Right coronary artery diastolic perfusion pressure on outcome of patients with left heart failure and pulmonary hypertension

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Abstract

Aims Right ventricle adaptation to prolonged exposure against pulmonary hypertension (PH) includes structural and functional abnormalities, translated into modifications of blood flow pattern through the right coronary artery. Given these changes, we investigate the relationship between right coronary artery diastolic perfusion pressure (RCDPP) and clinical outcome, in patients with PH secondary to left-sided heart failure (HF).

Methods and results We studied 108 HF patients who underwent right heart catheterization. PH was present in 75 (69.4%). Mean RCDPP was lower in patients with PH (59.4 ± 14.0 mmHg) as compared with no PH patients (65.5 ± 11.6 mmHg) (P = 0.03). Aortic diastolic pressure accounted for 79% of RCDPP variability explained by the model (P < 0.0001). During a median follow-up of 26 months, the RCDPP 1st tertile (<55 mmHg) [hazard ration (HR) 5.19, 95% confidence interval (CI) 1.08–25.12, P = 0.04] and left ventricular ejection fraction <45% [HR 7.26, 95% CI 1.77–29.73, P = 0.006] were independent predictors of mortality.

Conclusions Right coronary artery diastolic perfusion pressure is a strong independent haemodynamic marker of mortality in left-sided HF and PH. Excessive reduction of aortic diastolic pressure may be detrimental. Future research is necessary to determine the therapeutic approach to blood pressure in this population.

Keywords Heart failure; Pulmonary hypertension; Coronary perfusion pressure

Introduction

Pulmonary hypertension (PH) secondary to left heart failure (HF) is considered one of the most prevalent forms of PH,1 and its presence predicts poor prognosis.2–5 Development of PH in the setup of HF is a direct consequence of the increased left ventricle (LV) filling pressure and respectively of pulmonary capillary wedge pressure (PCWP).

Right ventricle (RV) adapts to prolonged exposure against high afterload by increasing wall thickness and contractility. This maladaptation of RV is translated into elevated intracavitary pressures, causing a reduction in right coronary artery (RCA) flow due to decreased coronary perfusion pressure gradient. Animal studies demonstrated that RV capability to increase its contractility as response to elevated pulmonary artery pressures is RCA flow dependent.6–8 Lately, it has been established that right coronary blood flow becomes strongly biphasic, with reduced systolic and markedly increased diastolic component,9 with the last one being correlated to the diastolic coronary perfusion pressure.

Given these modifications, we hypothesized that RCA diastolic perfusion pressure (RCDPP) may have implications on clinical outcome. The aim of the present study was to investigate the relationship between RCDPP and the outcome of patients with PH due to chronic left-sided HF. In addition, we sought to determine the impact of aortic and RV diastolic pressure on the variability of RCDPP.
Methods

Patients

The study population included all consecutive patients diagnosed with HF and functional capacity NYHA ≥2, who were submitted for haemodynamic evaluation by right heart catheterization (RHC) between 1 May 2016 and 31 December 2018. Exclusion criteria consisted of age < 18, acute decompensated HF, and any known or suspected potential aetiology for PH other than HF, such as congenital heart disease, connective tissue disease, lung disease, haematological disease, and valvular disease.

The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the institutional review board of Galilee Medical Center.

Haemodynamic evaluation

All catheterization measurements were performed in supine position at rest using fluoroscopic guidance in accordance with conventional standard techniques. Pressures were measured using a 7F Swan-Ganz catheter. Cardiac output (CO) was evaluated using the Fick method. Pressure measurements were taken at end expiration. Pulmonary vascular resistance (PVR) was calculated using standard formulas. RCDPP was calculated as the difference between the diastolic aortic pressure subtracted by end-diastolic right ventricle pressure.9

Based on the haemodynamic evaluation, the patients were classified into two groups: (i) no PH (mPAP ≤ 25 mmHg) and (ii) PH (mPAP > 25 mmHg, PCWP > 15 mmHg).1,10

Echocardiography

Right ventricular (RV) systolic function was quantitatively and qualitatively estimated by tricuspid annulus plane systolic excursion (TAPSE) and visual assessment. RV systolic dysfunction was considered to be present if at least moderate systolic dysfunction was observed.

The echocardiographic and haemodynamic assessments were performed during the same hospitalization.

Study endpoint

The pre-specified outcome, defined as all-cause mortality, was confirmed by manual review of patients’ records and discharge summaries, review of the national death registry, and by contacting each patient individually.

