Efficacy of Fluid Assessment Based on Intrathoracic Impedance Monitoring in Patients With Systolic Heart Failure

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Background: Previous studies have demonstrated that intrathoracic impedance monitoring (IIM) is associated with fluid overload. However, it remains unclear whether this new technology can predict heart failure (HF) before deterioration. Whether fluid status based on IIM predicts HF in patients with left ventricular (LV) systolic dysfunction was investigated.

Methods and Results: A prospective clinical observational study of 123 patients implanted with IIM-capable cardiac devices was carried out. The primary endpoint was the positive predictive value (PPV) at 12 months. Secondary endpoints were a correlation between onset of HF and IIM, optimal threshold of fluid index and duration between the alert and HF. Complete follow-up clinical data were obtained from 111 patients. During the observational period, 168 alerts were confirmed from 68 patients. In patient-based analysis (alert-based analysis), PPV was 33.8% (33.9%). Sensitivity, specificity and false positive was 67.6% (83.8%), 49.4% (28.4%) and 50.6% (71.6%), respectively. Mean duration between the alert and HF event was 21.4 ± 6.1 days. On multivariate logistic analysis, maximum fluid index, LV ejection fraction and atrial fibrillation were independent predictors of HF events. The optimal cut-off value determined by receiver operating characteristic curve was 114-ohm-day with sensitivity and specificity of 89.5% and 73.0%, respectively.

Conclusions: IIM-based fluid index in patients with HF due to LV systolic dysfunction was effective in predicting worsening HF. (*Circ J* 2011; **75**: 129–134)

Key Words: Cardiac device; Heart failure; Intrathoracic impedance

Heart failure (HF) is a common global medical problem with an increasing rate of new symptoms or morbidity among the aging population.^{1–4} HF is the major cause of hospitalization and death for people over 65 years old, and 75% of cases requiring hospitalization are caused by acute decompensated HF.⁵ Iterative treatments can be very costly and are a huge burden to the health care system.⁶ The number of HF patients is likely to increase with time^{1,7} and prevention of rehospitalization is an urgent issue from the perspectives of patient care and health economics.

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Intrathoracic impedance measured between the right ventricular lead and an implanted device is inversely correlated with pulmonary capillary wedge pressure and the loss of body fluid. This suggests that intrathoracic impedance monitoring (IIM) has the potential to be an alternative indicator for

body fluid overload.⁸ An IIM-based algorithm using a fluid index can detect probable onset of decompensated HF at an average of 15 days before onset, based on a cut-off value of 60 ohm·days.⁸ Several other reports have commented on the clinical efficacy of HF management utilizing this algorithm.^{9–12} However, little is known about it in Japanese patients and the predefined cut-off of 60 ohm·days was derived from a limited patient population, and the specificity and positive predictive values given by this cut-off value are unsatisfactory in daily medical practice.¹³

An optimal value for the fluid index that allows assessment based on the cause of each alert and the clinical utility of this approach has not been examined in detail. Furthermore, most previous studies have been conducted in patients with severe conditions, and evaluation of the effectiveness of the approach is required in a population with mild or moderate symptoms, which comprises most patients in daily practice. In this study, the clinical utility and efficacy of the fluid index were evalu-

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ated in such a patient of Japanese population.

Methods

Study Design

A single-center, prospective clinical observational study was performed to examine the utility of IIM for prediction of the deterioration of HF for 12 months after device implantation. The subjects were 123 consecutive patients with HF and left ventricular (LV) ejection fraction (EF) <35% who underwent a successful cardiac resynchronization therapy with a defibrillator (CRTD) or implantable cardioverter-defibrillator (ICD) procedure with inclusion of an OptiVol diagnostic feature (Medtronic, Inc, Minneapolis, MN, USA) from July 2007 to March 2009. Inclusion criteria were age ≥ 20 years old, expected survival of >1 year, and a class I or II ICD indication. The exclusion criteria were severe renal failure (serum creatinine >3.0 mg/dl) or hemodialysis; severe anemia (hemoglobin <10 g/dl); New York Heart Association (NYHA) functional class IV; chronic obstructive pulmonary disease; severe hematoma after device implantation; severe accumulation of pleural effusion; repetitive device implantation after infection; acute myocardial infarction within 6 months; awaiting cardiac surgery, heart transplant or a catheter procedure; pregnant or breast feeding; hypacusia; and difficulty making follow-up visits. Diabetes was defined as HbA_{1c} of $>6.5\%$, casual plasma glucose of >200 mg/dl or patients who were treated with oral hypoglycemic agents or insulin injection. Renal failure was defined as serum creatinine of >1.5 mg/dl.

