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CLINICAL RESEARCH

Assessment of right ventricular dysfunction predictors before the implantation of a left ventricular assist device in end-stage heart failure patients using echocardiographic measures (ARVADE): Combination of left and right ventricular echocardiographic variables

Évaluation de la fonction ventriculaire droite avant implantation d'une assistance ventriculaire mono-gauche chez les patients en insuffisance cardiaque terminale par échocardiographie : combinaison de paramètres ventriculaires gauches et droits

Nadia Aissaoui[a,b,c,d,*], Joe-Elie Salem[a], Lech Paluszkiewicz[b], Michiel Morshuis[b], Emmanuel Guerot[a], Gonzalo Martin Gorria[b], Jean-Yves Fagon[a,d], Jan Gummert[b], Benoit Diebold[a,c,d]

[a] *Georges-Pompidou European Hospital, Assistance Publique des Hôpitaux de Paris (AP—HP), Paris, France*
[b] *Heart and Diabetes Centre, NRW, Bad Oeynhausen, Germany*
[c] *Faculty of Medicine, University Paris Descartes, Paris, France*
[d] *INSERM U 678, University Paris VI, Paris, France*

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Abbreviations: AUC, area under the curve; BiVAD, biventricular assist device; CI, confidence interval; E_{LAT}, tissue Doppler lateral diastolic velocity; E_{RV}, tissue Doppler RV diastolic velocity; E_{SEPT}, tissue Doppler septal diastolic velocity; Em, pulsed Doppler transmitral E wave; Et, pulsed Doppler tricuspidal E wave; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricle/ventricular; LVAD, LV assist device; RR, relative risk; RV, right ventricle/ventricular; RVAD, RV assist device; RVEDD, RV end-diastolic diameter; RVF, RV failure; S_{LAT}, tissue Doppler lateral systolic velocity; S_{RV}, tissue Doppler RV systolic velocity; S_{SEPT}, tissue Doppler septal systolic velocity; TAPSE, maximal systolic excursion of the tricuspid annulus; VAD, ventricular assist device.

* Corresponding author at: Service de réanimation médicale, hôpital européen Georges-Pompidou, 25, rue Leblanc, 75015 Paris, France.
E-mail address: nadia.aissaoui@egp.aphp.fr (N. Aissaoui).

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KEYWORDS
Right ventricular failure;
INTERMACS level;
Assist device;
Doppler tissue velocities;
Echocardiography

Summary
Background. — Right ventricular failure (RVF) is a major cause of morbidity and mortality in left ventricular assist device (LVAD) recipients.
Objectives. — To identify preoperative echocardiographic predictors of post-LVAD RVF.
Methods. — Data were collected for 42 patients undergoing LVAD implantation in Germany. RVF was defined as the need for placement of a temporary right ventricular assist device or the use of inotropic agents for 14 days. Data for RVF patients were compared with those for patients without RVF. A score (ARVADE) was established with independent predictors of RVF by rounding the exponentiated regression model coefficients to the nearest 0.5.
Results. — RVF occurred in 24 of 42 LVAD patients. Univariate analysis identified the following measurements as RVF risk factors: basal right ventricular end-diastolic diameter (RVEDD), minimal inferior vena cava diameter, pulsed Doppler transmitral E wave (Em), Em/tissue Doppler lateral systolic velocity (S_{LAT}) ratio and Em/tissue Doppler septal systolic velocity (S_{SEPT}) ratio. Em/S_{LAT} $\geq$ 18.5 (relative risk [RR] 2.78, 95% confidence interval [CI] 1.38—5.60; $P = 0.001$), RVEDD $\geq$ 50 mm (RR 1.97, 95% CI 1.21—3.20; $P = 0.008$) and INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) level 1 (RR 1.74, 95% CI 1.04—2.91; $P = 0.04$) were independent predictors of RVF. An ARVADE score > 3 predicted the occurrence of post-implantation RVF with a sensitivity of 89% and a specificity of 74%.
Conclusion. — The ARVADE score, combining one clinical variable and three echocardiographic measurements, is potentially useful for selecting patients for the implantation of an assist device.

MOTS CLÉS
Assistance ventriculaire ;
Insuffisance ventriculaire droite ;
Niveau INTERMACS ;
Échocardiographie ;
Doppler tissulaire

Résumé
Contexte. — L'insuffisance ventriculaire droite (IVD) en post-implantation d'une assistance mono-gauche (ACM-MG) est une cause importante de morbi-mortalité.
Objectifs. — L'objectif principal de notre étude était d'identifier des paramètres échocardiographiques prédictifs de la survenue d'une IVD après l'implantation d'une ACM-MG chez les patients en insuffisance cardiaque terminale.
Méthodes. — Les données cliniques, hémodynamiques et échocardiographiques étaient recueillies prospectivement chez 42 patients en insuffisance cardiaque terminale devant bénéficier d'une ACM-MG. Ces données étaient comparées entre les patients développant une IVD en post-implantation et ceux ne la développant pas. L'IVD en postopératoire d'une ACM-MG était définie par la nécessité d'une assistance circulatoire droite ou d'inotropes au moins 14 jours après l'implantation de l'ACM-MG. Un score « ARVADE » était établi en additionnant des points déterminés en fonction de la valeur des facteurs prédictifs d'IVD.
Résultats. — Parmi les 42 patients inclus, 24 (57 %) ont développé une IVD en post-implantation de l'ACM-MG. Les facteurs de risque en analyse univariée de développer une IVD après l'implantation d'une ACM-MG étaient: le stade INTERMACS, le diamètre télédiastolique basal du VD (DTDVD), le diamètre minimal de la veine cave inférieur, l'onde E mitrale (Em) et les rapports Em/onde S latérale et Em/onde S septale. En analyse multivariée, les facteurs prédictifs d'une IVD étaient un rapport Em/SLAT $\geq$ 18,5 (RR 2,78, IC 1,38—5,60 ; $p = 0{,}001$), un DTDVD $\geq$ 50 mm (RR 1,97, IC 1,21—3,20 ; $p = 0{,}008$) et un stade 1 INTERMACS (RR 1,74, CI 1,04—2,91; $p = 0{,}04$). Un score ARVADE > 3 permettait de prédire une IVD en post-implantation avec une sensibilité de 89 % et une spécificité de 74 %.
Conclusion. — Le score ARVADE associant des paramètres échographiques reflétant le fonctionnement de VG et du VD et un paramètre clinique pronostique pourrait permettre une meilleure sélection des candidats à une ACM-MG.

