

## Research Article

### Prognostic Role of Right Ventricle in Mitral Valve Surgery for Ischemic Mitral Regurgitation

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## Abstract

**Background:** To evaluate if preoperative right ventricular (RV) dilatation or dysfunction may affect mid-term cardiac mortality of patients with ischemic mitral regurgitation (IMR) undergoing mitral valve surgery (MVS), independently from pulmonary hypertension (PH).

**Methods:** From March 2006 to March 2010, 172 patients with IMR, electively and consecutively operated on by a single surgeon (AMC) were enrolled in this study. Tricuspid annular plane systolic excursion (TAPSE) was used to evaluate RV function. Right ventricular end-diastolic diameter (RVEDD) was also evaluated.

**Results:** Twenty-seven patients (15.7%) died by 5 years for any cause, 22 (12.8%) due to cardiac cause. ROC curve identified two predictive cut-offs: TAPSE $\leq$ 15mm (AUC=0.87, sensitivity=91%, specificity=81 %) and RVEDD $>$ 35mm (AUC=0.84, sensitivity=86%, specificity=82%). An "abnormal" RV, defined as either RV dilatation or dysfunction, was found in 66 (38%) of cases, preoperatively. Right ventricle was normal in 106 cases.

Five-year overall cardiac survival was 85% $\pm$ 3 (normal 99% $\pm$ 1 versus abnormal RV 63% $\pm$ 7, p $<$ 0.001). This result was also confirmed by a multivariate analysis. Cardiac survival in patients without PH was 90% $\pm$ 4 versus 88% $\pm$ 3 in patients with any grade of PH (p = 0.812). The presence of an abnormal RV was a risk factor in patients both with and without PH; while the presence of PH was a risk factor neither in patients with normal nor abnormal RV.

**Conclusions:** : Right ventricular dysfunction and dilatation should be considered in risk stratification model; both conditions are able to impair cardiac mortality, independently from PH.

**Keywords:** Right Ventricular Function; Mitral Valve Surgery; Echocardiographic Assessment; Pulmonary Hypertension.

## Introduction

The prognostic role of right ventricle has been clearly demonstrated in patients with myocardial infarction (MI) [1, 2], heart failure (HF), either ischemic or not [3, 4] or receiving cardiac resynchronization therapy [5]. This finding changed the insight of the cardiologists, resulting

in a more careful evaluation of the right ventricle in order to assess the prognosis.

In cardiac surgery, although there are sufficient evidences [6-11] in favor of a routine preoperative assessment of the right ventricle, the main surgical risk score systems [12,13]

do not take into account neither dysfunction nor dilatation of the right ventricle.

On the contrary, systolic pulmonary artery pressure (sPAP) is considered a strong predictor for mortality after cardiac surgery; but, as already demonstrated in patients with HF, pulmonary hypertension (PH) does not always mirror RV dysfunction, which has an independent and additive prognostic value [14]. In addition RV dysfunction seems to be a better predictor of postoperative circulatory failure rather than pulmonary hypertension (PH), in patients undergoing mitral valve surgery (MVS) [8].

Such non-systematic assessment of RV is certainly due to difficult 2D-trans-thoracic echocardiographic (TTE) evaluation of the morphology and function of the right heart, whose position is immediately below the sternum. Given also its complex structure and asymmetrical shape, RV ejection fraction (EF) can be assessed only using more sophisticated imaging tools like radionuclide angiography [15] or cardiac magnetic resonance [16] which are costly and not widespread. Tricuspid annular plane systolic excursion (TAPSE) is a simple M-Mode measure [17] which well correlates with RVEF [15], since the longitudinal shortening accounts for the greater part of overall RV volume change [18]; So, TAPSE was easily collected during preoperative risk assessment, along with RV end-diastolic diameter (RVEDD).

With the spread of coronary interventional approach, cardiac surgery is nowadays appointed to deal with more complicated ischemic heart disease, like IMR. Beside that, it is well known that IMR should be treated at the same time of coronary artery bypass grafting in order to improve early and late outcome [19]. Consequently, MVS for ischemic mitral regurgitation (IMR) is becoming more and more routinely performed. In this subset of patients, RV alteration and pulmonary hypertensions coexist, so this retrospective study was aimed to evaluate if RV dilatation or dysfunction could affect mid-term cardiac mortality of the patients with ischemic mitral regurgitation (IMR) undergoing MVS, independently from pulmonary hypertension (PH).