The study was approved by our institutional review board and written informed consent was obtained from each patient. This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), which is accepted by the International Committee of Medical Journal Editors (registration number: UMIN00003640).

Device Implantation

All patients received transvenous procedures via the vena subclavia. For ICD implantation, a lead was first delivered to the right ventricular apex, and then the right atrium lead was placed in the right atrial appendage. Screw-in leads were used whenever possible. In CRTD implantation, after placing the ICD lead in the right ventricle, an 8 Fr guiding catheter was inserted into the coronary sinus, and a coronary sinus venogram was performed, followed by LV lead delivery. The LV lead was placed in a lateral or posterolateral vein if possible. Finally, the right atrium lead was delivered. The implanted devices were Concerto or Consulta for CRTD and Virtuoso or Secura for ICD (Medtronic, Inc, Minneapolis, MN, USA).

The fluid index threshold was programmed at the nominal value of 60 ohm·days, and the alert was set to go off at 10 a.m. for all subjects. The audible alert was tested for perceptibility and any sign of infection was examined before hospital discharge. A recommendation was made to visit the clinic within 3 days of hearing the alert.

Intrathoracic Impedance Monitoring

The fundamentals of IIM are described elsewhere.^{9,13} Briefly, during the first 34 days after implantation, the device only measures the reference impedance. Thereafter, daily impedance is calculated by averaging 64 measurements made every 20 min between 12 and 5 p.m. The fluid index increases when the daily impedance falls below the current reference value, and is reset when the daily impedance crosses the reference value. The nominal setting for the fluid index threshold is

60 ohm·days based on previous clinical findings,¹⁴ and the audible alert sounds when the index reaches this number.

Follow-up Visits

Data were collected during scheduled visits at 1, 3, 6 and 12 months after hospital discharge, and during unscheduled visits due to alerts or aggravation of HF. Subjects were tested for their HF status, and the device was interrogated to retrieve data from its internal memory for verification and examination. The presence of HF was basically diagnosed in our institute. Diagnoses of HF were made by HF specialists who were not involved in any other aspect of the study and who were blinded to the study endpoints. Patients who were diagnosed and received treatment for HF were counted as HF events. In the alert-based analysis, a single event was defined as the fluid index traversing the threshold of 60 ohm·days or the patient experiencing a HF event. The elapsed time between crossing of 60 ohm·days and the onset of the HF event was evaluated. Each subject with no crossing of the threshold during the follow-up period was counted as one alert. All other HF events, including those that took place after the 30-day window and those with unknown etiology, were classified as “unexplained detection”.

Study Endpoints

The primary endpoint was the positive predictive value (PPV), which was defined as the proportion of patients with a HF event that took place within 30 days following the first alert among all patients that an alert rang. Secondary endpoints were sensitivity (the proportion of patients that an alert actually rang among all subjects with HF events), specificity (the proportion of patients that an alert did not ring among all subjects without HF events) and false positive rate (the proportion of patients that an alert rang among all subjects without HF events), the optimal threshold of the fluid index, and the duration between the alert and the HF event.

