ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 5121–5131
Published online 3 September 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13581

ORIGINAL ARTICLE

Systolic pulmonary regurgitation affects the outcome of patients with severe systolic heart failure

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Abstract

Aims Little is known of the impact of systolic pulmonary regurgitation (PR) on acute decompensated heart failure (HF). We assessed the prevalence and prognostic significance of systolic PR in patients with severe HF.

Methods and results According to recent 10 year echocardiographic database of E-Da Hospital, 533 patients admitted for first systolic heart failure (HF) and left ventricular ejection fraction <35% were under investigation. Systolic PR was defined as the presence of pulmonary backward flow persistent after QRS in electrocardiogram. Isovolumic contraction/relaxation time and myocardial performance index were derived by tissue Doppler imaging. Right ventricular (RV) function was assessed by RV fractional area change. Estimated pulmonary vascular resistance (PVR) was assessed by the ratio of peak tricuspid regurgitation velocity to the RV outflow tract time–velocity integral. The factors associated with systolic PR were assessed by multivariate logistic regression. Cox proportional regression analyses were used to estimate the impact of cardiovascular events including HF rehospitalization and cardiovascular death. For estimated prevalence of 5480 control subjects, echocardiographic screens in those with normal left ventricular ejection fraction were performed. Of 533 systolic HF cases, 143 (26.8%) had systolic PR during indexed hospitalization. Among 143 cases, 86% systolic PR disappeared during late follow-up. In control subjects, 0.3% (18/5480) had systolic PR. Systolic PR correlated to RV dysfunction, estimated PVR, E/e′, sign of low cardiac output, and pulmonary oedema. Systolic PR was associated independently with further cardiovascular events (hazard ratio 2.266, 95% confidence interval 1.682–3.089, $P < 0.0001$) including cardiovascular death and HF rehospitalization.

Conclusions Systolic PR is not uncommon in systolic HF and is associated with high PVR and RV dysfunction. Systolic PR significantly impacts cardiovascular outcome.

Keywords Systolic pulmonary regurgitation; Heart failure; Pulmonary vascular resistance; Prognosis

Received: 12 June 2021; Revised: 22 July 2021; Accepted: 10 August 2021
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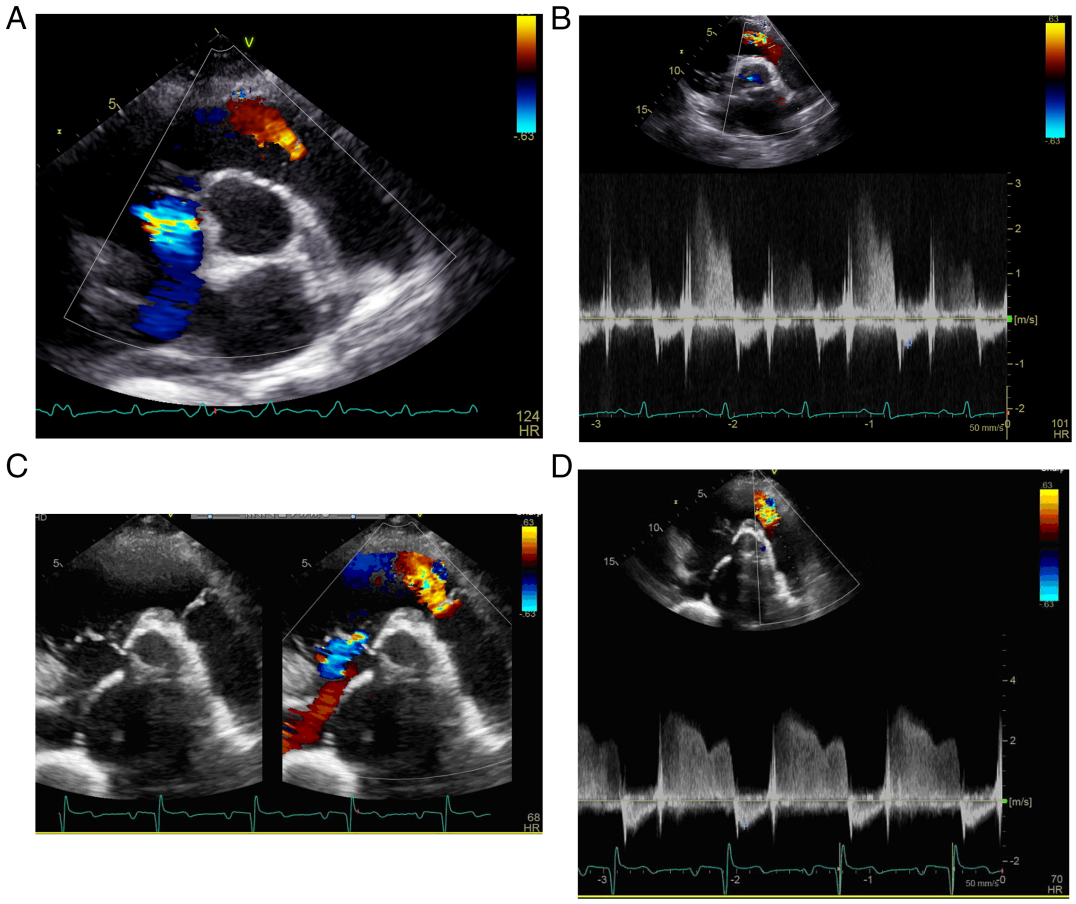
Introduction

Pulmonary regurgitation (PR) is defined as an abnormal reversal of blood flow from the pulmonary artery into the right ventricle. PR is early diastolic phase, most commonly seen secondary to various aetiologies causing pulmonary hypertension and dilation of the pulmonary artery. PR has a similar haemodynamic basis as aortic regurgitation (AR) except that the changes in pressures and volumes are noted on the right side of the heart (pulmonary artery, right ventricle, and right atrium).