## Methods

### Study Population

From March 2006 to March 2010, 184 patients with IMR were electively and consecutively operated on by a single surgeon (AMC). From the entire cohort, 12 patients were excluded from the analysis as they presented one or more of the following exclusion criteria: preoperative severe tricuspid regurgitation, recurrence of MR or continuous remodeling at follow up by 5 years. Thus, finally 172 patients were enrolled into the study.

### Echocardiography

All the patients underwent routine preoperative trans-thoracic echocardiography. The infarct location was estimated

by determining the location of akinesia/dyskinesia, identified qualitatively on the echocardiogram [20].

Right ventricle function was assessed using an apical 4-chamber view: the M-mode cursor was placed through the junction between the tricuspid valve plane and RV free wall to measure the TAPSE [17]. Patients with severe tricuspid regurgitation were excluded from the study due to the likelihood to overestimate TAPSE [16]; RVEDD was measured in the left parasternal long-axis view, applying the M-mode [21]. The sPAP was estimated as the sum of the gradient across the tricuspid valve (calculated from the simplified Bernoulli equation) and the right atrial pressure. Right atrial pressure was estimated using the size and respiratory response of the inferior vena cava in the sub-costal view. The methods used to assess all the other echocardiographic parameters have already been reported [22]. Recurrences of MR and continuous LV remodeling have been already defined [22]. All the preoperative echocardiographic data are listed in the table 1.

Table 1. Demographic, clinical and surgical and echocardiographic data

	Overall	TAPSE		RVEDD	
		≤15mm	>15mm	>35mm	≤35mm
	n=172	n = 43	n = 129	n = 47	n = 125
Age (years)	67±10	69±8	67±10	69±9	68±10
Males/Female	130/42	35/8	95/34	35/12	95/30
NYHA class					
II	110 (64%)	28 (65%)	82 (64%)	33 (70%)	81 (65%)
III-IV	62 (36%)	15 (35%)	47 (36%)	14 (30%)	44 (35%)
EuroSCORE	7.5% (4.7%-16.5%)	6.5% (4.5%-12.6%)	7.5% (4.7%-16.7%)	6.5% (4.5%-12.6%)	7.5% (4.7%-16.7%)
Location of MI					
Anterior	68 (39.5%)	18 (41.9%)	50 (38.8%)	21 (44.7%)	47 (37.6%)
Anterior and inferior	11 (6.4%)	3 (7.0%)	8 (6.2%)	2 (4.2%)	9 (7.2%)
Inferior	84 (48.9%)	20 (46.5%)	64 (49.6%)	21 (44.7%)	63 (50.4%)
Infero-lateral	9 (5.2%)	2 (4.6%)	7 (5.4%)	3 (6.4%)	6 (4.8%)
Any inferior	104 (60.5%)	25 (59.1%)	79 (61.2%)	26 (45.3%)	78 (62.4%)
EF (%)					
MV repair/replacement	168/4	42/1	126/3	42/1	126/3
CABG	150 (87.2%)	36 (83.7%)	114 (88.4%)	42 (89.4%)	108 (86.4%)
SVR	47 (27.3%)	13 (30.2%)	34 (26.4%)	13 (27.7%)	34 (27.2%)
TV repair	62 (36.0%)	18 (41.9%)	44 (34.1%)	23 (48.9%)	39 (31.2%)
RF ablation	15 (8.7%)	7 (16.2%)	8 (6.2%)	5 (10.6%)	10 (8.0%)
Biventricular pacing	5 (2.9%)	0	5 (3.9%)	2 (4.2%)	3 (2.4%)
CPB time (minutes)	117±37	124±31	115±38	127±41	113±34
EF (%)	36±10	36±10	37±10	36±10	37±9
≤35%	93 (54.0%)	25 (58.2%)	68 (52.7%)	32 (68.1%)	61 (47.3%)
≤30%	62 (36.0%)	20 (46.5%)	42 (32.6%)	20 (42.6%)	42 (33.6%)
EDD (mm)	56±7	55±8	57±7	56±8	57±6
ESD (mm)	41±8	40±7	42±9	41±9	41±8
MR (grade)	2.5±0.9	2.5±0.9	2.5±0.9	2.4±0.9	2.5±1.0
MVCD (mm)	7.5±2.0	6.8±1.5	7.5±1.3	6.7±2.3	7.6±2.0
TR grade	1.2±0.7	1.4±0.7	1.1±0.7	1.2±0.7	1.2±0.7
TAPSE (mm)	18±4	13±2	20±3*	16±3	19±4*
RVEDD (mm)	33±6	35±7	32±6*	42±5	29±2*