Statistical Analysis

Continuous data are presented as a mean $\pm$ SD. All analyses were based on an intention-to-treat principle. Continuous variables were examined by unpaired t-test. Categorical variables were compared by chi-square test or Fisher's exact test, if necessary. Time-dependent outcomes were analyzed by the Kaplan-Meier method. The optimal cut-off value was determined using a receiver operating characteristic (ROC) curve produced by plotting the sensitivity and specificity of the fluid index for HF event prediction. Multivariate logistic regression was used to examine the risks for HF events. Prespecified variables (age, gender, ischemic heart disease, CRTD, NYHA class III, hypertension, hyperlipidemia, diabetes, renal failure, use of β -blockade, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers or statins, LVEF before implantation, maximum fluid index, atrial fibrillation [AF], and history of hospitalization for HF) with $P < 0.10$ in univariate analysis were used in the multivariate model. The results of the multivariate analysis are expressed as odds ratios (OR) for the comparison of risk with 95% confidence intervals (CI). $P < 0.05$ was considered to be statistically significant.

Results

Baseline Characteristics

Between July 2007 and March 2009, ICD or CRTD implantation was performed successfully in 230 consecutive patients.

Ninety-nine of these patients met an exclusion criterion, and 123 of the remaining 131 patients were enrolled in the study. A total of 111 (90%) of these patients completed the final follow-up visit (Figure 1). The characteristics of the patients are shown in Table 1. The mean age was 67 ± 10 years old, 80% were male, 46% had ischemic cardiac disease, 56% were classified as NYHA III, 63% received a CRTD implant, 67% had sinus rhythm and 20% had AF.

The cumulative rates of first alerts and HF events during the observation period are shown in Figure 2. The incidences of HF events were 8.1%, 16.5% and 33.8% at the 3-, 6- and 12-month follow-up visits, respectively, and the respective incidences of first alerts were 11.4%, 32.0% and 65.5%. An alert sounded once or more in over half of the subjects.

Endpoints

At 12 months, 68 of 123 subjects experienced an alert due to crossing of the fluid index of 60 ohm·days, and 23 suffered a HF event within 30 days of the alert, giving a PPV of 33.8% (23 of 68; Table 2). Of the other 45 subjects, 6 experienced a HF event after the 30-day window. There were HF events in 11 of 55 subjects who did not have an alert: 7 in whom the HF event occurred even though the fluid index was <60 ohm·days; 2 with a HF event due to development of acute pulmonary edema before the alert; and 2 in whom the HF event occurred within 30 days of implantation, at which time the alert was programmed not to sound. The sensitivity, specificity and false positive rate were 67.6% (23 of 34), 49.4% (44 of 89) and 50.6% (45 of 89), respectively (Table 2).

There were a total of 223 alerts in the 68 subjects with alerts (range: 1–8, mean: 2.47 alerts/subject/year). In alert-based

Table 1. Patient Characteristics

	n=123
Age (years)	67 ± 10
Male gender (%)	93 (80)
Cardiomyopathy	
Ischemic (%)	58 (46)
Non-ischemic (%)	65 (54)
Device	
CRTD (%)	77 (63)
ICD (%)	46 (37)
NYHA class	
I/II/III	10/44/69
LVEF (%)	27 ± 6
LV end-systolic diameter (mm)	50.6 ± 8.3
LV end-diastolic diameter (mm)	60.4 ± 6.6
History of HF admission (%)	77 (63)
Renal failure* (%)	49 (39)
Diabetes (%)	32 (26)
Rhythm	
Sinus (%)	83 (67)
Atrial fibrillation (%)	24 (20)
Paced (%)	16 (13)
Medication	
Aspirin (%)	67 (54)
ACEI/ARB (%)	90 (72)
β -blockade (%)	98 (79)
Diuretics (%)	98 (79)
Aldosterone antagonist (%)	61 (50)
Digoxin (%)	19 (15)
Statins (%)	50 (41)
Ca antagonists (%)	26 (21)
Warfarin (%)	32 (26)
Amiodarone (%)	27 (22)

CRTD, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; LVEF, left ventricular (LV) ejection fraction; HF, heart failure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*Renal failure >1.5 mg/dl of serum creatinine.

