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Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure

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Aims To evaluate the utility of intrathoracic impedance monitoring for detecting heart failure (HF) deterioration in patients with an implanted cardiac resynchronization/defibrillation device.
Methods and results Patients enrolled in the European InSync Sentry Observational Study were audibly alerted by a device algorithm if a decrease in intrathoracic impedance suggested fluid accumulation. Clinical HF status and device data were assessed at enrolment, during regular follow-up, and if patients presented with an alert or HF deterioration. Data from 373 subjects were analysed. Fifty-three alert events and a total of 53 clinical events (HF deterioration defined by worsening of HF signs and symptoms) were reported during a median of 4.2 months. Adjusted for multiple events per patient, the alert detected clinical HF deterioration with 60% sensitivity (95% CI 46–73) and with a positive predictive value of 60% (95% CI 46–73). Higher NYHA class at baseline was predictive for adequate alert events during follow-up ($P < 0.05$). In 11 of 20 HF deteriorations without preceding alert, an upstroke of the fluid index occurred without reaching the programmed alert threshold.
Conclusion A device-based algorithm that alerts patients in case of decreasing intrathoracic impedance facilitates the detection of HF deterioration. Future randomized, controlled trials are needed to test whether the tailored use of intrathoracic impedance monitoring can improve the ambulatory management of patients with chronic HF and an implanted device.

Introduction

Heart failure (HF) is the most common cause for hospitalizations in the US among persons older than 65 years.[1] Despite therapeutic advances, the majority of these events are re-admissions due to acute deterioration of chronic HF.[2] Early detection of fluid overload and pulmonary congestion allows timely adjustment of HF therapy and may thereby avoid manifest HF decompensation, hospitalizations, and the associated morbidity, mortality, and costs. Current HF guidelines recommend to educate patients about HF signs and symptoms and to assess their fluid status regularly.[3] A large proportion of HF decompensations, however, is related to medication noncompliance and failure to seek medical attention timely after worsening of symptoms.[4] Furthermore, established measures for outpatient fluid status monitoring provide limited clinical reliability. Weight gain, for example, has recently been found to have a sensitivity of <20% to detect clinical deterioration of chronic HF.[5]

In the light of the growing number of devices being implanted in HF patients for cardiac resynchronization (CRT)/defibrillation (D) therapy, a device-based algorithm that alerts patients in case of cardiac deterioration and worsening pulmonary congestion could improve the outpatient management of HF. Recent studies suggest that intrathoracic impedance may be a useful parameter to track day-to-day changes in the pulmonary fluid status.[6,7] Intrathoracic impedance was measured over time by an implanted device and correlated inversely with changes in the left ventricular (LV) end diastolic pressure in a canine HF model[6] and with changes in the pulmonary capillary wedge pressure (PCWP) and the net fluid loss in HF patients hospitalized for fluid overload.[7]

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Recently, a CRT-D device that incorporates intrathoracic impedance monitoring (InSync Sentry™, Medtronic, USA) has been developed. This device is also equipped with an algorithm that can automatically alert the patient with an audible signal to contact the physician if intrathoracic impedance decreases significantly. Limited data indicate that this feature may enhance the detection of chronic HF deterioration.[7,8] The aim of the present analysis was to evaluate the alert algorithm in a large cohort of patients under a prospective observational study design.

Methods

Study design and patient selection

The European Observational InSync Sentry Study is a multi-centre, prospective observational study designed to collect clinical and device data from patients suffering from chronic HF and implanted with an InSync Sentry device. The study protocol complies with the Declaration of Helsinki and was approved by each local Ethics Committee. Approximately 1000 patients were enrolled at centres in Europe, Middle East, and Africa. Enrolment started July 2004 and was scheduled for a time period of 2 years, with the follow-up duration limited to a maximum of 2 years per patient.

Patients were enrolled on the day of device implantation or the day before. Subjects were eligible for enrolment if they were implanted with an InSync Sentry and if they had given written informed consent for data collection. Patient selection was up to the discretion of the participating centres.

In accordance with the protocol of the European Observational InSync Sentry Study, the database was frozen for a pre-specified interim analysis 1 year after enrolment had started. The focus of this interim analysis was to determine the value of the alert algorithm to anticipate clinical deterioration of chronic HF. Only patients with at least one follow-up, reported by the time the database was frozen, were considered for this analysis.