**Legends.** NYHA = New York Heart Association, MI = myocardial infarction, MV = mitral valve, CABG = coronary artery bypass grafting, SVR = surgical ventricular restoration, RF = radiofrequency, CPB = cardiopulmonary bypass, EF = ejection fraction, EDD = end-diastolic diameter, ESD = end-systolic diameter, MR = mitral regurgitation, MVCD = mitral valve coaptation depth, TR = tricuspid regurgitation, TAPSE = tricuspid annular plane systolic excursion, RVEDD = right ventricular end-diastolic diameter, sPAP = systolic pulmonary artery pressure, PH = pulmonary hypertension. \* p<0.05

## Surgery

Surgical indications have been already reported [22]. After a median sternotomy, the ascending aorta and both caeae were cannulated, the superior ore directly. The MV was approached transeptally via a right atriotomy. MA was always reshaped using the SMB40™ (Sorin, Saluggia, Italy). The band, 40 mm long, was inserted from A1 (that coincides with the left trigone) to A3 (the fibrous zone that represents the offshoots of the right trigone) with several interrupted sutures, leaving the only A2 insertion free. As the surgical technique is the same for all the annuli, independently from their size, all sutures (in general, 8 to 10) are embri-cated to reduce the stress on the single suture. Insertion of prosthesis inside the mitral valve was performed saving the annular-subvalvular connection. Different techniques were used to exclude ventricular scars. In the case of inferior scar, an incision parallel to the descending posterior artery was performed and the scar was longitudinally excluded with interrupted U sutures. If the scar was limited to the apex and to the apical septum, a Dor procedure was used. If the scar involved the septum more than the anterior free wall, a septal reshaping was performed [22]. Tricuspid repair was performed using a De Vega suture annuloplasty or a band annuloplasty [22]. Surgical details are reported in the table 1.

## Follow up

All the patients were clinically followed up in the outpatient clinic at 3 and 12 months after surgery and thereafter at yearly intervals. The most recent information was obtained by calling the patients or the referring cardiologists. Follow up was 100% complete. Median follow up time was 5 years (25th – 75th percentiles were 4-6 years).

## Endpoints

The primary end-point of this study was to evaluate if RV enlargement or dysfunction might affect 5-year cardiac mortality of patients with IMR undergoing MVS.

## Statistical Analysis

Results are expressed as mean ( $\pm$ standard deviation). Categorical variables were reported as counts and percentages. Non-normally distributed variables were reported as median and 25th-75th percentiles. The optimal cut-off was determined by receiver-operating characteristic (ROC) curve analysis. The influence of preoperative RV variables upon mid-term actuarial mortality was investigated by means of Kaplan-Meier curves and Cox regression model. All the variables listed in the tables 1-2 were tested in the univariate analysis; those variables with  $p < 0.2$  were included in first multivariate model. The final model was validated in 1000 bootstrap samples. The role “1 independent variable every 10 events” has been respected. Correlation between RV dimension and function was assessed by means of bivariate correlation (Pearson r-square and p-value). For all tests, a p-value  $< 0.05$  was significant. The SPSS software (SPSS Inc, Chicago, IL, USA) was used.

## Results

### Preoperative Characteristics

The table 1 summarized preoperative characteristics of

overall population and stratified by cutoff of RVEDD and TAPSE.

### RV and Cardiac Mortality

Twenty-seven (15.7%) patients died by 5 years for any cause: 6 (3.5%) within 30 days and 21 (12.2%) thereafter; cardiac deaths were 22 (12.8%): 6 (3.5%) within 30 days and 16 (9.3%) thereafter; in 12 out of 22 cases cardiac death occurred as sudden death (7.0%). Thirteen patients experienced a new episode of heart failure; it was fatal in half of them.

