter in differentiating between precapillary and postcapillary PH: the LAVi min is higher in postcapillary PH and is able to differentiate pre- and postcapillary PH better than the atrial volume ratio or the maximum LA volume. The differentiation ability could be improved if the 3DE measured atrial minimum volume data combined with the left ventricular end-diastolic volume.

Distinguishing between pre- and postcapillary PH is important because of their different treatment strategies. The current guidelines recommend a classification that requires invasively measured mean PAP and PAWP. The differential diagnosis is challenging without these invasive measurements (RHC).

Recent studies have examined the role of atrial size in the differential diagnosis of the two PH phenotypes. Veld et al. demonstrated that the ratio of LA and RA maximum area ratio assessed by CT is a potentially useful parameter (58). Saito et al. also showed that the atrial volume ratio (RA maximum volume divided by LA maximum volume) is a useful parameter for differentiating pre- and postcapillary PH (59). These studies mainly focused on the LA maximum volume.

It is known that LA size is a marker of left ventricular diastolic dysfunction, as increased left ventricular filling pressure leads to LA enlargement. Most of the studies describing the prognostic value of LA size have focused on the LA maximum volume, but the most recent results support measuring the minimum volume of LA instead, since during diastole the exposure of the LV diastolic pressure is the major factor that determines the LA minimum volume (60). It was found that the LA minimum volume is a better marker of LV filling pressure and elevated PAWP. Moreover, it predicts major cardiovascular events better than the LA maximum volume (61). Currently, the standard echocardiographic method used to estimate the LA volume is the 2DE biplane method, but it gives inaccurate results due to the LA shape complexity. Wu et al. evaluated the prognostic value of the LA volume, demonstrating that the 3DE-measured LA minimum volume is superior to the conventional 2DE-based estimation (62).

In our patient population, PAWP correlated better with the LA minimum volume than the LA maximum volume. The LA volumes were increased in the postcapillary PH group, where the PAWP was significantly higher than that in the precapillary PH group. The elevated left ventricular filling pressure affected both the PAWP and the left atrial volumes, mainly the LA minimum volume. Our results confirmed that the left atrial minimum volume reflects the increased left ventricular filling pressure (60, 61). Left atrial pressure also correlates with PAWP and the LV end-diastolic pressure. The relationship between PAWP and the LV EDV was good in our population. Adding this to the left atrial minimum volume increased the atrial volume performance in differentiating postcapillary PH.

In contrast, the RA volume is affected by right ventricular pressure overload due to elevated PAP, and it was similarly increased in both the precapillary and postcapillary PH groups. Both the RA minimum and maximum volumes were correlated with mean right atrial pressure and the PAWP, and their relationship with the RA minimum volume was stronger for the pressure values than for the maximum volume. The RA minimum volume was significantly lower in the precapillary PH group, while the right atrial pressure was lower than that in the postcapillary PH group. This is a potential explanation for why the right atrial minimum volume could discriminate between the pre- and postcapillary PH groups, but with less efficacy than the LA minimum volume.

A recent study assessing LA and RA maximum volumes by TTE showed that these parameters are useful in differentiating precapillary and postcapillary PH (58). Their results were comparable with our findings: the LA maximum volume was larger in the postcapillary PH group, and the RA maximum volume did not differ significantly between the PH groups. In addition, we found that the LA minimum volume was a more powerful parameter for differentiating between precapillary and postcapillary PH.

5.2.2. Limitations of the study

This study was a single-center study with a relatively small sample size. The software used for the measurement of the LA volumes was 3D-based but was not specifically dedicated to 3D left atrial volume measurements. No heart failure patients with preserved ejection fraction (HFpEF) were included in our study population.

6. Summary of results and novel observations

Three-dimensional echocardiography (3DE), beyond the limits of the 2D method, is suitable for taking high-quality images of all pulmonary veins using a specific transoesophageal (TEE) examination protocol. This specific 3D TEE protocol can be an alternative tool of CT in examining and visualizing the pulmonary vein's anatomical features before the pulmonary vein isolation.

The left atrial minimum volume measured by 3DE is suitable for differentiating patients with precapillary and postcapillary pulmonary hypertension. 3D left atrial minimum volume is more effective in differentiating the patients with different type of pulmonary hypertension than left ventricular maximal volume or the atrial volume ratio. The differentiation ability could be improved if the 3DE measured atrial minimum volume data combined with the left ventricular end-diastolic volume.

6.1. New results, findings:

1. Our modified method for visualization pulmonary veins by three-dimensional transesophageal echocardiography is able to produce 3D images of all pulmonary veins.

2. Modification of the patient's position during the examination is the cornerstone of the modified protocol for displaying the pulmonary veins.

3. The developed method was able to display pulmonary veins with high quality in 93%.

4. The body surface area indexed left atrial minimum volume measured by 3D echocardiography is a suitable non-invasive parameter in the differential diagnosis of pulmonary hypertension distinguishing between the precapillary and postcapillary forms.

5. The differential diagnostic value of the indexed left atrial minimum volume is better than the atrial volume ratio or the left atrial maximum volume alone.

6. The ability to differentiate between the precapillary and postcapillary pulmonary hypertension form is further enhanced if the atrial minimum volume measured by the 3D echo is combined with the left ventricular end-diastolic volume value.

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8. Scientometry

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A PhD értekezés alapjául szolgáló közlemények

1. **Jenei, C.**, Kádár, R., Balogh, L., Borbély, A., Győry, F., Péter, A., Daragó, A., Csanádi, Z.: Role of 3D echocardiography-determined atrial volumes in distinguishing between pre-capillary and post-capillary pulmonary hypertension.
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További közlemények

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A közlő folyóiratok összesített impakt faktora: 51,607
A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre): 5,766

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