Device characteristics and programming

The device used in the present study (InSync Sentry) is a triple-chamber CRT-D device with several additional diagnostic capabilities for the management of HF. Intrathoracic impedance measurement and the alert algorithm were described in detail previously.[7,8] Briefly, intrathoracic impedance is calculated once daily as an average of 64 measurements between the can of the device and the right ventricular (RV) coil of the defibrillation lead. Daily impedance is compared with a reference, which is a slow moving average of several preceding daily impedance values. The algorithm is inactive for the first 34 days after device implant to allow time for post-implant pocket healing. Thereafter, differences between reference and daily impedance are accumulated if the daily impedance decreases below the current reference value. The resulting fluid index will progressively increase if consecutive daily impedance measurements are below the reference. An audible alarm can alert the patient each day at a given time if the fluid index exceeds a programmable threshold.

Device programming was left to the physicians' discretion in this study. It was recommended, however, to program the alert feature 'ON' and to adhere to the nominal fluid index threshold of 60. Furthermore, physicians were advised to demonstrate the alarm tone to all patients prior to hospital discharge and to instruct patients to present to the clinic in case of a device alert.

Data collection and study endpoints

Data were evaluated at enrolment, during regular follow-up, and if patients presented with a device alert or with decompensated HF. Standard case report forms were used for data collection. Timing of regular follow-up was up to the local investigators.

At each regular or unscheduled visit, the clinical HF status was evaluated, the device was interrogated, the integrity and appropriate functioning of the implanted system was verified, and device programming and all retrieved memory data were stored onto a disk.

Current HF status was assessed according to standard procedures of the participating centres. Usually, this evaluation included changes in functional NYHA class, HF symptoms, body weight, and HF medication. Additional diagnostic procedures (e.g. physical exam, chest X-ray) were performed if indicated by the local investigator. On the basis of the acquired information, physicians were asked to classify the current HF status as stable or, in the presence of worsening HF signs or symptoms, as deteriorated.

A device alert was considered for event classification if the clinical HF status was evaluated within a time period of 2 weeks after alert onset. Threshold crossings of the fluid index and clinical events with HF deterioration that occurred while the device alert function had been programmed 'OFF' were not considered for data analysis. Furthermore, an event was excluded from the analysis if it occurred within the first 34 days after surgical (re-) intervention at the device pocket (e.g. due to lead dislodgement) and if—contrary to the recommendation of the manufacturer—the alert had erroneously been programmed 'ON' for this time period.

All available clinical data and device save-to-disk information were reviewed for adequate event classification. As per definition, a 'true-positive alert event' was associated with clinically deteriorated HF, diagnosed within 2 weeks after the initial alert. A 'false-positive alert event' required HF to be classified as stable within the same period of time. If HF deterioration was diagnosed without alert in the preceding 2 weeks, the event was defined as a 'false-negative' alert. The clinical management of alert events and HF decompensation was left to the discretion of the local physician.

Statistics

Continuous data are given as mean $\pm$ standard deviation. Data not normally distributed are expressed as median with 25th–75th percentile. Sensitivity (ratio between the number of true-positive alert events and clinical events with HF deterioration) and positive predictive value (PPV, ratio between the number of true-positive alert events and all alert events) are expressed with 95% CI. Adjusted sensitivity and PPV were estimated from a logistic regression model without covariates, using the generalized estimating equations (GEE) method to correct parameter estimates for multiple alert events per patient. Logistic regression models were fitted to assess whether baseline variables (gender, age, NYHA class, QRS width, LV ejection fraction, non-ischaemic cardiomyopathy, ischaemic cardiomyopathy, coronary artery disease, hypertension, diabetes, sick sinus syndrome, ventricular conduction disorder, AV-conduction disorder, atrial fibrillationAF/flutter) were associated with alert sensitivity or PPV, or with the occurrence of an alert event or HF deterioration. Because the number of repeat events was too low to estimate repeat-event-specific parameters, the model considered only the first event.

Impedance changes were compared using the Wilcoxon's signed-rank test. A Z-test or Fisher's exact test was used, as appropriate, to compare clinical HF manifestations between true-positive and false-negative alert events. A two-tailed P-value <0.05 was considered statistically significant.

