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Right heart catheterization in advanced systolic heart failure. What are the most useful haemodynamic parameters for risk stratification?

Abbreviated title: Right heart catheterization in advanced systolic heart failure

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Summary

Background. – Previous studies have shown that pulmonary hypertension is a predictor of mortality in patients with systolic heart failure (SHF). Persistent pulmonary hypertension after a reactivity test is associated with a worse outcome after transplantation. Recent studies have shown the utility of different haemodynamic parameters.

Aims. – To define best haemodynamic parameters for risk stratification in patients with advanced systolic heart failure.

Methods. – We included 425 consecutive patients who underwent a right heart catheterization with an inotropic challenge if indicated.

Results. – During a median (interquartile range) follow-up of 1.67 (0.49–4.49) years, there were 151 major cardiac events (126 cardiovascular deaths and 25 post-operative deaths after ventricular assist device implantation or heart transplantation). The most powerful independent predictors of major cardiac events were baseline right atrial pressure (RAP) (hazard ratio [HR] 1.09, 95% confidence interval [CI] 1.06–1.12; $P < 0.0001$) and baseline pulmonary vascular resistance (PVR) (HR 1.10; 95% CI 1.03–1.17; $P = 0.002$). After inotropic challenge, the only independent predictor was mean pulmonary arterial pressure (mPAP) (HR 1.06; 95% CI 1.03–1.09; $P < 0.0001$). The combination of PVR (\leq or $>$ 3 Wood units), RAP ($<$ or \geq 9 mmHg) and mPAP after the inotropic challenge (\leq or $>$ 30 mmHg) was the best predictor of major events.

Conclusion. – We suggest using a simple algorithm based on baseline PVR, baseline RAP and mPAP after the inotropic challenge for the risk stratification of stable patients with advanced systolic heart failure.

Résumé

Contexte. – Des études précédentes ont démontré que l'hypertension pulmonaire prédisait la mortalité chez les patients avec une insuffisance cardiaque systolique. Une hypertension pulmonaire persistante après un test de réactivité est associée à plus d'événements après une transplantation. Des études récentes ont montré l'intérêt de différents paramètres hémodynamiques.

Objectifs. – Définir les paramètres hémodynamiques les plus puissants pour la stratification du risque des patients en insuffisance cardiaque systolique avancée.

Méthodes. – Nous avons inclus 425 patients consécutifs qui ont eu un cathétérisme cardiaque droit avec un test aux inotropes si nécessaire.

Résultats. – Pendant un suivi médian (écart interquartile) de 1.67 (0.49--4.49) ans, il y a eu 151 événements cardiaques majeurs (126 décès cardio-vasculaires et 25 décès post-opératoires après soit l'implantation d'une assistance ventriculaire soit une transplantation). Les paramètres prédicteurs indépendants les plus puissants étaient la pression auriculaire droite (POD) « (hazard ratio "[HR] 1.09 ; intervalle de confiance [IC] à 95 % 1.06–1.12 ; $P < 0.0001$) et les résistances vasculaires pulmonaires (RVP) (HR 1.10 ; IC 95 % 1.03–1.17 ; $P = 0.002$). Sous inotropes, le seul paramètre indépendant était la pression pulmonaire moyenne (mPAP) (HR 1.06 ; IC 95 % 1.03–1.09 ; $P < 0.0001$). La combinaison des RVP (\leq or $>$ 3 unités Wood), de la POD ($<$ or \geq 9 mmHg) et de la mPAP sous inotropes (\leq or $>$ 30 mmHg) était le prédicteur le plus puissant des événements cardio-vasculaires majeurs.

Conclusions. – On suggère l'utilisation d'un algorithme simple basé sur les RVP et la POD en base et la mPAP sous inotropes pour la stratification du risque des patients stables avec une insuffisance cardiaque systolique avancée.

KEYWORDS

Advanced heart failure;

Pulmonary hypertension;

Right heart catheterization;

Heart transplantation;

Systolic heart failure

MOTS CLÉS

Insuffisance cardiaque avancée ;

Hypertension pulmonaire ;

Cathétérisme cardiaque droit ;

Transplantation cardiaque ;

Insuffisance cardiaque systolique

Abbreviations: CI, confidence interval; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HR, hazard ratio; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SD, standard deviation; SHF, systolic heart failure; SvO₂, mixed venous oxygen saturation; TPG, transpulmonary pressure gradient; VAD, ventricular assist device; WU, Wood units.

Introduction

Heart failure is a major health care problem [1,2] and patients referred for heart transplantation represent a limited number of patients [3]. In patients with advanced left ventricular systolic dysfunction, pulmonary hypertension (PH) is a common and severe complication [4]. PH increases the risk of cardiovascular events in patients with heart failure and the risk of post-operative death after heart transplantation [5-9]. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) has shown that the use of right heart catheterization in patients with advanced systolic heart failure (SHF) was not useful for their therapeutic management [10]. Right heart catheterization is now mainly performed in patients before listing them for heart transplantation.

Besides pulmonary pressure, some studies have examined other haemodynamic parameters, such as transpulmonary pressure gradient (TPG), the difference between mean pulmonary arterial pressure (PAP) (mPAP) and mean pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PVR) [11]. As these parameters are correlated, some authors have analysed other haemodynamic parameters, namely diastolic pulmonary gradient [12], proportional pulmonary arterial pulse pressure [13], pulmonary arterial compliance [14] and right- and left- sided filling pressure mismatch [15]. However, there are conflicting data concerning the prognostic impact of these parameters [7,8,16] and no study has compared all of these haemodynamic parameters.

