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ORIGINAL RESEARCH ARTICLE

Baseline diastolic pressure gradient and pressure reduction in chronic heart failure patients implanted with the CardioMEMS™ HF sensor

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Abstract

Aims Remote haemodynamic monitoring (RHM) decreases hospitalization rates in patients with chronic heart failure (HF). Many patients with chronic HF develop pulmonary hypertension (PH) secondary to left heart disease with some acquiring combined pre-capillary and post-capillary PH (Cpc-PH). The efficacy of RHM in achieving pulmonary pressure reductions in patients with Cpc-PH vs. isolated post-capillary PH (Ipc-PH) is unknown. The purpose of this study is to evaluate whether a higher baseline diastolic pressure gradient ($DPG_{baseline}$) measured at the time of CardioMEMS™ HF sensor implantation is associated with lower reductions in pulmonary artery diastolic pressures (PADP).

Methods and results This was a retrospective analysis of 32 patients meeting clinical indications for CardioMEMS™ implantation. $DPG_{baseline}$ categorized patients as Cpc-PH (DPG $\geq$ 7 mmHg) or Ipc-PH (DPG $<$ 7 mmHg). Minimum achievable PADP ($PADP_{min}$) and ΔPADP ($PADP_{baseline} - PADP_{min}$) were determined. Pearson's correlation analysis and comparison of mean pressure changes were assessed. Median age was 69 years, and median left ventricular ejection fraction (LVEF) was 25%. Eight patients (25%) had a LVEF ≥40%. Twenty-five patients (78%) met criteria for Ipc-PH and seven (22%) for Cpc-PH. Neither $PADP_{min}$ (ρ = 0.27; P = 0.13) nor ΔPADP (ρ = 0.07; P = 0.72) was correlated with $DPG_{baseline}$. A trend towards higher ΔPADP was seen in Cpc-PH vs. Ipc-PH patients (15.2 vs. 9.88 mmHg; P = 0.12). There was a moderate positive correlation between baseline PADP and ΔPADP [ρ = 0.55 (0.26–0.76); $P < 0.001$].

Conclusions Decreased PADP reduction was not seen in Cpc-PH vs. Ipc-PH patients. Higher $PADP_{baseline}$ was associated with greater ΔPADP. Larger studies are needed to elaborate our findings.

Keywords Combined pre-capillary and post-capillary pulmonary hypertension; Isolated post-capillary pulmonary hypertension; Implantable haemodynamic monitoring; Heart failure

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Introduction

Heart failure (HF) patients with pulmonary hypertension (PH) secondary to left heart disease (PH-LHD) experience worse outcomes than those without coexistent PH.[1–6] Isolated post-capillary PH (Ipc-PH) represents a unique subset of those with PH and can be defined by a diastolic pulmonary gradient (DPG) <7 mmHg, while combined pre-capillary and post-capillary PH (Cpc-PH) patients have a DPG ≥7 mmHg.[3] More importantly, Cpc-PH patients not only develop maladaptive pulmonary vascular remodelling but also have poorer right ventricular–pulmonary vascular coupling and worse clinical outcomes.[1,5,7–10]

To date, there is no proven medical therapy to improve morbidity and mortality in patients with PH-LHD.[11] A recent retrospective analysis of the PH-LHD subset of patients from the CardioMEMS™ Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients (CHAMPION) Trial[12] found that pressure-guided therapy with remote haemodynamic monitoring (RHM) using the CardioMEMS™ HF sensor reduced the composite endpoint of death and HF

hospitalization.[13] The study did not evaluate serial haemodynamic changes in patients with Cpc-PH vs. Ipc-PH over time; the CardioMEMS™ HF sensor has been shown to have minimal pressure drift over time.[14] Additionally, the clinical implications of a higher DPG at the time of sensor implantation were not explored. Given the unique phenotypic differences in patients with Cpc-PH and Ipc-PH, we felt it was important to characterize the clinical responses to determine if one group was more likely to achieve a higher or lower pressure reduction than the other. Should a substantial difference exist between groups, it would have clinical implications for patient selection and prioritization for device implantation.

We sought to evaluate patients with PH-LHD to determine if a higher baseline DPG measured at the time of CardioMEMS™ HF sensor implantation is associated with a lower serial pressure reduction of the pulmonary artery diastolic pressure (PADP).