Background

Ventricular assist devices (VADs) are a life-saving therapeutic option for patients with end-stage heart failure. One-year survival after implantation of a left ventricular assist device (LVAD) in selected patients is similar to that after heart transplant [1],10 although survival is limited by early morbidity and mortality caused by

right ventricular failure (RVF) [2,3]. Indeed, RVF failure has an incidence of up to 50% after LVAD implantation and results in perioperative mortality and morbidity rates of 19 to 43%, including end-organ dysfunction associated with prolonged intensive care and hospitalization [2,4,5].

Numerous factors contribute to RVF after LVAD implantation, rendering the prediction and management of postoperative right ventricular (RV) dysfunction complex [2,4—6]. The identification of predictors of RVF in preoperative VAD patients would improve the selection of patients most likely to benefit from LVAD.

Various clinical factors (being female, non-ischaemic aetiology of LV dysfunction) and haemodynamic factors (high central venous pressure, low mean pulmonary artery pressure and low RV stroke work index) have been identified as independent predictors of RVF after LVAD implantation [1—7]. However, no single factor reliably predicts RVF in these conditions.

Risk scores, based on the independent predictors of RVF, combining clinical, haemodynamic and laboratory measurements, may be useful for predicting RVF, but no score of this type has been tested prospectively [4,5]. The Michigan RV score can be useful in very severely affected patients, with high scores reflecting multiple organ failure (requirement for vasopressors, renal and hepatic congestion), but its utility is limited in less severe cases [4,7].

RV echocardiographic variables, including two-dimensional global strain imaging, have been reported to provide valuable information about RV risk, but conflicting results have been obtained [8—11]. The complex geometry of the right ventricle (RV) also makes it difficult to assess RV function.

Left ventricular (LV) evaluation may be useful for RVF prediction [12]. Severe and advanced LV dysfunction has consequences for RV function, and impaired LV contractility has a negative effect on RV function. Left-sided heart disease causes pulmonary venous congestion and pulmonary venous hypertension. Chronic sustained high blood pressure in pulmonary capillaries leads to a cascade of pathological retrograde anatomical and functional effects, resulting in RV overload and failure [13]. It may, therefore, be possible to predict the likelihood of RVF after LVAD implantation, at least partially, from assessments of LV function. In particular, tissue Doppler systolic myocardial velocity and the E wave, an indicator of LV relaxation disorder and overload, may be useful.

The main aim of this study was to identify preoperative echocardiographic predictors of post-LVAD RVF and to evaluate a risk score for postoperative RVF.

Methods

Study

This study complied with the Helsinki Declaration and was approved by the ethics committee of our institution. Informed consent was not sought from the patients, as this was an observational study and did not involve any changes to diagnostic tests or therapeutic interventions.

Patient selection

Data were collected prospectively for all patients who underwent elective LVAD or biventricular VAD (BiVAD) implantation and preoperative echocardiography between November 2010 and August 2011, at the Clinic for Thoracic and Cardiovascular Surgery in Bad Oeynhausen, Germany. The devices implanted were the HeartMate II (Thoratec, Pleasanton, CA, USA), the HeartWare HVAD (HeartWare, Oakville, CA, USA) and the Thoratec Paracorporeal BiVAD (Thoratec, Pleasanton, CA, USA). Patients receiving a total artificial heart were excluded from the analysis because, at our institution, the choice to implant a total artificial heart was often based on the presence of mechanical prostheses, active endocarditis, severe pulmonary insufficiency, extensive LV apical thrombus or hypertrophic cardiomyopathy. Patients were also excluded if image quality was deemed insufficient for the analysis of RV function.

Clinical data

Baseline clinical, demographic, haemodynamic and laboratory data were recorded prospectively in the electronic record. An Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile [14] and Michigan RV risk score [4] were calculated for each patient. The Michigan score assigns points based on four variables, with vasopressor use adding 4 points, creatinine > 2.3 mg/dL adding 3 points, bilirubin > 2 mg/dL adding 2.5 points and aspartate aminotransferase > 80 IU/dL adding 2 points. Higher scores (especially if ≥ 5.5) are associated with a greater risk of RVF.

Patients with a glomerular filtration rate < 60 mL/min/1.73 m^2 for 3 months were classified as having chronic renal insufficiency.

Deaths during hospitalization and the causes of death were recorded. Univariate risk factors for death were analysed.

Echocardiographic assessment

Preoperative transthoracic echocardiography results were reviewed and analysed by a reader blinded to clinical outcome. Standard echocardiographic measurements of the RV were made in accordance with current guidelines [15], including basal RV end-diastolic diameter (RVEDD), end-systolic and end-diastolic RV areas, fractional area change, maximal systolic excursion of the tricuspid annulus (TAPSE), tissue Doppler systolic and diastolic velocities of the RV lateral wall (S_{RV} and E_{RV}), pulsed Doppler tricuspid E wave (Et), systolic pulmonary arterial pressure and maximal and minimal diameters of the inferior vena cava. Longitudinal strain of the RV free wall was measured on the stored DICOM loops with standard commercially available software (QLAB CMQ, Philips, Amsterdam, Netherlands). Images were searched for evidence of severe mitral, aortic, tricuspid and pulmonary regurgitation. The systolic and diastolic functions of the left ventricle (LV) were also assessed: LV end-diastolic diameter and volume, LV end-systolic diameter and volume, ejection fraction (Biplan Simpson), aortic time-velocity integration, tissue Doppler imaging, systolic and diastolic lateral (S_{LAT} and E_{LAT}) and septal (S_{SEPT} and E_{SEPT}) velocities, pulsed

Doppler transmitral E wave (Em) and mitral deceleration time.