Results

Between July 2004 and July 2005, 640 patients were enrolled at 42 centres when the database was frozen for an interim analysis. In 267 patients, no follow-up data had been reported by the time the database was frozen. The time interval between enrolment and database freeze was <30 days in 91 and >3 months in 108 of these subjects. The present analysis considered those 373 patients with at

least one reported follow-up. Baseline characteristics of these patients are summarized in *Table 1*. Fifteen subjects, including nine NYHA class I or II patients, were indicated for an ICD but not for CRT and received the InSync Sentry without an LV lead. In six patients, the InSync Sentry replaced another implanted CRT device because of battery depletion. Placement of the LV lead failed in four patients (1.1%). A lateral or posterior LV lead position was reported for 91% of the subjects, whereas the RV lead was predominantly placed in the RV apex (87%).

Median follow-up duration was 4.2 (25th–75th percentile, 2.5–6.6) months. A total of 818 follow-up visits were reported, with a median follow-up interval of 2.1 (25th–75th percentile, 1.3–3.3) months; 117 follow-up visits were unscheduled.

The alert feature was programmed 'ON' in 72% of the patients at the initial follow-up and in 79% at the last follow-up. The alert index threshold was programmed to the nominal value of 60 in 95% of the subjects at the first follow-up.

Alert events and patient outcome

Fifty-three alert events occurred in 45 patients, and a total of 53 clinical events of HF deterioration were identified in 43 subjects. Clinical manifestations of HF deterioration are summarized in *Table 2*. The median time interval between alert onset and clinical evaluation was 3 (25th–75th percentile, 2–6) days. The alert algorithm detected clinical deterioration of chronic HF with a raw sensitivity of 62% (33/53) and a raw PPV of 62% (33/53). In three alert events, the device alert threshold had been adjusted in response to a preceding event. After exclusion of these events because of potential bias and after correcting for multiple events per patient (GEE method), the adjusted device alert sensitivity to detect HF deterioration was 60% (95% CI 46–73), with an adjusted PPV of 60% (95% CI 46–73). *Figure 1* shows representative examples of different alert events. In subjects with active device alert function during follow-up, the average monthly rate of false-positive alert events was 1.5 per 100 patients (~0.2 per patient-year).

Six clinical events of HF decompensation were excluded from data analysis because they occurred while the device alert function was inactive. In four of these events, the fluid index had crossed the programmable alert threshold (60 in all patients) prior to the event. Seven alert events were excluded because they occurred within 34 days after surgical intervention at the device pocket (e.g. lead revision).

Multiple regression analysis revealed that a higher NYHA class at baseline was the only variable that was significantly associated with episodes of clinical HF deterioration and the occurrence of true-positive alert events during follow-up ($P < 0.05$, respectively). None of the baseline characteristics could predict the occurrence of false-positive device alert events or false-negative alerts. Furthermore, there was no significant difference in the clinical presentation of true-positive and false-negative alert events (*Table 2*).

HF deterioration caused hospitalization of 19 patients for 40% (21/53) of all clinical HF events. Hospitalization rates were not significantly different between cases of HF deterioration with or without preceding alert (36 vs. 45%, $P = 0.53$).

Nine deaths were reported during the study period. Two deaths were due to terminal pump failure and occurred in hospitalized patients. In one case, intrathoracic impedance had dropped significantly in the week before the fatal event, but the alert had been programmed to monitor

Table 1 Patients' characteristics at enrolment ($n = 373$)

Male	303 (81%)
Age, years	65 ± 10
Cardiomyopathy	
Ischaemic	216 (58%)
Non-ischaemic	157 (42%)
NYHA class	
I	17 (5%)
II	81 (22%)
III	254 (68%)
IV	21 (6%)
QRS width	158 ± 29 ms
Ejection fraction	25 ± 8%
Cardiovascular disease	
Coronary artery disease	216 (58%)
Hypertension	175 (47%)
Diabetes	104 (28%)
Ventricular conduction disorders[a]	
Left bundle brunch block	271 (73%)
Right bundle brunch block	15 (4%)
Other ventricular conduction block	10 (3%)
AV conduction disorders	
AV block I	40 (11%)
AV block II	10 (3%)
AV block III	34 (9%)
Rhythm disorders	
Sick sinus syndrome	49 (13%)
Atrial fibrillation/atrial flutter	103 (28%)
Paroxysmal	54 (15%)
Persistent/permanent	49 (13%)
HF medication use	
Beta-blocker	295 (79%)
ACE-inhibitor/AT blocker	293 (79%)
Diuretics	352 (94%)
Aldosteron antagonist	180 (48%)
Digitalis	144 (39%)

Data are mean (standard deviation) or *n*%.
[a]In the presence of intrinsic AV conduction.