Statistics

Continuous variables are presented as mean ± SD or as medians with interquartile ranges (IQR), while categorical variables as numbers and percentages. Baseline characteristics of groups were compared using analysis of variance for continuous parametric and Kruskal–Wallis test for non-parametric variables, while \( \chi^2 \) for categorical variables.

Univariate linear regression was used to explore the relationship between RCDPP and diastolic pressures in aorta and right ventricle.

Right coronary artery diastolic perfusion pressure was categorized according to tertiles of distribution, with the highest tertile serving as the reference group.

Restricted cubic spline transformations11 of the continuous independent variable were implemented to detect potential nonlinear relationship between RCDPP and the likelihood of mortality. Marginal effects were used to compute the change in the probability that the outcome occurs according to unit changes in RCDPP, in order to detect significant modifications in spline’s slope.12,13

Survival curves were constructed using the Kaplan–Meier method and compared using log-rank test. Univariate and multivariate Cox proportional hazard models were used to analyse the relationship between RCDPP and mortality. Variables with demonstrated clinical significance and those with \( P < 0.1 \) in univariable analysis were included in the Cox multivariate model. The following parameters were considered as covariates in the models: age, gender, LV systolic function, RV systolic function, PH, right atrial pressure (RAP), PCWP, and peripheral vascular resistance (PVR). Differences were considered statistically significant at two-sided \( P < 0.05 \) level. Statistical analyses were performed using SPSS 15.0 (Chicago, Illinois) and STATA 12.0 (STATA Corp., College Station, Texas).

Results

During the study period, a total of 108 patients with chronic left-sided HF underwent RHC. PH was present in 75 (69.4%). The mean RCDPP was lower in the PH group (59.4 ± 14.0 mmHg) as compared with the no PH group (65.5 ± 11.6 mmHg) (\( P = 0.03 \)).

The clinical and haemodynamic characteristics of study population, according to the presence of PH, are presented in Table 1. PCWP was higher in the PH group, as well as RAP and PVR. In both groups, the majority of patients had preserved LV systolic function. The RV dysfunction was more frequent in patients with PH.

Figure 1 shows the linear relationships, with inverse slopes, between the diastolic pressures of aorta and right ventricle, respectively, and the RCDPP. In univariable analysis,
Table 1  Clinical and haemodynamic characteristics of patients with chronic left heart failure without pulmonary hypertension and with pulmonary hypertension

| Characteristics                      | No PH n (33) | PH n (75) | P-value |
|--------------------------------------|--------------|-----------|---------|
| Age (years)                          | 72.0 ± 9.1   | 68.7 ± 13.2 | 0.19    |
| Female (%)                           | 18 (54.5)    | 42 (56)   | 0.88    |
| eGFR (mL/min/1.73 m²)                | 63 ± 21      | 56 ± 28   | 0.11    |
| Hb (g/dL)                            | 11.8 ± 1.9   | 11.6 ± 2.4 | 0.76    |
| LVEF (%)                             | 59.9 ± 5.6   | 55.8 ± 10.4 | 0.57    |
| LVEF < 45%                           | 2 (6.7)      | 8 (11.3)  | 0.38    |
| RV dysfunction                       | 2 (6.7)      | 22 (31.4) | 0.005   |

Haemodynamic variables

| PCWP (mmHg)                          | 11.0 ± 4.3   | 18.9 ± 6.9 | <0.0001 |
| mPAP (mmHg)                          | 19.4 ± 3.3   | 37.8 ± 10.9 | <0.0001 |
| SV (mL)                              | 56.7 ± 13.7  | 59.6 ± 22.1 | 0.51    |
| CO (L/min)                           | 4.2 ± 1.0    | 4.5 ± 1.5  | 0.23    |
| Aortic systolic pressure (mmHg)      | 145.1 ± 28.6 | 149.3 ± 26.5 | 0.45    |
| Aortic diastolic pressure (mmHg)     | 73.5 ± 10.3  | 72.5 ± 16.0 | 0.72    |
| RV systolic pressure (mmHg)          | 35.3 ± 8.3   | 60.3 ± 18.7 | <0.0001 |
| RV diastolic pressure (mmHg)         | 8.0 ± 5.3    | 14.0 ± 5.7  | <0.0001 |
| RCDPP (mmHg)                         | 65.5 ± 11.6  | 59.4 ± 14.0 | 0.05    |
| PVR (WU)                             | 2.1 ± 1.2    | 4.8 ± 4.0   | <0.0001 |
| RAP (mmHg)                           | 7.3 ± 4.9    | 13.5 ± 5.4  | <0.0001 |

Medical therapy

| Beta-blockers                        | 24 (72.7)    | 52 (69.3)  | 0.45    |
| ACEI/ARB                             | 23 (69.7)    | 36 (48.0)  | 0.03    |
| MRA                                  | 6 (18.1)     | 36 (48.0)  | 0.003   |
| Diuretics                            | 21 (63.6)    | 63 (84.0)  | 0.20    |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CO, cardiac output; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; MRA, mineralocorticoid antagonist; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RCA, right coronary artery; RCDPP, right coronary artery diastolic perfusion pressure; RV, right ventricle; SV, stroke volume; WU, Wood’s unit.

