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Evaluation of thoracic impedance trends for implant-based remote monitoring in heart failure patients - Results from the (J-)HomeCARE-II Study

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ABSTRACT

Aims: Remote monitoring by implantable devices substantially improves management of heart failure (HF) patients by providing diagnostic day-to-day data. The use of thoracic impedance (TI) as a surrogate measure of fluid accumulation is still strongly debated. The multicenter HomeCARE-II study evaluated clinically apparent HF events in the context of remote device diagnostics, focusing on the controversial role of TI.
Methods and results: We followed 497 patients (66.6 ± 10.1 years, 77% male, QRS 139.8 ± 36.0 ms, ejection fraction 26.8 ± 7.0%) implanted with a CRT-D (67%) or an ICD (33%) for 21.4 ± 8.1 months. An independent event committee confirmed 171 HF events of which 82 were used to develop a TI-based algorithm for the prediction of imminent cardiac decompensation. Highly inter-individual variations in patterns of TI trends were observed. The algorithm resulted in a sensitivity of 41.5% (50.0%) with 0.95 (1.34) false alerts per patient year, and a positive predictive value of 7.9% overall and 27.9% in the HF event group of patients. Averaged ratio statistics showed a significant pre-hospital decrease and a highly significant in-hospital increase in TI after intensified diuresis. Recurrent decompensations turned out to be preceded by a significantly stronger decrease of TI compared to first events with a higher chance for detection (63.6% sensitivity, $p < 0.05$).
Conclusions: Overall performance in predicting imminent decompensation by monitoring TI alone is limited due to its high inter-patient variability. TI stand-alone applications should be redirected towards a target population with more advanced symptoms where post-hospital observation aimed to maintain the patient's discharge status might be the most valuable approach.
Clinical trial registration: ClinicalTrials.gov Identifier NCT00711360 (HomeCARE-II) and NCT01221649 (J-HomeCARE-II).

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Introduction

Heart failure (HF) represents a substantial burden in regard to morbidity, mortality, and economic costs to our healthcare systems. Acute decompensated HF is one of the leading causes of hospital admissions

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and subsequent readmissions [1]. With a prevalence of ≥10% among persons aged 70 years or older, this burden is likely to escalate in the near future due to the ageing population and improved HF care.

Hence, there is a strong need to develop and establish optimized HF management programs. Remote monitoring of implantable cardioverter defibrillators (ICD) or cardiac resynchronization defibrillators (CRT-D) has already been shown to be effective in reducing morbidity and mortality [2,3]. Beyond their original therapeutic purpose [1], these implants record and transmit technical device parameters and additionally a large set of variables used for medical diagnostics, including information on heart rate, pacing occurrence, physical activity, and arrhythmia detections. This has been considerably improved by the automatic transmission of periodic or event-triggered electrocardiograms, a technology that is meanwhile also used by implantable cardiac monitors in the diagnosis of malignant arrhythmias, cryptogenic stroke and unexplained syncope [4].

The role of thoracic impedance (TI) as a diagnostic surrogate measure of pulmonary fluid status, and its predictive power to avert imminent HF decompensations has been strongly debated for the last decade. An early study showed very promising results and introduced an algorithm with 76.9% sensitivity in predicting hospitalizations for fluid overload [5]. Multiple other studies reported satisfactory correlations of TI with markers of fluid overload [6–8]. However, later trials provided divergent results: Whereas observational studies still confirmed the prognostic value of TI [9–11], recent outcome trials reported only modest sensitivities (20.7% to 42.1%) [12], and no improvement of outcomes in terms of all-cause death or cardiovascular hospitalization, as hypothesized [13–15].

The HomeCARE-II (Monitoring of Fluid Status in Heart Failure Patients by Intrathoracic Impedance Measurement) study evaluated HF-related clinical events in the context of remote device diagnostics. Here, we present a combined analysis of the European and Japanese part of the study focusing on TI trends preceding hospital admission due to HF (pre-hospital), during hospital stay (in-hospital), and after discharge (post-hospital) (ClinicalTrials.gov registrations NCT00711360, NCT01221649).

Material and methods

Study population

This prospective, non-randomized study enrolled a total of 501 patients in 58 centers in Europe (33 clinics, 303 patients) and Japan (25 clinics, 198 patients) between 2008 and 2014. Eligible patients had an indication for an ICD or CRT-D, HF symptoms according to New York Heart Association (NYHA) class II-IV, a left ventricular ejection fraction (LVEF) ≤ 35%, and at least one out of eight pre-specified high risk criteria: diastolic dysfunction, considerably increased BNP level, CRT-D indication with NYHA class > II, LVEF < 15%, left ventricular end-diastolic diameter > 60 mm, significant mitral regurgitation, known paroxysmal or chronic atrial fibrillation (AF), and/or HF hospitalization within the last year. Major exclusion criteria were recent acute coronary syndrome, prior or planned heart transplant, recent or scheduled cardiac surgery, and hemodialysis.

The study was conducted in adherence with the Declaration of Helsinki and approved by the local Ethics Committees of all participating study centres. All patients gave written informed consent.

Measurement of thoracic impedance

Patients were implanted with a commercially available ICD or CRT-D (Lumax 540 VR-T/DR-T/HF-T, Biotronik SE & Co. KG, Berlin, Germany) capable of wireless daily and fully automatic data transmission via Home Monitoring [16]. TI was measured between the right ventricular distal coil and the pectorally implanted can. Every hour, the device averaged TI over 1024 cardiac cycles. The 24 samples were transmitted daily to a remote service center, and stored to a data warehouse for further analysis. In addition, implant downloads were collected during follow-ups. Daily impedance was calculated as the mean of the 24 hourly values. Home Monitoring was activated but the investigators remained blinded to TI during the whole course of the study.