Table 2 Clinical presentation of HF deterioration

Manifestation of HF deterioration (multiple manifestations possible)	All ($n = 53$)	+Alert ($n = 33$)	−Alert ($n = 20$)	*P*-value (+ *vs.* −alerts)
Pulmonary congestion ↑ (%)	46 (87)	29 (88)	17 (85)	0.76
Peripheral oedema ↑ (%)	25 (47)	14 (42)	11 (55)	0.37
Worsening of NYHA functional status (%)	18 (34)	7 (21)	11 (55)	0.12
Body weight ↑ (%)	14 (26)	9 (27)	5 (25)	0.86

+Alert, true-positive alert events; −Alert, false-negative alert events; Pulmonary congestion ↑, worsening of dyspnoea/orthopnoea, and/or signs of acute pulmonary congestion on auscultation/chest X-ray.

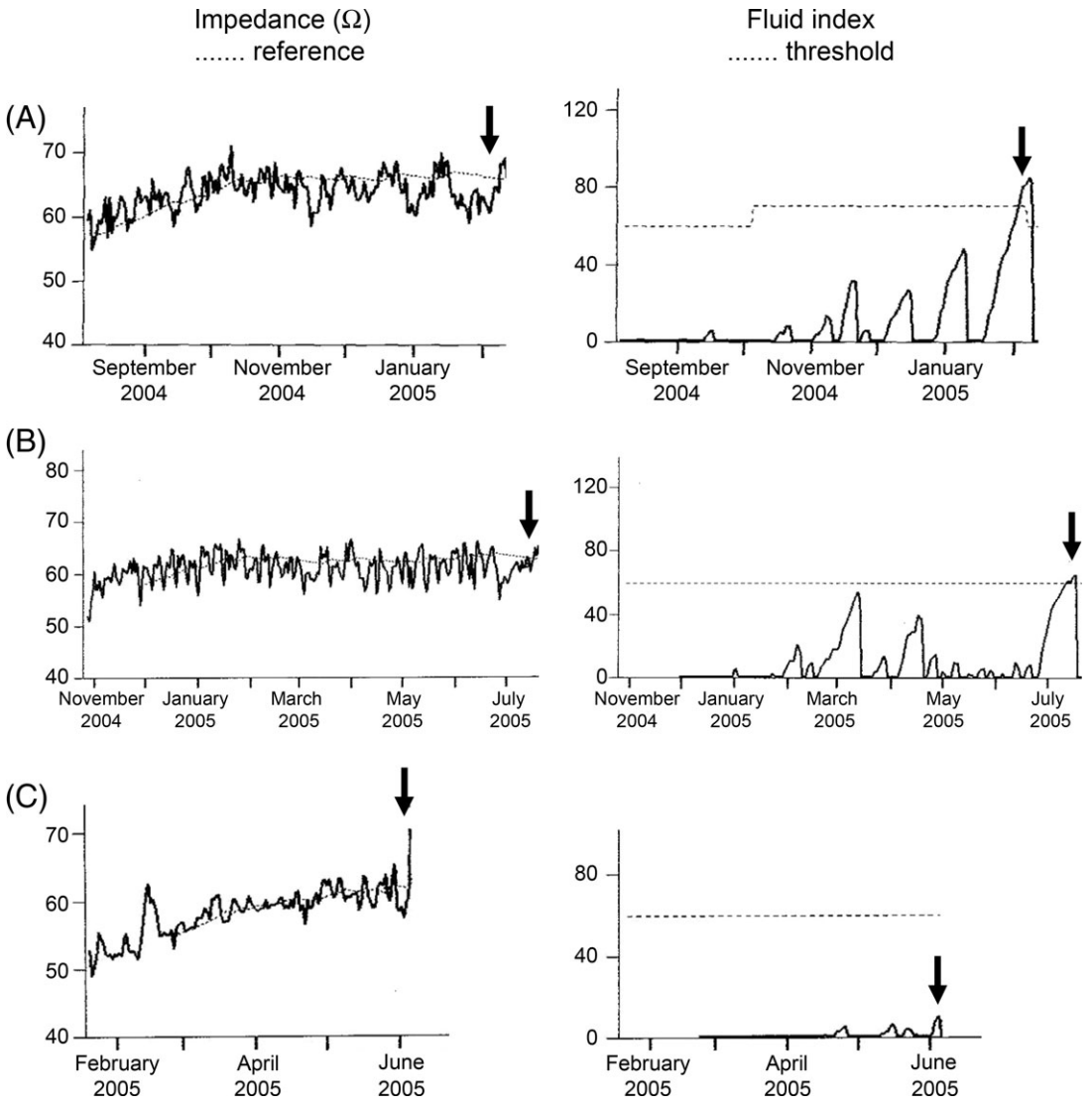

Figure 1 Examples of different alert events. (*A*) True-positive alert in a 39-year-old female who received the device because of DCM, EF of 20%, complete heart block, and NYHA class III symptoms. In February 2005, an unscheduled follow-up (↓) was triggered by an alert that had first sounded the previous day. The patient denied worsening of HF symptoms, but admitted incompliance with regard to fluid intake in the last weeks. Her body weight had increased by 4 kg since the preceding visit, and chest X-ray revealed signs of acute pulmonary congestion. Diuretic doses were increased and fluid intake was restricted. Six days later, her body weight had normalized and daily impedance was above the reference. Note that transiently the fluid index threshold had been programmed empirically from 60 to 70 in this patient. (*B*) False-positive alert in a 59-year-old male who received the device because of DCM, EF of 15%, LBBB, and NYHA class III symptoms. In July 2005, the alert triggered an unscheduled follow-up (↓) when no evidence of HF deterioration was found. Note that daily impedance had increased, returning close to the reference at the time of follow-up visit. (*C*) False-negative alert in a 57-year-old male with ICM, EF of 20%, LBBB, and NYHA class II symptoms at the time the resynchronization device was exchanged because of battery depletion. In June 