Table 2. Patient- and Alert-Based Analysis

	HF (+)	HF (–)	Total
Patient-based analysis			
Alert (+)	23	45	68
Alert (–)	11	44	55
Total	34	89	123
Alert-based analysis			
Alert (+)	57	111	168
Alert (–)	11	44	55
Total	68	155	223

Alert (+), crossing of fluid index at 60 ohm·days.

analysis, a HF event took place within 30 days after 57 alerts (PPV=33.9%, 57 of 168; Table 2), and 6 alerts were followed by a HF event after the 30-day window (Figure 3). There were 105 alerts that did not have a corresponding incidence of HF: 22 with apparently identifiable causes (including pneumonia in 6, oral medication compliance in 5, excessive

Table 3. Univariate and Multivariate Logistic Regression Analysis of HF Event (per Patients)

	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Atrial fibrillation	3.01	1.16–7.80	0.02	3.12	1.09–8.97	0.035
Use of β -blockade	2.65	0.73–9.59	0.14			
CRTD	1.78	0.72–4.44	0.22			
History of HF hospitalization	1.78	0.72–4.44	0.22			
NYHA class III	1.67	0.70–3.98	0.24			
Renal failure	1.57	0.68–3.64	0.29			
Hypertention	1.36	0.49–3.84	0.49			
Hyperlipidemia	1.31	0.47–3.66	0.60			
Use of ACEI/ARB	1.20	0.46–3.15	0.71			
Maximum fluid index	1.15	1.06–1.24	0.0004	1.16	1.07–1.25	0.0004
Use of statin	1.04	0.45–2.42	0.93			
Age	0.99	0.95–1.02	0.46			
Male gender	0.97	0.35–2.72	0.96			
LVEF	0.94	0.88–1.00	0.06	0.93	0.86–0.99	0.041
Ischemic heart disease	0.89	0.38–2.04	0.77			
Diabetes	0.88	0.33–2.31	0.79			

OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

fluid or sodium intake in 4, and a β -blocker dosage increase in 4); and 83 with an unidentifiable cause (an unexplained detection rate of 49.4%; 83 of 168). The sensitivity, specificity, and false positive rate were 83.8% (57 of 68), 28.4% (44 of 155), and 71.6% (111 of 155), respectively (Table 2), and the relative risk was 1.70. The mean duration between the alert and the 63 HF events was 21.4 ± 6.1 days (Figure 3).

Subjects with a HF event had a higher frequency of AF (34% vs. 15%, $P=0.02$) and a higher maximum fluid index (138 ± 71 vs. 91 ± 52 ohm·days, $P=0.02$), and showed a trend toward a lower LVEF ($25 \pm 7\%$ vs. $28 \pm 6\%$, $P=0.06$). The differences in other baseline characteristics were not significant. Multivariate logistic regression with prespecified risk factors was used to evaluate predictive factors in subjects with HF events. The maximum fluid index (OR: 1.16, 95%CI: 1.07–1.25, $P=0.0004$), LVEF (OR: 0.9, 95%CI: 0.86–0.99, $P=0.04$), and AF (OR: 3.12, 95%CI: 1.09–8.97, $P=0.004$) were independent predictors of HF events (Table 3). Further analysis using a ROC curve revealed an optimal cut-off value of 114 with a sensitivity and specificity of 89.5% and 73.0%, respectively (Figure 4).

Discussion

In most cases, patients do not notice symptoms until less than 1 week prior to HF.¹¹ In the present study, the fluid index crossed 60 ohm·days at an average of 21 days prior to the occurrence of an HF event, which is 6 days longer than the period found by Yu et al⁸ who studied a smaller number of subjects with a higher mean age of 78 years old. Subjects with EF $>50\%$ and/or dilated cardiomyopathy were also included in the study of Yu et al, indicating that the population differed from that in the present study. Therefore, the symptoms and observations may have been less obvious in the population in Yu et al when the fluid index crossed 60 ohm·days.