Current guidelines recommend that a reactivity test is performed, with either vasodilators or inotropes, in patients with significant PH [17]. In some patients, PH is not considered to be directly related to the increase in the left ventricular filling pressure (passive PH) but related to a pulmonary vascular disease leading to a disproportional increase in pulmonary pressure (reactive or out-of-proportion PH). It is generally accepted that the presence of fixed elevated PVR, defined as 'persistent despite a reactivity test', is a contraindication to heart transplantation [18]. Such patients are at a greater risk of right ventricular failure and death after heart transplantation.

The main aim of our study was to determine the best prognostic haemodynamic parameters in stable patients undergoing a modern treatment for SHF and admitted with an indication for either heart transplantation or ventricular assist device (VAD) implantation. The secondary objective was to analyse the prognostic impact of the response to the reactivity test. Most previous studies have analysed the impact of haemodynamic parameters on major events either in patients with chronic SHF

or during the post-operative period after either heart transplantation or VAD implantation [6,11,19,20]. We analysed the impact of haemodynamic parameters on both kinds of events: post-operative death after either heart transplantation or VAD implantation and cardiovascular death in patients mostly on the heart transplant waiting list.

Methods

We included consecutive patients referred to our institution for possible heart transplantation or VAD implantation between 2000 and 2014 with the exception of patients with complex congenital heart disease. Patients were included if they were ambulatory, clinically stable and receiving optimal medical therapy with maximal tolerated doses of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists (before 2010, in patients in New York Heart Association [NYHA] class III–IV; after 2010, in all patients, without contraindications).

The study conforms with the principles outlined in the Declaration of Helsinki and all patients provided signed informed consent for the collection and use of their data for scientific purposes.

Right heart catheterization was performed by heart failure specialists using a 6 French Swan-Ganz catheter that was placed under fluoroscopic guidance from either a right antecubital vein or a femoral vein. The correct position of the catheter was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms. The manometer was zeroed at the level of the midaxillary line. We measured right atrial pressure (RAP), PAP and PCWP. mPAP was determined electronically as the mean of the area under pressure curves after manual correction of systolic or diastolic PAP if indicated. All measures were the mean of several beats during quiet breathing. Cardiac output was measured by the thermodilution technique. The mean of 3–6 measures with a difference $\leq 10\%$ were used (≥ 5 in atrial fibrillation). Mixed venous oxygen saturation was measured from blood drawn from the pulmonary artery. In our institution, a reactivity test with inotropes is performed in patients with a PVR > 3 Wood units (WU). We started with dobutamine at an infusion rate of 10 $\mu\text{g}/\text{kg}/\text{min}$ over 10 minutes, which was increased to 20 $\mu\text{g}/\text{kg}/\text{min}$ in case of an unsatisfactory response (cardiac output increase $< 10\%$ or PVR > 3 WU). If neither worked, the last step was the association of dobutamine with a bolus of milrinone (50 $\mu\text{g}/\text{kg}$) for 10 minutes.

Definitions

Various parameters were calculated using the following formulae:

- $PVR = (mPAP - PCWP) / \text{cardiac output}$
- $TPG = mPAP - PCWP$
- Diastolic pulmonary gradient = diastolic PAP - PCWP
- Stroke volume = cardiac output / heart rate
- Pulmonary arterial pulse pressure (PAPP) = systolic PAP - diastolic PAP
- Pulmonary arterial compliance = stroke volume / PAPP
- Per cent of proportional PAPP PPAPP = $(PAPP / \text{systolic PAP}) \times 100$
- Right ventricular stroke work index (RVSWI) = $(\text{cardiac index} / \text{heart rate}) \times (mPAP - RAP) \times 13.6$

The right- and left-sided filling pressure mismatch was estimated by RAP/PCWP. Patients were classified as concordant when RAP < 10 mmHg and PCWP < 22 mmHg, high concordant when RAP ≥ 10 mmHg and PCWP ≥ 22 mmHg, high right mismatch when RAP ≥ 10 mmHg and PCWP < 22 mmHg and high left mismatch when RAP < 10 mmHg and PCWP ≥ 22 mmHg [21].

Statistical analyses

Results are expressed as mean ± standard deviation (SD) or as median (interquartile range [IQR]) for parameters not normally distributed. Discrete variables were compared using chi-square test.

Comparisons between quantitative variables were performed by either a Student's *t* test or by a non-parametric Mann and Whitney test, as appropriate. Comparisons of haemodynamic parameters at baseline and at the end of the reactivity test were performed by either paired Student's *t* test or a non-parametric Wilcoxon test. Follow-up was performed by direct examination or contact with the general practitioner.