2005, the patient was hospitalized for global HF decompensation (↓). Device interrogation revealed that daily impedance had decreased below the reference, but the accumulated difference between daily impedance and reference impedance (fluid index) was not sufficient to trigger the alert. Note the rapid increase in intrathoracic impedance during hospitalization and intensified diuretic therapy. DCM, dilative cardiomyopathy; EF, LV ejection fraction; ICM, ischaemic cardiomyopathy; LBBB, complete left bundle branch block.

only. The other patient died in hospital 2 weeks after the device had been implanted and while the alert algorithm was still in the initialization period. Causes for the remaining seven deaths were sudden cardiac ($n = 1$), non-cardiac ($n = 4$), and unknown ($n = 2$).

Intrathoracic impedance and false alert events

Overall, intrathoracic impedance gradually increased from $58 \pm 11\ \Omega$ at implant to 62 ± 8, 66 ± 9, and $68 \pm 9\ \Omega$ at 34, 90, and 180 days post-implant. This trend likely reflects initial healing of the device pocket and overall improvement in clinical HF status upon CRT.

Thirteen per cent (7/53) of the device alert events occurred while a different threshold than the nominal value of 60 was programmed. This selected threshold was 40 ($n = 2$), 70 ($n = 2$), and 120 ($n = 1$) in 15% (5/33) of the true-positive alert events and 40 ($n = 1$) and 80 ($n = 1$) in 10% (2/20) of the false-positive alerts. In three of the true-positive alert events, thresholds were adjusted in response to a preceding alert event, either to increase ($60 \rightarrow 40$) or decrease ($60 \rightarrow 120$) the sensitivity of the alert algorithm.

At an alert event, daily impedance was $4.6 \pm 3.5\ \Omega$ below the reference at the alert onset and $3.0 \pm 3.6\ \Omega$ below the reference when the clinical HF status was evaluated.

Comparison of impedance trends for this time interval did not reveal significant differences between true-positive and false-positive alert events.

