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Intrathoracic impedance and pulmonary wedge pressure for the detection of heart failure deterioration

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Aims The aims of this analysis were to assess the agreement between implantable defibrillator (ICD)-measured intrathoracic impedance and pulmonary capillary wedge pressure (PCWP) collected during long-term follow-up, as well as to evaluate whether PCWP measures may improve the performance of the impedance detection algorithm in predicting heart failure (HF) worsening.

Methods and results We studied 23 HF patients implanted with an ICD capable of intrathoracic impedance measurement and alerting for fluid accumulation diagnosis. At regular follow-up and at visits for HF decompensation or device alert, clinical status was assessed and PCWP was non-invasively estimated with a validated echo-Doppler method. During 23 ± 11 months, 45 paired assessments of impedance and PCWP were performed. The Kappa analysis revealed good agreement between impedance and PCWP ($k = 0.701$, SE 0.113, $P < 0.001$). Moreover, PCWP estimations and the paired values of the impedance fluid index resulted significantly correlated ($r = 0.677$, $P < 0.001$). The impedance-alert detected clinical HF deterioration with 92% sensitivity and 69% positive predictive value. The combined finding of decreased impedance and increased PCWP resulted in enhanced positive predictive value (92%) and no change in sensitivity (92%).

Conclusion These data confirm the inverse correlation between impedance and PCWP at long-term follow-up and suggest the potential clinical value of a combined impedance and pressure assessment for the improved detection of HF deterioration.

Keywords Heart failure • Intrathoracic impedance • Implantable defibrillator • Pulmonary wedge pressure

Introduction

The thoracic fluid status monitoring via intrathoracic impedance is a diagnostic capability of some modern implantable defibrillators (ICDs).[1] For patients with heart failure (HF), the ability to monitor fluid status can provide additional insight into the problem of managing their disease. Recent studies demonstrated the capability of this feature to detect chronic HF deterioration, and showed the clinical utility of the fluid accumulation alert feature in reducing clinical events and HF hospitalizations.[2–5]

Early clinical data[6] showed that intrathoracic impedance correlates with measures of fluid overload. Specifically, the inverse correlation between implantable pulse generator-measured intrathoracic impedance and pulmonary capillary wedge pressure (PCWP) was demonstrated during periods of intravenous diuretic therapy in HF patients hospitalized for HF exacerbation.

The aims of this analysis were to assess the agreement between ICD-measured intrathoracic impedance and estimated PCWP collected during long-term follow-up, as well as to evaluate whether

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PCWP measures may improve the performance of the impedance detection algorithm in predicting HF worsening.

Methods

Patient selection, implantable defibrillator implantation, and follow-up

Consecutive patients with symptomatic chronic HF regardless of optimal medical treatment and with current indications for CRT[7] underwent successful implantation of a biventricular ICD (InSync Sentry™, Medtronic Inc., Minneapolis, MN, USA) with intrathoracic impedance monitoring capability (OptiVol™ algorithm), and were prospectively enrolled in this study. All patients gave written informed consent approved by the Institutional Review Board.

Before device implantation, the following baseline demographics were collected: medical history, clinical examination, 12-lead electrocardiogram, NYHA class, and echocardiographic parameters. Prior to hospital discharge, physician demonstrated the ICD alarm tone to patients and instructed them to present to the clinic in the event of an alert. Patients demonstrating inability to perceive the alarm tone received a handheld monitor (SentryCheck™) that allows the user to determine whether or not the alert condition is fulfilled, and were trained to perform status checks every other day.

After implantation, data were evaluated during in-office follow-up examinations and if patients presented with an ICD alert or with decompensated HF. Every 6 months and at unscheduled visits, the ICD was interrogated to verify the integrity and appropriate functioning of the implanted system and all data retrieved from the memory were stored on a disk. At each visit, the clinical status assessment was performed in accordance with the guidelines on the diagnosis of acute HF,[8] and included changes in functional NYHA class, signs, and symptoms of HF, heart rate, bodyweight, and HF medication.