Major cardiac events included cardiovascular death and death during the hospital stay for heart transplantation or VAD implantation (left VAD or bi VAD). Survivors of urgent (defined as United Network for Organ Sharing status 1) or elective transplantations, urgent or elective VAD implantation and patients with non-cardiac-related deaths were censored at the time of the event. Survival was estimated with the Kaplan–Meier method and differences were tested with a log-rank test. The proportional hazards assumption was tested using log-minus-log-plots. Univariate Cox proportional

hazards analyses were performed to determine predictors of survival. As most of the parameters were highly correlated, bivariate analyses were performed and parameters with the highest Wald statistics were selected. Multivariable Cox analyses were performed to select independent predictors of survival. The aim of our study was not to determine independent prognostic variables in advanced SHF using clinical, biological and morphological variables. Rather, the aim was to determine independent haemodynamic predictors. Thus, we only included haemodynamic variables in our multivariable analyses. We performed analyses with quantitative and qualitative parameters at baseline, after the inotropic challenge and with the combination of qualitative parameters at baseline and after the inotropic challenge. Best cut-off values were determined by receiver operating characteristic curve analyses. The incremental prognostic value of mPAP to PVR after the inotropic challenge was assessed using net reclassification improvement. For multivariable analyses, we chose the model with the highest global Wald statistics. Independent hazard ratios (HRs) are presented with 95% confidence intervals (CIs). $P \leq 0.05$ was considered statistically significant. Statistics were performed with the SPSS software version 15.0 (Chicago, Illinois).

Results

The clinical characteristics and treatments of the 425 consecutive patients are presented in [Table 1](#), while haemodynamic characteristics are presented in [Table 2](#).

Inotropic challenge

At baseline, 145 patients had $PVR > 3$ WU. The inotropic challenge was not performed in 26 patients due to electrical instability ($n = 3$), clinician's decision because of borderline results (systolic PAP ≤ 50 mmHg [$n = 6$] or TPG ≤ 13 mmHg [$n = 3$]) or contraindications to heart transplantation found before catheterization ($n = 14$) (mainly significant peripheral vascular disease and/or significant pulmonary disease and no VAD indication at that time). Haemodynamic results of the inotropic challenge in the remaining 119 patients are summarized in [Table 3](#). Inotropes significantly increased cardiac index and mixed venous oxygen saturation (SvO₂), RVSWI, pulmonary arterial compliance, PPAPP and heart rate and decreased all pressures and PVR. TPG, RAP/PCWP, PAPP and systolic blood pressure were unchanged.

Survival analysis

During a median (IQR) follow-up of 1.67 (0.49–4.49) years, there were 126 cardiovascular deaths (69 heart failure deaths, 49 sudden cardiac deaths and eight other cardiac deaths) and 24 non-cardiovascular deaths. Overall, 140 patients had a heart transplantation, 31 of which were urgent and 22 patients died during their hospitalization; 26 patients had VAD implantation, of whom 3 died during their hospitalization. Major cardiac events ($n = 151$) were a combination of cardiovascular deaths ($n = 126$) and post-operative deaths after VAD implantation ($n = 3$ [right ventricular dysfunction or multiorgan dysfunction syndrome]) or heart transplantation ($n = 22$ [19 right ventricular dysfunction or acute graft failure, two acute renal failure, one haemorrhagic stroke]). The mortality rate of our population was 17% at 1 year and 26% at 2 years.

Haemodynamic predictors of major events: quantitative parameters

Baseline haemodynamic characteristics of the patients without and with a major event and univariate predictors are presented in [Table 2](#). After inotropic challenge, the best univariate predictors of survival were mPAP, systolic PAP and PVR ([Table A.1](#)). Haemodynamic parameters were highly correlated and [Tables A.2](#) and [A.3](#) show the different coefficients of correlation at baseline and after inotropic challenge, respectively. [Table 4](#) shows the most powerful models of non-correlated independent predictors of survival. At baseline, RAP, PVR and cardiac index were independent predictors. After inotropic challenge, the only independent predictor of survival was mPAP. All the other models were less powerful for predicting survival ([Table A.4](#)). Diastolic pulmonary gradient, pulmonary arterial compliance, PAPP, PPAPP, RAP/PCWP, RAP + PCWP and RVSWI were not, or were less predictive of, survival.

Haemodynamic predictors of major events: qualitative parameters

The best cut-off values were 9 mmHg for RAP and 3 WU for PVR at baseline, and 3 WU for PVR and 30 mmHg for mPAP after inotropic challenge. [Fig. A.1](#) shows the survival curves according to baseline RAP. [Fig. 1A](#) shows the survival curves according to PVR at baseline and after the inotropic challenge. Although PVR after inotropic challenge was predictive of survival in univariate analysis, the prognostic information was mainly related to baseline PVR. [Fig. 1B](#) shows the survival curves of the study population divided into subgroups according to baseline PVR and mPAP after the inotropic

challenge. The different areas under the receiver operating characteristic curves are presented in [Table A.5](#). Univariate qualitative predictors of major events are presented in [Table A.6](#). We performed multivariable analyses with qualitative variables combining measures at baseline and after inotropic challenge. The most powerful combination was RAP and PVR at baseline and mPAP after the inotropic challenge ([Table 5](#)). [Fig. 2](#) shows the survival curves according to baseline RAP and PVR and mPAP after inotropic challenge. The reclassification of subjects was estimated with the NET RECLASSIFICATION IMPROVEMENT with mPAP after the inotropic challenge instead of PVR: 14.2% of deceased patients and 8.4% of alive patients were correctly reclassified given a total NET RECLASSIFICATION IMPROVEMENT of 22.6% ($z = 4.5$; $P < 0.0001$). Similar results were found in separate analyses using either intra-hospital deaths after transplantation/VAD implantation or cardiac-related deaths as endpoints. [Figs. A.2](#) and [A.3](#) show the survival curves of the study population divided according to PVR at baseline and PVR or mPAP after the inotropic challenge, with either intra-hospital deaths after major surgery (25 events; [Figs. A.2A](#) and [A.2B](#)) or cardiac-related deaths (126 events; [Figs. A.3A](#) and [A.3B](#)). Due to the limited number of events after major surgery, Cox analysis was not performed.