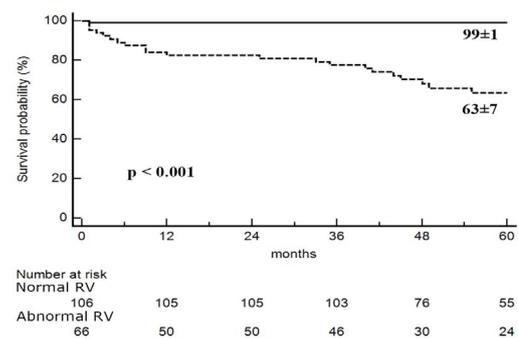
### Cut-offs of TAPSE and RVEDD

ROC curve identified two predictive cut-offs: TAPSE  $\leq 15$ mm (AUC=0.87, sensitivity=91%, specificity=81%) and RVEDD  $> 35$ mm (AUC=0.84, sensitivity=86%, specificity=82%).

The entire study population was divided according to TAPSE cutoff: group A,  $\leq 15$ mm versus group B,  $> 15$ mm (B), and according to RVEDD cutoff: group C,  $> 35$ mm vs  $\leq 35$ mm group D. No differences were found in group A versus B, and in group C versus D (tables 1 and 2). In patients with TAPSE  $\leq 15$ mm, RVEDD was significantly higher ( $35 \pm 7$  versus  $32 \pm 6$  mm,  $p = 0.019$ ) as well as in patients with RVEDD  $> 35$ mm, TAPSE was significantly lower ( $16 \pm 3$  versus  $19 \pm 4$ ,  $p = 0.040$ ).

An “abnormal” RV, defined as either RV dilatation or dysfunction, was found in 66 (38%) of cases, preoperatively. Right ventricle was normal in 106 cases.

Five-year survival was  $82\% \pm 3$ ; five-year overall cardiac survival was  $85\% \pm 3$ . In figure 1 cardiac survival stratified according to different preoperative RV features is reported: normal  $99\% \pm 1$  versus abnormal RV (66)  $63\% \pm 7$ ,  $p < 0.001$ . Multivariate model showed as age (OR 1.14, 1.03-1.35,  $p = 0.017$ ) and abnormal RV (OR 6.60, 3.15-13.8,  $p < 0.001$ ) were risk factors for 5-year cardiac mortality.



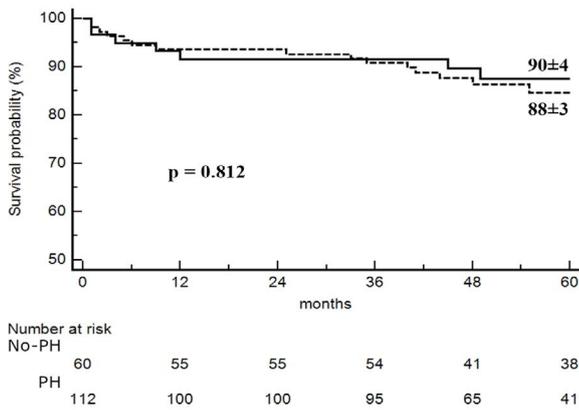
**Fig1:** Five-year survival according to preoperative echocardiographic evaluation of right ventricle (RV): normal RV (solid line) versus abnormal RV (dashed lined).

### RV and sPAP

Systolic PAP was correlated neither with TAPSE ( $r = -0.283$ ,  $p = 0.122$ ) nor RVEDD ( $r = 0.196$ ,  $p = 0.134$ ); sPAP was similar in patients with TAPSE either above or below 15mm ( $34 \pm 11$  versus  $38 \pm 12$  mmHg,  $p = 0.089$ ) as well as in patients with RVEDD either above or below 35mm ( $32 \pm 9$  versus  $36 \pm 11$  mmHg,  $p = 0.097$ ).

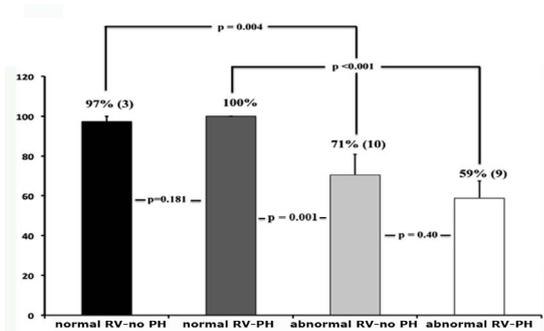
According to EuroSCORE II [13], pulmonary hypertension (PH) can be classified in two grades: 31-55mmHg (mild-moderate) and  $\geq 55$ mmHg (severe). In our experience, 60 (35%) patients did not have PH and 112 (65%) showed PH: 100 (58%) had mild-moderate PH and 12 (7%) had severe PH; stratifying the entire population according to TAPSE or RVEDD cutoffs, no differences were found regarding different sPAP grades (Table 2).