Systolic AR had been identified in valvular heart disease or heart failure (HF) and showed capability for predicting HF.[1–6] Systolic AR was explained as the inability of the ventricular contraction to overcome the aortic pressure in patients with valvular incompetence. This phenomenon is associated with pulsus alternans and ineffective contraction, which is common in severe left-side HF.[7]

We found that simultaneous tricuspid regurgitation and PR at systolic phase in patients with acute decompensated HF (*Figure 1A–1D*), and systolic PR disappeared after discharge. The prevalence and clinical significance of systolic PR were

Figure 1 Simultaneous tricuspid regurgitation and pulmonary regurgitation (PR) at systolic phase in patients with acute decompensated heart failure. (A) Systolic PR simultaneous with tricuspid regurgitation at a patient with acute heart failure due to post-partum cardiomyopathy and (B) continuous-wave Doppler recording over right ventricular outflow tract; (C) the same phenomenon occurred at a patient with acute ischaemic heart failure and (D) continuous-wave Doppler over right ventricular outflow tract.



not investigated before. After searching for systolic PR and HF in MEDLINE, only one article mentioned end-diastolic PR pressure gap, which was associated with left ventricular (LV) filling pressure, showing prognostic significance in HF cases.[8] In line with systolic AR presenting in systolic LV HF, we hypothesized that systolic PR could be a phenomenon of biventricular HF if right ventricular (RV) dysfunction cannot overcome elevated pulmonary vascular resistance (PVR). Accordingly, the study was retrospectively conducted to assess the frequency and outcome impact of systolic PR, and invasive haemodynamic study in cases with acute decompensated HF.

Methods

Patient enrolment

Retrospective screening of E-Da Hospital 10 year database of hospitalization for acute severe systolic LV HF was performed to clarify the true prevalence of systolic PR in this cohort. Severe LV systolic dysfunction is defined as LV ejection fraction (LVEF) $<$35%. The echocardiograms at first admission of systolic LV HF were reviewed, and all patients were subdivided according to the presence of systolic PR. We also screened echocardiographic database of past 1 year to detect the systolic PR prevalence in cohort with normal LVEF. The study protocol was approved by the institutional review board of E-Da Hospital. The requirement for written informed consent was waived by clinic institutional review board that gave its approval for this study.

Clinical characteristics

History of diabetes, hypertension, and smoking was recorded. At the index HF admission, subjects were considered hypertensive if they had high blood pressure or were under hypertension drug treatment. Diabetes mellitus was defined according to American Diabetes Association criteria.[9] At

enrolment, creatinine clearance (CCr) was estimated by Cockcroft–Gault equation, and renal dysfunction was defined as CCr $<$ 60 mL/min/1.73 m^2.[10] All electrocardiograms (ECGs) were reviewed for atrial fibrillation and bundle branch block. Coronary artery disease was defined as any history of the following: (i) myocardial infarction; (ii) at least 70% stenosis in one or more coronary vessels on coronary angiography; (iii) exercise-induced ischaemia indicated by treadmill electrocardiogram, nuclear perfusion stress imaging, or coronary computedtomography angiogram; or (iv) coronary revascularization. Any signs of HF at index HF hospitalization were under detailed reviews. Pulmonary oedema is defined as paroxysmal nocturnal dyspnoea, orthopnoea, pulmonary rales, a third heart sound, and pulmonary oedema on chest radiography, and low cardiac output is defined as inadequate peripheral perfusion including cold limbs, postural hypotension, effort-related tachycardia, oliguria, and poor digestion.

Echocardiographic parameters

Left ventricular ejection fraction was calculated by Simpson biplane technique. RV fractional area change was assessed by RV area change between systolic and diastolic phases at apical four-chamber views. RV dysfunction was defined as RV fractional area change $<$35%. Pulmonary artery systolic pressure was estimated using Doppler echocardiography by calculating RV to right atrial pressure gradient during systole. Right atrial pressure, estimated on the basis of echocardiographic characteristics of the inferior vena cava,[11] was then added to the calculated gradient. Pulsed-wave tissue Doppler imaging (TDI) was performed in apical views, and a pulsed-wave Doppler sample volume was placed at the level of the mitral annulus over the septal, lateral borders and RV basal annulus. The average early diastolic velocity (e′) of the septal and lateral mitral annuli was used in E/e′ for assessing diastolic filling.[12] Myocardial performance index of the right ventricle was calculated according to isovolumic contraction time (IVCT), relaxation time, and ejection time derived from TDI over RV basal annulus.[13] PVR was assessed by the ratio of peak tricuspid regurgitation velocity (TRV, m/s) to the RV outflow tract time–velocity integral (TVI_{RVOT}, cm) obtained by Doppler echocardiography (TRV/TVI_{RVOT} × 10 + 0.16; Wood units, multiply 80 dyn·s/cm^5).[14–16]

