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Correlation of laboratory haemoconcentration measures with filling pressures obtained via pulmonary arterial pressure sensors in ambulatory heart failure patients

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Aims

Laboratory measures of haemoconcentration correlate with invasive haemodynamics and clinical outcomes in hospitalized heart failure (HF) patients. We aimed to determine the association between haemoconcentration and haemodynamic measures in ambulatory HF patients with implantable pulmonary arterial pressure (PAP) sensors.

Methods and results

We reviewed ambulatory HF patients ($n = 23$) managed at the Brigham and Women's Hospital with implantable PAP sensors (CardioMEMS™, Abbott, Atlanta, GA, USA) who had sufficient data for serial haemodynamic–haemoconcentration correlation. The primary measures of interest were the absolute changes in haemoglobin and diastolic PAP at follow-up compared to baseline values (obtained at implantation). In 23 patients (median age 64 years, 57% with HF with preserved ejection fraction), 518 paired laboratory–haemodynamic measurements were evaluated. At a median follow-up of 27 (interquartile range 13–42) months, 17 (74%) patients had at least one hospitalization (59 total hospitalizations including 30 HF hospitalizations). For the population as a whole, diastolic PAP was negatively correlated with haemoglobin level ($r = -0.09$, $P = 0.053$). This negative correlation was more apparent when changes in haemoglobin and diastolic PAP were evaluated at the time of HF hospitalization compared to baseline values ($r = -0.40$, $P = 0.029$). The mean rise in diastolic PAP of 3.6 mmHg at HF hospitalization corresponded to a numerical decline of 0.6 g/dL in haemoglobin ($P = 0.20$).

Conclusion

Change in haemoglobin was correlated with change in diastolic PAP in ambulatory HF patients, especially at the time of HF hospitalization. These findings support the potential for investigation into the role of ambulatory monitoring of haemoglobin as an inexpensive, non-invasive tool to guide de-congestion strategies and potentially prevent HF hospitalizations.

Keywords

Pulmonary arterial pressure sensor • Plasma volume • Haemoconcentration • Congestion
 • Haemoglobin • Haematocrit • Heart failure

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Background

A rise in intracardiac filling pressures precedes overt clinical congestion and heart failure (HF) hospitalization by several weeks.¹ Implantable ambulatory haemodynamic monitoring allows early detection of rising filling pressures and may facilitate HF management to reduce hospitalizations.^{2,3} However, as an invasive procedure with high associated costs, this approach is not practical for use on a population scale. Changes in haemoglobin (Hb), haematocrit (Hct), and plasma volume correlate with invasive haemodynamics and clinical outcomes in hospitalized HF patients.⁴⁻⁶ We sought to explore the relationship between haemoconcentration and haemodynamic measures in an ambulatory HF patient population leveraging data from implantable pulmonary arterial pressure (PAP) sensors (CardioMEMS™, Abbott, Atlanta, GA, USA).

Methods

Patient selection and device management

We retrospectively reviewed HF patients ≥ 18 years old at the Brigham and Women's Hospital, Boston, MA, implanted with a CardioMEMS™ HF system device between January 2013 and July 2019. Patients with ≥ 6 months follow-up and ≥ 3 pairs of laboratory (Hb, Hct) and haemodynamic measures (pairs were defined as measurements of each obtained within 48 h) were included. Measurements obtained after left ventricular assist device implantation or heart transplantation were excluded. Patients who were implanted at Brigham and Women's Hospital but followed elsewhere were ineligible for this analysis. PAP-guided ambulatory HF management was directed by the advanced HF team following protocols to achieve patient-specific diastolic PAP (dPAP) goals.

Laboratory, haemodynamic and clinical outcome definitions

Patients recorded systolic PAP (sPAP), dPAP and mean PAP (mPAP) at home in the recumbent position at rest using a wireless sensor, which automatically uploads all recordings to a secure, web-based database for clinician review. The frequency of monitoring was determined by the treating nurse clinician. The nurse clinician, in conjunction with the patient's cardiologist, titrates diuretics and other guideline-recommended HF therapies to achieve patient's individual dPAP goal and to avoid HF hospitalization. Laboratory measures included Hb and Hct, which were obtained as part of routine clinical care. Estimated plasma volume status (ePVS) was calculated using the previously validated Duarte formula⁷: $ePVS \text{ (mL/g Hb)} = 100 \times (1 - \text{Hct})/\text{Hb} \text{ (g/dL)}$.