Assessment of heart failure events

Follow-up visits were scheduled three months after implantation and thereafter every six months. Scheduled as well as unscheduled follow-ups comprised device interrogation, medication capture, physical examination, and adverse event documentation.

Any adverse event, if judged by the site investigator to be a substantial worsening of HF, was documented detailed including therapy medications, echocardiographic diagnosis and, if available, laboratory results and X-ray data. All reported HF events were judged by an independent Clinical Event Committee (EC) whose members were also blinded to TI. EC members followed pre-specified medical criteria for judgment: like necessity of an overnight hospitalization, and clinically proven significance of HF worsening that required intravenous drug treatment or a substantial increase in oral diuretics.

Termination of the event-driven study was announced after achievement of a target number of primary HF events, fulfilling further pre-specified integrity criteria. An EC-confirmed HF event was classified as primary if (1) there was sufficient remote data coverage, (2) it was not preceded by another HF event within the previous month, (3) it did not occur within the post-implant phase of three months. (4) A maximum of two primary HF events were allowed to contribute per patient.

Study objective

Primary objective was to record long-term trends of TI in the context of clinically relevant HF events. All EC-confirmed HF events were used for pre-, in- and post-hospital evaluation of TI. The primary HF events served to develop an impedance-based algorithm for early detection of worsening HF. Due to blinding, TI diagnostics could not affect any clinical decision.

Data analysis and statistics

Unless otherwise noted, data are reported as mean $\pm$ standard deviation or median (interquartile range) for continuous variables, and as percentages of non-missing values for categorical variables. Characteristics were calculated for all patients who experienced at least one EC-confirmed HF event (HFE group) or not (control group). Groups were compared by Pearson chi square test for categorical variables and two-sided Student's *t*-test or Wilcoxon rank sum test for continuous variables, as appropriate.

The algorithm was retrospectively developed by use of all primary HF events to provide an index for detecting significant decreases of TI. Its sensitivity was calculated as the percentage of these events preceded by a threshold crossing of the index within a 30-day period prior to the event. Its false alert rate was determined as the number of threshold crossings not associated with any EC-confirmed HF event divided by the overall number of patient days covered with index data. All rates are expressed as number per patient-year (ppy). Additionally, the positive predictive value (PPV) was estimated as the proportion of all alerts that were followed by an EC-confirmed HF event within the pre-specified 30-day period to the total alert count.

Error bar plots were used to simply overlay TI trends (based on a 7-day moving average) for all patients with available data for post-implant, pre-hospital and post-hospital data. Ratio statistics and paired Student's *t*-tests were used to evaluate pre-hospital TI (four weeks prior versus admission) and in-hospital TI (admission versus discharge) where all EC-confirmed HF events with available data were used.

In order to account for more patient individuality, the patient-individual maximum difference (fall) of impedance to admission within a pre-hospital four-week window was calculated, grouped and compared for different types of events. Summarized data are illustrated by boxplots with mean, median, quartiles, and outliers. For all tests, a significance level of 0.05 was considered statistically significant.

Data processing, algorithm design and all statistical analysis were implemented in Matlab (R2013b, statistics toolbox V8.3, Math Works Inc., Natick, MA, USA).

Results

Study conduct

We included 497 successfully implanted patients in the present analysis with 333 (67%) CRT-Ds, and 164 (33%) single or dual chamber ICDs (Fig. 1). Median follow-up time was 21.4 (19.6–26.7) months. In total, the study accumulated 885.2 patient years. Median patient-individual remote monitoring coverage was 90 (77–96) %. Fifty-eight patients (11.6%) died during the study.

Clinical heart failure events

Site investigators submitted 233 HF-related case reports. In 62 of 233 cases, EC members did not find evidence of a significant HF worsening. Finally, EC judgments resulted in 171 confirmed HF events in 100 patients (20%). Of those, a number of 82 primary HF events in 65 patients (13%) fulfilled all pre-specified integrity criteria (Fig. 1).

Recurrent events occurred in 32 patients. In total, 71 of the confirmed 171 HF events, and 22 of the primary 82 HF events were counted as recurrent.

Averaged HF event rates were calculated as 0.19 ppy (EC-confirmed HF events), and 0.09 ppy (primary HF events), respectively. Median hospital stay was 12 (8–20) days whereby significant differences existed between Europe with 9 (6–16) days and Japan with 17 (10−23) days ($p < 0.01$).

Patient characteristics

Main baseline characteristics were typical for an ICD/CRT-D population (Table 1) with a vast majority of male patients, high percentages of hypertension and coronary artery disease, AF in a quarter of patients, and a major comorbidity burden. Most presented at enrollment with NYHA class II or III (equally distributed), severely reduced LVEF, and a longer QRS duration due to the high percentage of CRT-D patients. Body mass index is low but resulted from significantly lower indices of the 40% Asian versus European patients (23.3 ± 3.8 kg/m^2 vs. 27.5 ± 4.6 kg/m^2, $p < 0.001$).

All characteristics showed a trend towards expected differences between the HFE and the control group. A significant increased risk of HF events was found for patients with higher NYHA class, jugular venous distension, peripheral edema, mitral and aortic regurgitation, a history of pulmonary edema, diabetes, renal insufficiency, and known AF. Also the number of current or ex-smokers was significantly higher in the HFE group. The resulting significance for digitalis medication was attributable to patients with AF.