Fifty-five per cent (11/20) of the false-positive alerts were related to other clinical events or resulted in therapeutic interventions. In two patients, the decrease in intrathoracic impedance was attributed to fluid accumulation due to other causes than pulmonary congestion (e.g. pneumonia). In another patient with a false-positive alert, clinical evidence for HF deterioration was lacking, but ineffective CRT therapy due to LV lead dislocation was diagnosed. In another eight subjects, HF medication was intensified, although clinical symptoms and signs for HF deterioration were reported to be absent at the time of follow-up. Underlying reasons for these interventions were given for half of the patients (new onset of AF, $n = 2$; previous true-positive alert, $n = 2$). Clinical HF deterioration late (15–30 days) after alert onset was not reported for any of the patients with false-positive alert events.

Twenty false-negative alert events were observed during the study period. Patients with false-negative alert events tended to present more often with worsening of peripheral oedema and less frequently with pulmonary congestion, but this trend was statistically not significant (*Table 2*). In three false-negative alert events, HF deterioration manifested without clinical evidence for pulmonary congestion. In 11 (55%) of the false-negative alerts, intrathoracic impedance had decreased below the reference when HF deterioration was diagnosed, but the upstroke of the fluid index was not sufficient to cross the programmed threshold (*Figure 1C*).

Discussion

Main findings

This prospective observational study describes first clinical experience with a device-based alert algorithm for the detection of clinical HF deterioration. Subjects with chronic HF and an implanted CRT-D device were audibly alerted if changes in intrathoracic impedance indicated potential fluid accumulation. We found that the device alert detected HF deterioration with an adjusted sensitivity and an adjusted PPV of 60% each. Failure of the alert algorithm to detect clinical HF deterioration was in 55% of the cases associated with an increase of the fluid index that was yet below the programmable alert threshold. Half of the false-positive alerts were related to other clinical findings or therapeutic interventions.

Clinical utility of intrathoracic impedance monitoring

Previous studies showed that intrathoracic impedance, measured by an implanted device, correlates inversely with the LV end diastolic pressure in a canine HF model[6] and with the PCWP and the net fluid loss in HF patients hospitalized for fluid overload.[7] Yu *et al.*[7] developed and evaluated the present alert algorithm, using data from subjects who had been implanted with an investigational device for regular measurements of intrathoracic impedance. In their retrospective analysis of data from 26 patients and 13 hospitalizations, the alert algorithm detected hospitalization for fluid overload, with a sensitivity of 77% and 1.5 false-positive alerts per patient-year (reflecting a PPV of 25–30%).

Several aspects have to be considered when comparing the algorithm performance reported by Yu *et al.* with our results. First, different endpoints were analysed: Yu *et al.* used hospitalization for decompensated HF as a clinical endpoint; our study also considered milder forms of HF deterioration. This difference may explain the lower sensitivity and the higher PPV of the alert feature in our study. Furthermore, in contrast to the work by Yu *et al.*, patients and physicians were not blinded for the alert in our investigation, and we only evaluated device alerts if the clinical HF status was assessed shortly (14 days) after the alarm first sounded, whereas Yu *et al.* retrospectively defined an early warning time window of 30 days prior to hospitalization.

False alerts

In 40% of the reported alert events, clinical evaluation within the 14 days after alert onset did not confirm HF deterioration. Yu *et al.* retrospectively analysed the temporal relationship between changes in intrathoracic impedance and clinical worsening of HF after developing the alert algorithm that was used in the present study.[7] They found that a time interval of several days usually existed between the alert (13 ± 6 days before HF-related hospitalization) and clinical manifestation with worsening of HF symptoms (3 ± 3 days before hospitalization). Furthermore, Stevenson and Perloff[9] reported that the physical examination often fails to detect elevated LV filling pressures in patients with chronic HF. Thus, in some of the alert events classified as false positive in our study, symptoms and clinical signs of HF deterioration may have been absent, despite progressive pulmonary congestion at the time of the clinical evaluation. In this context, it is remarkable that HF medication was intensified in more than one-third of the false-positive alert events. The benefit of this treatment remains speculative, but in at least half of these events, the physician had apparent reasons to believe that the alert may predict HF deterioration in a yet asymptomatic patient.