Discussion

Haemodynamic parameters could help us in the selection of severe patients with SHF. Using simple haemodynamic parameters, such as RAP, PVR and mPAP, it was possible to stratify our study population into subgroups with different 1-year mortality rates, from 6% (patients with RAP < 9 mmHg and baseline PVR \leq 3 mmHg) to 46% (patients with baseline PVR > 3 WU and mPAP > 30 mmHg after inotropic challenge ([Fig- 2](#)). Right heart catheterization is mandatory before adding a patient to the waiting list for heart transplantation and a reactivity test is indicated in patients with severe PH. However, there are no clear recommendations based on the haemodynamic results following the reactivity test [18].

Right atrial pressure

Baseline RAP, a strong surrogate of right ventricular dysfunction, was the most powerful independent predictor of survival. It is important to have a normal RAP. Patients with an elevated RAP (annual mortality rate of 20%) had the same survival as patients with a baseline PVR > 3WU and mPAP \leq 30

mmHg after the inotropic challenge (annual mortality rate of 17%). In a subgroup of 151 patients from the ESCAPE trial, Cooper et al. demonstrated that the level of RAP after therapeutic management was a prognostic parameter [22].

Other haemodynamic parameters

Diastolic pulmonary gradient, the difference between PCWP and diastolic PAP, is used to differentiate 'passive PH' from 'out-of-proportion PH'. Previous studies that examined the prognostic power of diastolic pulmonary gradient have discordant results [7,12,16,23,24]. We found that diastolic pulmonary gradient was not predictive of major events. PAPP (the difference between systolic PAP and diastolic PAP) and proportional pulmonary arterial pulse pressure (PAPP divided by systolic PAP) reflect the right ventricular–pulmonary arterial coupling [13]. Pulmonary arterial compliance is considered to be a more reliable parameter of right ventricular afterload [7,14,25] and the right- and left-sided filling pressure ratio (RAP/PCWP) or the sum of RAP and PCWP are markers of right ventricular dysfunction [15,26]. In our study, all these parameters were less predictive of major events than RAP, PVR and mPAP.

Impact of the inotropic challenge

A reactivity test is recommended in case of severe PH. Heart transplantation is contraindicated in case of elevated PVR after the reactivity test (> 3–5 WU). We found that PVR after the inotropic challenge was not predictive of survival (Fig. 1A). Previous studies that have analysed reversible PH have shown conflicting results [19,27–32]. There are several reasons to explain these discordant results, namely selected populations, different endpoints and multicollinearity. Previous studies have analysed the impact of haemodynamic parameters in selected populations, either in SHF patients [7,25] or in patients on the waiting list for heart transplantation [16,19], with the exclusion of severe patients contraindicated for heart transplantation. Some analyses were restricted to patients with reversible PH [27,29]. The second limitation is different endpoints. Most of the studies analysed survival after heart transplantation, excluding patients on the waiting list and those who were haemodynamically contraindicated to, or without indication for, heart transplantation [6,16,27,28,30,33,34]. In other studies, endpoints were the combination of cardiovascular death and urgent transplantation and/or VAD implantation [13,14,23], regardless of the result of the surgical procedure (patients alive or

deceased after an urgent surgery were considered dead at the time of the surgery). Finally, one difficult problem with haemodynamic parameters is the correlation between parameters [30]. Multivariable analyses must be restricted to non-correlated parameters and it is easy to understand some 'discordant' results between studies. Some parameters are highly correlated (e.g. RAP + PCWP is correlated to systolic PAP and to mPAP; [Tables A.2](#) and [A.3](#)). Finally, it is important to consider a possible publication bias, as negative studies are less often published.

In clinical practice, we often used PVR after the reactivity test to contraindicate or not heart transplantation. We found that PVR after the inotropic challenge was not predictive of survival. This has already been shown after a vasodilator challenge [19,31]. mPAP seems to be a more interesting parameter ([Fig. 1B](#)). mPAP after the inotropic challenge identified 43 patients (36%) with a different short-term survival, with a 1-year mortality rate of 17% compared to a 1-year mortality rate of 34% in patients with a PVR < 3 WU after the inotropic challenge. We propose, for the risk stratification of ambulatory severe SHF patients, a simple algorithm using baseline PVR and RAP, and in patients with PVR > 3 WU, mPAP after an inotropic challenge ([Fig. 2](#)).

Limitations

Although we included consecutive patients, our study was retrospective. Our algorithm must therefore be prospectively confirmed in an independent group of patients. We included a selected population of patients with ambulatory chronic SHF. Our results should, therefore, not be extrapolated to other subgroups of patients, particularly to patients with haemodynamic instability (acute de novo SHF or cardiogenic shock), older adults referred for VAD destination therapy [35] or patients with preserved left ventricular ejection fraction [36]. Similarly, we performed an inotropic challenge, so our results cannot be extrapolated to patients in whom a vasodilator challenge is performed.