Definition of systolic pulmonary regurgitation and severity

Pulmonary regurgitation was assessed according to PR jet flow echo density compared with forward flow, PR jet deceleration time at continuous-wave Doppler measurement over RV outflow tract of parasternal short-axis view, and PR vena contracta/pulmonary artery diameter. If PR jet flow was dense with early termination, PR deceleration time was $<$260 ms, and PR vena contracta/pulmonary artery diameter was $>$0.7, it indicated severe PR. If PR jet flow density was soft, and PR vena contracta/pulmonary artery diameter was $<$0.5, it indicated mild tricuspid regurgitation. The other was defined as moderate PR.[17] Systolic PR was defined as the duration of PR beyond the QRS of ECG tracing, based on the presence of backward flow over pulmonary valve beyond QRS at colour Doppler image in parasternal short-axis view. Because systolic PR flow density and the ratio of vena contracta were less than PR, the grade of systolic PR was based on the diameter of vena contracta in the current study. If vena contracta of systolic PR was $>$0.7 cm, it was defined as Grade 3. If vena contracta of systolic PR was $<$0.5 cm, it was classified as Grade 1. The other was defined as Grade 2. The duration of systolic PR was measured as the interval from the initiation of QRS to the termination of systolic PR. The maximal velocities of PR and systolic PR were measured by continuous-wave Doppler at parasternal short-axis view.

Outcome assessment

The endpoints were HF rehospitalization and cardiovascular death after first HF admission. Hospitalization for HF was defined as a hospital stay of at least one night for treatment of a clinical syndrome with at least two of the following symptoms: low cardiac output, paroxysmal nocturnal dyspnoea, orthopnoea, elevated jugular venous pressure, pulmonary rales, a third heart sound, cardiomegaly on chest radiography, or pulmonary oedema on chest radiography. These clinical signs and symptoms might have represented a clear change from the normal clinical state of the patient and might have been accompanied by either failing cardiac output, as determined by peripheral hypoperfusion, or peripheral or pulmonary oedema requiring treatment with vasodilators, inotropes, or intravenous diuretics. Supportive documentation of a decreased cardiac index, an increased pulmonary capillary wedge pressure, decreasing oxygen saturation, and end-organ hypoperfusion, if available, was included in the adjudication. The definition of events was based on medical record reviews. For those with loss of follow-up or possible mortality, medical assistants telephoned patients or family to assess any cardiovascular event through medical interview. The certification of cardiovascular death was based on death records, death certificates, and hospital medical records.

Statistical analysis

The SPSS software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Baseline characteristics and echocardiographic parameters were analysed according to the presence of systolic PR or not. All continuous variables were

DOI: 10.1002/ehf2.13581

presented as means ± standard deviation. A P value <0.05 was considered statistically significant. Clinical characteristics were compared by χ^2 analysis of categorical variables. Kaplan–Meier curves of cardiovascular events according to systolic PR were estimated by the log-rank test. The relationship between the presence of systolic PR and clinical characteristics was assessed by multivariate logistic regression analyses. Cox proportional hazards regression models were used to analyse outcomes according to time-to-event data and associations between cardiovascular events and systolic PR while controlling for baseline characteristics and echocardiographic parameters.

Table 1 Clinical characteristics and echocardiographic parameters according to the presence of systolic PR or no systolic PR

Variables	No systolic PR $N = 390$	Systolic PR $N = 143$	P values
Age (years)	64 ± 15	65 ± 16	0.435
Systolic BP (mmHg)	104 ± 28	108 ± 31	0.116
Heart rate (b.p.m.)	95 ± 15	97 ± 17	0.141
Male gender (%)	132 (33.8%)	52 (36.4%)	0.273
Hypertension (%)	171 (33.8%)	74 (51.7%)	0.025
Diabetes (%)	126 (32.3%)	36 (25.2%)	0.044
Coronary artery disease (%)	201 (51.5%)	69 (48.3%)	0.476
Atrial fibrillation (%)	136 (34.9%)	55 (38.5%)	0.19
Bundle branch block (%)	82 (21%)	23 (16.1%)	0.082
Renal dysfunction (%)	116 (29.7%)	45 (31.5%)	0.432
Heart failure NYHA FC (1–4) at enrolment	2.9 ± 0.8	2.9 ± 0.8	0.896
Mitral stenosis more than moderate degree (%)	15 (3.8%)	10 (7%)	0.083
Mitral regurgitation grade (0–3)	1.7 ± 0.8	2.2 ± 0.8	<00001
Aortic stenosis more than moderate degree (%)	10 (2.6%)	5 (3.5%)	0.362
Aortic regurgitation grade (0–3)	0.6 ± 0.6	0.7 ± 0.8	0.091
Tricuspid regurgitation grade (0–3)	1.5 ± 0.6	1.9 ± 0.6	<0.0001
Prosthetic mitral valve	8 (2.1%)	3 (2.1%)	0.874
Prosthetic aortic valve	7 (1.8%)	3 (2.1%)	0.261
PASP (mmHg)	44 ± 14	51 ± 14	<0.0001
RV fractional area change (%)	44 ± 9	30 ± 10	<0.0001
LV end-diastolic volume (mL)	124 ± 34	128 ± 39	0.283
LV end-systolic volume (mL)	101 ± 26	103 ± 32	0.443
LVEF (%)	29 ± 5	28 ± 5	0.722
E/e′	20.5 ± 9.7	24.4 ± 9.5	0.004
RV IVCT (ms)	78 ± 16	106 ± 21	<0.0001
RV IVRT (ms)	100 ± 26	102 ± 25	0.617
RV myocardial performance index	0.73 ± 0.26	0.97 ± 0.29	0.032
Tricuspid regurgitation velocity (m/s)	3.0 ± 0.5	3.3 ± 0.5	0.344
Time–velocity integrity of RVOT (cm)	17.1 ± 2.6	11.6 ± 3.0	<0.0001
Estimated PVR (dyn·s/cm^5)	172 ± 32	238 ± 54	<0.0001
Signs of heart failure			
Pulmonary oedema (%)	295 (75.6%)	131 (91.6%)	0.001
Low cardiac output (%)	264 (67.8%)	121 (84.6%)	<0.0001
RV failure (%)	102 (26.2%)	112 (78.3%)	<0.0001
Pulmonary artery diameter (cm)	2.4 ± 0.4	2.5 ± 0.4	0.019
Pulmonary regurgitation severity (0–3)	0.4 ± 0.3	0.7 ± 0.4	<0.0001
Vena contracta of pulmonary regurgitation (cm)[a]	0.8 ± 0.2	0.9 ± 0.2	0.023
Maximal pulmonary regurgitation velocity (cm/s)[a]	179 ± 56	219 ± 58	<0.0001
Systolic pulmonary regurgitation severity (0–3)		1.4 ± 0.5	
Vena contracta of systolic pulmonary regurgitation (cm)		0.6 ± 0.2	
Maximal systolic pulmonary regurgitation velocity (cm/s)		156 ± 51	
Duration of systolic pulmonary regurgitation (ms)		12 ± 7	
Events			
HF rehospitalization	122 (31.3%)	86 (60.1%)	<0.0001
CV death	50 (12.8%)	31 (21.7%)	0.003
All cardiovascular events (HF and CV death)	139 (35.8%)	98 (68.5%)	<0.0001