The first measurement obtained after device implantation was considered the patient's 'baseline' value and reflected their optimal uncongested state as our institutional protocol requires patients to be clinically stable and electively admitted for the implantation procedure. Measurements obtained within 1 day of hospitalization were defined as 'hospitalization' values.

Haemoconcentration measures were:

- (1) Absolute change in Hb in g/dL = Hospitalization Hb – Baseline Hb (primary laboratory measure of interest)

Table 1 Baseline characteristics and clinical outcomes of the study cohort

Age (years)	61.2 \pm 2.9
Women	13 (57)
Body mass index (kg/m ²)	36.3 \pm 2.3
HF history	
Ischemic aetiology	5 (22)
Non-ischaemic aetiology (including idiopathic)	18 (78)
Left ventricular ejection fraction (%)	43.3 \pm 4.0
HF with preserved ejection fraction (%)	13 (57)
Duration of HF before device implantation (years)	4.9 \pm 1.0
Renal function (creatinine) (mg/dL)	1.44 \pm 0.11
Estimated glomerular filtration rate (CKD-EPI) (mL/min/1.73 m ²)	52 \pm 5
Comorbidities	
Coronary artery disease	8 (35)
Diabetes mellitus	11 (48)
Dyslipidaemia	11 (48)
Hypertension	18 (78)
COPD	9 (39)
Atrial fibrillation	7 (30)
Medications	
Beta-blockers	20 (87)
ACE inhibitors/ARB	13 (57)
Angiotensin receptor–neprilysin inhibitor	1 (4)
Mineralocorticoid receptor antagonists	18 (78)
ICD or CRT	17 (74)
Clinical outcomes	
Follow-up duration (years)	2.3 \pm 0.3
Total number of all-cause hospitalizations	59
Primary diagnosis	
HF	30 (51)
Other cardiovascular causes (without HF) (e.g. NSTEMI, arrhythmias)	7 (12)
Acute kidney injury	6 (10)
Other (infections, COPD exacerbations)	16 (27)
Patients with at least one HF hospitalization	12 (52)
No. of HF hospitalizations per patient	2.0 [1.3–3.8]
Mean time from implantation to first HF hospitalization (years)	1.0 \pm 0.8
Patients with at least one all-cause hospitalizations	15 (65)
No. of all-cause hospitalizations per patient	4.0 [2.0–6.0]
Mean time from implantation to first all-cause hospitalization (years)	1.1 \pm 0.9
Left ventricular assist device implantation, heart transplantation, or death	3 (13)

Values are given as mean \pm standard deviation, *n* (%), or median [interquartile range].

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; NSTEMI, non-ST-elevation myocardial infarction.

Table 2 Laboratory and haemodynamic measures at baseline, at the time of heart failure and all-cause hospitalizations

Characteristics	Baseline (n = 23)	HF hospitalizations (n = 12)	All-cause hospitalizations (n = 15)	P-value for hospitalizations compared to baseline ^a	
				HF	All-cause
Laboratory measures					
Hb, g/dL	12.7 ± 0.3	12.1 ± 0.5	12.3 ± 0.4	0.20	0.59
Hct, %	39.1 ± 1.0	37.8 ± 1.3	38.1 ± 1.0	0.42	0.55
ePVS, mL/g Hb	4.9 ± 0.2	5.3 ± 0.3	5.1 ± 0.3	0.47	0.76
Haemodynamic measures					
HR, bpm	80.8 ± 2.5	90.4 ± 4.8	85.9 ± 4.2	0.027	0.16
dPAP, mmHg	20.5 ± 1.5	24.1 ± 3.2	21.0 ± 2.8	0.23	0.57
mPAP, mmHg	28.0 ± 1.9	33.3 ± 3.8	29.0 ± 3.5	0.14	0.74
sPAP, mmHg	39.8 ± 2.4	46.6 ± 4.7	41.0 ± 4.4	0.089	0.26

Values are given as mean ± standard deviation.

dPAP, diastolic pulmonary arterial pressure; ePVS, estimated plasma volume status; Hb, haemoglobin; Hct, haematocrit; HF, heart failure; HR, heart rate; mPAP, mean pulmonary arterial pressure; sPAP, systolic pulmonary arterial pressure.

^aWilcoxon paired test.