Several markers were calculated: cardiac index, right-to-left ventricular end-diastolic diameter, Et/E_{RV} ratio, Em/E_{SEPT} ratio, Em/E_{LAT} ratio, Em/S_{SEPT} ratio and Em/S_{LAT} ratio.

Data collection

The data were collected in the 24 hours before LVAD implantation. The median period between admission and VAD implantation was 5.0 days (interquartile range, 2.0—7.0).

Outcomes

Patients were divided into three groups: LVAD patients without RVF, LVAD patients with RVF and patients for whom BiVAD implantation was planned. RVF was defined as the unplanned insertion of a right VAD (RVAD) or the use of an intravenous inotrope for 14 days after surgery [2—8,10,11].

Statistical analysis

Preoperative variables were compared between the three groups with GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA). Continuous variables were compared in unpaired *t* tests for normally distributed variables and Wilcoxon rank-sum tests for non-normally distributed variables. Chi^2 or Fisher's exact tests were used for categorical variables. Analysis of variance was used to compare continuous variables between groups. A P value < 0.05 was considered significant. Relative risks (RRs) are presented with 95% confidence intervals (CIs).

Multivariable analyses were based on stepwise multiple logistic regression analysis and were used to assess predictors of RVF. BiVAD patients were not included in multivariable analyses, because they were generally in a more critical state and the definition of postoperative RVF failure is more complex in this specific context. The following variables were identified as significant predictors ($P < 0.05$) in univariate analyses between the two LVAD groups and were, therefore, included in multivariable analyses: INTERMACS profile, basal RVEDD, minimal inferior vena cava diameter and Em/S_{LAT} ratio.

Bootstrap estimation with resampling from 1000 simulations (570 simulations for the RVF LVAD group and 430 simulations for the LVAD group without RVF) was used. Univariate and multivariable analysis were performed on bootstrap samples.

An ARVADE (assessment of right ventricular dysfunction predictors before the implantation of a left ventricular assist device in end-stage heart failure patients using echocardiographic measures) score was devised by rounding the exponentiated regression model coefficients of independent predictors of RVF to the nearest 0.5. A receiver operating characteristic curve was plotted for ARVADE score, and the area under the curve (AUC) was calculated. AUCs were also calculated for Michigan score and for the independent predictors of RVF.

Results

Population characteristics

During the study period, 67 patients received mechanical circulatory support. We excluded 18 patients because they had received a total artificial heart (11 patients) or because complete echocardiographic evaluations with strain rate imaging were not available (7 patients; all undergoing emergency implantation); thus, 49 patients were included in the study. Twenty-seven patients received the HeartWare HVAD (HeartWare), 15 patients received the HeartMate II (Thoratec) and seven patients received a Thoratec Paracorporeal BiVAD. Detailed results are shown in Table 1.

Characteristics of the population, according to the presence or absence of a BiVAD

The patients in the BiVAD group were more severely ill at the time of mechanical circulatory support implantation than those of the LVAD groups (Table 1). All BiVAD patients had an INTERMACS level 1 profile and a significantly higher Michigan score than the other patients. BiVAD patients had a significantly lower RV stroke work index and a decreased pulmonary capillary wedge pressure. Finally, concerning echocardiographic variables (Table 2), diastolic indices (Em, E_{LAT}, Em/E_{SEPT}, Em/S_{LAT} ratio and Em/S_{SEPT} ratio) were increased in the BiVAD population.

Post-implantation RVF in LVAD patients

Twenty-four LVAD patients (57%) developed RVF, 11 of whom required a temporary RVAD.

Outcome

Inhospital mortality rates were 4 of 7 (57%) in the BiVAD group, 8 of 24 (33%) in the LVAD with RVF group and 0 of 18 in the LVAD without RVF group ($P < 0.01$). The risk factors for death in hospital identified in the univariate analysis were RVF (RR 1.95, 95% CI 1.42—2.66; $P = 0.002$) and an INTERMACS level 1 profile (RR 1.96, 95% CI 1.09—3.52; $P = 0.049$).

Risk factors for RVF in LVAD patients

Clinical risk factors for RVF were INTERMACS level and preoperative mechanical ventilation (Table 1). Biological and haemodynamic characteristics and Michigan score were similar in patients with and without RVF.

The associations between preoperative echocardiographic characteristics and RVF are reported in Table 2. Variables assessing RV systolic function (S_{RV}, longitudinal strain and TAPSE) tended to be decreased in RVF patients. Univariate analysis identified the following echocardiographic measurements as risk factors for RVF: basal RVEDD, minimal inferior vena cava diameter, Em, Em/S_{LAT} ratio and Em/S_{SEPT} ratio.

Independent predictors of postoperative RVF

Multivariable analysis identified INTERMACS level 1, the Em/S_{LAT} ratio and the basal RVEDD as independent predictors

Table 1 Preoperative patient characteristics according to postoperative occurrence of RVF.