Cardiac survival in patients without PH was  $90\% \pm 4$  versus  $88\% \pm 3$  in patients with any grade of PH ( $p = 0.812$ ) (Fig. 2).



**Fig2:** Five-year survival according to preoperative echocardiographic evaluation of pulmonary hypertension (PH): no PH (solid line) versus PH (dashed line).

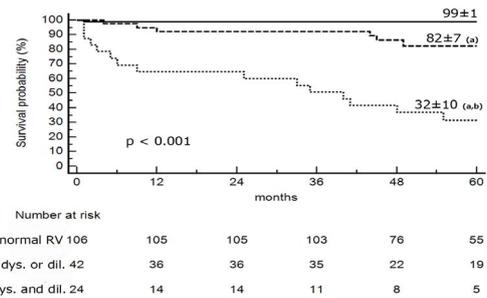
The presence of abnormal RV was a risk factor either in patients with or without PH (Fig. 3), while the presence of PH was a risk factor neither in patients with normal RV nor with altered RV (Fig. 3).



**Fig3:** Five-year survival according to preoperative echocardiographic evaluation of right ventricle (RV) and pulmonary pressure (PH): normal RV-no PH (black column, 38 cases), normal RV-PH (dark gray column, 68 cases), abnormal RV-no PH (light gray column, 22 cases), abnormal RV-PH (white column, 44 cases). Standard error is reported in the brackets.

**RV Dysfunction and Dilatation**

Finally, the value of contemporary presence of RV dysfunction and dilatation was evaluated: 106 patients had normal RV, 42 showed either RV dysfunction or dilatation and 24 both RV dysfunction and dilatation. The figure 4 shows that the presence of both condition significantly impair mid-term cardiac survival.



**Fig4:** Five-year survival according to preoperative echocardiographic evaluation of right ventricle (RV): normal RV (solid line), either RV dysfunction or dilatation (dashed line), both RV dysfunction and dilatation (dot line). a. p-value (versus normal RV); b. p-value (versus either RV dysfunction or dilatation).

**Discussion**

Right ventricular dysfunction or dilatation, unlike PH, is not included in both Parsonnet [12] and EuroScore [13] risk stratification models. However, there are growing evidences that higher mortality associated with PH could depend more on RV adaptation to pulmonary vascular resistance than on the absolute presence of high pulmonary pressure [8]. However in both scores RV assessment was not evaluated considering pulmonary hypertension as the epiphenomenon of right ventricular dysfunction and dilatation, even if this is not always true.

In both medically [14] and surgically [6, 7] treated patients with idiopathic or ischemic dilated cardiomyopathy, RV showed an independent prognostic value.

**Right Ventricular Dysfunction**

The lower TAPSE the lower 5-years cardiac survival; in particular, patients with TAPSE<15 mm showed an increase of 5-year cardiac mortality with respect to those ones with TAPSE $\geq 15$  mm. The same prognostic cutoff has been already reported in 1547 outpatients referred for the evaluation of HF [23], whereas others [3, 4] found a slightly lower cutoff (14 mm) in patients with idiopathic or ischemic dilated cardiomyopathy. In cardiac surgery, the relationship between TAPSE and outcome has been confirmed also by others [6-11].

Myocardial dysfunction after cardiopulmonary bypass (CPB) is commonly mild without any consequence in terms of hemodynamics. However, in some susceptible patients, CPB may cause RV failure due to new onset of RV ischemia/infarction (bad myocardial protection, graft thrombosis); coronary air embolism; pre-existing pulmonary hypertension exacerbated by atelectasis, inadequate oxygenation or inflammation; pulmonary vasoconstriction due sometimes to protamine; loss of atrio-ventricular synchrony; sepsis. So, the presence of preoperative RV dysfunction could be very likely the basis for a critical postoperative RV failure, making this condition irreversible; this might explain the impact of RV dysfunction in the early phase of follow up. More difficult is to figure out the reasons underlying the prognostic impact of RV dysfunction in mid-term period.