Methods

Patient selection

This was a two-site study with an initial cohort of 55 patients meeting clinical indications for implantation of the CardioMEMS™ HF sensor. For the purposes of this analysis, we included only patients with PH-LHD, defined as mean pulmonary artery pressure (mPAP) $\geq$25 mmHg and pulmonary capillary wedge pressure (PCWP) $>$15 mmHg. Twenty-three patients who did not have PH-LHD by these criteria were excluded, yielding a final study cohort of 32. Patients were included regardless of ejection fraction, and all patients were required to have the CardioMEMS™ HF sensor implanted for at least 180 days. Written informed consent was not required for this retrospective analysis.

Remote haemodynamic monitoring and transmission

At the time of CardioMEMS™ HF sensor implantation, all patients were provided with device teaching and required to demonstrate their ability to obtain accurate pressure readings using their home unit prior to hospital discharge. Patients were instructed to transmit readings on a daily basis. A trained medical assistant monitored the CardioMEMS™ HF system website (Merlin.net) daily for patient compliance with pressure transmission. If patients did not have pressure transmissions for two consecutive days, they were contacted and encouraged to resume daily readings.

Haemodynamic measurements

Baseline haemodynamic indices were calculated based upon values obtained at the time of CardioMEMS™ HF sensor implantation, referred to as baseline pressures. DPG was calculated PADPbaseline minus PCWP. Transpulmonary pressure gradient (TPG) was calculated as mPAP – PCWP. Pulmonary vascular resistance (PVR) was calculated as TPG/cardiac output. Patients were categorized as having Cpc-PH if they met the criteria for PH-LHD and had a DPG $\geq$7 mmHg. Patients were categorized as having Ipc-PH if they met the criteria for PH-LHD and had a DPG $<$7 mmHg. The analysis was repeated using a TPG cut-off of $>$12 mmHg and a PVR cut-off of $\geq$3 Wood units to classify patients into the Cpc-PH group[3] (Supporting Information). All available CardioMEMS™ pressure readings for each patient were evaluated by a single reviewer (A. M. W.) for a period of up to 180 days from the time of CardioMEMS™ HF sensor implantation. The minimum transmitted PADP ($PADP_{min}$) during the study period was recorded based upon review of the pressure transmissions. The maximum magnitude of pressure reduction over the study period was calculated as $PADP_{baseline} - PADP_{min}$ and was defined as delta PADP (ΔPADP).

Statistical analysis

Baseline clinical characteristics are reported as either mean ± standard deviation or median and interquartile range. Baseline clinical characteristics were compared with *t*-tests or the Mann–Whitney U test for continuous variables or Pearson's χ^2 test or Fischer's exact test for categorical variables. The Shapiro–Wilk test was used to evaluate for a normal distribution. Pearson's correlation analysis was performed between baseline DPG, TPG, and PVR and either $PADP_{min}$ or ΔPADP. Correlation between $PADP_{min}$ and ΔPADP with $PADP_{baseline}$ was assessed using Pearson's correlation. Similar analyses were performed, categorizing patients into Cpc-PH and Ipc-PH groups based upon TPG and PVR cut-offs as specified above. Significance levels were two-sided with a *P* value of $<$0.05.

Results

Patient characteristics

Baseline patient characteristics are shown in *Table 1*. Median age for the entire cohort was 69 years, 22 (69%) were male, and 19 (59%) were White. Eight patients (25%) had a left ventricular ejection fraction $\geq$40%, and median ejection fraction was 25%. Based on a DPG $\geq$7 mmHg, 25 patients (78%) were categorized into the Ipc-PH group and 7 patients (22%) into the Cpc-PH group. There were no significant differences

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Table 1 Baseline clinical characteristics of patients presented as the entire cohort and stratified according to isolated post-capillary pulmonary hypertension and combined pre-capillary and post-capillary pulmonary hypertension subgroups