Characteristic	Study patients, ($n = 49$)	LVAD patients without RVF, ($n = 18$)	LVAD patients with RVF, ($n = 24$)	BiVAD patients, ($n = 7$)
Age (years)	56 [46–67]	60 [48–69]	52 [43–61]	51 [48–57]
Men	44 (90)	18 (100)	21 (88)	5 (71)
BMI (kg/m^2)	25.3 [22.4–27.2]	24.2 [22.7–26.9]	26.0 [22.3–37.0]	26.4 [21.6–28.7]
Ischaemic aetiology	23 (47)	10 (56)	9 (38)	2 (29)
History of COPD	5 (10)	3 (17)	2 (8)	0
Chronic renal insufficiency	24 (49)	11 (61)	9 (38)	2 (29)
Previous cardiac surgery	18 (37)	7 (39)	11 (46)	0
Resynchronization therapy	20 (41)	10 (56)	6 (25)	4 (57)
Bridge to transplantation	33 (67)	11 (61)	15 (63)	7 (100)
Preoperative mechanical ventilation	12 (25)	1 (6)	9 (38)[a]	2 (29)
Preoperative haemodialysis	9 (18)	3 (17)	3 (13)	3 (43)
Preoperative IABP	21 (43)	5 (28)[b]	11 (46)	6 (86)
Preoperative ECMO	4 (8)	1 (6)	3 (13)	0
Preoperative inotrope	47 (96)	16 (89)	24 (100)	7 (100)
SOFA score	4 [3–7]	3 [2–7]	4 [3–5]	7 [7–10]
SAPS II	30 [23–40]	24 [20–37][b]	29 [23–38]	35 [33–42]
Michigan score	3.0 [0–5.5]	2.3 [0.0–4.1][b]	2.8 [0.5–4.4][c]	8.5 [7.5–9.5]
INTERMACS level	1 [1–3]	3 [1–3][b]	1 [1–2][a]	1 [1]
Serum sodium concentration (mmol/L)	134 [129–136]	135 [128–139][b]	135 [131–137][c]	126 [125–132]
Blood urea nitrogen concentration (mg/dL)	76 [54–107]	80.0 [57.5–111.5]	76.0 [54.8–102.8]	111 [63.8–195.5]
Creatinine concentration (mg/dL)	1.5 [1.2–2.2]	1.8 [1.3–2.3]	1.3 [1.0–1.8]	2.3 [2.2–3.7]
CRP concentration (mg/L)	2.3 [1.0–7.8]	1.7 [0.3–6.2]	2.2 [1.1–6.9]	5.1 [4.4–7.2]
AST concentration (IU/L)	31 [25–62]	27 [22–42]	37 [31–49]	31.0 [21.3–185.5]
Bilirubin concentration (mg/dL)	1.7 [1.0–2.5]	1.4 [0.6–2.1][b]	1.6 [0.9–3.5][c]	3.6 [2.6–4.5]
INR	1.5 [1.2–2.3]	2.0 [1.3–2.5]	1.4 [1.1–2.3]	1.5 [1.3–2.0]
Haemoglobin concentration (g/dL)	11.9 [10.6–13.5]	12.6 [10.6–13.2]	11.6 [10.4–14.1]	11.8 [10.3–13.5]
Platelets (10^9/L)	194 [160–256]	183 [166–233]	232 [166–284]	156 [95–224]
Lactate concentration (mmol/L)	1.6 [1.3–2.5]	1.3 [1.0–1.7][b]	2.1 [1.6–3.1]	2.7 [1.4–3.0]
Heart rate (beats/min)	84 [70–102]	76 [64–83][b]	85 [69–105][c]	102 [98–120]
Mean systemic arterial pressure (mmHg)	70 [64–78]	65 [61–75]	65 [58–75]	72 [69–78]
Central venous pressure (mmHg)	16 [12–21]	19 [11–21]	15 [12–22]	16 [15–19]
sPAP (mmHg)	50 [42–62]	50 [47–58]	51 [36–64]	34 [33–54]
mPAP (mmHg)	35 [26–44]	35 [28–38]	38 [27–46]	27 [26–42]
PCWP (mmHg)	28 [19–30]	28 [27–31][b]	29 [16–38][c]	23 [19–27]
Cardiac index (L/min/m^2)	1.7 [1.4–1.9]	1.7 [1.4–2.0]	1.8 [1.5–2.3][c]	1.4 [1.1–1.6]
PVR (Dynes/s/cm^5/m^2)	183 [117–311]	127 [101–223]	193 [134–255]	131 [86–257]
RV stroke work index (mmHg/m^2/L)	2.9 [2.0–4.2]	8.7 [6.7–12.5][b]	5.6 [4.3–7.4][c]	2.7 [2.1–3.5]

Data are median [interquartile range] or number (%). AST: aspartate aminotransferase; BiVAD: biventricular assist device; BMI: body mass index; COPD: chronic obstructive pulmonary disorder; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; INR: international normalized ratio; LVAD: left ventricular assist device; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RV: right ventricular; RVF: RV failure; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; sPAP: systolic pulmonary artery pressure.

[a] $P < 0.05$ for comparison between LVAD patients with and without RVF.

[b] $P < 0.05$ for comparison between BiVAD patients and LVAD patients without RVF.

[c] $P < 0.05$ for comparison between BiVAD patients and LVAD patients with RVF.

Table 2 Preoperative echocardiographic data, according to the postoperative occurrence of RVF.