- (2) Absolute change in Hct in % = Hospitalization Hct – Baseline Hct
- (3) Absolute change in ePVS in mL/g Hb = Hospitalization ePVS – Baseline ePVS

Similar calculations of haemodynamic measures (sPAP, dPAP, and mPAP) were performed, and the absolute change in dPAP was the primary haemodynamic measure of interest. The main analysis was evaluating the relationship between change in Hb and change in dPAP at the time of HF hospitalization compared to the baseline values. Change in Hb (as opposed to Hct or ePVS) was selected as the primary haemoconcentration measure of choice given its lowest within-subject variability and measurement errors (coefficient of variation).⁸ We also estimated the same associations between measures of absolute changes in sPAP and mPAP with changes in Hb, Hct and ePVS (online supplementary Table S7).

Clinical outcomes included death, heart transplantation, left ventricular assist device implantation, all-cause hospitalizations, and HF hospitalizations (defined as an unplanned hospital admission or emergency department visit requiring intravenous diuretics administration or lasting more than 24 h in observation).

Statistical analysis

Baseline clinical characteristics are reported as count (%), mean ± standard deviation, or median and interquartile range (IQR), as appropriate. Laboratory and haemodynamic continuous variables at baseline were compared with the first HF and all-cause hospitalization values using a paired Wilcoxon test. For laboratory–haemodynamic measures correlation, Spearman’s rank correlation test was utilized given non-normal data distribution. In analysing the correlation between changes in laboratory and haemodynamic measures at the time of hospitalization (compared to baseline), the unit of analysis was considered each episode of hospitalization (not each individual patient). Retrospective chart review for this study was approved by an Institutional Review Board with a waiver of informed consent.

Table 3 Spearman’s rank correlation analysis between pooled laboratory and haemodynamic measures at all time points (irrespective of hospitalization status)

	Hb (g/dL)	Hct (%)	ePVS (mL/g Hb)
sPAP			
r _s	–0.20	–0.21	0.21
P-value	<0.0001	<0.0001	<0.0001
dPAP			
r _s	–0.09	–0.09	0.09
P-value	0.053	0.036	0.041
mPAP			
r _s	–0.15	–0.16	0.16
P-value	0.0005	0.0002	0.0003
Hb, mg/dL			
r _s	N/A	0.97	–0.96
P-value		<0.0001	<0.0001
Hct, %			
r _s	0.97	N/A	–0.99
P-value	<0.0001		<0.0001
ePVS, mL/g Hb			
r _s	–0.96	0.99	N/A
P-value	<0.001	<0.0001	

dPAP, diastolic pulmonary arterial pressure; ePVS, estimated plasma volume status; Hb, haemoglobin; Hct, haematocrit; mPAP, mean pulmonary arterial pressure; N/A, not applicable; sPAP, systolic pulmonary arterial pressure; r_s, Spearman’s rank correlation coefficient.

Results

Patient characteristics

Of 30 patients implanted with a PAP sensor at our centre during the study period, 7 did not have laboratory or clinical follow-up data for review. The remaining 23 met our study criteria and were

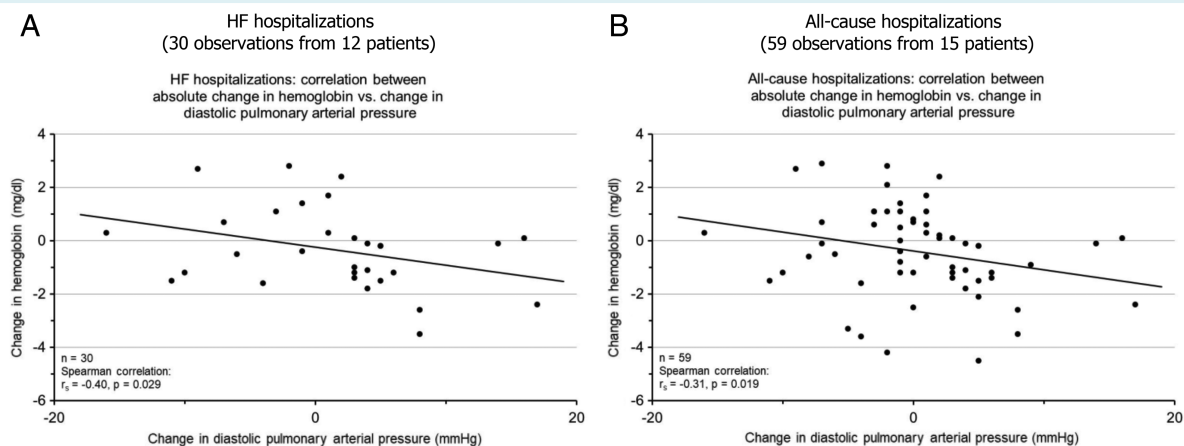


Figure 1 Scatter plots showing the correlation between absolute change in haemoglobin vs. change in diastolic pulmonary arterial pressure (between the time of hospitalization and baseline) in (A) heart failure (HF) hospitalizations, (B) all-cause hospitalizations.