Variable	Entire cohort (n = 32)	Ipc-PH (n = 25)	Cpc-PH (n = 7)	P value
Age (years)	69 (60–75)	69 (60–74)	68 (58–74)	0.91
Male	22 (69%)	18 (72%)	4 (57%)	0.74
Race (White)	19 (59%)	14 (56%)	5 (71%)	0.72
Body mass index (kg/m^2)	29.6 (24–35.1)	29.1 (24–35)	32.7 (30.7–35.3)	0.24
Diabetes mellitus	19 (59%)	16 (64%)	3 (43%)	0.6
Hypertension	22 (69%)	19 (76%)	3 (43%)	0.44
Atrial fibrillation	20 (63%)	17 (68%)	3 (43%)	0.54
Ischaemic cardiomyopathy	18 (56%)	15 (60%)	3 (43%)	0.66
Coronary artery disease	19 (59%)	16 (64%)	3 (43%)	0.6
Heart failure with preserved ejection fraction	8 (25%)	5 (20%)	3 (43%)	0.36
Left ventricular ejection fraction (%)	25 (20–39)	25 (20–35)	38 (20–53)	0.29
Creatinine (mg/dL)	1.61 ± 0.47	1.64 ± 0.51	1.48 ± 0.32	0.32
Pulmonary artery diastolic pressure (mmHg)	25.4 ± 5.6	24.3 ± 5.3	29.4 ± 5.5	0.0526
Mean pulmonary artery pressure (mmHg)	36.1 ± 7.3	35.1 ± 6.5	40.0 ± 9.3	0.27
Pulmonary capillary wedge pressure (mmHg)	23.8 ± 5.9	24.6 ± 5.9	20.7 ± 5.4	0.12
Transpulmonary gradient (mmHg)	12.3 ± 5.8	10.5 ± 4.5	18.9 ± 5.3	0.004
Pulmonary vascular resistance (Wood units)	3.4 ± 1.6	3.2 ± 1.6	4.1 ± 1.5	0.17
Cardiac output (L/min)	3.9 ± 1.4	3.6 ± 1.4	4.78 ± 1.4	0.072

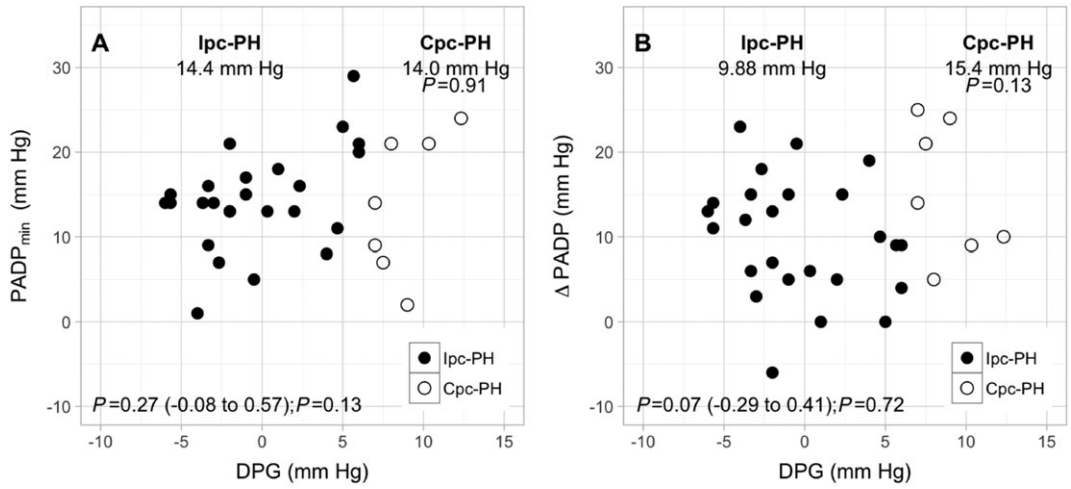
Data presented as mean ± standard deviation or median with interquartile range.

between the groups with respect to age, male gender, race, body mass index, ejection fraction, or co-morbid medical conditions. Baseline PADP (29.4 vs. 24.3 mmHg; P = 0.0526) and mPAP (40.0 vs. 35.1 mmHg; P = 0.27) were numerically greater in the Cpc-PH group than in the Ipc-PH group, while the PCWP (20.7 vs. 24.6 mmHg; P = 0.12) was numerically smaller in the Cpc-PH than in the Ipc-PH group, suggesting the former group was closer to euvolaemia than the latter. Not surprisingly, TPG was significantly higher in the Cpc-PH group compared to the Ipc-PH group (18.9 vs. 10.5 mmHg, P = 0.004, respectively). Additionally, cardiac output (4.78 vs. 3.6 L/min; P = 0.072) and body mass index (32.7 vs. 29.1 kg/m^2) were both numerically higher in the Cpc-PH group than in the Ipc-PH group, respectively. Body surface area was not available in all patients; therefore, the calculation of cardiac index and subsequent comparisons were not performed.