Variables	Patients without RVF, ($n = 18$)	RVF patients, ($n = 24$)	BiVAD patients, ($n = 7$)
Right heart			
Parasternal RVEDD (mm)	39 [35–44]	40 [34–45]	45 [38–42]
Basal RVEDD (mm)	42 [38–49]	51 [42–56][a]	45 [43–51]
FAC (%)	21 [16–30]	28 [21–36]	23 [20–33]
S_{RV} (cm/s)	12.6 [9.5–14.2][b]	10.0 [7.8–11.9]	9.0 [7.9–11.5]
RV longitudinal strain (%)	9.4 [8.6–11.5]	8.9 [6.9–10. 3]	6.8 [6.4–7.3]
TAPSE (mm)	17 [13–22]	16 [12–20]	14 [12–18]
E_{RV} (cm/s)	11.6 [9.3–15.3][b]	12.6 [9.0–15.0][c]	16.7 [14.9–19.3]
RA area (cm^2)	24 [20–32]	25 [19–35]	35 [27–38]
Maximal IVC diameter (mm)	22 [19–26][b]	24 [20–30][c]	28 [27–33]
Minimal IVC diameter (mm)	15 [16–26][b]	20 [16–29][a,c]	28 [20–29]
Et (cm/s)	49 [35–67]	49 [34–64]	62 [46–78]
Severe TR	1 (6)	6 (25)	2 (29)
sPAP (mmHg)	56 [46–63]	54 [38–67]	46 [44–52]
Et/E_{RV}	4.7 [3.8–5.6]	4.6 [3.3–5.3]	3.9 [3.1–4.9]
RVEDD-to-LVEDD ratio	0.54 [0.47–0.63]	0.48 [0.44–0.64]	0.58 [0.47–0.63]
Left heart			
LVEDD (mm)	72 [70–76]	77 [67–84]	68 [67–78]
LVEDV (mL)	250 [184–308]	300 [222–415]	254 [193–355]
LVESV (mL)	204 [180–300]	233[189–314]	212 [197–259]
LVEF (%)	17.2 [12.3–23.8]	18.4 [10.6–25.1]	20.7 [15.9–22.6]
S_{SEPT} (cm/s)	4.1 [3.6–6.5]	4.1 [3.2–4.7]	3.5 [3.0–5.5]
S_{LAT} (cm/s)	5.3 [4.7–6.8]	4.5 [3.8–5.4]	5.6 [4.8–7.0]
E_{SEPT} (cm/s)	6.8 [4.4–9.3]	6.0 [4.4–8.0]	7.0 [4.5–8.0]
E_{LAT} (cm/s)	10.3 [5.2–14.6][b]	9.5 [7.6–13.9][c]	17.5 [11.5–23.2]
LA area (cm^2)	33 [30–45]	32 [26–47]	39 [29–41]
Aortic VTI (cm)	10 [8–12]	11 [8–14]	9 [5–11]
Cardiac index ($L/min/m^2$)	1.9 [1.4–2.1]	1.6 [1.1–2.1]	1.4 [1.3–2.4]
Severe MR	1 (6)	3 (13)	3 (43)
Mitral deceleration time (ms)	95 [88–135]	135 [125–145]	105 [85–132]
Em (cm/s)	86 [70–93][b]	105 [84–132][a]	99 [91–132]
Em/E_{SEPT}	12.5 [9.4–18.8][b]	16.9 [13.0–26.1]	18.2 [12.2–22.0]
Em/E_{LAT}	8.2 [5.6–12.6]	10.3 [8.3–12.7]	7.2 [4.0–8.7]
Em/S_{SEPT}	17.5 [12.3–26.2][b]	27.1 [20.8–32.0][a]	28.7 [20.9–33.3]
Em/S_{LAT}	16.3 [10.5–18.2][b]	24.4 [18.2–29.2][a,c]	19.1 [13.2–22.2]

Data are median [interquartile range] or number (%). BiVAD: biventricular assist device; E_{RV}: tissue Doppler RV diastolic velocity; E_{LAT}: tissue Doppler lateral diastolic velocity; Em: pulsed Doppler transmitral E wave; E_{SEPT}: tissue Doppler septal diastolic velocity; Et: pulsed Doppler tricuspid E wave; FAC: RV fractional area change; IVC: inferior vena cava; LA: left atrial; LV: left ventricular; LVAD: LV assist device; LVEDD: LV end-diastolic diameter; LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; LVESV: LV end-systolic volume; MR: mitral regurgitation; RA: right atrial; RV: right ventricular; RVEDD: RV end-diastolic diameter; RVF: RV failure; RVSWI: RV stroke work index; S_{LAT}: tissue Doppler lateral systolic velocity; sPAP: systolic pulmonary arterial pressure; S_{RV}: tissue Doppler RV systolic velocity; S_{SEPT}: tissue Doppler septal systolic velocity; TAPSE: maximal systolic excursion of the tricuspid annulus; TR: tricuspid regurgitation; VTI: velocity-time integral.

[a] $P < 0.05$ for comparison between LVAD patients with and without RVF.

[b] $P < 0.05$ for comparison between BiVAD patients and LVAD patients without RVF.

[c] $P < 0.05$ for comparison between BiVAD patients and LVAD patients with RVF.

Table 3 Independent predictors of post-implantation RVF.

Factors	RR for RVF	95% confidence interval	*P* value
$Em/S_{LAT} \geq 18.5$	2.78	1.38–5.60	0.001
Basal RVEDD $\geq$ 50 mm	1.97	1.21–3.20	0.008
INTERMACS level 1	1.74	1.04–2.91	0.04

Em: pulsed Doppler transmitral E wave; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; RR: relative risk; RVEDD: right ventricular end-diastolic diameter; RVF, right ventricular failure; S_{LAT}: tissue Doppler lateral systolic velocity.