Conclusions

Haemodynamic parameters are useful for the risk stratification of ambulatory patients with advanced SHF. In clinical practice, it is important to have a simple algorithm. We demonstrated that the combination of baseline RAP, baseline PVR and mPAP after a reactivity test is a powerful prognostic algorithm.

Disclosure of interest

Conflict of interest: none.

References

- [1] Feldman SF, Lesuffleur T, Olie V, Gastaldi-Menager C, Juilliere Y, Tuppin P. French annual national observational study of 2015 outpatient and inpatient healthcare utilization by approximately half a million patients with previous heart failure diagnosis. *Arch Cardiovasc Dis* 2021;114:17-32.
- [2] Feldman SF, Lesuffleur T, Olie V, Gastaldi-Menager C, Juilliere Y, Tuppin P. Outpatient healthcare utilization 30 days before and after hospitalization for heart failure in France: Contribution of the national healthcare database (Systemenationaldesdonneesdesante). *Arch Cardiovasc Dis* 2020;113:401-19.
- [3] Dorent R, Gandjbakhch E, Goeminne C, Ivanes F, Sebbag L, Bauer F, et al. Assessment of potential heart donors: A statement from the French heart transplant community. *Arch Cardiovasc Dis* 2018;111:126-39.
- [4] Berthelot E, Bauer F, Eicher JC, Flecher E, Gellen B, Guihaire J, et al. Pulmonary hypertension in chronic heart failure: definitions, advances, and unanswered issues. *ESC Heart Fail* 2018;5:755-63.
- [5] Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. *Circ Heart Fail* 2011;4:644-50.
- [6] Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol* 1992;19:48-54.
- [7] Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail* 2013;1:290-9.
- [8] Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T, ESCAPE Investigators. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the

- Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. *Am Heart J* 2009;157:1026-34.
- [9] Chang PP, Longenecker JC, Wang NY, Baughman KL, Conte JV, Hare JM, et al. Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. *J Heart Lung Transplant* 2005;24:998-1007.
- [10] Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *Jama* 2005;294:1625-33.
- [11] Kirklin JK, Naftel DC, McGiffin DC, McVay RF, Blackstone EH, Karp RB. Analysis of morbid events and risk factors for death after cardiac transplantation. *J Am Coll Cardiol* 1988;11:917-24.
- [12] Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest* 2013;143:758-66.
- [13] Mazimba S, Kennedy JL, Zhuo D, Bergin J, Abuannadi M, Tallaj J, et al. Decreased Pulmonary Arterial Proportional Pulse Pressure After Pulmonary Artery Catheter Optimization for Advanced Heart Failure Is Associated With Adverse Clinical Outcomes. *J Card Fail* 2016;22:954-61.
- [14] Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. *Circ Heart Fail* 2012;5:778-85.
- [15] Drazner MH, Velez-Martinez M, Ayers CR, Reimold SC, Thibodeau JT, Mishkin JD, et al. Relationship of right- to left-sided ventricular filling pressures in advanced heart failure: insights from the ESCAPE trial. *Circ Heart Fail* 2013;6:264-70.
- [16] Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, et al. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. *J Heart Lung Transplant* 2014;33:289-97.

- [17] Torres Macho J, Delgado Jimenez JF, Sanz Salvo J, Gonzalez Mansilla A, Sanchez Sanchez V, Gamez Diez S, et al. Effect of different pharmacologic agents to reverse severe pulmonary hypertension among end-stage heart failure patients. *Transplant Proc* 2009;41:2477-9.
- [18] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant* 2016;35:1-23.
- [19] Chen JM, Levin HR, Michler RE, Prusmack CJ, Rose EA, Aaronson KD. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. *J Thorac Cardiovasc Surg* 1997;114:627-34.
- [20] Erickson KW, Costanzo-Nordin MR, O'Sullivan EJ, Johnson MR, Zucker MJ, Pifarre R, et al. Influence of preoperative transpulmonary gradient on late mortality after orthotopic heart transplantation. *J Heart Transplant* 1990;9:526-37.
- [21] Drazner MH, Hamilton MA, Fonarow G, Creaser J, Flavell C, Stevenson LW. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. *J Heart Lung Transplant* 1999;18:1126-32.
- [22] Cooper LB, Mentz RJ, Stevens SR, Felker GM, Lombardi C, Metra M, et al. Hemodynamic Predictors of Heart Failure Morbidity and Mortality: Fluid or Flow? *J Card Fail* 2016;22:182-9.
- [23] Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail* 2015;3:9-16.
- [24] Wright SP, Moayedi Y, Foroutan F, Agarwal S, Paradero G, Alba AC, et al. Diastolic Pressure Difference to Classify Pulmonary Hypertension in the Assessment of Heart Transplant Candidates. *Circ Heart Fail* 2017;10:e004077.
- [25] Pellegrini P, Rossi A, Pasotti M, Raineri C, Ciccoira M, Bonapace S, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest* 2014;145:1064-70.
- [26] Ma TS, Paniagua D, Denktas AE, Jneid H, Kar B, Chan W, et al. Usefulness of the Sum of Pulmonary Capillary Wedge Pressure and Right Atrial Pressure as a Congestion Index that