BP, blood pressure; CV, cardiovascular; E/e′, peak early diastolic mitral flow velocity divided by peak early diastolic mitral annular velocity; HF, heart failure; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA FC, functional classification according to the New York Heart Association; PASP, pulmonary artery systolic pressure; PR, pulmonary regurgitation; PVR, pulmonary vascular resistance; RV, right ventricular; RVOT, right ventricular outflow tract.
[a]Number of no systolic PR = 204 and number of systolic PR = 143.

Results

Prevalence of systolic pulmonary regurgitation

Totally, 533 cases first hospitalized for systolic HF and LVEF < 35% were enrolled. Echocardiographies were available at each case, and subsequent echocardiographic studies after indexed hospitalization were under analyses. The clinical characteristics and echocardiographic parameters were listed in *Table 1*. Of 533 HF cases, 143 (26.8%) had systolic PR with variable severity grade during indexed hospitalization. There were 85 with Grade 1 of systolic PR, 55 with Grade 2, and 3 with Grade 3. Almost all systolic PR disappeared after discharge, and only 14% (20/143) cases demonstrated systolic PR during late follow-up.

Consequentially screening 5480 cases with normal LVEF from E-Da echocardiographic database in 1 year (*Table 2*), we found that only 18 cases had systolic PR and the prevalence was 0.3%. The identifiable/possible causes and echocardiographic parameters were shown in *Table 2*.

Table 2 Clinical characteristics and echocardiographic parameters of patients with normal LV systolic function and systolic PR

Variables	Systolic PR $N = 18$
Age (years)	72 ± 12
Systolic BP (mmHg)	125 ± 28
Heart rate (b.p.m.)	76 ± 16
Male gender (%)	10 (55.6%)
Hypertension (%)	5 (27.8%)
Diabetes (%)	4 (22.2%)
Coronary artery disease (%)	2 (11.1%)
Atrial fibrillation (%)	6 (33.3%)
Bundle branch block (%)	1 (5.6%)
Renal dysfunction (%)	3 (16.7%)
Mitral stenosis more than moderate degree (%)	3 (16.7%)
Mitral regurgitation grade (0–3)	1.5 ± 0.6
Aortic stenosis more than moderate degree (%)	0 (0%)
Aortic regurgitation grade (0–3)	1.2 ± 0.8
Tricuspid regurgitation grade (0–3)	1.7 ± 0.9
Mitral annuloplasty (%)	1 (5.6%)
Prosthetic mitral valve and aortic valve (%)	1 (5.6%)
RV failure (%)	11 (61.1%)
PASP (mmHg)	45 ± 12
RV fractional area change (%)	35 ± 8
LV end-diastolic volume (mL)	64 ± 12
LV end-systolic volume (mL)	32 ± 7
LVEF (%)	55 ± 6
E/e′	14.3 ± 6.4
Pulmonary artery diameter (cm)	2.3 ± 0.3
Pulmonary regurgitation severity (0–3)	0.7 ± 0.6
Vena contracta of pulmonary regurgitation (cm)	0.8 ± 0.2
Maximal pulmonary regurgitation velocity (cm/s)	181 ± 41
Systolic pulmonary regurgitation severity (Grades 0–3)	1.3 ± 0.6
Vena contracta of systolic pulmonary regurgitation (cm)	0.6 ± 0.2
Maximal systolic pulmonary regurgitation velocity (cm/s)	128 ± 33
Duration of systolic pulmonary regurgitation (ms)	11 ± 3

Abbreviations as shown in *Table 1*. Totally, 5480 cases with normal left ventricular systolic function were screened.

Systolic pulmonary regurgitation relates to other echocardiographic parameters

Compared with cases without systolic PR, systolic PR group had higher pulmonary artery systolic pressure, higher E/e′, and lower RV fractional area change. Pulsed-wave TDI showed longer RV IVCT and higher myocardial performance index in the systolic PR group than those without systolic PR (106 ± 21 vs. 78 ± 16 ms, $P < 0.0001$ and 0.93 ± 0.29 vs. 0.73 ± 0.26, $P = 0.032$, respectively). Estimated PVRs were higher in the systolic PR group than those without systolic PR (238 ± 54 vs. 172 ± 32 dyn·s/cm^5; $P < 0.0001$). Patients with systolic PR showed larger pulmonary artery diameter, more severe PR, and higher maximal PR velocity (219 ± 58 vs. 179 ± 56, $P < 0.0001$). Multivariate logistic regression analyses revealed that systolic PR correlated to baseline PR, E/e′, RV fractional area change, estimated PVR, low cardiac output, and pulmonary oedema at enrolment (*Table 3*).