Indeed, if MVS increases the forward quote of LV stroke volume with an increase of systemic perfusion, along with a reverse LV remodeling in 59% of cases [22], it is very difficult to expect the same outcome for the right ventricle. Hence, patients with RV dysfunction, surviving the operation, could be more prone to worsen RV function throughout the follow up with a consequent worse outcome.

### Right Ventricular Dilatation

In addition to RV dysfunction, dilatation of RV chamber should be evaluated to stratify the surgical risk [10,11]. Chrustowicz et al [10] assessed the prognostic value of pre-operative RV dilatation in a cohort of 70 consecutive patients with HF undergoing elective MV repair, finding that RVEDD>35mm, assessed in M-mode, was associated with lower 5-year survival and survival-free from heart transplantation, both at uni- and multivariate analyses. In our study, the same cut-off was found out, but unlike them [10], herein RVEDD > 35mm was also predictor for higher cardiac mortality, even in absence of RV dysfunction. Right ventricular dilatation in presence of mitral regurgitation is due to increased afterload that causes prolonged isovolumetric contraction; thus, RV dilatation is a compensative mechanism to keep stroke volume unchanged, but entailing increased myocardial walls stress and oxygen consumption (Laplace Law), with decreased right coronary perfusion. In addition, the enlargement of the RV chamber leads to tricuspid annulus dilatation and papillary muscles displacement, increasing tricuspid regurgitation over time. Finally, RV enlargement causes leftward bulging of the left ventricle, with consequent impairment of LV diastolic and systolic function.

### RV and sPAP

In this particular subset of patients, both pulmonary hypertension, due to venous increase of pulmonary pressure, and RV dilatation or dysfunction may coexist. However, it is crucial to understand how these two conditions are linked and their independent and additive effect on prognosis. In our series, RV dilatation and dysfunction were not correlated with PH, in fact, the average sPAP was similar in patients with normal or abnormal right ventricle, and neither TAPSE nor RVEDD were correlated to sPAP. The explanations of this finding may be different: advantaged disease with low RV output could determine normal PAP; a primary reduction of in RV myocardial contractility due to involvement of RV wall or septum by MI, high prevalence of atrial fibrillation; overtreatment with diuretic. Ghio et al [14] found that RV dysfunction was a risk factor only in presence of PH in patients with heart failure; unlike, our results demonstrates that PH is neither a risk factor per se nor add any prognostic value to the presence of abnormal RV. Conversely, abnormal RV had an independent impact on prognosis, even in presence of PH or not. All the patients with high PH without RV alteration survived; on the contrary patients with normal PH, but abnormal RV showed a significantly lower survival. Even if patients with abnormal RV and PH showed the lowest survival, it was not significantly different from patients with abnormal RV and no PH (**Fig. 3**).

To explain the latter result, some considerations deserve to be quoted: firstly, in our series, pulmonary pressure was assessed by echocardiography, and this is subject to significant biases compared to invasive measurement, and also does not give us any information about the pulmonary resistances and their possible reversibility. So, it is likely pressure was assessed by echocardiography, and this is subject to significant biases compared to invasive measurement, and also does not give us any information about the pulmonary resistances and their possible reversibility. So, it is likely that pulmonary hypertension, as sign of increased RV afterload due to mitral regurgitation, could be solved with mitral surgery, while RV remodeling could no longer be reversible, influencing the prognosis of these patients.

### Study Limitations

There are some limitations to quote; firstly, this is a retrospective single center experience with a small size of the cohort. Right ventricular dysfunction was assessed by TAPSE that, although is well correlated with RVEF, ignores the outlet portion and the septal contribution to RV ejection, which may become important to maintain overall RV function [16]. Then, this study evaluated only the clinical impact of preoperative RV function and dimension, just speculating upon possible behavior of right ventricle throughout the follow up; in fact no information can be provided about right ventricle in the mid-term.

### Conclusions

Right ventricular dysfunction, easily assessed by TAPSE, and RV dilatation should be considered in risk stratification in order to adopt specific perioperative management and reduce postoperative and mid-term cardiac mortality; both conditions are able to impair cardiac mortality, independently from PH.

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