Algorithm design and performance

The designed algorithm compares the daily TI with two simple long-term trends serving as a reference band. Its boundaries are determined by a weighted four-week moving average of the daily first and third quartile of the circadian TI. Leaving this reference band by daily TI confirms an up- or downward trend, respectively. The percentage distance of daily TI to the lower reference is calculated as a risk index denoting a substantial decrease of TI. The risk index is doubled for the first 60 post-implant days or if at least 14 out of the last 21 days show positive risk values. An alert is triggered if this index crosses a pre-specified

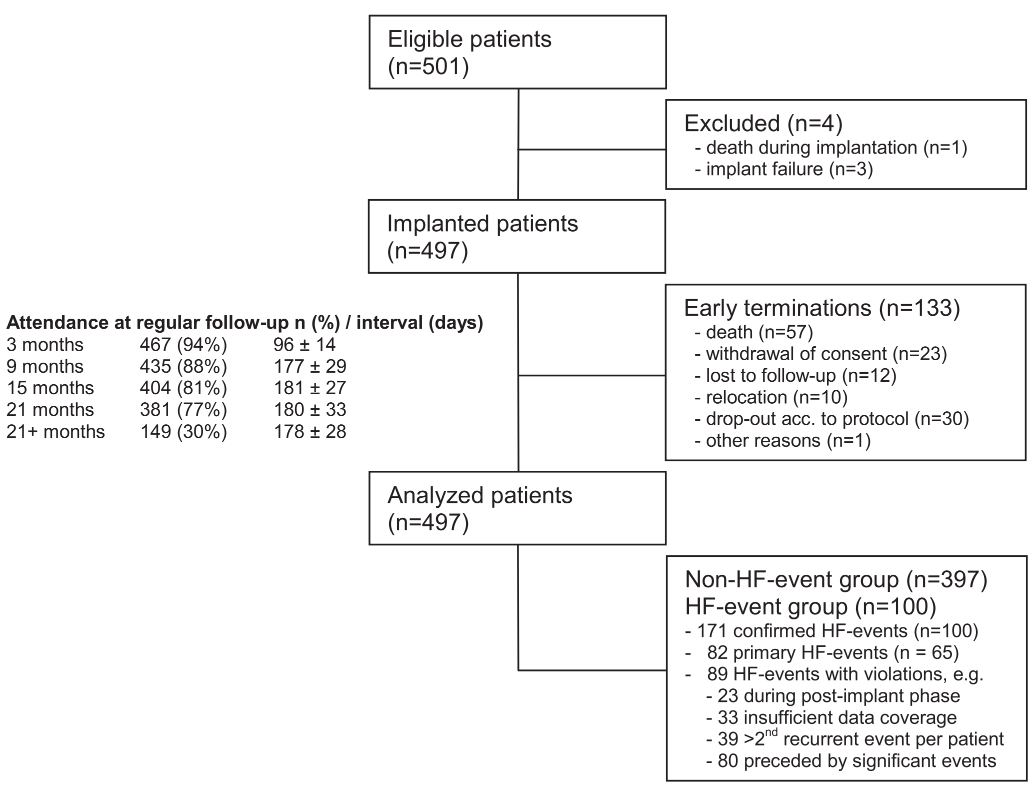

Fig. 1. CONSORT flow chart of the study.

Table 1
Comparison of baseline clinical characteristics between patients with and without heart failure events.

Variable	All patients ($n = 497$)	HF event group ($n = 100$)	Control group ($n = 397$)
Demographics			
Age, years	66.6 ± 10.1	68.2 ± 9.5	66.2 ± 10.2
Male gender	383 (77.1%)	84 (84.0%)	299 (75.3%)
Body mass index, kg/m^2	25.9 ± 4.8	26.4 ± 4.8	25.8 ± 4.7
Baseline symptoms			
NYHA II/III/IV, n	237/240/20	29/60/11	208/180/9§
NYHA II/III/IV, %	47.7%/48.3%/4.0%	29.0%/60.0%/11.0%	52.4%/45.3%/2.3%§
Pulmonary rales	43 (8.7%)	13 (13.0%)	30 (7.6%)
Jugular venous distention	70 (14.1%)	27 (27.0%)	43 (10.8%)$^\$$
Peripheral edema	110 (22.2%)	34 (34.0%)	76 (19.2%)§
Cardiovascular diagnosis			
Atrial fibrillation, any kind	136 (27.4%)	41 (41.0%)	95 (23.9%)$^\$$
Coronary artery disease	256 (51.5%)	52 (52.0%)	204 (51.4%)
Hypertension	333 (67.0%)	67 (67.0%)	266 (67.0%)
Mitral regurgitation	361 (72.6%)	81 (81.0%)	280 (70.5%)*
Mitral stenosis	12 (2.4%)	4 (4.0%)	8 (2.0%)
Aortic regurgitation	137 (27.6%)	41 (41.0%)	96 (24.2%)$^\$$
Aortic stenosis	21 (4.3%)	4 (4.0%)	17 (4.3%)
History of pulmonary diseases			
Pulmonary edema	98 (19.7%)	27 (27.0%)	71 (17.9%)*
Pneumonia	37 (7.4%)	10 (10.0%)	27 (6.8%)
Pronounced pleural effusion	41 (8.3%)	12 (12.0%)	29 (7.3%)
Smoker: former or current	274 (55.1%)	66 (66.0%)	208 (52.4%)*
Non-cardiovascular diagnosis			
Diabetes	174 (35.0%)	45 (45.0%)	129 (32.5%)*
Renal insufficiency	152 (30.6%)	47 (47.0%)	105 (26.4%)$^\$$
Asthma	18 (3.6%)	5 (5.0%)	13 (3.3%)
Cancer	32 (6.4%)	6 (6.0%)	26 (6.5%)
Hypercholesterolemia	238 (47.9%)	45 (45.0%)	193 (48.6%)
Measurements			
Heart rate, bpm	71.9 ± 14.5	72.3 ± 13.9	71.8 ± 14.7
QRS duration, ms	139.8 ± 36.0	143.0 ± 33.7	139.0 ± 36.6
LV ejection fraction, %	26.8 ± 7.0	25.8 ± 6.0	27.0 ± 7.3
Type of device therapy			
CRT-D	333 (67.0%)	78 (78.0%)	255 (64.2%)§
ICD	164 (33.0%)	22 (22.0%)	142 (35.8%)§
Medication	($n = 495$)	($n = 99$)	($n = 396$)
Beta-blocker	432 (87.3%)	83 (83.8%)	349 (88.1%)
ACE-inhibitors/AT II antagonist	406 (82.0%)	80 (80.8%)	326 (82.3%)
Ca-channel blockers	39 (7.9%)	6 (6.1%)	33 (8.3%)
Digitalis	105 (21.2%)	29 (29.3%)	76 (19.2%)*
Diuretics	438 (88.5%)	90 (90.9%)	348 (87.9%)
Anti-coagulant	211 (42.6%)	49 (49.5%)	162 (40.9%)
Anti-anginal	60 (12.1%)	10 (10.1%)	50 (12.6%)
Anti-arrhythmics	154 (31.1%)	36 (36.4%)	118 (29.8%)