Outcome analyses

Outcome analyses were according to time to event, and the mean duration from first indexed hospitalization for HF to the end of study was 5.9 ± 4.0 years. Kaplan–Meier curves of cardiovascular events according to systolic PR were shown in *Figure 2A–2C*. Systolic PR was associated significantly with cardiovascular events, particularly HF rehospitalization (log-rank $P < 0.0001$). Regarding cardiovascular death, it also reached statistical significance (log-rank $P = 0.0091$). Cardiovascular events according to the grade of systolic PR were shown in *Figure 3*.

To predict cardiovascular events, age, systolic PR, pulmonary artery systolic pressure, RV dysfunction at enrolment, E/e′, and mitral and tricuspid regurgitation severity were associated with events in univariate analyses (*Table 4*). Multivariate analyses revealed that both age and systolic PR were associated independently with further cardiovascular events. The presence of systolic PR had 2.266-fold risk increase of further HF hospitalization and cardiovascular death (hazard ratio 2.266, 95% confidence interval 1.682–3.089, $P < 0.0001$).

Invasive haemodynamic measurements

Figure 4 shows invasive haemodynamic measurements in a case with systolic PR at Day 7 of indexed HF hospitalization. Simultaneous pressure wave recordings show that LV systolic response occurred earlier than pulmonary artery (*Figure 4A*), and aortic systolic response occurs earlier than pulmonary artery (*Figure 4B*). Ineffective contraction of the right ventricle at second sinus beat suggested RV dysfunction, and

Table 3 Multivariate logistic regression analyses of the relationship between systolic pulmonary regurgitation and clinical characteristics in heart failure

Variables	Odds ratio (95% CI)	*P* values
Age (years)	1.009 (0.989–1.028) per 1 year increase	0.39
Atrial fibrillation	0.719 (0.386–1.362)	0.312
Pulmonary artery diameter (cm)	1.098 (0.531–2.269) per 1 cm increase	0.801
Pulmonary regurgitation severity (0–3)	2.489 (1.334–4.641) per 1 grade increase	0.004
Pulmonary artery systolic pressure (mmHg)	1.012 (0.990–1.035) per 1 mmHg increase	0.295
Tricuspid regurgitation severity (0–3)	0.899 (0.335–2.417) per 1 grade increase	0.834
Bundle branch block (LBBB or RBBB)	1.582 (0.644–3.886)	0.317
Left ventricular ejection fraction (%)	1.045 (0.979–1.116) per 1% increase	0.185
Right ventricular fractional area change (%)	0.938 (0.900–0.979) per 1% increase	0.003
Estimated PVR (dyn·s/cm^5)	1.424 (1.244–1.630) per 10 dyn·s/cm^5 increase	<0.0001
Low cardiac output at enrolment	1.178 (1.036–2.572)	0.006
Pulmonary oedema at enrolment	2.704 (1.422–5.131)	<0.0001
E/e′	1.072 (1.012–1.145) per 1 unit increase	0.011

CI, confidence interval; LBBB, left bundle branch block; PVR, pulmonary vascular resistance; RBBB, right bundle branch block.

Figure 2 Kaplan–Meier curves of cardiovascular events according to the presence of systolic pulmonary regurgitation (PR). Plots of (A) heart failure rehospitalization, (B) cardiovascular death, and (C) all cardiovascular events.