As an alternative explanation for a false-positive alert, the time interval between decreases in impedance, alert onset, and evaluation of clinical HF status may in some cases have been associated with enhanced patient compliance with regard to fluid intake, HF medication, or physical activity. This situation was reported anecdotically, while transient changes in patient compliance were not systematically evaluated. The example shown in *Figure 1B* could represent such a case, although no additional information on compliance was provided. When this patient presented to the clinic owing to the alert, no evidence for HF deterioration was found. As illustrated by the impedance trend, however, the decrease in impedance had occurred several days earlier, whereas it had returned almost back to the reference at the time of clinical evaluation. Analysis of overall changes in impedance for the time between alert onset and clinical HF evaluation revealed no significant trend. Nevertheless, it appears advisable to consider the trend in intrathoracic impedance if a patient presents with an alert but without clinical evidence for deteriorating HF. Furthermore, the findings of our analysis underline that other causes for pulmonary fluid accumulation

(e.g. pneumonia) should be excluded if HF deterioration cannot be clinically confirmed in case of an alert.

In the present analysis, the alert algorithm detected clinical deterioration of chronic HF with an adjusted sensitivity of 60%. Weight gain, a commonly used indicator for fluid accumulation in ambulatory HF patient, was recently found to detect clinical deterioration of chronic HF with a sensitivity of only 17%.[5] In the same report, the combination of increase in body weight and B-type natriuretic peptide (BNP) increased sensitivity to 55%. Measurement of BNP, however, requires blood testing and can thus only be evaluated sporadically, e.g. if subjects present to the outpatient clinic. In contrast, the present alert algorithm provides continuous ambulatory surveillance of patients who received an HF device for therapeutic indications. Thus, while other tools also provide limited sensitivity or require patient visits, the complementary use of intrathoracic impedance monitoring may enhance the ambulatory management of chronic HF in patients with implanted devices.

In more than half of the false-negative alerts, intrathoracic impedance had decreased below the reference when HF deterioration was diagnosed, but the upstroke of the fluid index was not yet sufficient to cross the programmed threshold. The recommendation to program the alert threshold to a nominal value of 60 is based on the algorithm performance curve of a prior investigation[7] and reflects the ideal trade-off between sensitivity and specificity in the respective study population. Our findings suggest that individual adjustment of the fluid index threshold may be necessary to achieve sufficient algorithm sensitivity in selected patients.

Furthermore, pulmonary congestion is a typical but not an obligatory manifestation of HF deterioration. In our study, for example, HF deterioration manifested without evidence for pulmonary congestion in three false-negative events. Although the overall comparison of true-positive and false-negative alert events revealed only insignificant differences in the clinical presentation of HF deterioration, it is unlikely that intrathoracic impedance monitoring will detect HF deterioration in the absence of pulmonary congestion (e.g. isolated right heart failure).

None of the baseline parameters assessed in this study could predict the occurrence of a false-positive or false-negative alert event. However, multiple regression analysis revealed that a higher NYHA class at baseline was significantly associated with the occurrence of true-positive alert events during follow-up. This finding may appear not particularly surprising, but it indicates that appropriate patient selection may influence the clinical performance of the alert algorithm. Specifically, since patients with a higher NYHA class at baseline are more likely to experience a true-positive alert, the benefit from the present alert algorithm may be greatest in the subpopulation with moderate-to-severe HF.

In summary, our data support the use of device-based intrathoracic impedance monitoring as a complementary tool for the ambulatory management of chronic HF. Tailored use of the alert algorithm and consideration of the patient history and impedance trends at the time of an event may enhance the utility of the alert function. Future randomized, controlled trials are needed to assess the exact value of intrathoracic impedance monitoring in patients with chronic HF and an implanted device.

Study limitations

The design of this observational study implied that physicians and patients were not blinded for the alert. In addition, clinical HF evaluation was not standardized, and only recommendations were given for device programming. We can therefore not deny that the alert influenced patient compliance and that local physicians were biased regarding the evaluation and classification of HF and programming of the device. Furthermore, this analysis only considered alerts that led to a timely presentation of the patient, and no specific course of action was required in subjects presenting with an alert. Nevertheless, the present analysis gives first insights into the clinical utility of the alert function, highlighting potential advantages and limitations of the present algorithm. Future randomized, controlled studies with a longer follow-up period will have to determine the effect of the alert function on HF-related heath care utilization and survival.

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Conflict of interest: D.V. and B.L. served as lecturers for Medtronic. H.N. received research grants from Medtronic. U.W. served as a lecturer and consultant for Medtronic. A.Q. served as a consultant for Medtronic and Guidant. A.G. and M.R.S.H. are employed by Medtronic. P.S., C.B., and G.Z. declared no conflicts of interest.

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