Data are expressed as mean ± SD or n (%); NYHA, New York Heart Association; LV, left ventricular; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; ACE, angiotensin-converting enzyme; AT, angiotensin.
Where indicated, characteristics differed significantly between the HF event group and the control group on a significance-level p < 0.05*, p < 0.01§ or p < 0.001$^\$$.

threshold from below to above indicating an impending decompensation. Every alert blanks the following 30-day window.

Fig. 2 presents the performance curve of the algorithm. At its optimized threshold, the algorithm correctly detected 41 of all 82 primary HF events, resulting in a sensitivity of 50.0% at a calculated false alert rate of 1.34 ppy. The mean time interval between alert onset and clinical evaluation was 12 ± 9 days. To further lower the alert rate at the cost of sensitivity, an increase of the threshold provided a sensitivity of 41.5% with a target rate below one false alert (0.95) ppy and a leading time of 13 ± 9 days. Here, significantly more true positives were found for the group of recurrent events versus first events (sensitivity 63.6% vs. 33.3%, $p < 0.05$). Approximately 28% of all alerts were either preceded or followed by reported adverse events within one month. Alert ratio resulted in an overall PPV of 7.9%, and 27.1% if only applied to the HF event group.

Patient-individual patterns of thoracic impedance

A qualitative inspection of the complete set of case reports showed manifold fluctuations of TI on different time scales affected by a mix of precipitating factors like prior hospitalizations, therapies, presence or onset of AF, and comorbidities in all patients. Hence, high patient-individuality was observed with long-term (>8-weeks) and mid-term (>1-week) decreases of TI before decompensation. Cases of a sudden drop of TI right before hospitalization were evident like also cases with no signs of a clear decrease despite clinical evidence of pulmonary congestion at admission.

Fig. 3 shows two exemplary cases with >76 weeks of daily TI. Both CRT-D patients presented with NYHA class III symptoms, poor EF, and a history of pulmonary edema at enrollment. The 51-year-old male (Fig. 3A) experienced three serious HF decompensations (NYHA IV, dyspnea at rest, interstitial pulmonary edema), the first one shortly after implantation. Another 74-year-old male (Fig. 3B) showed higher TI fluctuations and suffered from four HF decompensations during study course. Based on the developed algorithm, the risk index would have triggered both true and false alerts for these two patients. It is obvious that some false alerts, which are not followed by a HF event in the next month, are in fact episodes of HF worsening, which did not manifest clinically and thus counted as false alerts according to protocol.