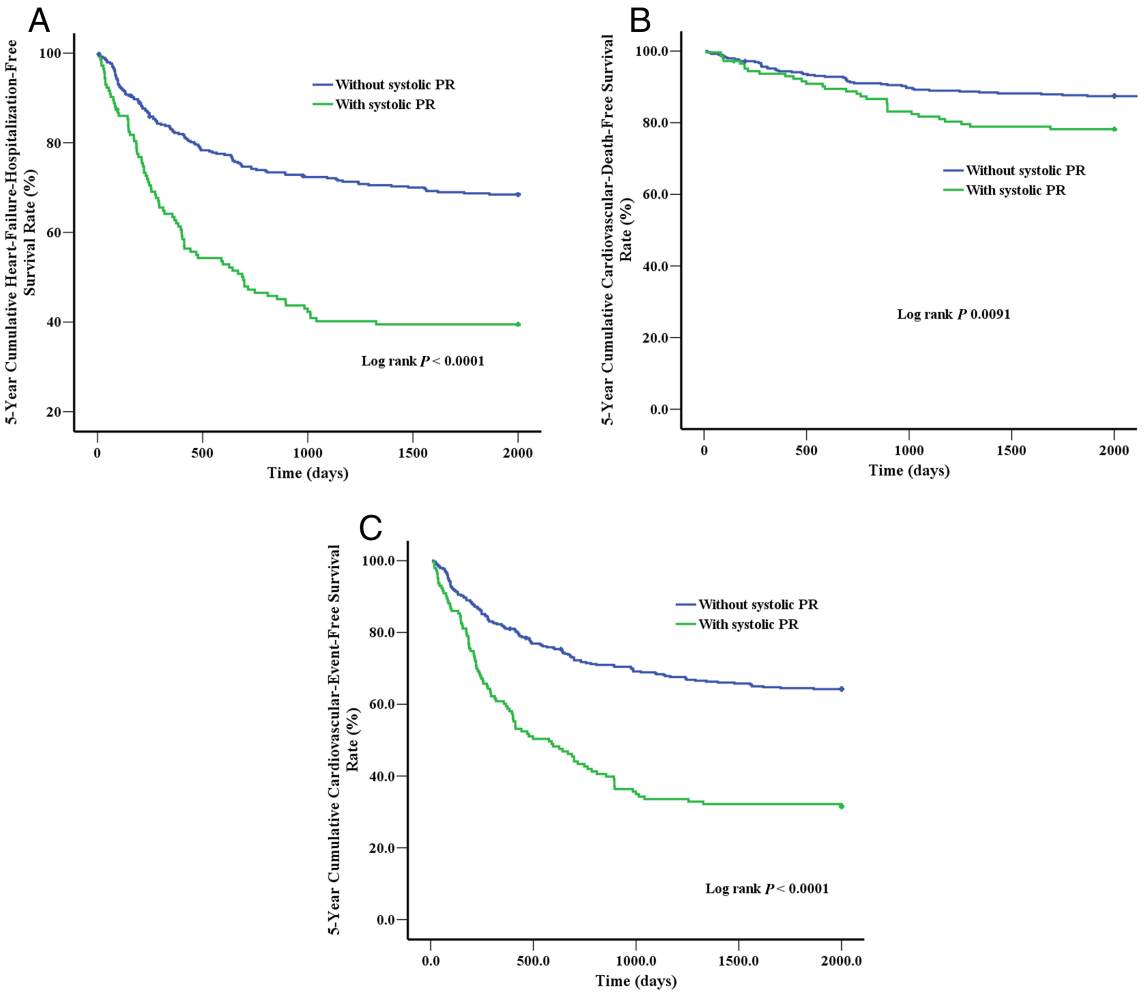
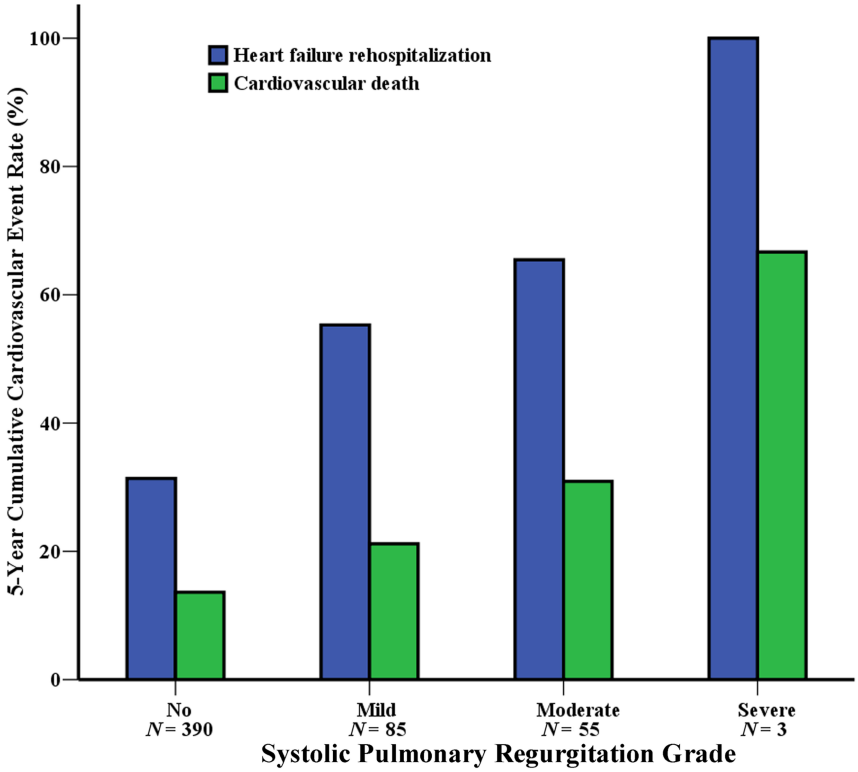


Figure 3 Five year cumulative cardiovascular events according the grade of systolic pulmonary regurgitation.



simultaneous pressure waves of right heart system revealed that pulmonary artery pressure was higher than RV pressure at early systolic phase (*Figure 4C*). Therefore, systolic PR existed at this period.

Discussion

High incidence of systolic pulmonary regurgitation and clues

The phenomenon of systolic PR was not uncommon at first hospitalization for systolic LV HF (26.8%, 143/533), associated significantly with further cardiovascular outcome (*Table 1*), and disappeared after discharge. Only 14% (20/143) cases persisted in systolic PR during late follow-up in this retrospective study. It was very rare in normal LVEF (0.3%, 18/5480) (*Table 2*). Like systolic AR, physicians are acquired to focus more on systolic PR.[1–7] Before elucidating systolic PR, systolic AR might provide some clues. Based on data, the prevalence of systolic AR is higher in HF population (5.9% vs. 2.1%).[18,19] Transient systolic AR can be an ineffective ejection phenomenon, which is commonly associated with ventricular extrasystole and the use of LV assist devices in patients, being a consequence of artificial suction by the device from the LV apex rather than a spontaneous finding, in HF patients with pre-existing AR.[7] Ineffective ejection responsible for generating pulsus alternans in HF cases could be explained by contractility variation as myocardial intracellular calcium availability during excitation–contraction coupling. It is also possible to observe sustained systolic AR in HF cases with sinus rhythm wherein rate of development of LV pressure is very slow and the aortic systolic pressure exceeds the LV systolic pressure during prolonged IVCT.[19]

Invasive haemodynamic recordings (*Figure 4*) demonstrated that systolic PR was due to the delay of RV systolic response with prolonged RV IVCT, and reverse pressure gap between pulmonary artery and the right ventricle after QRS of ECG. Ineffective RV ejection at sinus rhythm (*Figure 4C*) also provided the clues. Transient elevation of pulmonary artery pressure above RV pressure can be also due to a decrease in pulmonary artery compliance and an increase in main pulmonary artery size, impedance, and transmission time of the velocity wave.

