International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Correlation between pulmonary artery pressure and thoracic impedance: Insights from daily monitoring through an implanted device in chronic heart failure☆

Giovanni Battista Perego [a,*,1,2], Matteo Oldani [a,1], Dario Pellegrini [a,1], Francesco Maria Angelo Brasca [a,1], Gabriella Malfatto [a,1], Alessandra Villani [a,1], Roberto Brambilla [a,1], Valeria Rella [a,1], Gianfranco Parati [a,b,1]

[a] Dept of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano, Milano, Italy
[b] Dept of Clinical Medicine and Prevention, University of Milano Bicocca, Italy

ARTICLE INFO

Article history:
Received 15 April 2017
Received in revised form 19 June 2017
Accepted 12 July 2017
Available online xxxx

Keywords:
Pulmonary artery pressure
Thoracic impedance
Heart failure
Telemedicine

ABSTRACT

Background: Thoracic impedance (TI) decrease and pulmonary artery pressure (PAP) elevation precede acute decompensation in congestive heart failure (HF). However, the relationship between TI and PAP has been studied only in the context of acute decompensation.
Methods: This prospective, observational study enrolled subjects with reduced ejection fraction HF, previously implanted with an ICD capable of measuring TI. Patients underwent implantation of a sensor for direct measurement of PAP (CardioMEMs™). Both TI and PAP were remotely monitored daily during follow up. Investigators were blinded to PAP values during the first three months, then PAP was used as a guide to therapy.
Results: Ten patients were followed up for 405 ± 141 days (3720 patient-days). During hemodynamic guided therapy, diastolic PAP (dPAP) decreased from 27.8 ± 10.2 mm Hg to 24.0 ± 8.0 mm Hg ($p < 0.001$); non-significant variations of TI were observed. A significant negative correlation was found between the variations of TI and PAP vs. baseline ($p < 0.001$). Episodes of sustained increase of PAP preceded subsequent periods of TI decrease by 5.6 ± 3.9 days, but the former were poor predictors of the latter (sensitivity 0.37).
Conclusions: Our study confirms the strict correlation that exists between left ventricular filling pressures and lung water content, estimated by dPAP and TI, respectively. However, dPAP acute variation analysis showed a limited value in predicting subsequent episodes of TI decrease.

1. Introduction

Heart Failure (HF) is a major health care issue. Acute Heart Failure (AHF) hospitalization is the most relevant determinant of HF related costs [1] and is associated to further myocardial injury, which contributes to the progression of the disease [2]. Despite therapy optimization, >25% patients are readmitted to hospital for recurrence of AHF within 30 days after discharge [3]. The main reason for HF readmission is congestion, either caused by volume overload or by fluid redistribution.

Overt AHF is the final step of a process lasting days or weeks, initiated by left ventricular (LV) filling pressure elevation, followed by subclinical fluid overload and finally by the appearance of signs and symptoms [4,5].Thus, strategies for early detection of subclinical and potentially actionable impending AHF have been searched for.

Ambulatory monitoring of thoracic impedance (TI) by Implanted Electronic Devices (IEDs) has been proposed as a surrogate measure of fluid overload. Early promising experiences showed that decreases in TI might be predictive of subsequent AHF [6]. Further registry data confirmed the association between TI decrease and AHF risk [7] and suggested that TI remote monitoring might reduce hospitalizations [8]. Unfortunately, randomized control trials (RCTs) failed to confirm a favorable clinical effect of TI guided therapy, both with and without remote monitoring, possibly because of the low sensitivity and specificity of TI derived indexes in predicting AHF [9,10,11].

On the other hand, implantable systems have been developed which allow remote monitoring of cardiac filling pressures, estimated from either left atrium, right ventricle or pulmonary artery pressure (PAP). Two RCTs, using different devices, demonstrated that hemodynamic

☆ Istituto Auxologico Italiano received financial support for this study from St. Jude Medical Corporation.
* Corresponding author at: Istituto Auxologico Italiano – Ospedale S. Luca, Piazza Brescia 20, 20149 Milano, Italy.
E-mail address: perego@auxologico.it (G.B. Perego).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Dr. Perego received fees from St. Jude Medical Corporation as a compensation for speeches about CardioMEMs technology.

http://dx.doi.org/10.1016/j.ijcard.2017.07.042
0167-5273/

Table 1
Baseline features for the study population. Continuous variables are reported as mean ± Standard Deviation.