Figure 1  Scatter plot and fit lines of right ventricle diastolic pressure and aortic diastolic pressure versus RCA diastolic perfusion pressure.
the aortic diastolic pressure model explained 79% of RCDPP variability, while the RV diastolic pressure model 21%.

**Relationship between right coronary artery diastolic perfusion pressure and survival**

The median follow-up period was 26 months (IQR 14–30 months). During this period, there was no difference in mortality between the PH and no PH groups (20.0% and 12.1%, respectively; \( P = 0.32 \)). However, after the PH group was classified according to RCDPP tertiles, the all-cause mortality occurred in 25.7%, 5.9% and 9.1% of patients in the first, second, and third RCA diastolic perfusion pressure tertile, respectively (\( P = 0.03 \)).

The implementation of cubic spline regression was used to explore potential non-linear relationship between RCDPP and mortality. It was observed that the probability of mortality increased progressively with RCDPP reduction, in an inversed J-shaped curve. The predicted margins of mortality probability allowed to detect the change in the slope of the spline which became stepper for patients with right coronary diastolic perfusion pressure below 55 mmHg (Figure 2).

Using RCDPP tertiles classification, the Kaplan–Meier analysis showed a significant increased cumulative probability of mortality of the 1st tertile in comparison with the two others (Figure 3).

Multivariate Cox proportional hazard models were constructed to determine independent clinical and haemodynamic predictors of mortality. In univariable Cox proportional hazards model, the first RCDPP tertile, age and LVEF < 45% were associated with mortality (Table 2). After multivariable adjustment, only the first tertile of RCDPP and the LVEF < 45% remained associated with increased mortality.

**Discussion**

The results of the present study demonstrate that the diastolic perfusion pressure of the RCA is a significant haemodynamic characteristic of chronic left-sided HF and PH.

Right coronary artery diastolic perfusion pressure was a robust independent marker of long-term risk for all-cause mortality in group 2 PH type patients and may contribute to the increased mortality associated with this population. An inverse non-linear association between the magnitude of RCDPP and the probability of death was demonstrated.

The variability of RCDPP was mainly explained by changes in the diastolic pressure of aorta and less by RV diastolic pressure, inferring a possible approach strategy in systemic afterload reduction for patients with left-sided HF and PH.

Development of pulmonary hypertension secondary to left-sided HF represents an advanced stage of the disease and is complicated by high mortality.

Although the pathobiology is multifactorial, the outcome is closely related to RV function.

Under normal conditions, the RV operates against a low resistance and high capacitance vascular system. The thin wall nature of the chamber is not designed to confront an elevated PAP, secondary to backward transmission of the increased PAWP. However, when chronically exposed to this high afterload, the RV adapts by hypertrophy and later by ventricular dilation, similar to changes taking place in pulmonary arterial hypertension (PAH). This remodelling pattern of RV, in order to generate sufficient mechanical energy, entails enhanced oxygen demand.

Under normal loading conditions, in contrast to the left ventricle (LV), systolic intra-myocardial pressure is low in the RV and thus does not produce compressive forces that interfere with blood flow through RCA, allowing perfusion throughout the entire cardiac cycle.

**Figure 2** Cubic spline analysis of the probability of mortality and RCA diastolic perfusion pressure. The dash dot lines represent the 95% confidence interval.
In animal models, the systolic RCA flow has been described to be attenuated in conditions of RV systolic hypertension, imposed by the reduction in systolic driving pressure defined as the difference between aortic and right ventricular systolic pressures. Similar findings were reported by studies in humans with PH, where RCA systolic flow was blunted and inversely related to the magnitude of RV systolic pressure. The RCA flow profile demonstrated biphasic pattern with markedly reduced systolic component, yet notably increased diastolic flow, strongly correlated to the diastolic coronary perfusion pressure. The pressure-flow autoregulation is attenuated in the right, as compared with the left coronary circulation, with RCA blood flow variation being a function of perfusion pressure. The steep slope of this almost linear relationship in the right coronary circulation implies a proportional reduction of blood flow with a decrease in coronary perfusion pressure. It is interesting to note that elevation in RV afterload causes the slope to become even steeper. This coronary blood flow reduction, imposed by the intrinsic RCA properties, is translated into a transmural and uniform myocardial hypo-perfusion of RV.