Correlation analysis

Correlation analysis was applied to assess the association of baseline DPG on the minimum achievable PADP ($PADP_{min}$)

Figure 1 (A) Minimum pulmonary artery diastolic pressure ($PADP_{min}$) is plotted vs. baseline diastolic pressure gradient (DPG) for both isolated post-capillary pulmonary hypertension (Ipc-PH, closed circles) and combined pre-capillary and post-capillary pulmonary hypertension (Cpc-PH, open circles) groups. (B) Change in pulmonary artery diastolic pressure (ΔPADP) is plotted vs. baseline DPG for both Ipc-PH (closed circles) and Cpc-PH (open circles) groups. The correlation coefficient (with 95% confidence interval and P value) and mean $PADP_{min}$ (A) and mean ΔPADP (B) for Ipc-PH vs. Cpc-PH (with P values comparing means) are shown superimposed on each figure. Each symbol represents one patient.



and the maximum achievable pressure reduction (ΔPADP) (*Figure 1*). There was no significant association with baseline haemodynamic indices assessed across a range of DPG from −6 to 12 mmHg. Scatterplots of the raw data are shown in *Figure 1*. There were no significant differences in the mean $PADP_{min}$ (14.4 vs. 14.0 mmHg, $P = 0.91$); however, there was a numerical, but not statistically significant, difference in the mean ΔPADP (9.88 vs. 15.4 mmHg, $P = 0.13$) between patients in the Ipc-PH and Cpc-PH subgroups. See *Figure S1* for similar analysis using TPG-specific and PVR-specific cut-offs. There was no significant correlation between $PADP_{min}$ and baseline PADP (*Figure 2*) [$\rho = 0.23$ (−0.12 to 0.54), $P = 0.20$]. However, baseline PADP had a moderate and significant positive correlation with ΔPADP [$\rho = 0.56$ (0.26 to 0.76); $P < 0.001$].

