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3D echocardiography derived right ventricular function is associated with right ventricular failure and mid-term survival after left ventricular assist device implantation

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A B S T R A C T

Background: Right heart failure remains a major cause of morbidity and mortality after left ventricular assist device (LVAD) implantation. Multiple 2D echocardiography derived parameters are associated with right ventricular failure (RV failure), but none of them has been proven to be a reliable predictor to date. We hypothesized that novel 3D-echocardiography (3DE) based parameters are associated with RV failure and predict long term outcome in patients undergoing LVAD implantation.
Methods: This single-center study retrospectively enrolled 26 patients undergoing continuous-flow LVAD implantation. RV failure was defined as prolonged inotropic support for >14 days after LVAD implantation or consecutive implantation of a right ventricular assist device. Based on transesophageal 3DE datasets acquired prior to surgery right ventricular size, ejection fraction and longitudinal strains were calculated.
Results: The overall RV failure rate was 19.2%. Patients suffering from RV failure had a significantly impaired 3D-right ventricular ejection fraction (3D-RVEF; 28 ± 2% vs. 19 ± 3%, $p = 0.0145$) and 3D derived RV free wall longitudinal strain (3D-RV-fws; −13.2 ± 0.97% vs. −6.4 ± 1.98%; $p = 0.0056$) when compared to patients without RV failure. ROC analysis for 3D-RV-fws (AUC 0.914) and 3D-RVEF (AUC 0.876) showed high discriminative capabilities in regard to detection of RV failure. Kaplan-Meier analysis showed an improved long-term survival of patients with a 3D-RV-fws <−11.9%.
Conclusions: 3D-echocardiography derived RV ejection fraction and RV free wall strain are associated with right ventricular failure and long term outcome in patients undergoing LVAD implantation. These parameters have the potential to be future predictors for right heart failure in LVAD surgery.

1. Introduction

Left ventricular-assist device (LVAD) implantation has become a standard of care for patients suffering from severe congestive heart failure not manageable by medical therapy alone. Most patients undergoing an LVAD implantation have a New York Heart Association (NYHA) Class IV and an American Heart Association (AHA) Heart Failure Stage D. LVAD therapy is being increasingly used worldwide as destination therapy resulting from the globally decreasing numbers of donor organs as well as a temporary treatment option as bridge-to-transplant [1]. Despite novel surgical implantation techniques and improvements in perioperative care [2], right ventricular failure (RV failure) still remains a major cause for morbidity and mortality in this patient population and hence determines the overall outcome. As an attempt to reduce morbidity and mortality after LVAD implantation, various scores have been developed to estimate and predict the risk of perioperative RV failure [3–5]. Unfortunately none of these scores has been validated in larger patient populations and can be recommended for clinical use to date. Two-dimensional echocardiography (2DE) remains a standard diagnostic tool for the evaluation of right ventricular function used in routine clinical practice [6,7]. Due to the complex anatomical shape and the functional complexity of the right ventricle, 2DE has to rely on multiple surrogate parameters (e.g. TAPSE) to estimate RV function. Various 2DE parameters have been studied to evaluate their predictive value for RV failure with variable results [8–10]. The American Society of

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Echocardiography (ASE) therefore recommends combining 2DE with preoperatively assessed clinical signs of RV failure as an attempt to improve risk assessment in LVAD patients and to improve patient therapy [11].

In recent years, 3-dimensional echocardiography (3DE), especially 3D transesophageal echocardiography (3DTEE) in cardiac surgery patients, has become increasingly available for these patients [12,13]. 3DE has been thoroughly validated against cardiac magnetic resonance imaging (CMRI) and offers the possibility to quantitatively assess right ventricular function and filling states based on volumetric models calculated from 3-dimensional full volume datasets [14,15]. To date, however, there is to the best of our knowledge only one study that has assessed the association of 3DE RV size and function in regard to perioperative RV failure in patients undergoing LVAD implantation [16].