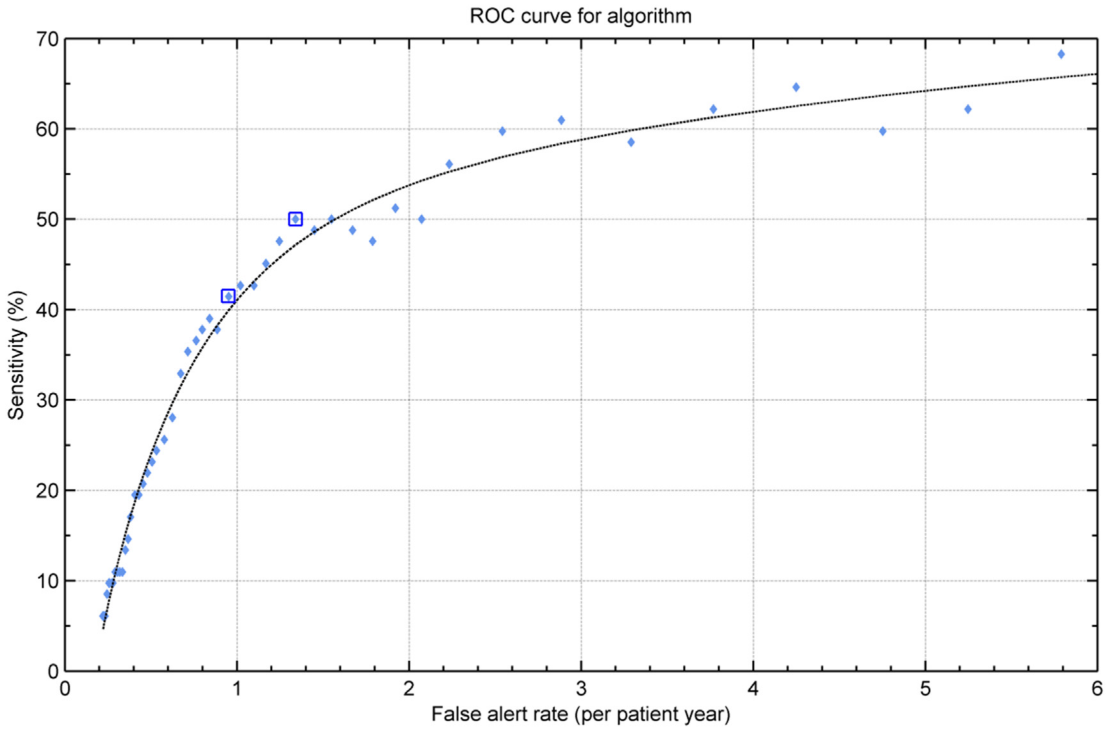

Fig. 2. Threshold-dependent performance of the designed algorithm in predicting decompensated heart failure ($n = 82$ primary events) within a 30 day window before hospitalization: Reducing the alert threshold leads to increased sensitivity at the cost of higher false alert rate (FAR) per patient year (ppy). Two examples are highlighted (open squares): sensitivity 50% at FAR 1.34 ppy, and 41.5% at 0.95 ppy, respectively.

Pre-, in- and post-hospital thoracic impedance

The averaged patient-individual impedance was 61.9 ± 7.8 Ω. Patients of the HFE group had a lower TI than patients of the control group (60.1 ± 7.6 Ω vs. 62.3 ± 7.8 Ω, $p < 0.05$). Patients with a TI smaller than 60 Ω had a nearly two-fold higher chance for clinical HF events (odds ratio 1.90, confidence interval: 1.21–2.98, $p < 0.01$).

The average post-implant TI trend (Fig. 4A) shows an initial short decline of TI during the first two weeks, followed by a gradual increase during the following months. This stabilization of TI towards a steady baseline value takes more than three months. The initial steeper increase in TI was expected as a result of wound healing of the pocket.

In contrast, the pre-hospital TI trend (averaged for all EC-confirmed HF events) showed a gradual decrease within eight weeks prior to admission (Fig. 4B). Ratio statistics prove a significant change of TI prior to hospitalization with values being 3.0% higher (confidence interval: 1.9–4.2%, $p < 0.001$) four weeks before admission. The absolute level of pre-hospital TI is clearly below the calculated overall patients' median (see the dashed line in Fig. 4).

The in-hospital change of TI was calculated for 137 EC-confirmed HF events, and was highly significant (+6.9%, confidence interval: 5.4–8.4%, p < 0.001). Post-hospital observation of averaged TI (Fig. 4C) showed stabilized values on a higher TI level within 8 weeks after hospital discharge.

The more patient-individual analysis in Fig. 5 depicts the maximum percentage difference of TI (ΔTI_{max}) within a four-week pre-hospital period to the day of admission. Summarizing all covered events, average ΔTI_{max} was 5.6% ± 6.2% and found approximately 16 days before admission. When comparing different groups of event types, we observe a gradual increase in ΔTI_{max} starting with very low values ($\Delta TI_{max} =$ 3.3% ± 5.4%) for the post-implant group (early events within the first four months after implantation) to higher values ($\Delta TI_{max} =$ 5.3% ± 4.4%) for the group of first study events (outside this implant period) up to significantly higher values ($\Delta TI_{max} =$ 8.0% ± 7.9%) for the group of recurrent events. For the last group, another subdivision was meaningful, showing that events which occurred within 30 to 90 days after discharge from previous hospitalization, had still higher values ($\Delta TI_{max} =$ 11.9% ± 9.8%). For the group of EC-confirmed HF events including hospitalization and finally leading to patient's death, the analysis suggests even higher values. The differences between categories “post-implant events” versus “recurrent events” as well as “first events” versus “recurrent events” were all significant ($p < 0.05$).

Discussion

The opportunities to benefit from remote device diagnostics will increase with the growing capabilities of modern implants and the efficiency of novel sensors. However, each sensor variable has to be introduced with great caution and needs a critical review of its clinical validity, not least to avoid the effects of information overload.

Our results show that TI individually offers added value by providing clinically relevant information on pulmonary congestion in selected cases, whereas overall benefit is modest. In general, the averaged absolute level of impedance was significantly lower in those patients who had experienced one or more HF events. Although less pronounced than expected, there was a significant pre-hospital decrease in TI. Most striking was the effect of intensified diuresis on TI during in-hospital stay that was paralleled by a highly significant rise in TI. In- and post-hospital observation of TI might therefore be the most valuable scenario for clinical practice to control recompensation and a stabilization of TI on a higher absolute level. Here, the big advantage of this application should be pointed out: TI data result from measurements by an already implanted device without additional sensor equipment, using standard leads and the capability of fully automatic transmissions on a daily basis.