Every 12 months and at unscheduled visits, the echocardiograph examination was performed to non-invasively estimate the PCWP with validated methods that combine Doppler echocardiographic variables of mitral and pulmonary venous flow.[9,10] Mitral flow velocity was assessed by pulsed wave Doppler study, and following measurements were made: maximal early and late diastolic velocity and their ratio (E/A), deceleration rate of early diastolic velocity (DR) calculated by dividing peak early diastolic velocity by deceleration time, duration of the late diastolic velocity wave (dA), isovolumic relaxation time (IVRT) measured as the time interval between the aortic closure click and the start of mitral flow. From the pulmonary venous flow velocity, we obtained the duration of reverse flow at atrial contraction (dZ) and the systolic fraction of peak velocities (SF) calculated as the systolic flow velocity divided by the sum of systolic plus diastolic forward flow velocity. All measurements were made over 5 consecutive cycles for sinus rhythm and 10 cycles for patients in atrial fibrillation.[10]

For patients in sinus rhythm, the PCWP was estimated as a combination of multiple variables:[9] $PCWP = 0.93 \times DR - 0.15 \times SF + 0.03 \times (dZ - dA) + 0.87 \times E/A + 16.2$. Similarly, for patients in atrial fibrillation following multivariable equation was applied:[10] $PCWP = 1.23 \times DR - 0.175 \times SF - 0.089 \times IVRT + 24.04$. For the aims of the present analysis, a PCWP value ≤ 13 mmHg was considered normal.

Left ventricular ejection fraction was assessed by Simpson's equation using the apical four-chamber view. Mitral regurgitation was detected by colour flow Doppler study and graded on the basis of the maximal regurgitant jet area obtained in the apical four-chamber view as mild or grade 1 (jet area/left atrium area $\leq$20%), moderate or grade 2 (jet area/left atrium area 20% to 40%), and severe or grade 3 (jet area/left atrium area $>$40%).

The physician performing the echocardiograph examination was blinded to the device alerts and the fluid index status.

Intrathoracic impedance monitoring

The intrathoracic impedance monitoring feature of the ICD has been previously described.[1,2,6] In brief, the OptiVol algorithm measures the impedance between the right ventricular coil and the ICD case. Changes in the daily impedance over time determine a moving average, or reference impedance, that indicates the currently expected daily impedance value. The cumulative difference between the measured daily impedance and the reference impedance is used to calculate a fluid index. The ICD may be programmed to alert the patient if the fluid index increases above a pre-programmed threshold (nominal value: 60 Ω day), in order to timely detect impending episodes of fluid retention and pulmonary congestion.

Statistical analysis

Continuous data were expressed as means $\pm$ standard deviation and categorical data were expressed as percentages. Differences between mean data were compared by a *t*-test for Gaussian variables, and by Mann–Whitney non-parametric test for non-Gaussian variables. Statistical correlations between variables were tested by using linear regression analysis. The Kappa statistic and its standard error (SE) were calculated to measure the agreement between variables. A *P*-value < 0.05 was considered significant for all tests. All statistical analyses were performed by means of SPSS software (SPSS Inc., Chicago, IL, USA).

Results

From September 2004, 23 consecutive patients undergoing implantation of a biventricular ICD with impedance monitoring capability were followed-up for 23 $\pm$ 11 months. The baseline characteristics are summarized in *Table 1*. At the pre-discharge visit, five patients