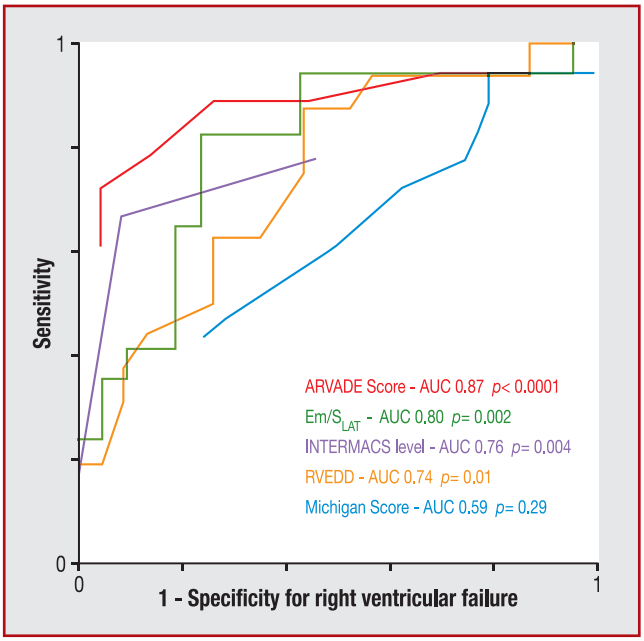

Figure 1. Receiver operating characteristic curves for the ARVADE (assessment of right ventricular dysfunction predictors before the implantation of a left ventricular assist device in end-stage heart failure patients using echocardiographic measures) score, the Michigan right ventricular score and independent right ventricular failure predictors. AUC: area under the curve; Em: pulsed Doppler transmitral E wave; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; RVEDD: right ventricular end-diastolic diameter; S_{LAT}: tissue Doppler lateral systolic velocity.

of RVF (Table 3). These results were confirmed by bootstrapping.

ARVADE score

An ARVADE score was calculated as the sum of points attributed according to the values of three variables: 3.0 points for $Em/S_{LAT} \geq 18.5$, 2.0 points for basal RVEDD $\geq$ 50 mm and 1.5 points for INTERMACS level 1. An ARVADE score > 3.0 was predictive of post-implantation RVF, with a sensitivity of 89% and a specificity of 74%.

Receiver operating characteristic curves for the ARVADE score, the independent RVF predictors identified in our study and the Michigan score are shown in Fig. 1. In our population, the Em/S_{LAT} ratio was the independent predictor with the best AUC. The ARVADE score outperformed the independent factors identified in our study and the Michigan score in predicting the occurrence of postoperative RVF (Fig. 1).

Discussion

The findings of this prospective study indicate that Em/S_{LAT} was the index that most accurately predicted RVF after LVAD implantation, showing that LV echocardiographic variables were the best predictors of post-LVAD RVF. A straightforward score combining the results of preoperative clinical (INTERMACS level 1) and echocardiographic assessments (Em/S_{LAT} ratio and basal RVEDD) may be a useful predictor of RVF.

RVF incidence

RVF developed after LVAD implantation in 57% of our patients. This figure is high but consistent with published findings.

Different definitions of postoperative RVF have been used in different studies. When we reviewed all studies reporting postoperative RVF (Table 4) [3–5,7–10,16–21], we found at least five definitions of this condition: (A) unplanned insertion of an RVAD or the use of an intravenous inotrope for 14 days after surgery; (B) unplanned insertion of an RVAD or the use of an intravenous inotrope for at least 14 days after surgery or discharge from hospital on inotrope treatment; (C) planned insertion of a BiVAD; (D) unplanned insertion of an RVAD; and (E) presence of two of the following criteria in the first 48 hours after surgery: mean arterial pressure $\leq$ 55 mmHg, central venous pressure $\geq$ 16 mmHg, mixed venous saturation $\leq$ 55%, cardiac index < 2 L/min/m^2, inotropic support score > 20 units or the need for an RVAD. RVF incidence was between 9 and 49%, depending on the definition used. The definition of postoperative RVF as unplanned insertion of an RVAD yielded a lower incidence, whereas incidences of almost 50% were reported for the definition of RVF as use of an intravenous inotrope for 14 days after surgery or the unplanned insertion of an RVAD. For LVAD patients developing RVF, we obtained an incidence of RVF of 57%, consistent with the three largest studies, which reported RVF incidences of 40% to 50% [3,8,21]. We used the most widely used definition here [4,17,20,21].

RV function in LVAD recipients

After LVAD implantation, adequate RV function is required for pulmonary output and sufficient return to the LV to supply the pump. Nevertheless, in cases of end-stage heart failure and/or cardiogenic shock, there is some degree of RV dysfunction before surgery, clearly increasing the risk of RVF [12,13].

RV behaviour after LVAD implantation is difficult to predict. In most patients, RV function improves because the afterload is decreased [9,22]. However, complex haemodynamic modifications, caused by the leftward shift of the interventricular septum, may affect RV function during LVAD implantation. RV dysfunction may also be favoured by postoperative RV distension, caused by the perioperative use of blood products and crystalloids, and intraoperative RV injury [18].

RVF in LVAD recipients results in higher mortality [2]. In our study, RVF was associated with inhospital mortality. It is, therefore, important to identify those patients who are likely to develop RVF.

Assessment of RV function

It is difficult to predict the adequacy of RV function and its capacity to respond to variations in loading conditions in LVAD patients before surgery.

Table 4 Definitions and incidences of postoperative RVF in previous studies.

Study	Definition of RVF	Patient numbers	Study period	Incidence of RVF[a]
Fukamachi et al. [19]	D	100	1991—1996	11 (11)
Kavarana et al. [20]	A	69	1996—1999	21 (30.4)
Ochiai et al. [5]	D	245	1991—2001	23 (9)
Dang et al. [16]	A	108	1996—2004	42 (39)
Potapov et al. [3]	C	970	1987—2006	485 (49)
Matthews et al. [4]	A	197	1996—2006	68 (35)
Potapov et al. [10]	E	54	1998—2006	8 (17)
Fitzpatrick et al. [18]	C	266	1995—2007	99 (37)
Deng et al. [17]	Unclear	542	2002—2004	44 (11)
Patel et al. [21]	A	73	2000—2007	29 (40)
Kormos et al. [7]	B	484	2005—2008	98 (20)
Kukucka et al. [9]	E	115	2007—2009	15 (13)
Grant et al. [8]	A	117	2007—2011	47 (40)

A: unplanned insertion of a right ventricular assist device (RVAD) or the use of an intravenous inotrope for 14 days after surgery; B: unplanned insertion of an RVAD or the use of an intravenous inotrope for at least 14 days after surgery or hospital discharge on inotrope treatment; C: planned insertion of a biventricular assist device; D: unplanned insertion of an RVAD; E: presence of two of the following criteria in the first 48 hours after surgery: mean arterial pressure $\leq$ 55 mmHg, central venous pressure $\geq$ 16 mmHg, mixed venous saturation $\leq$ 55%, cardiac index < L/min/m^2, inotropic support score > 20 units or the need for an RVAD; RVF: right ventricular failure.