The presented algorithm was retrospectively developed, based on the patient's circadian TI trend. Its performance was measured on a subset of HF events selected by the use of pre-specified validation criteria in order to avoid a potential bias, caused e.g. by overfitting towards single patients or post-implant HF events. With a sensitivity of 41.5% at a

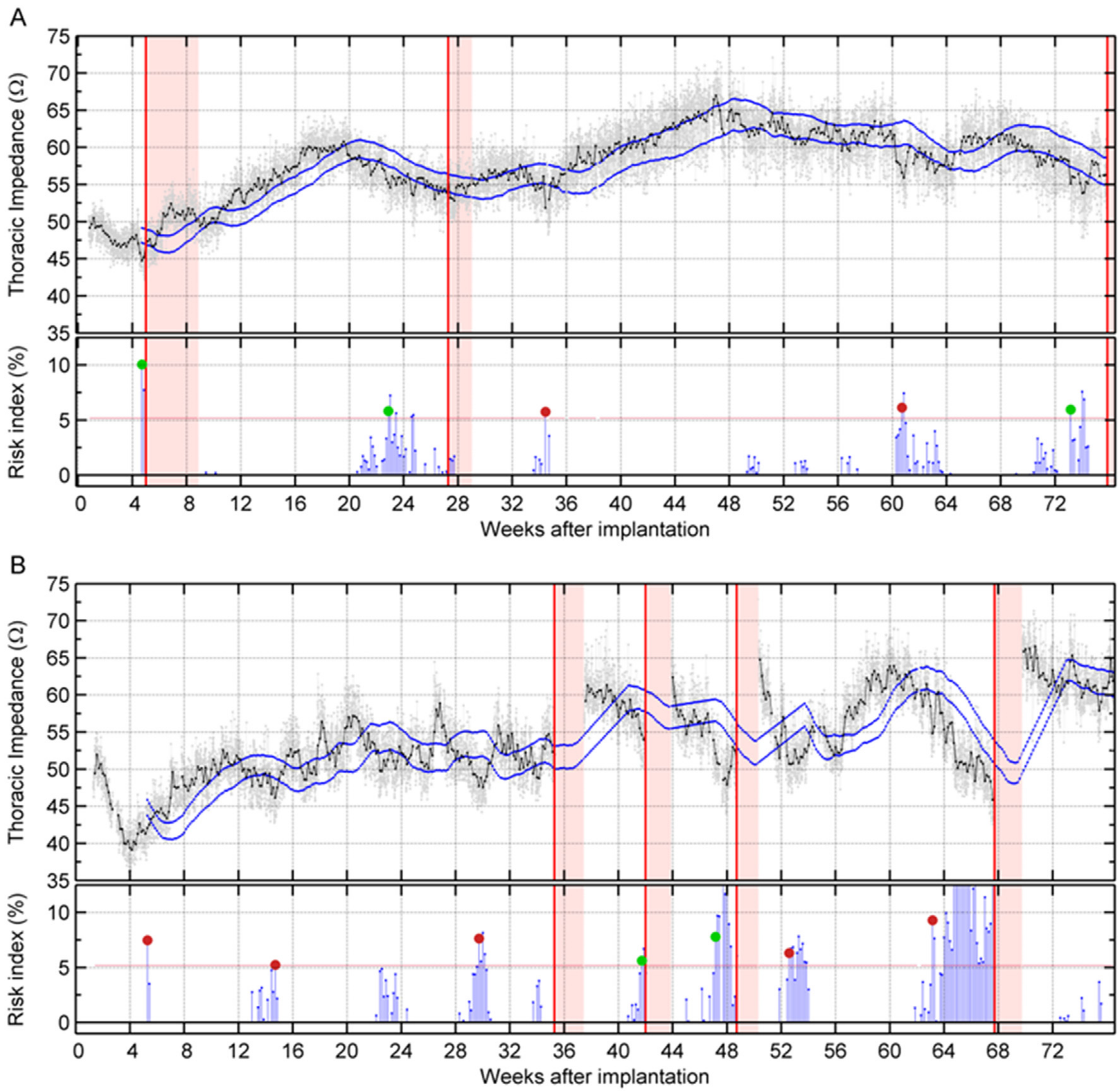

Fig. 3. Representative examples of thoracic impedance trends for two patients (A) and (B) with multiple heart failure decompensations. Upper graphs with 24 hour impedances (light grey), daily mean impedances (black), and derived reference band (blue). Lower graphs with risk index (blue), threshold (red), and resulting true positives (green circles) and false positives (red circles). Red shaded regions identify time of hospitalization.

projected low false alert rate of 0.95 ppy and a sensitivity of 50% at 1.34 false alerts ppy, respectively, the overall performance of the algorithm was satisfactory if compared to recent data from other studies [12,17,18].

However, the main finding of this study is the strong diversity of the diagnostic and prognostic power of TI between different subgroups, a fact that calls into question whether a more global target population with less advanced HF symptoms is really best suited for applying TI-based alerts. The visual inspection of TI trends on a larger timescale, as for example presented by our case reports, provide a more comprehensive picture, including manifold short and long term fluctuations of TI that trigger a considerable number of uncertain alerts. These alerts might actually result in false alerts due to the individual capability to self-correct congestion by intrinsic adaptive responses or by self-changes in therapy, in response to mild not reported worsening of HF symptoms. Another option might be a lesser compliance with therapy as we can assume that a considerable number of re-hospitalizations involves low adherence to therapeutic and life style (sodium diet) recommendations. The observed high inter-patient variability clearly impairs the generalizability of the results. Although only patients with high risk criteria contributed to this study, 80% did not experience any HF event during 21 months of follow-up. This resulted in a low overall HF event rate of 0.19 ppy, and as a consequence, a low overall PPV of 7.9% if the algorithm is applied to the complete study cohort. Applying the algorithm to the HF event group only, obviously results in a substantially higher PPV of 27.1% in this patient cohort with more advanced HF symptoms, as pre-confirmed by the underlying baseline characteristics.