Biventricular pumping dysfunction, high pulmonary vascular resistance, and pre-existing pulmonary regurgitation as determinants

Severe left-side HF with low cardiac output and pulmonary oedema indicates pumping failure with congestive left

DOI: 10.1002/ehf2.13581

Table 4 Univariate and multivariate analyses for predicting cardiovascular events including heart failure rehospitalization and cardiovascular-cause mortality

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* values	Hazard ratio (95% CI)	*P* values
Age (years)	1.011 (1.002–1.019) per 1 year increase	0.014	1.010 (1.001–1.018) per 1 year increase	0.027
Gender (female)	1.010 (0.773–1.320)	0.943		
Diabetes	1.032 (0.783–1.359)	0.825		
Hypertension	1.187 (0.920–1.532)	0.187		
Atrial fibrillation	1.252 (0.965–1.625)	0.090		
Coronary artery disease	1.135 (0.862–1.662)	0.752		
Left ventricular ejection fraction (%)	1.005 (0.978–1.034) per 1% increase	0.706		
Systolic pulmonary regurgitation	2.598 (2.003–3.369)	<0.0001	2.266 (1.682–3.089)	<0.0001
Pulmonary regurgitation grade (0–3)	1.190 (0.940–1.507) per 1 grade increase	0.148		
Mitral regurgitation grade (0–3)	1.198 (1.027–1.398) per 1 grade increase	0.022	1.033 (0.856–1.247) per 1 grade increase	0.734
Tricuspid regurgitation grade (0–3)	1.236 (1.028–1.488) per 1 grade increase	0.025	0.995 (0.772–1.281) per 1 grade increase	0.967
Pulmonary artery systolic pressure (mmHg)	1.010 (1.001–1.029) per 1 mmHg increase	0.030	1.001 (0.989–1.012) per 1 mmHg increase	0.918
Pulmonary oedema at enrolment	1.286 (0.886–1.866)	0.185		
Low cardiac output at enrolment	1.386 (0.954–1.956)	0.089		
Right heart failure at enrolment	1.808 (1.400–2.334)	<0.0001	1.223 (0.898–1.664)	0.201
E/*e'* at enrolment	1.113 (1.012–1.334) per 1 unit increase	0.023	1.014 (0.982–1.298) per 1 unit increase	0.096

CI, confidence interval.

ventricle, which brings high LV filling pressure. The pressure might go backward to left atrium and pulmonary circulation, which induces high PVR. All cases with systolic PR already had PR at baseline. If the right ventricle did not function well (RV fractional area change and RV myocardial performance index in *Table 1*), RV output might decrease markedly after facing very high PVR. Therefore, the existence of systolic PR indicated (i) RV pumping dysfunction, (ii) high PVR, and (iii) pre-existing PR. In late follow-up echocardiographies, 14% (20/143) showed persistent systolic PR, the grade of systolic PR less than that in indexed hospitalization. We assumed that the reduction of LV filling pressure improved PVR and RV function, which causes the disappearance of systolic PR in follow-up period. The prevalence of atrial fibrillation and bundle branch block was similar at patients with and without systolic PR (*Tables 1* and *3*), which indicated that systolic PR was not induced by arrhythmia or bundle branch block. However, advanced tissue Doppler imaging and two-dimensional/three-dimensional speckle tracking imaging for all segments of both right and left ventricles were not performed in the current study. The impacts of mechanical dyssynchrony (interventricular or intraventricular) on systolic PR require further investigation.[20–22] In addition, early wave reflection may increase RV wall stress and compromise RV function. It deserves to explore whether it contributes in some physiology variants to systolic PR or not. Further study design uses invasive pressure–volume conductance catheter technique to assess magnitude and timing of the reflected pressure, and analyses its correlation with RV function,[22,23] in patients with or without systolic PR.