The aim of this retrospective analysis was to evaluate the prognostic association of 3DTEE derived parameters of RV function in patients undergoing LVAD implantation immediately prior to the start of cardiac surgery. We included parameters such as 3D ejection fraction, RV free wall and septal wall longitudinal strains that can now be extracted out of the 3D dataset with a modern software package.

2. Methods

2.1. Study design

Approval of this study was given by the Institutional Review Board at the University Hospital Tübingen (IRB# 230/2016BO2). All patients undergoing laminar-flow ventricular assist device implantation at our institution from October 2013 to July 2017 were retrospectively screened for possible inclusion. Only patients with high quality 3DE images were included in this study. Postoperative right ventricular failure (RV failure) was defined as prolonged inotropic support for >14 days after implantation or consecutive implantation of a right ventricular assist device (RVAD) according to the current literature [5,17,18]. Long-term survival was defined as survival without death of any cause.

2.2. Management during LVAD implantation

Isolated implantation of the LVAD device was performed using a median sternotomy or a less-invasive approach on cardio-pulmonary bypass (CPB) without the use of cardioplegia (on-pump beating-heart). A few patients needed additional procedures such as valvular reconstruction or replacement in which cases cold blood cardioplegia (Buckberg technique) was used. All patients received inotropic and vasoactive pharmacological support as per institutional standard as follows: A continuous i.v. milrinone infusion at 0.5 μg/kg/min initiated after institution of CPB. A continuous dobutamine infusion up to 10 μg/kg/min was started immediately before separation from CPB according to RV function. All patients received a single dose of 20 μg inhalative iloprost upon separation from CPB and a continuous application of 20 ppm inhalative nitric oxide (NO) to reduce pulmonary vascular resistance. Treatment with inhaled iloprost was repeated as needed for RV function. Noradrenaline and vasopressin (if noradrenaline dose exceeded 0.5 μg/kg/min) were used as vasopressors to maintain sufficient perfusion pressures and stable hemodynamics.

2.3. Echocardiography

Transesophageal (TOE) real-time 3D full-volume datasets including the entire right ventricle were obtained from a mid-esophageal RV focused view (Philips iE33-system, X7-2t Matrix probe, Philips Healthcare Inc., Andover, USA). To obtain this view the TOE probe was rotated until the right heart was visualized. The image was optimized until the whole tricuspid annulus was captured in its entity throughout the cardiac cycle. Four-beat acquisition during apnea was performed and the settings of the ultrasound machine were adjusted to a high temporal resolution of >15 Hz (Fig. 1a). In one patient transthoracic real-time 3D echocardiography (Philips iE33-system, X5-1 Matrix transducer, Philips Healthcare Inc., Andover, USA) was used, due to low frame rate of the transesophageal image. All datasets were acquired before skin incision under general anesthesia and stable hemodynamics. Comprehensive quantification of the RV was performed offline on a vendor independent RV quantification platform (Tomtec Image Arena and Tomtec 4D RV-Function 2.0; Tomtec Imaging Systems GmbH, Unterschleissheim, Germany). This software has been validated against CMRI and shows a higher accuracy for the 3D volumetric analysis compared to the previous version [15]. Based on anatomical landmarks and speckle-tracking algorithms, a volumetric model of the right ventricle was generated (Fig. 1b and c). RV end-diastolic (RVEDV) and end-systolic (RVESV) volumes were measured. RVEF was calculated as [(RVEDV − RVESV)/RVEDV] × 100%. To compare individual RV sizes, volumes were indexed to the body-surface area (RVEDVI and RVESVI). Using the 3D dataset, an optimally aligned 4-chamber view was generated with the RV quantification platform, allowing the accurate measurements of distances (e.g. TAPSE) and right ventricular areas (e.g. FAC). Tricuspid annular plane systolic excursion (TAPSE) was calculated as the distance of the movement of the lateral tricuspid annulus towards the RV apex. Fractional area change (FAC) was calculated as follows: [(RV end-diastolic area − RV end-systolic area)/RV end-diastolic area] × 100%. Based on the 3D aligned 4-chamber view RV free wall longitudinal strain (3D-RV-fws) and RV septal wall longitudinal strain (RV-sws) were assessed as the difference in the measured distance of the curvature in systole and diastole of the free or septal RV wall: [(RV end-diastolic curvature (mm) − RV end-systolic curvature (mm))/RV end-diastolic curvature (mm)] × 100% (Fig. 1d). 2D speckle tracking to calculate the 2D derived right ventricular longitudinal free wall strain (2D-RV-fws) was performed on a vendor independent quantification platform (Tomtec Image Arena and Tomtec 2D Cardiac Performance Analysis, Tomtec Imaging Systems GmbH, Unterschleissheim, Germany). Tricuspid valve regurgitation was assessed according to current published guidelines [19].