Table 1 Demographics, baseline clinical, and echocardiographic parameters

Parameter	*n* = 23
Male gender, *n* (%)	20 (87)
Age, years	70 $\pm$ 8
Ischemic aetiology, *n* (%)	8 (35)
Primary prevention, *n* (%)	18 (78)
Hospitalizations for HF (prior 12 months), *n* per year	1.1 $\pm$ 1.0
NYHA Class	2.6 $\pm$ 0.8
QRS Duration, ms	151 $\pm$ 32
History of atrial fibrillation/atrial flutter, *n* (%)	3 (13)
Left ventricular ejection fraction, %	25 $\pm$ 6
Mitral regurgitation, grade	1.9 $\pm$ 0.9
Pulmonary capillary wedge pressure, mmHg	11 $\pm$ 3
Hypertension, *n* (%)	7 (30)
Renal dysfunction, *n* (%)	2 (9)
Chronic lung disease, *n* (%)	5 (22)

Table 2 Details of the implantable defibrillator-alert for fluid index increase and/or decompensated heart failure events occurred during follow-up

Event	Patient	Months since implant	OptiVol fluid index (Ω day)	PCWP (mmHg)	Signs of HF Deterioration
1	Pt1	31	83	14	No
2	Pt2	31	105	18	Yes
3	Pt3	30	67	10	No
4	Pt6	24	62	16	Yes
5	Pt10	34	64	10	No
6	Pt11	40	72	13	No
7	Pt12	35	200	18	Yes
8	Pt13	12	89	16	Yes
9	Pt14	12	120	16	Yes
10	Pt15	16	200	18	Yes
11	Pt17	15	88	15	Yes
12	Pt18	2	92	16	Yes
13	Pt20	2	200	22	Yes
14	Pt21	5	67	10	No
15	Pt21	11	21	14	Yes
16	Pt22	10	73	15	Yes
17	Pt23	10	72	18	Yes
Mean values at scheduled visits ($n = 28$)			12 ± 15	10 ± 2	No

received the SentryCheck monitor because of their inability to clearly perceive the alarm tone.

During follow-up, 17 events of ICD alert for fluid index increase and/or decompensated HF occurred in 16 patients. Specifically, during follow-up, 12 patients presented with signs and symptoms of worsening HF for a total of 12 episodes. Moreover, in 16 patients, the ICD detected 16 episodes of acute impedance decline that resulted in the increase of the fluid index above the pre-programmed threshold of 60 Ω day. *Table 2* depicts the details of the episodes occurred during the study.

Paired assessments of ICD-measured intrathoracic impedance and non-invasive echo-derived PCWP were performed every 12 months and at unscheduled in-office examinations. In particular, among 45 pressure assessments, we reported 14 episodes of PCWP increased above the pre-defined value of 13 mmHg.

The agreement between the two indices of impending HF decompensation, i.e. elevated PCWP and impedance-derived fluid index above threshold, was tested by Kappa statistical analysis that revealed a good agreement ($k = 0.701$, standard error 0.113, $P < 0.001$).

Similarly, regression analysis was performed between the PCWP estimations and the paired values of the OptiVol fluid index, as measured by the ICD in the dates of echocardiographic assessment, and the two variables resulted significantly correlated ($r = 0.677$, $P < 0.001$), as shown in *Figure 1*.

The OptiVol algorithm appropriately identified 11 out of 12 worsening HF events, resulting in a sensitivity of 92%. However, the clinical status assessment did not confirm any sign of ongoing or impending decompensation for 5 of 16 impedance-alerts, thus leading to a positive predictive value of 69%.

A posteriori, the positive predictive value could be improved to 89% by increasing the OptiVol threshold from 60 to 80 Ω day (8 episodes of worsening HF out of 9 alerts), at the cost of diminished sensitivity (67%: 8 alerts out of 12 worsening HF events).

The mean PCWP measured in presence of concomitant clinical deterioration was 17 ± 2 mmHg vs. a mean value of 10 ± 2 mmHg ($P < 0.001$) obtained in the absence of signs or symptoms of decompensation. In all cases of worsening HF, the PCWP resulted increased above the value of 13 mmHg.