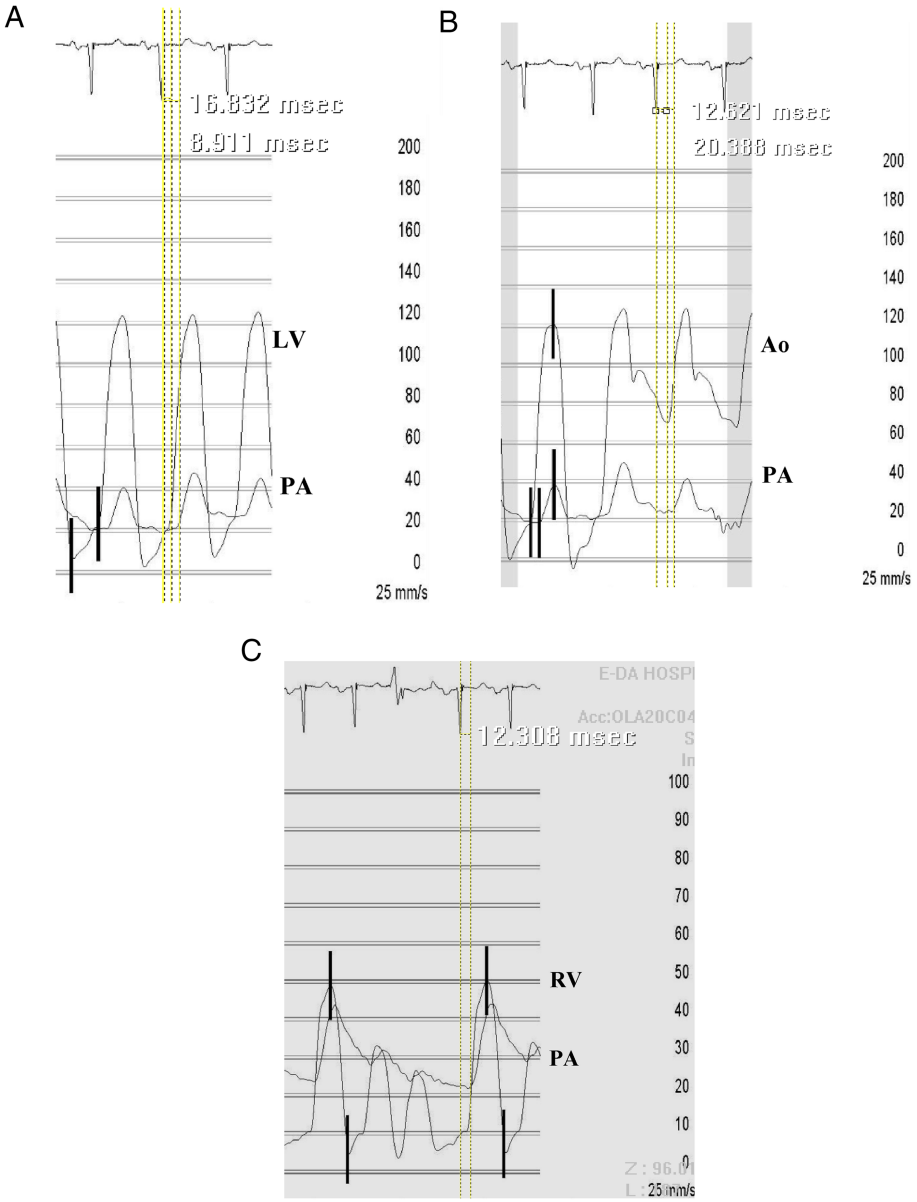
Clinical implications

For clinical application, physicians need to pay more attention to systolic LV HF cases with systolic PR and focus on the need of rapid reduction of high PVR, caused by poor LV compliance, high LV filling pressure, and mitral regurgitation. Loop diuretic is not a good choice because biventricular HF with profound low cardiac output already exists. Although loop diuretic reduces LV filling pressure and improves pulmonary oedema dramatically, it can be complicated with lower cardiac output and multiple organ failure. In this kind of biventricular HF cases, rapid up-titration of vasodilator after adequate preload with promotion forward flow and the reduction of LV filling pressure is a better choice.[24] In the meantime, physicians should keep maximal tolerable doses of evidence-based medications and consider device therapy as second line if medical treatment fails.

Study limitations

We acknowledge certain limitations of this study. This investigation was a single-centre retrospective observational

Figure 4 Invasive haemodynamic measurements in a case with systolic pulmonary regurgitation (PR). (A) Simultaneous pressure wave recording of the left ventricle (LV) and pulmonary artery (PA). (B) Simultaneous pressure wave recording of aorta (Ao) and PA. (C) Ineffective contraction of RV at second sinus beat indicates poor right ventricular performance, otherwise simultaneous pressure wave recording of RV and PA; due to delayed systolic response of RV, PA pressure was higher than RV at early systolic phase, which brought systolic pulmonary regurgitation.



study, a need for prospective validation. There were several questions needed to solve. For example, mechanical delay of the right ventricle for overcoming high PVR caused systolic PR, but it could not explain why tricuspid regurgitation and systolic PR occurred at the same time. We assume that the rate of increase of early systolic RV pressure might be delayed, so the ejection proceeds with RV systolic pressure exceeding right atrial pressure but is delayed to exceed (expectedly higher) diastolic pulmonary artery pressure. Second, the onset/end time of systolic PR compared with QRS termination of single-lead ECG was sometimes very hard to identify if artefact or arrhythmia occurred during echocardiography. Thus, we only enrolled well-documented pulmonary artery backward flow after clear image of QRS of ECG in multiple beats. Third, RV dysfunction was just dependent on RV fractional area change $<35\%$. The geometry of the right ventricle is not similar to that of the left ventricle, and the function of the right ventricle assessed by area change at apical four-chamber view might not be accurate enough to diagnose RV failure. It is also necessary to improve RV

function assessment in further study. Otherwise, diuretic use during acute systolic HF might omit RV failure sign. Thus, only 78.3% patients of systolic PR group could find RV failure sign, although RV fractional area change in systolic PR group was much lower than that in the group without systolic PR. Fourth, high E/e′ and PVR in systolic HF with systolic PR indicate that the primary driver of this phenomenon is LV diastolic dysfunction and high LV filling pressure. In patients with normal LVEF, the underlying cause of systolic PR could not be identified, although some cases had valvular heart disease, RV dysfunction, or elevated E/e′. It requires more integrated studies, including multimodality images and invasive haemodynamic measurement. Thus, we cannot conclude the primary driver of systolic PR until further prospective studies provide more data.

Conclusion

Systolic PR is common in first hospitalization of systolic LV HF and is associated with high PVR and RV dysfunction. It can subside after treatment. In spite of short-term phenomenon, systolic PR indicating acute biventricular HF has a significant impact on long-term cardiovascular outcome.

Conflict of interest

None declared.

Funding

This work was supported by the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-650-014 and 106-2314-B-038-094) and E-Da Hospital (EDAHP106026 and EDAHP105027).

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