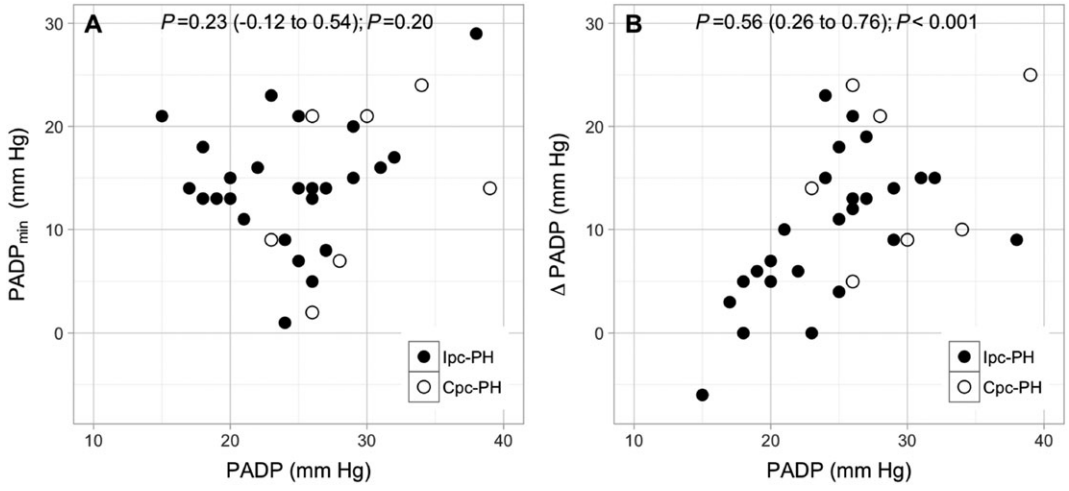
Discussion

In this cohort of patients with the CardioMEMS™ HF sensor implanted for clinical indications, we found that the baseline haemodynamic index of Cpc-PH studied, DPG, was not correlated with either $PADP_{min}$ or ΔPADP during a follow-up period of 180 days. However, there was a numerical difference in the mean ΔPADP (15.4 vs. 9.88 mmHg, $P = 0.13$) between the Cpc-PH and Ipc-PH groups, respectively; albeit with only seven Cpc-PH patients (vs. 25 Ipc-PH patients). Nevertheless, this finding warrants investigation in a larger cohort to see if this difference becomes significant—upon completion of the CardioMEMS™ Post Approval Study (NCT02279888),[15] a larger and more definitive analysis may soon be possible. Our finding that ΔPADP increased with higher baseline PADP may simply represent (1) regression to the mean and/or (2) that pressure reduction is unlikely in a patient with goal or near-goal baseline PADP. Whether acquired pulmonary vascular disease in Cpc-PH patients poses a barrier to pressure reduction (ΔPADP) remains a key question to answer. If so, it would require clinicians to re-calibrate pressure reduction goals with baseline haemodynamic status in mind. While our findings suggest that the efficacy of RHM may depend on baseline haemodynamic parameters, more investigation is needed.

The clinical implications of baseline haemodynamic status are especially important because current Food and Drug Administration criteria for CardioMEMS™ implantation only requires New York Heart Association functional class III symptoms and an HF hospitalization in the prior year. No consideration is given to concomitant Ipc-PH or Cpc-PH, and given worse outcomes in the Cpc-PH[16] subgroup, we felt it important to explore the magnitude of pressure response. Furthermore, *a priori* knowledge of anticipated pressure reduction based on phenotype may assist in daily management and how best to titrate medical therapy.

To the best of our knowledge, this is the first study to report on the serial haemodynamic changes in a heterogeneous group of patients with PH-LHD undergoing RHM for clinical indications. While these findings are from a small, two-site cohort of patients implanted for clinical indications outside of clinical trials, they suggest that continued serial RHM for patients along a spectrum of PH-LHD is essential because many of these patients will proceed to end-stage HF and ultimately require more advanced therapies.[17,18] A better understanding of the progression of the haemodynamic profile of patients with worsening HF will likely become a crucial element for

Figure 2 (A) Minimum pulmonary artery diastolic pressure ($PADP_{min}$) is plotted vs. baseline PADP and (B) ΔPADP vs. baseline PADP. Patients with isolated post-capillary pulmonary hypertension (Ipc-PH) are represented by closed circles and those with combined pre-capillary and post-capillary pulmonary hypertension (Cpc-PH) by open circles. The respective correlation coefficient with 95% confidence interval and *P* value is superimposed on each panel. Each symbol represents one patient.



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identifying the optimal timing of advanced HF strategies such as durable mechanical circulatory support[19] or heart transplantation, especially among the high-risk Cpc-PH population.[17]

Limitations

There are several limitations to the current analysis. The haemodynamic data were obtained from a relatively small number of patients treated at two different medical centres. Inherent in this study were issues related to the retrospective analysis of the data. There was no pre-specified, standardized reporting method for haemodynamic assessment. The small sample size limits the statistical power and generalizability of our findings. Association with outcome data was not explored. Additionally, management of elevated pressures did not follow a standardized protocol and therefore was provider specific across both institutions. Pulmonary vascular vasoreactivity studies to evaluate reversibility of pulmonary pressures were not routinely performed and were not incorporated into our analysis.

Conclusions

During a 6 month follow-up period, there was no observed correlation with serial pressure reduction and baseline DPG in patients managed with the CardioMEMS™ HF system. The finding of a numerical, but not statistically significant, difference between mean ΔPADP in the Cpc-PH vs. Ipc-PH groups warrants additional investigation. As such, larger studies of patients with PH-LHD along a wider spectrum of pulmonary vascular disease with associated outcome data are needed to better understand the implications of Cpc-PH in patients managed with RHM.

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None.

Conflict of interest

D. M. S. has served as a paid consultant, is on the speaker's bureau, and receives research support from Abbott Vascular. A. M. W has received speaking fees from Abbott Vascular. L. G. has received speaking fees from Abbott Vascular. L. S. has received research support from Abbott Vascular. R. J. is on the speaker's bureau and receives research support from Abbott Vascular.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Minimum pulmonary artery diastolic pressure ($PADP_{min}$) is plotted vs. baseline transpulmonary gradient (TPG) and baseline pulmonary vascular resistance (PVR) and shown in panels A and C, respectively. Change in pulmonary artery diastolic pressure (ΔPADP) is plotted vs. baseline TPG and baseline PVR and shown in panels B and D, respectively. Patients with Ipc-PH are represented by closed circles and those with Cpc-PH by open circles. The respective correlation coefficient with 95% confidence interval and *P* value is superimposed on each panel. Each symbol represents one patient.

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