Among the 16 follow-up visits characterized by an OptiVol fluid index above threshold, 12 were associated to an elevated PCWP (*Figure 1*). Thus, the combined finding of decreased impedance (fluid index greater than 60 Ω day) and increased PCWP would have reduced the number of false impedance-alerts from 5 to 1, resulting in enhanced positive predictive value (92%) and no change in sensitivity (92%).

Discussion

This study demonstrates the inverse correlation between the intrathoracic impedance and the PCWP at long-term follow-up, with patients in stable clinical conditions and during periods of decompensated HF. Moreover, it shows that a good agreement exists between the ICD warning for fluid index above the threshold, and the PCWP deviating from the optimal pressure range.

Pulmonary capillary wedge pressure is an established index of cardiac function that has been widely used to assess left ventricular filling pressures.[11] In patients with chronic HF, a high PCWP is associated with poor prognosis, severe symptoms, and low exercise tolerance.[12–14] Its normalization achieved by

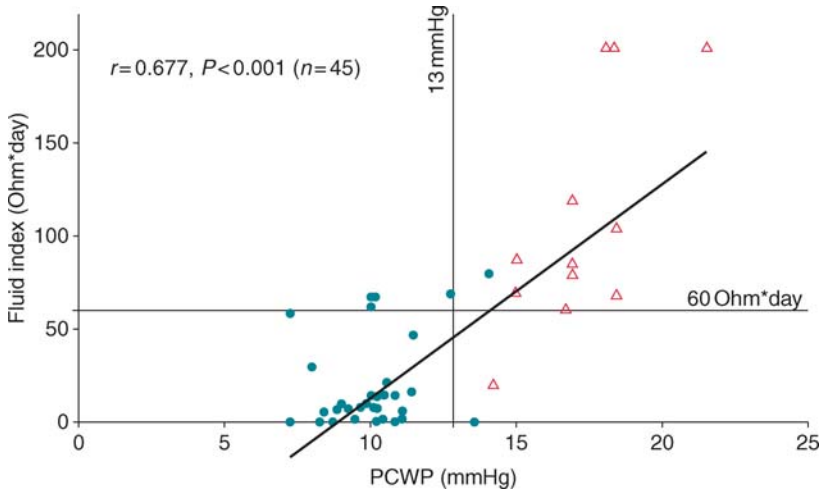

Figure 1 Correlation between the pulmonary capillary wedge pressure estimations and the paired values of the OptiVol fluid index. Closed circles indicate stable clinical conditions, open triangles indicate measures taken during episodes of decompensated heart failure.

appropriate unloading treatment may decrease congestive symptoms and improve quality of life.[15,16] Strategies to prevent cardiac decompensations include frequent physician examinations and close monitoring of the patient's clinical status to maintain optimal volume and adjust medications.[17] Repeated right heart catheterizations may help tailor HF therapy,[18] but they are inconvenient for patients and associated with significant risks. Therefore, in patients with chronic HF, who already suffer the discomfort of repeated diagnostic and therapeutic procedures, a means to continuously monitor the haemodynamic status is of great value.

Intrathoracic impedance assessment using OptiVol fluid status monitoring has been studied in the MIDHeFT study, in 33 patients with severe HF implanted with a pacemaker modified to accept an ICD lead and special software.[6]

During the acute phase of the study, when patients were hospitalized for acute decompensated HF and were receiving intravenous diuretics, a pulmonary artery catheter was inserted, and the PCWP values were measured together with intrathoracic impedance. The results suggested that the intrathoracic impedance (measured by average daily impedance) and intracardiac filling pressures (measured by PCWP) were inversely correlated ($r = -0.61$, $P < 0.001$).

Our results seem to extend previous findings, demonstrating that the commercially available OptiVol system provides intrathoracic impedance measures that are significantly and inversely correlated with the ambulatory estimations of intracardiac filling pressure ($r = 0.677$, $P < 0.001$), and that its fluid accumulation alert feature is able to identify episodes of volume overload.