[a] Data are number (%).

Limitations of biological measurements

Previous studies identified congestion biomarkers, including urea, creatinine, aminotransferase and bilirubin concentrations, and prothrombin time as risk factors for RVF development [4]. However, these markers are not specific for RVF and may reflect poor kidney perfusion and liver congestion in the context of severely decompensated global heart failure. In our population of patients selected for LVAD, neither biological markers nor the Michigan RV score was associated with the post-LVAD risk of RVF. This may be because a high Michigan RV score is used as a criterion for selecting patients for planned BiVAD implantation at our institution. Thus, in our study, the Michigan RV score was higher in the planned BiVAD group than in the other groups. Alternatively, these results may reflect the timing of biological data collection. We recorded biological data on the day of implantation, in patients stabilized, as required, with inotrope treatment. The status of almost all patients was therefore better than that at admission. Previous studies using the Michigan RV score to predict the occurrence of RVF after LVAD implantation did not report the timing of biological data collection [4,8].

Invasive haemodynamic measurements

Pulmonary arterial blood pressure, pulmonary vascular resistance, central venous blood pressure and RV stroke work index have been identified as risk factors for RVF [5,7]. However, the results of different studies diverge and, in our study, no invasive haemodynamic measurement discriminated between LVAD patients with and without RVF, although the RV stroke work index was lower in BiVAD patients. The use of invasive haemodynamic indices to select patients for BiVAD implantation might account for our results.

The value of echocardiographic assessments

Transthoracic echocardiography is non-invasive and readily available at the patient's bedside. However, echocardiographic assessment is particularly difficult for the RV, because of its complex geometry [15].

RV function variables

Some indices assessing RV systolic function have been identified as predictors of RVF after LVAD implantation; they include TAPSE < 7.5 mm, RV fractional area shortening and longitudinal strain < −9.6% [8—11]. In our population, these markers were not discriminating. There are several possible reasons for this: previous cardiac surgery (a factor present in 43% of our patients) can interfere with RV systolic indices and/or function [22], RV function measurements are load dependent and load conditions differed before and after LVAD implantation. Uncertainties concerning delineation of the RV endocardium in some patients may have contributed to our negative results [15].

Basal RVEDD is associated with the risk of developing RVF after LVAD implantation. Thus in our hands, the echocardiographic measurements predictive of RVF after LVAD implantation were not those assessing RV systolic function, but those reflecting RV congestion [9,10].

Pulmonary circulatory function variables

Chronic sustained increases in blood pressure in the pulmonary capillaries caused by pulmonary venous congestion and pulmonary venous hypertension lead to RV overload and failure. Variables assessing pulmonary circulatory function have been reported in previous studies aiming to predict RVF after LVAD implantation [4,5,13,18—20]. In a retrospective analysis assessing 337 patients, pulmonary blood pressure and pulmonary capillary wedge pressure were found to be

the most important haemodynamic determinants of RV function in both decompensated and stable systolic heart failure [13]. In our study, among echocardiographic variables, systolic pulmonary pressure failed to differentiate between the different groups, whereas variables assessing the diastolic function of the LV were identified as risk factors for postoperative RVF.

LV function variables

One study to date has highlighted the potential value of assessing LV function for the evaluation of RV function and the identification of patients at risk of RVF after LVAD implantation [12]. This study reported that LV measurements (LV diameters, LV ejection fraction and left atrial diameter/LV end-diastolic diameter ratio) could help to identify patients at risk of developing postoperative RVF.

In our study, some variables assessing LV function were identified as risk factors for RVF after LVAD implantation: Em, Em/S_{SEPT} ratio and Em/S_{LAT} ratio.

The E wave is dependent on fast passive filling and diastolic LV function; a high E wave reflects high capillary wedge pressures and, indirectly, a high RV afterload [23]. A study in 16 anaesthetized dogs with closed chests showed that the E wave was strongly related to LV contractility and afterload ($R = 0.906$) [24]. This relationship led the authors to conclude that relaxation was closely related to systolic function. We considered the E wave to reflect not only high capillary wedge pressures, but also severe impairments of LV contractility.

Similarly, early E_{LAT}s assessing LV relaxation were also found to differ between BiVAD and LVAD patients.

The normalization of the E wave value by longitudinal function makes a major contribution to the evaluation of LV filling pressure: Em/E_{LAT} and Em/E_{SEPT} ratios [23]. Here, we have expanded this concept slightly, by calculating the Em/S_{LAT} and Em/S_{SEPT} ratios.

The Em/S_{LAT} ratio was the best echocardiographic index for identifying postoperative RVF. A low S_{LAT} reflects severe LV systolic dysfunction. Moreover, it is a load-independent measure [25].

We would expect that the interventricular septum systolic impairment would be more relevant than the lateral wall and the Em/S_{SEPT} stronger than the Em/S_{LAT} for predicting RVF failure after LVAD implantation. The RV is linked to the LV via the shared septal wall, the pericardial space and the mutually encircling epicardial fibres, and because the RV free wall is attached to the anterior and posterior septum [26]. We find, paradoxically, that Em/S_{LAT}, reflecting LV function, was the index that most accurately predicted RVF after LVAD implantation, showing the strong contribution of the LV to RVF.