- Prognosticates Heart Failure Survival (from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). *Am J Cardiol* 2016;118:854-9.
- [27] Butler J, Stankewicz MA, Wu J, Chomsky DB, Howser RL, Khadim G, et al. Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. *J Heart Lung Transplant* 2005;24:170-7.
- [28] Drakos SG, Kfoury AG, Gilbert EM, Horne BD, Long JW, Stringham JC, et al. Effect of reversible pulmonary hypertension on outcomes after heart transplantation. *J Heart Lung Transplant* 2007;26:319-23.
- [29] Klotz S, Wenzelburger F, Stypmann J, Welp H, Drees G, Schmid C, et al. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. *Ann Thorac Surg* 2006;82:1770-3.
- [30] Gorlitzer M, Ankersmit J, Fiegl N, Meinhart J, Lanzenberger M, Unal K, et al. Is the transpulmonary pressure gradient a predictor for mortality after orthotopic cardiac transplantation? *Transpl Int* 2005;18:390-5.
- [31] Levine TB, Levine AB, Goldberg AD, Tobes MC, Narins B, Goldstein S, et al. Acute reversibility of pulmonary hypertension predicts neither long-term hemodynamic response nor outcome in patients awaiting heart transplantation. *Am J Cardiol* 1997;79:105-6.
- [32] Ghio S, Crimi G, Temporelli PL, Traversi E, La Rovere MT, Cannito A, et al. Haemodynamic effects of an acute vasodilator challenge in heart failure patients with reduced ejection fraction and different forms of post-capillary pulmonary hypertension. *Eur J Heart Fail* 2018;20:725-34.
- [33] Drazner MH, Brown RN, Kaiser PA, Cabuay B, Lewis NP, Semigran MJ, et al. Relationship of right- and left-sided filling pressures in patients with advanced heart failure: a 14-year multi-institutional analysis. *J Heart Lung Transplant* 2012;31:67-72.
- [34] Vakil K, Duval S, Sharma A, Adabag S, Abidi KS, Taimeh Z, et al. Impact of pre-transplant pulmonary hypertension on survival after heart transplantation: a UNOS registry analysis. *Int J Cardiol* 2014;176:595-9.
- [35] Galand V, Flecher E, Chabanne C, Lelong B, Goeminne C, Vincentelli A, et al. Septuagenarian population has similar survival and outcomes to younger patients after left ventricular assist device implantation. *Arch Cardiovasc Dis* 2020;113:701-9.

- [36] Schrub F, Oger E, Bidaut A, Hage C, Charton M, Daubert JC, et al. Heart failure with preserved ejection fraction: A clustering approach to a heterogenous syndrome. *Arch Cardiovasc Dis* 2020;113:381-90.

Figure legends

Figure 1. Survival curves of the study population divided according to: A. PVR at baseline and after inotropic challenge (IC-PVR) and B. baseline PVR and mPAP after the inotropic challenge (IC-mPAP). B: baseline; IC: inotropic challenge; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; WU: Wood units.

Figure 2. Survival curves of the study population divided into four subgroups according to PVR and RAP at baseline (B-PVR and B-RAP, respectively) and mPAP after the inotropic challenge (IC-mPAP). B: baseline; IC: inotropic challenge; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: Wood units.

Central illustration. Summary of the main results of the study. Haemodynamic independent predictors of major events in our study population and survival curves in subgroups divided according to baseline PVR, RAP and mPAP after the inotropic challenge. †: mortality; B: baseline; IC: inotropic challenge; mPAP: mean pulmonary arterial pressure; PA: pulmonary arterial; PAP: pulmonary arterial pressure; PAPP: pulmonary arterial pulse pressure; PPAPP: per cent of proportional PAPP; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SHF: systolic heart failure; TPG: transpulmonary pressure gradient; WU: Wood units.

Table 1 Clinical characteristics and treatments of the study population.

	Study population (<i>n</i> = 425)
Age (years)	52.6 ± 10.8
Women	101 (23.8)
NYHA III–IV	168 (39.5)
Ischaemic	181 (42.6)
Diabetes mellitus	101 (23.8)
Atrial fibrillation	88 (20.7)
LVEF (%)	29.4 ± 12.2
ACEI or ARB	403 (94.8)
Beta blockers	378 (88.9)
MRA	269 (63.3)
Diuretics	381 (89.6)
Oral anticoagulants	221 (52.0)
Defibrillator	300 (70.6)
Resynchronization therapy among those with LBBB	107/132 (81.1)

Data are expressed as mean ± standard deviation, number (%) or number/number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Table 2 Haemodynamic characteristics in the overall study population and in patients without and with major events.