A subgroup-based analysis of this HF event group points out another major finding: Recurrent events showed a significantly higher decrease in TI before readmission, suggesting the predictive power of TI is considerably superior for advanced HF patients. This was confirmed by a significantly higher sensitivity for the prediction of recurrent events. This finding should be challenged in a multivariate analysis including other traditional or novel markers.

In fact, our findings help to explain the divergence of previous study results where the predictive power of TI covered a broad range of sensitivities ranging from 20.7% to 76.9% with false alert rates from 0.25 to 2.4 ppy [5,9–12,17,18]. Unfortunately, many differences between those studies exist in terms of patient characteristics, blinding of TI data and alerts, calculation of performance statistics, and the exact definition of HF events. Basically, these studies were mainly driven by the initial results from Yu et al. who showed very promising statistics with a high

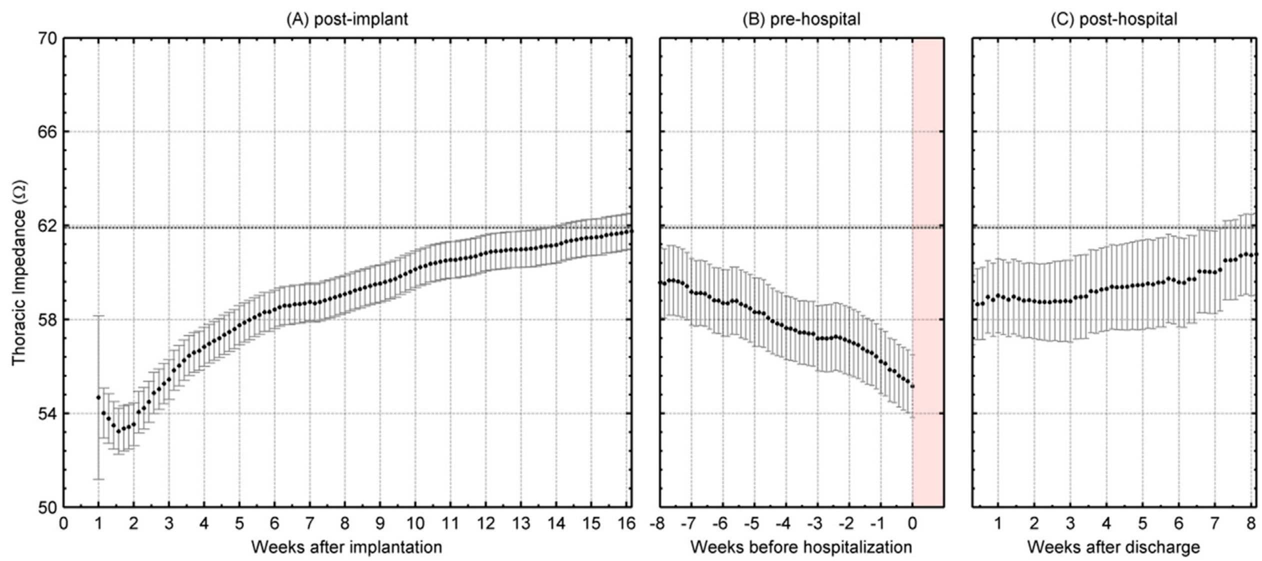

Fig. 4. Overlay trends of thoracic impedance averaged for patients providing data for four-month post-implant phase (A, only patients from non-heart failure-event group), pre-hospital phase (B), and post-hospital phase (C). Dots represent mean of values, error bars represent 1.96 standard error. Dashed line indicates overall averaged patient-individual median impedance.

sensitivity of >76% and a considerably high decrease of impedance by >12% approximately 18 days before hospital admission [5]. However, these data merely refer to 24 HF events in only nine patients from a small study population with exclusively NYHA III-IV patients, all with a history of significant HF-related events. Thus, the whole analysis was based on recurrent HF events only. Interestingly, and in accordance with the selected population of Yu et al., our results on recurrent HF events demonstrate a similar, more distinct decrease in TI revealing a significantly higher chance for detection. This suggests that current TI applications for detecting imminent decompensation are superior in only a minority of advanced HF patients. However, conclusions drawn from this first study have been adopted in an oversimplifying way for a broader patient collective in the majority of following trials. The inconsistent results from these trials led to a shift in clinical requirements towards more specific, and therefore less sensitive, algorithms even during the course of our study, since opposite effects like an increase in HF hospitalizations occur when providing a too sensitive algorithm with low PPV to patients or treating physicians [13]. A very recent prospective and randomized controlled trial with >1000 patients and 18 months of follow-up clearly failed to show superiority of a prescriptive intervention algorithm based on remote TI alerts over standard clinical assessment [15]. Böhm et al. addressed a considerable non-adherence to telemedicine and treatment protocol by patients and physicians. Their presented data suggest that a lack of confidence in TI-based alerts might be the reason for the addressed non-adherence.