2.4. Statistical analysis

Normal distribution of the variables was checked using the Kolmogorov-Smirnov and Shapiro-Wilk test. Continuous variables are reported as mean values ± standard deviation. For echocardiographic parameters, 95% confidence intervals of the mean were used. Comparison of continuous variables between the different groups was performed using a Student's *t*-test. Correlation of continuous variables was tested using the Pearson's correlation coefficient. Variables that were not normally distributed were reported as median and interquartile ranges (IQR). Comparison of these variables was performed using the Mann-Whitney-*U* Test. Categorical variables were reported as percentages. Logistic regression analysis and receiver operating characteristic (ROC) analysis was performed using the easyROC web-tool (ver. 1.3; http://www.biosoft.hacettepe.edu.tr/easyROC/). The mean value was used as a cut-off value for long term survival analysis. Long term survival was assessed using a Kaplan-Meier analysis and the Log-Rank test. Differences of the variables were interpreted as significant at p values < 0.05. Statistical analyses were performed using the IBM SPSS software (ver. 24, IBM Corporation, Armonk, US) and SAS JMP software (ver. 13.1.0, SAS Institute Inc., Cary, US).

3. Results

3.1. Patient selection

A total of 77 patients were retrospectively screened for inclusion into this study. 26 patients were excluded because they were on veno-arterial extracorporeal life support (va-ECLS) prior to LVAD implantation. Of the remaining 52 patients, 2D datasets were only acquired in 23 patients and 3D datasets were captured in 28 patients. The availability of a 3D ultrasound machine determined whether the patients received 3D echocardiography or not. Another 2 patients were excluded due to very low frame rates (<10 Hz) and stitching artifacts. Finally, a total of 26 patients, 2 female (7.7%) and 24 male (92.3%) were included in this study (Fig. 2a).

There were not statistically significant differences between the patients that were included and not included into this study with regard to gender, age, body-surface area, cause of heart failure, implanted devices, rate of right heart failure, preoperative hemodynamics and preoperative left ventricular ejection fraction (Supplement 2). The patients included into the analysis consisted of a statistically significant higher rate of Intermacs Class 1 patients (3/26 vs. 0/23, p = 0.0000).

3.2. Characteristics of the studied patients

There were no statistically significant differences between the groups with and without right ventricular failure in regard to age,

Fig. 1. a) 3D full volume loop of the right ventricle captured from a transesophageal RV focused view. b) Generation of 3D model of the right ventricle by endocardial border detection with TomTec 4D RV Function® 2.0 software. c) Volumetric model of the right ventricle and volumetric changes during cardiac cycle allowing for determination of end-diastolic (EDV) and end-systolic (ESV) volumes and calculation of ejection fraction (EF). d) Calculation of 3D aligned right ventricular longitudinal strains as the difference of the curvature distance. Longitudinal strain of the RV free wall (green) and RV septal wall (yellow). e) Comparison of means and standard deviations of 3D-RV ejection fraction (3D-RVEF). f) Comparison of means and standard deviations of 3D aligned RV free wall strain (3D-RV-fws). g) Comparison of means and standard deviations of 2D derived myocardial RV free wall strain (2D-RV-fws). h) Bland and Altman analysis for the comparison of the 3D and 2D methods to calculate the RV free wall strain. Red line describing mean difference of 1.792%. Dotted red line describing the upper and lower 95% confidence intervals 0.297% and 3.287% respectively.

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