Table 2 Unadjusted and adjusted Cox’s proportional hazards model for all-cause mortality

| Characteristics          | Unadjusted            | Adjusted               |
|--------------------------|-----------------------|------------------------|
| Age (per 10 years)       | 1.98 (1.09–3.59)      | 0.016                  |
| EF < 45%                 | 4.53 (1.22–16.80)     | 0.02                   |
| RCDPP                    |                       |                        |
| First tertile (<55 mmHg) | 4.74 (1.02–22.01)     | 0.004                  |
| Second tertile (56–68 mmHg) | 0.93 (0.13–6.67)      | 0.95                   |
| Third tertile (>68 mmHg) | 1.0 (Referent)        | 1.0 (Referent)         |

CI, confidence interval; EF, ejection fraction; HR, hazard ratio; RCDPP, right coronary artery diastolic perfusion pressure

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It could conceivably be hypothesized that in patients with left-sided HF and PH, a disequilibrium status between oxygen supply and demand of RV may appear. This mismatch is a result of RCA blood flow dependence on diastolic coronary perfusion pressure and blunted auto-regulatory capability on one side, and augmented oxygen demand due to maladaptive remodelling of the ventricle on the other side. This theory corroborates with the findings of myocardial ischaemia of the chamber and its inability to cope with a high work demand.

Because RV function is a major prognostic marker of left-sided HF complicated by PH, it is not surprising to observe that RCA diastolic perfusion pressure magnitude portends prognostic information, as was demonstrated in the present study. The significant increase in mortality among patients with RCA diastolic perfusion pressure below a threshold of 55 mmHg is in agreement with analysis by Lee et al. who reported an aortic diastolic pressure below 70 mmHg to be significantly related to increased mortality and rehospitalization for left-sided HF patients.

The imposed significance of aortic diastolic pressure on RCDPP variability demonstrated by this study has direct haemodynamic and therapeutic consequences. RCDPP can be lowered through a reduction of the diastolic systemic blood pressure, in conformity with current practice, recommendations, and guidelines for hypertension and heart failure.

Figure 3 Kaplan–Meier plot according to tertiles of RCA diastolic perfusion pressure.

Table 2 Unadjusted and adjusted Cox’s proportional hazards model for all-cause mortality

| Characteristics          | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|--------------------------|------------------------|---------|----------------------|---------|
| Age (per 10 years)       | 1.98 (1.09–3.59)       | 0.016   | -                    | -       |
| EF < 45%                 | 4.53 (1.22–16.80)      | 0.02    | 7.26 (1.77–29.73)    | 0.006   |
| RCDPP                    |                        |         |                      |         |
| First tertile (<55 mmHg) | 4.74 (1.02–22.01)      | 0.004   | 5.19 (1.08–25.12)    | 0.04    |
| Second tertile (56–68 mmHg) | 0.93 (0.13–6.67)      | 0.95    | 0.80 (0.11–5.75)     | 0.82    |
| Third tertile (>68 mmHg) | 1.0 (Referent)         | -       | 1.0 (Referent)       | -       |

CI, confidence interval; EF, ejection fraction; HR, hazard ratio; RCDPP, right coronary artery diastolic perfusion pressure
failure. Nonetheless, due to paucity of evidence, avoidance of aortic diastolic pressure below 70 mmHg is advised27,28 sparsely, with others not specifying a blood pressure target, but instead recommending drug up-titration to dosages that patients tolerate without developing adverse events. The results reported in the present study are prima facie evidence that in left-sided HF and PH population, the therapeutic approach request knowledge of haemodynamic parameters, while medication should be tailored to target an aortic diastolic pressure sufficient to maintain RCA diastolic perfusion pressure above 55 mmHg, in order to achieve beneficial results.

**Study limitations**

Our study has some limitations that merit emphasis. First, the present analysis is retrospective, and thus, the results must be regarded as hypothesis generating and exploratory, and require validation in supplementary studies. Second, RV function assessment data were available at baseline only. Therefore, there is no direct evidence that the association between RCDPP and mortality is driven by progressive deterioration in RV function. Finally, no data was available regarding other conditions beside left side HF that may have contributed to development of PH.

**Conclusions**

Right coronary artery diastolic perfusion pressure is a strong independent haemodynamic maker of mortality in left-sided HF and PH. Excessive reduction of aortic diastolic pressure may be detrimental. Future research is necessary to determine the therapeutic approach to blood pressure in this population.

**Conflict of interest**

None declared.

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