included in the analysis. The median age of the cohort was 64 (IQR 52–73) years, 10 (43%) were men, and 13 (57%) had HF with preserved ejection fraction (defined as left ventricular ejection fraction $\geq 50\%$) (Table 1). A total of 518 laboratory–haemodynamic measurement pairs were evaluated with a median of 17 (11–31) measurements per patient. After a median follow-up of 27 (13–42) months, 17 (74%) patients had ≥ 1 all-cause hospitalization (total of 59 hospitalizations, including 30 HF hospitalizations).

Laboratory–haemodynamic measurements

Table 2 summarizes mean laboratory and haemodynamic measures at baseline and at the time of first HF and all-cause hospitalizations. Diastolic PAP increased from 20.5 ± 1.5 mmHg at baseline to 24.1 ± 3.2 mmHg at HF hospitalization ($P = 0.23$); inversely, there was a decrease in Hb from baseline of 12.7 ± 0.3 to 12.1 ± 0.5 g/dL at HF hospitalization ($P = 0.20$).

Correlation analysis

In the pool of all stable and hospitalization laboratory–haemodynamic measurement pairs, there was a weak negative correlation between Hb and dPAP ($r = -0.09$, $P = 0.053$) (Table 3).

This negative correlation became more apparent when the change in Hb from implantation to HF hospitalization was compared with the change in dPAP ($r = -0.40$; $P = 0.029$) (Figure 1A). A similar negative correlation between Hb and dPAP was observed at the time of all-cause hospitalization ($r = -0.31$, $P = 0.019$) (Figure 1B). Analyses of the remaining haemodynamic (change in mPAP and sPAP) and laboratory (change in Hct and ePVS) measurements are summarized in online supplementary Table S1).

Conclusion

We report that increases in dPAP, a predictor of HF hospitalization, correlate significantly with decreases in Hb concentration, a

surrogate of haemodilution, in ambulatory HF patients. We extend existing literature on the haemoconcentration–haemodynamic measure association from hospitalized patients to the ambulatory setting. The degree of dPAP rise is commensurate with previously reported mean increases in dPAP preceding HF hospitalizations,^{1,9} and importantly, herald an estimated 24% increased risk of death.² Our data suggest the potential for change in Hb concentration to serve as a lower cost and more widely available alternative to dPAP monitoring. This finding was recently corroborated in a subgroup analysis of the EVEREST trial showing haemodilution 1-month post-discharge (defined as absolute reduction in Hct by $\geq 5\%$) to correlate with increase in weight, B-type natriuretic peptide and worse survival.¹⁰ Further research should determine if the same correlation between haemodilution and haemodynamic/laboratory markers of congestion can be established several weeks preceding HF hospitalization to define its practical utility in guiding ambulatory HF patient management. Interestingly, a prospective 5-day-a-week home monitoring in HF patients post-discharge combining Hb, Hct, potassium and creatinine measurements was able to capture a substantial number of clinically relevant cardio-renal (congestion/de-congestion, worsening renal function) and electrolyte events (hypokalaemia/hyperkalaemia), which are frequently overlooked and potentially actionable.¹¹ Finally, considering the small sample size herein, inherently limited retrospective design, non-simultaneous laboratory and haemodynamic measurements, and bias by clinical indication, our exploratory work requires prospective and adequately powered examinations.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: A.S.D. reports consulting from Abbott, Alnylam, Amgen, AstraZeneca, Biofourmis, Boston Scientific, Boehringer Ingelheim, DalCor, Merck, Novartis, Relypsa, Regeneron; he also reports research grants from AstraZeneca, Novartis, Alnylam. M.R.M. reports payment made to his institution from Abbott for consulting; consultant fees from Portola, Bayer, Xogenex, and Baim Institute for Clinical Research, Medtronic, Janssen, NuPulseCV, Leviticus, FineHeart, Mesoblast. P.R. reports personal fees (consulting) for Idorsia and G3P, honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Servier, Stealth Peptides, Ablative Solutions, Corvidia, Relypsa, and Vifor Fresenius Medical Care Renal Pharma, outside the submitted work. P.R. is the cofounder of CardioRenal, a start-up developing a telemonitoring loop encompassing haemoglobin, potassium and creatinine monitoring in heart failure. The other authors have nothing to disclose.

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