Age (years)	71 ± 9	LV EF (%)	27,2 ± 4,0
Male gender	10/10	LVEDV (mL/m^2)	110.9 ± 34.89
Ischemic cardiomyopathy	7/10	dPAP (mm Hg)	28,0 ± 8,7
Serum creatinine (mg/dL)	1.41 ± 0.44	PWP (mm Hg)	26.4 ± 6.0
eGFR (mL/min)	55 ± 21	CI (L/min/m^2)	2.0 ± 0.5
6 min HWT (m)	391 ± 158	BNP (pg/mL)	1078 ± 382

guided therapy optimization is able to reduce AHF hospitalizations in NYHA class III HF patients [12] [13].

We present the data of a pilot study designed to investigate the relationship between TI and PAP and the time course of their variations.

2. Material and methods

Our study was a single center prospective, observational, open-label registry, including patients with TI and PAP remote monitoring.

2.1. Patients

Candidates to PAP monitor implant were selected among HFrEF patients (EF < 40%) who fulfilled the following criteria: age ≥ 18; history of NYHA class III or ambulatory class IV HF longer than 6 months; stable NYHA class III in optimized drug therapy [14] in the last 3 months; at least 1 episode of AHF treated with intravenous therapy during the prior year; previous implant of ICD or CRT-D, with thoracic impedance monitoring capabilities, followed remotely by our telemedicine service. We excluded: patients with recent acute coronary syndrome, cardiac thrombus, creatinine ≥2.5 mg/dL (or GFR < 25 mL/min), previous pulmonary embolism, deep venous thrombosis, known venous prothrombotic state, active infection, congenital heart disease, mechanical heart valves; subjects unable to tolerate a right heart catheterization; patients who had suffered a major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of initial assessment; patients with hypersensitivity or allergy to aspirin and/or clopidogrel.

All patients gave written informed consent to take part in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

2.2. Study design

Eligible subjects underwent right heart catheterization with full hemodynamic assessment and PA angiography. If a suitable PA branch (diameter 7–15 mm) was identified, the patients were enrolled and the device (Cardio MEMS™ HF – St. Jude Medical) was implanted according to standard technique [15]. Before discharge, subjects were instructed to take pulmonary artery pressure measurements daily.

According to our telemedicine standard protocols, patients received phone calls fortnightly from the Tutor Nurse to assess symptoms and reinforce compliance. TI was recorded daily by IEDs and transmitted every two weeks or in case of predefined alert conditions. TI measures were accessible to HF specialists throughout the study.

For the first three months investigators were blind to the data transmitted by CardioMEMs™ sensors (Observation Phase - OP). Afterwards (Active Phase - AP), HF management was guided by the hemodynamic information provided by the CardioMEMs™ system. We applied the hemodynamic-guided care strategy rules previously adopted by the CHAMPION trial [16]. Briefly, therapy was adjusted to force dPAP in the range of 8–20 mm Hg (optivolemic state); if patients had signs of low perfusion, IV fluid repletion and/or administration of IV inotropic agents were considered. Pressure measurements were reviewed weekly in case of optivolemia and 2 to 3 times per week if dPAP was outside the optimal range.

2.3. Statistical analysis and calculations

OP and AP data were compared using Paired *t*-test. We considered each TI measure as percentage of baseline to make variations comparable in different patients.

In order to identify trends for PAP and TI, for each day we calculated the difference between the average measure of the last week and the one of the previous two weeks. Periods of TI decrease and dPAP increase were defined as those with a consistent positive or negative variation lasting 7 or more days.