	Study population (<i>n</i> = 425)	No major events (<i>n</i> = 274)	Major event(s) (<i>n</i> = 151)	HR (95% CI)	Wald	<i>P</i>
Heart rate (bpm)	70.5 ± 14.1	69.8 ± 14.3	71.6 ± 13.7	1.00 (0.99–1.01)	0.39	0.53
SBP (mmHg)	110 ± 19	110 ± 19	111 ± 20	0.99 (0.99–1.00)	2.89	0.09
DBP (mmHg)	72 ± 12	72 ± 12	72 ± 12	1.00 (0.98–1.01)	0.46	0.50
Systolic PAP (mmHg)	47.7 ± 17.9	44.6 ± 16.1	53.1 ± 19.7	1.03 (1.02–1.03)	46.1	< 0.0001
Diastolic PAP (mmHg)	20.2 ± 8.8	18.6 ± 8.1	23.1 ± 9.2	1.06 (1.04–1.08)	46.2	< 0.0001
mPAP (mmHg)	31.6 ± 11.8	29.4 ± 10.6	35.3 ± 12.6	1.05 (1.03–1.06)	50.2	< 0.0001
PAPP (mmHg)	27.5 ± 11.8	26.0 ± 10.5	30.1 ± 13.3	1.03 (1.02–1.04)	25.9	< 0.0001
PPAPP (%)	57.6 ± 10.2	58.6 ± 10.8	56.4 ± 10.9	0.99 (0.97– 0.999)	4.74	0.03
PCWP (mmHg)	20.6 ± 8.5	19.5 ± 8.4	22.6 ± 8.3	1.06 (1.04–1.08)	36.9	< 0.0001
TPG (mmHg)	11.0 ± 6.5	9.9 ± 5.2	12.7 ± 7.8	1.05 (1.03–1.07)	24.0	< 0.0001
Diastolic gradient (mmHg)	–1 (–3 to 2)	–1 (–4 to 2)	0 (–3 to 3)	1.02 (0.99–1.05)	1.74	0.19
RAP (mmHg)	10.2 ± 6.3	9.0 ± 5.8	12.3 ± 6.5	1.10 (1.07–1.13)	62.6	< 0.0001
RAP/PCWP	0.51 ± 0.30	0.49 ± 0.30	0.56 ± 0.30	1.94 (1.22–3.10)	7.83	0.005
RAP + PCWP	30.8 ± 13.2	28.5 ± 12.7	34.9 ± 13.1	1.05 (1.04–1.06)	56.6	< 0.0001
Cardiac index (L/min/m ²)	2.17 ± 0.58	2.25 ± 0.59	2.04 ± 0.52	0.43 (0.32–0.58)	29.6	< 0.0001
SvO ₂ (%)	61.2 ± 8.9	61.8 ± 8.6	59.4 ± 9.3	0.95 (0.93–0.97)	17.4	< 0.001
PVR (WU)	2.91 ± 2.25	2.47 ± 1.5	3.70 ± 3.0	1.19 (1.13–1.24)	48.2	< 0.0001
RVSWI (g*m/m ² /beat)	8.95 ± 4.34	9.01 ± 4.4	8.83 ± 4.2	1.01 (0.97–1.05)	0.18	0.67
PA compliance (mL/mmHg)	2.67 ± 1.59	2.89 ± 1.7	2.27 ± 1.3	0.71 (0.63–0.81)	26.3	< 0.0001

Data are expressed as mean ± standard deviation or median (interquartile range). bpm, beats per minute; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; mPAP, mean

pulmonary arterial pressure; PA, pulmonary arterial; PAP, pulmonary arterial pressure; PAPP, pulmonary arterial pulse pressure; PCWP, pulmonary capillary wedge pressure; PPAPP, per cent of proportional pulmonary arterial pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; SvO₂, mixed venous oxygen saturation; TPG, transpulmonary pressure gradient; WU, Wood units.

Table 3 Haemodynamic results among the 119 patients who underwent inotropic challenge.

	Baseline	Inotropic challenge	<i>P</i>
Heart rate (bpm)	72.0 ± 13.3	88.8 ± 18.5	< 0.0001
SBP (mmHg)	108 ± 17	108 ± 19	0.73
DBP (mmHg)	72 ± 11	65 ± 12	< 0.0001
Systolic PAP (mmHg)	63.3 ± 16.6	57.6 ± 16.6	< 0.0001
Diastolic PAP (mmHg)	27.7 ± 7.3	21.6 ± 8.7	< 0.0001
mPAP (mmHg)	42.2 ± 10.1	36.0 ± 10.9	< 0.0001
PAPP (mmHg)	35.7 ± 12.8	36.0 ± 12.1	0.77
PPAPP (%)	55.5 ± 9.8	62.5 ± 10.7	< 0.0001
PCWP (mmHg)	25.4 ± 7.0	18.8 ± 9.8	< 0.0001
TPG (mmHg)	16.8 ± 6.2	16.9 ± 6.2	0.91
Diastolic gradient (mmHg)	2 (−1 to 5)	3 (−2 to 7)	0.05
RAP (mmHg)	12.8 ± 5.7	8.4 ± 4.8	< 0.0001
RAP/PCWP	0.51 ± 0.23	0.51 ± 0.37	0.97
RAP + PCWP	38.1 ± 10.9	27.1 ± 13.7	< 0.0001
Cardiac index (L/min/m ²)	1.88 ± 1.05	2.55 ± 1.38	< 0.0001
SvO ₂ (%)	58.9 ± 8.8	72.0 ± 5.54	< 0.0001
PVR (WU)	5.07 ± 2.6	3.08 ± 1.5	< 0.0001
RVSWI (g*m/m ² /beat)	11.7 ± 4.4	14.4 ± 5.1	< 0.0001
PA compliance (mL/mmHg)	1.41 ± 0.50	2.02 ± 0.74	< 0.0001

Data are expressed as mean ± standard deviation or median (interquartile range). bpm, beats per minute; DBP, diastolic blood pressure; mPAP, mean pulmonary arterial pressure; PA, pulmonary arterial; PAP, pulmonary arterial pressure; PAPP, pulmonary arterial pulse pressure; PCWP, pulmonary capillary wedge pressure; PPAPP, per cent of proportional pulmonary arterial pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; SvO₂, mixed venous oxygen saturation; TPG, transpulmonary pressure gradient; WU, Wood units.