Technical improvements of impedance-based approaches are under investigation but their interpretation is very challenging, e.g. the use of a quadripolar electrode arrangement between biventricular leads for

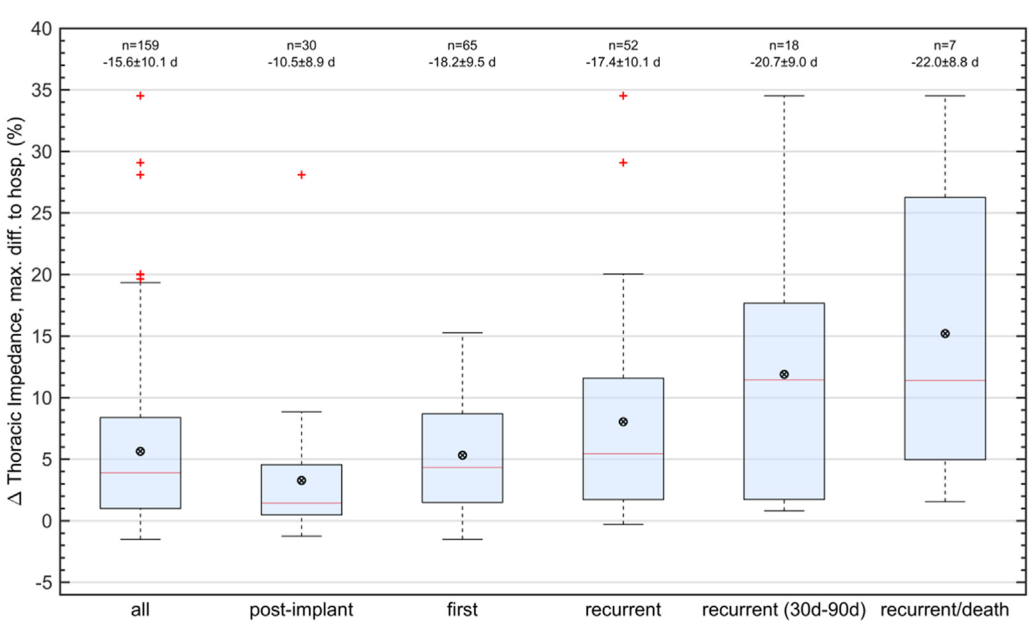

Fig. 5. Maximum difference of thoracic impedance (ΔTI_{max}) within a four-week window to day of admission for different heart failure event types: all = all confirmed events with sufficient data; post-implant = first events inside of post-implant phase (4 months); first = first events outside of post-implant phase; recurrent = recurrent events (>7 days after previous) outside of post-implant phase; recurrent (30d-90d) = recurrent events (30 to 90 days after previous); recurrent/death = recurrent events followed by death.

measuring intracardiac impedance as a better hemodynamic correlate [19]. Another recent study by Heist et al. presented a multi-vector approach for TI measurements but showed that including the LV lead as an additional pole did not improve predictive power (sensitivity 32.4%, false alert rate 1.66 ppy) [17]. In another recent study, Auricchio et al. reported on a dual sensor approach which combined data from TI-derived minute ventilation and physical activity, but the trial also failed to outperform current numbers (sensitivity 34%, false alert rate 2.4 ppy) [18].

The performance of our single-sensor approach might exceed that of other device diagnostic variables. For example, Sack et al. reported lower sensitivities of several parameters ranging from 23.6% for patient activity to 50.0% for heart rate variability, all with a projected false alert rate of 1.83 ppy [20]. However, the authors referred to a broader definition of major cardiovascular events. In contrast, all TI-based approaches are tailored towards HF events with clear signs of pulmonary congestion, and still there is a tendency towards a limited inherent sensitivity <40% in clinical real-life, irrespective of the details of any implemented algorithm. Besides technical deficiencies and limitations in revealing lung fluids with an optimal technical sensitivity, much of this might be attributed to the complex pathophysiological mechanisms behind acute HF decompensation that go beyond a simple gradual accumulation of fluids [21].

The proposed switch to a multi-parameter approach using a combined set of independent device diagnostics might depict an appropriate strategy to establish a risk score with improved sensitivity at an acceptable alert rate [20,22,23]. However, collective results from trials focusing on a representative HF cohort (this and the above mentioned studies) all attest a low PPV. This clearly indicates the importance of a well-defined and efficient clinical workflow subsequent to remote alerts. Interestingly, so far only one recent trial that did not focus on TI, showed that daily implant-based multi-parameter monitoring significantly improved clinical outcomes [2]. In contrast, other recent trials where TI played a major diagnostic role, failed to improve outcomes [15,24,25]. Beyond the trivial conclusion that several predictive parameters are more powerful than a single one, this may suggest one further aspect: Telemedical strategies may be more successful when they aim to maintain patient's health status in time rather than to take action only before imminent decompensation in patients with advanced HF by focused use of a single-sensor application like TI.

Conclusion

Our study confirms that monitoring thoracic impedance offers added benefit for individual patients due to its unique pre-hospital and in-hospital changes. However, overall performance in predicting imminent decompensation by TI alone is limited due to the observed high inter-patient variability. As the exhibited pre-hospital decrease in TI appears to be significantly larger before recurrent events, its use should be redirected towards patients with more advanced symptoms for whom close observation of TI has already been shown to be of diagnostic or prognostic value. Post-hospital monitoring aimed to maintain the patient's discharge status might be the most valuable approach.

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Conflict of interest

S.K.G.M. has received grant support and consulting fees from Biotronik and Medtronic. S.P. and N.L. are employees of Biotronik. M.K. has received grant support and speaker's honoraria from Biotronik and Medtronic. A.Q. has received consulting fees and research honoraria from Biotronik, Medtronic and St Jude Medical. K.A. has received payment for speaker's bureau appointments from Medtronic Japan. All other authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.01.004.

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