In the present study, a PPV based on fluid index alone was 33.8%. This result of PPV is not fully satisfied in daily practice. Whellan et al reported the combination of changes of several parameters of Cardiac Compass diagnostic report as

Figure 4. The optimal cut-off value for fluid index for predicting the presence of heart failure determined by receiver operating characteristic curve analysis was 114. The area under the receiver operating characteristic curve (AUC) was 0.871.

well as fluid index made it possible to predict worsening HF.¹⁵ In addition, Small et al reported changes in intrathoracic impedance were associated with subsequent risk of hospitalizations for decompensated HF.¹⁶ Therefore, device diagnostic parameters and risk stratification period in addition to fluid index play an important role to identify high-risk patients who may lead to develop a clinical HF with pulmonary congestion. Furthermore, apparent HF conditions were not found in 14 of our subjects (24 alerts) who made follow-up visits within 3 days of an alert, and about half of these alerts were classified as unexplained detections. Based on current HF indicators, it is difficult to determine if an unex-

plained detection reflected a condition prior to development of clinical HF (pre-HF status) or an irrelevant phenomenon. This issue requires further study. Assuming that the majority of these detections were indicative of a pre-HF status, spontaneous relief must occur with a certain frequency, and more data are required to determine when interventional treatment should be initiated.

In the present study, multivariate analysis showed that AF, LVEF and maximum fluid index were independent predictors of a clinical HF event. Of them, AF was the strongest predictors of recurrent HF events. In a 20-year follow-up study,^{17,18} AF was the strongest independent predictor of the development of HF (relative risk=3.4). Interestingly, HF was also the strongest independent predictor of AF (relative risk=4.6). AF is associated with an increased long-term risk of HF and scrupulous management for AF is needed for the prevention of recurrent HF events. Maximum fluid index was significantly higher in subjects with HF events (138 ± 71 vs. 91 ± 52 ohm·days, $P=0.02$). This result is similar to a previous report showing that the maximum fluid index of patients with decompensated HF was significantly higher than that in a control population (129 ± 46 vs. 100 ± 43 ohm·days, $P<0.05$).¹³ The maximum fluid index of patients without HF events was 90–100 ohm·days; therefore, it is necessary to assess the threshold based on patient background and underlying conditions, rather than having a programmed value of 60 ohm·days for all individuals.

ROC curve analysis indicated an optimal fluid index threshold of 114 ohm·days. Since the OptiVol fluid index threshold can only be programmed in increments of 10, we propose an optimal setting of 110 or 120 ohm·days. Since the specificity is low when the threshold is set to 60 ohm·days, Ypenburg et al suggested an optimal threshold of 120 ohm·days,¹³ which is similar to our finding. Application of a threshold of 110 ohm·days in the cohort gave a sensitivity, specificity, PPV and false negative rate for alert-based analysis of 85.1%, 63.3%, 63.6% and 36.4%, respectively, with a relative risk of 4.2. Improved specificity and PPV were observed without compromising sensitivity, which suggests that more accurate identification of patients who are about to develop HF may be possible. The duration between the alert and the HF event was 8.9 ± 4.8 days with the threshold of 110 ohm·days in our study population, which was approximately 13 days shorter than that with a threshold of 60 ohm·days.

There are a few limitations in this study. It was conducted in a single center and the sample size was small. Therefore, to confirm the results, a large multi-center study must be performed. Secondly, variability in diagnosis and treatment of HF between doctors cannot be ignored. To address this bias, subjects were seen by multiple HF specialists during their visits to our hospital. Lastly, the study included subjects with LV systolic dysfunction, and therefore the results may not be directly applicable to patients with diastolic dysfunction.

Conclusion

IIM using a fluid index in patients with systolic HF was effective in predicting the onset of HF in Japanese patients. The maximum fluid index, LVEF and AF were independent predictors of HF events. Effective detection of patients with preclinical HF may be achievable using a threshold of 110 or 120 ohm·days based on individual conditions.

Disclosure

Conflict of Interest: None of the authors have a real or perceived conflict

of interest regarding the work in the manuscript.

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