Table 4 Independent predictors of major events with quantitative parameters.

	Wald	HR (95% CI)	<i>P</i>
Baseline ^a			
RAP	40.7	1.09 (1.06–1.12)	< 0.0001
PVR	9.20	1.10 (1.03–1.17)	0.002
Cardiac index	3.89	0.69 (0.48–0.99)	0.05
After inotropic challenge ^b			
mPAP	13.0	1.06 (1.03–1.09)	< 0.0001

CI, confidence interval; HR, hazard ratio; mPAP, mean pulmonary arterial pressure; PA: pulmonary arterial; PAPP, pulmonary arterial pulse pressure; PPAPP, per cent of proportional pulmonary arterial pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

^a Model: RAP, PVR, cardiac index, PAPP, PPAPP (global Wald = 91.9).

^b Model: mPAP, PVR, PPAPP, PA compliance (global Wald= 20.4).

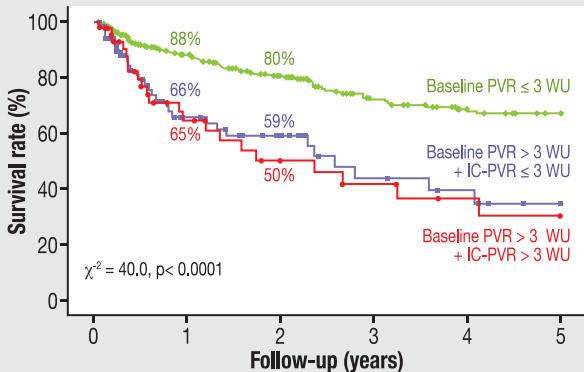
Table 5 Predictors of major events with combinations of qualitative parameters.

	Wald	HR (95% CI)	<i>P</i>
Baseline and after inotropic challenge^a			
B-PVR ≤ 3 WU	20.6	Reference	–
B-RAP ≥ 9 mmHg	19.3	2.41 (1.63–3.57)	< 0.0001
B-PVR > 3 WU and IC-mPAP ≤ 30 mmHg	6.18	1.89 (1.14–3.12)	0.01
B-PVR > 3 WU and IC-mPAP > 30 mmHg	18.5	2.54 (1.66–3.89)	< 0.0001
Baseline and after inotropic challenge^b			
B-PVR ≤ 3 WU and B-RAP < 9 mmHg	53.7	Reference	–
B-PVR ≤ 3 WU and B-RAP ≥ 9 mmHg	15.1	2.40 (1.55–3.74)	< 0.001
B-PVR > 3 WU and IC-mPAP ≤ 30 mmHg	10.7	2.79 (1.51–5.17)	0.001
B-PVR > 3 WU and IC-mPAP > 30 mmHg	47.7	5.54 (3.50–8.76)	< 0.0001

B-PVR, baseline pulmonary vascular resistance; B-RAP, baseline right atrial pressure; CI, confidence interval; HR, hazard ratio; IC-mPAP, mean pulmonary arterial pressure after inotropic challenge; WU, Wood units.

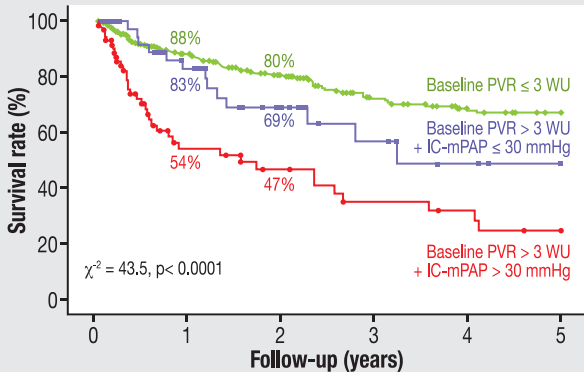
^a Global Wald = 70.1

^b Global Wald = 62.3

A

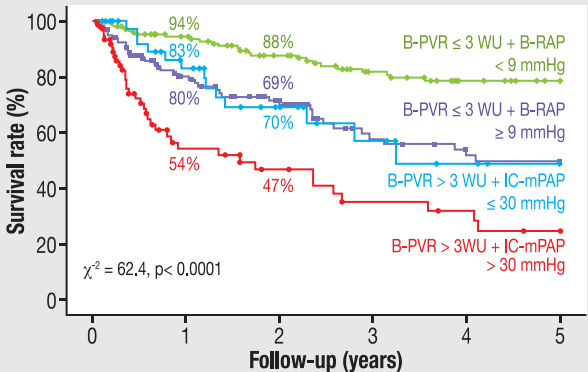
Number at risk

280	185	146	108	89	81
45	20	12	9	6	4
74	31	20	11	8	3

B

Number at risk

280	185	146	108	89	81
43	27	15	9	5	2
76	24	17	11	9	5



Number at risk

159	117	97	77	64	58
121	68	49	31	25	23
43	27	15	9	5	2
76	24	17	11	9	5