3. Results

From January to November 2016, 11 patients were implanted with CardioMEMs™ in our Center. One patient was lost to follow up due to technical reasons. The current analysis refers to 10 patients, whose baseline characteristics are summarized in Table 1.

The follow up lasted 405 ± 141 days. The compliance (days with PAP measure/days of follow up) was 94%. Our analysis was run on 3720 patient-days.

During hemodynamic guided therapy medications were changed as indicated in Table 2 and dPAP decreased (OP 27,8 ± 10.2 mm Hg, AP 24,0 ± 8.0 mm Hg; p < 0,001; in all cases average dPAP during AP was over 20 mm Hg), whereas no significant variation of TI was observed (OP 0.72 ± 5.0, AP 1.22 ± 6.8 expressed as % variation from baseline; p: n.s.) (Fig. 1). BNP decreased in 9/10 patients, but the variation was not statistically significant (OP 1078 ± 1209, AP 962 ± 1438 pg/mL; p: n.s.). Six patients were hospitalized for HF (9 episodes during OP and 14 during AP). The annual hospitalization rate was 4,0 in OP and 2,1 in AP (p n.s.)

A significant negative correlation was found between the variations of TI and PAP Vs. baseline (Pearson Correlation: – 0.417; p < 0.001) (Fig. 2).

No significant correlation was found between the trend (weekly and fortnightly variation) of PAP and TI (Fig. 3).

We recorded 222 periods of dPAP increase: 54 of them (15 in OP and 39 in AP) were followed by periods of TI decrease within the following 15 days. The average delay between the beginning of periods of PAP increase and TI decrease was 5.6 ± 3.9 days (with no difference between OP and AP) but no correlation was found between the trend of dPAP and the trend of TI observed 5 days later. The occurrence of a period of PAP increase (previously defined as 7 consecutive days of PAP increase) predicted a subsequent period of TI decrease with a sensitivity of 0.37 and a PPV of 0.24. Average PAP was not different during periods of PAP increase followed vs. those not followed by a TI decrease (23.0 ± 7.6 vs. 23.5 ± 7.8 mm Hg; p n.s). The same was true for PAP absolute and relative variations v. baseline.

Periods of PAP decrease lasting 7 or more days were 256, 42 in OP and 125 in AP): 49% of them were associated to periods of TI increase, taking place 1.6 ± 3.6 days later. This delay was not significantly different in OP and AP. Approximately 1/3 of cases were preceded by increases of dosage or by extemporary supplements of loop diuretics.

4. Discussion

This is the first attempt to examine the relationship between TI and PAP in congestive HF using daily measurements of both variables in a long term follow up. Our data demonstrate that the significant decrease of dPAP obtained during hemodynamic-guided care correlates with the expected increase of TI. Though, a sustained increase of PAP is not predictive of a subsequent decrease in TI.

Table 2
HF drug therapy at baseline, during Observation and Active Phase. Prevalence and total daily dose. No significant difference in doses and changes was found between Observation and Active Phase.

		Baseline		Observation Period			Active Phase		
Class	Drug	n	Daily dose (mg)	n	Daily dose (mg)	Therapy changes (n/month)	n	Daily dose (mg)	Therapy changes (n/month)
Diuretics	Loop diuretic	10	70.0 ± 46.9	10	101 ± 83	1.0	10	96.5 ± 74.4	1.4
Vasodilators	Nitrate	0	0	0	0.0 ± 0.0	0	2	15.8 ± 36.7	0.37
	ACEi or ARB	10	5.8 ± 3.0	10	5.5 ± 4.3	1.0	10	11.1 ± 11.0	0.3
Neurohormonal	Beta blocker	10	9.3 ± 12.4	10	13.9 ± 13.1	0.3	10	15.3 ± 13.5	0.2
Antagonists	Aldosteron antag.	8	31.2 ± 19.7	8	29.1 ± 21.7	0.11	7	29.0 ± 29.6	0.1

Please cite this article as: G.B. Perego, et al., Correlation between pulmonary artery pressure and thoracic impedance: Insights from daily monitoring through an implanted device in chronic heart failure, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.07.042