RV dysfunction is a consequence of LV dysfunction in cases of end-stage heart failure ischaemic cardiomyopathy, and these two dysfunctions progress together in cases of dilated cardiomyopathy.

As it is difficult to assess RV function, an assessment of LV systolic function can be used to evaluate RV function. LV echocardiographic variables are not affected by cardiac surgery [22]. It is, therefore, not particularly surprising that a LV measurement was the best predictor of RVF after LVAD implantation. Nevertheless, this factor alone does not provide a satisfactory prediction of RVF after LVAD implantation.

The usefulness of a score for predicting RVF in LVAD patients

The large number of factors responsible for RVF after LVAD implantation justify the development of scores for predicting the risk of postoperative RVF [4,5,18].

Our score is a simple tool combining one clinical prognostic marker—the INTERMACS level [14]—and three easily-obtained echocardiographic measurements reflecting RV congestion and LV function. Our score outperformed the Michigan score in our study; these two scores are complementary. Critically ill patients with a high Michigan score should undergo BiVAD implantation. The difficulty in routine clinical practice is identifying the 'less severely ill' patients likely to develop postoperative RVF. The ARVADE score could be useful for this. Prospective validation of this tool with a large population is required before its use can be generalized.

Study limitations

The definition of RVF remains problematic for the classification of patients. Indeed, the definition 'unplanned insertion of an RVAD or the use of an intravenous inotrope for 14 days postoperatively' covers a very large and heterogeneous population.

Other limitations of our study include the small number of patients and the monocentric character of our cohort.

Conclusion

The occurrence of RVF following LVAD implantation is a severe complication, associated with excess mortality.

The echocardiographic variables assessing the LV were the best predictors of post-LVAD RVF, showing the strong contribution of the LV to RVF.

The ARVADE score, calculated as the sum of scores for one clinical prognostic marker (INTERMACS level) and three easily obtainable echocardiographic measures (Em/S_{LAT} and basal RVEDD) reflecting LV global systolic and diastolic dysfunction and RV congestion, may facilitate the identification of suitable patients for device implantation.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Strueber M, O'Driscoll G, Jansz P, et al. Multicenter evaluation of an intrapericardial left ventricular assist system. J Am Coll Cardiol 2011;57:1375—82.

[2] Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation 2007;116:497—505.

[3] Potapov EV, Loforte A, Weng Y, et al. Experience with over 1000 implanted ventricular assist devices. J Cardiovasc Surg (Torino) 2008;23:185—94.

[4] Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163—72.

[5] Ochiai Y, McCarthy PM, Smedira NG, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation 2002;106:I198—202.

[6] Tsukui H, Teuteberg JJ, Murali S, et al. Biventricular assist device utilization for patients with morbid congestive heart failure: a justifiable strategy. Circulation 2005;112:I65—72.

[7] Kormos RL, Teuteberg JJ, Pagani FD, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg 2010;139:1316—24.

[8] Grant AD, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 2012;60:521—8.

[9] Kukucka M, Stepanenko A, Potapov E, et al. Right-to-left ventricular end-diastolic diameter ratio and prediction of right ventricular failure with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2011;30:64—9.

[10] Potapov EV, Stepanenko A, Dandel M, et al. Tricuspid incompetence and geometry of the right ventricle as predictors of right ventricular function after implantation of a left ventricular assist device. J Heart Lung Transplant 2008;27:1275—81.

[11] Puwanant S, Hamilton KK, Klodell CT, et al. Tricuspid annular motion as a predictor of severe right ventricular failure after left ventricular assist device implantation. J Heart Lung Transplant 2008;27:1102—7.

[12] Kato TS, Farr M, Schulze PC, et al. Usefulness of two-dimensional echocardiographic parameters of the left side of the heart to predict right ventricular failure after left ventricular assist device implantation. Am J Cardiol 2012;109:246—51.

[13] Guglin M, Win CM, Darbinyan N, Wu Y. Predictors of right ventricular systolic dysfunction in compensated and decompensated heart failure. Congest Heart Fail 2012;18:278—83.

[14] Holman WL. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): what have we learned and what will we learn? Circulation 2012;126:1401—6.

[15] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685—713 [quiz 86—8].

[16] Dang NC, Topkara VK, Mercando M, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant 2006;25:1—6.

[17] Deng MC, Edwards LB, Hertz MI, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report—2005. J Heart Lung Transplant 2005;24:1182—7.

[18] Fitzpatrick 3rd JR, Frederick JR, Hsu VM, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. J Heart Lung Transplant 2008;27:1286—92.

[19] Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181—4.

[20] Kavarana MN, Pessin-Minsley MS, Urtecho J, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg 2002;73:745—50.

[21] Patel ND, Weiss ES, Schaffer J, et al. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. Ann Thorac Surg 2008;86:832—40 [discussion 40].

[22] Wenaweser P, O'Sullivan CJ. Aortic stenosis and the right heart at risk: is transcatheter aortic valve implantation the better option? Heart 2012;98:1265—6.

[23] 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—7.

[24] Hansen DE, Daughters 2nd GT, Alderman EL, Ingels NB, Stinson EB, Miller DC. Effect of volume loading, pressure loading, and inotropic stimulation on left ventricular torsion in humans. Circulation 1991;83:1315—26.

[25] Aissaoui N, Guerot E, Combes A, et al. Two-dimensional strain rate and Doppler tissue myocardial velocities: analysis by echocardiography of hemodynamic and functional changes of the failed left ventricle during different degrees of extracorporeal life support. J Am Soc Echocardiogr 2012;25:632—40.

[26] Gorcsan 3rd J, Murali S, Counihan PJ, Mandarino WA, Kormos RL. Right ventricular performance and contractile reserve in patients with severe heart failure. Assessment by pressure-area relations and association with outcome. Circulation 1996;94:3190—7.