In the present study, we adopted a non-invasive method to estimate the PCWP combining Doppler echocardiographic variables of mitral and pulmonary venous flow,[9,10] thus making possible repeated assessments during follow-up, both in case of decompensated HF and at routine in-office visits with patients in stable clinical conditions. This method was demonstrated to reliably estimate PCWP in patients with chronic HF, even when mitral regurgitation or atrial fibrillation is present.

A recent observational study showed that an ICD endowed with the intrathoracic impedance monitoring feature reliably detected HF hospitalizations and milder forms of HF deterioration in a large population of HF patients.[5] Moreover, by allowing timely detection and prompt therapeutic intervention, the alert capability seemed to reduce the number of HF hospitalizations.

In our observation, the vast majority of HF decompensations were correctly identified by the algorithm, while 5 of the 16 impedance-alerts came out to be false after in-hospital assessment, thus we obtained a sensitivity of 92% and a predictive value of 69% confirming a previous experience.[19]

False-alerts are obviously a costly and time-consuming problem, and remain one of the major concerns of healthcare providers who adopt remote monitoring technology. The rate of impedance-alerts occurring in the absence of signs of worsening HF, as estimated in previous large cohort observational studies,[2,5] is ~0.2 per patient-year. The performance of the currently available OptiVol algorithm can be enhanced, as suggested by Ypenburg *et al.*,[20] by increasing the fluid threshold value from its default value of 60 Ω day and pursuing a reasonable balance between sensitivity and positive predictive value in each subject.

Another strategy for future improvement of the detection algorithm could be the integration of data from independent sensors to corroborate OptiVol threshold crossing.

A totally implantable monitor that continuously measures and stores intracardiac pressure has been developed, and chronic studies comparing its measures with those obtained by a Swan-Ganz catheter have found the system to be safe, accurate, and stable over time.[21–23] Despite it was shown that intracardiac pressures change before HF exacerbations,[24] no

studies were designed to examine the exact predictive value of continuous haemodynamic monitoring. Similarly, in our study, we only noticed a PCWP higher than 13 mmHg in all episodes of worsening HF but, in the absence of continuous pressure monitoring, we were not able to determine its predictive value.

The recently published COMPASS-HF study[25] investigated whether continuous intracardiac pressure remote monitoring could decrease morbidity, and showed a 36% reduction in the relative risk of a first HF hospitalization. In that study, when patient's data deviated from an optimal pressure range, therapy was adjusted in order to restore pressure to the range. Indeed, at present, no automatic algorithm for early detection of impending decompensations has been applied to intracardiac pressure signals.

Our findings show that the evidence of a PCWP out-of-range after an OptiVol threshold crossing, did not lead to any loss in true positive detection, but permitted to reduce the number of false-positive from 5 to 1, thus increasing the positive predictive value to 92%. Therefore, the present study seems to suggest that an implantable device incorporating both intrathoracic impedance and intracardiac pressure monitoring could enhance the performance of the algorithm, reducing the false-alert rate while maintaining sensitivity for predicting HF deterioration.

Recently, Santini *et al.*[19] showed that the combined use of the OptiVol system and a home monitor for remote ICD follow-up allowed to successfully manage episodes of possible fluid accumulation without requiring additional in-hospital visits. The availability of additional diagnostic data from independent sensors, such as intracardiac pressure, may facilitate the remote data review and management of HF patients.

The present analysis was performed in a small patient population, even if comparable to the sample size of previous studies testing the thoracic fluid monitoring via intrathoracic impedance,[6] and thus this should be considered when interpreting present results.

In conclusion, the findings of this study confirm the inverse correlation between intrathoracic impedance and PCWP at long-term follow-up and suggest the potential clinical value of an implantable device capable of combined impedance and pressure measurements for the improved detection of HF deterioration.

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Conflict of interest: S.V. and J. C. are employees of Medtronic, Inc.

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