Decreased Intrathoracic Impedance Associated With OptiVol Alert Can Diagnose Increased B-Type Natriuretic Peptide

– MOMOTARO (Monitoring and Management of OptiVol Alert to Reduce Heart Failure Hospitalization) Study –

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**Background:** Ambulatory measurement of intrathoracic impedance (ITI) with an implanted device may detect increases in pulmonary fluid retention early, but the clinical utility of this method is not well established. The goal of this study was to test whether conventional ITI-derived parameters can diagnose fluid retention that may cause early stage heart failure (HF).

**Methods and Results:** HF patients implanted with high-energy devices with OptiVol (Medtronic) monitoring were enrolled in this study. Patients were monitored remotely. At both baseline and OptiVol alert, patients were assessed on standard examinations, including analysis of serum brain natriuretic peptide (BNP). From April 2010 to August 2011, 195 patients from 12 institutes were enrolled. There were 154 primary OptiVol alert events. BNP level at the alerts was not significantly different from that at baseline. Given that ITI was inversely correlated with log BNP, we added a criterion specifying that the OptiVol alert is triggered only when ITI decreases by ≥4% from baseline. This change improved the diagnostic potential of increase in BNP at OptiVol alert (sensitivity, 75%; specificity, 88%).

**Conclusions:** BNP increase could not be identified based on OptiVol alert. Decrease in ITI ≥4% compared with baseline, in addition to the alert, however, may be a useful marker for the likelihood of HF (Clinical trial info: UMIN000003351). (Circ J 2015; 79: 1315–1322)

**Key Words:** Brain natriuretic peptide; Heart failure; Intrathoracic impedance; OptiVol alert; Remote monitoring

Heart failure (HF) is one of the most common reasons for hospitalization. Despite therapeutic advances, the majority of these events are re-admissions because of acute deterioration of chronic HF. It would be an important advance in diagnostic medicine to be able to identify patients at risk for hospitalization for HF. Most HF-related hospitalizations are due to fluid accumulation, and careful surveillance of fluid status and monitoring of symptoms are critical. HF symptoms and an increase in body weight, however, usually occur late in the course of worsening HF and are unreliable diagnostic indicators even with day-to-day follow-up of patients with HF. Daily monitoring of the thoracic fluid status with intrathoracic impedance (ITI) is a diagnostic feature of implantable cardioverter defibrillators (ICD) or can be carried out in combination with cardiac resynchronization therapy (CRT-D). The monitoring of ITI may provide helpful information for the early detection of HF decompensation, because it is commonly preceded by a gradual increase in pulmonary fluid over several days or weeks.
The MOMOTARO (Monitoring and Management of OptiVol Alert to Reduce Heart Failure Hospitalization) Study was a prospective observational study that was carried out at 12 medical centers. Patients with either ischemic or non-ischemic heart disease were eligible for the study. The ICD patients with preserved EF underwent implantation for secondary prevention and the patients with hypertrophic cardiomyopathy underwent implantation for primary prevention. The CRT-D patients with EF > 35% have been improved in EF after CRT-D implantation. All patients had ICD or CRT-D with OptiVol 1.0 feature (models 7297, 7303, 7277, 7289, or C154D WK; Medtronic). Devices were implanted in the pectoral region, preferably on the left side. Patients who were having a device implanted for the first time as well as those with existing devices were included in this study. We excluded patients who were < 18 years old, scheduled for or had undergone cardiac surgery in the last 90 days, and those who were listed for heart transplantation. Further exclusion criteria were moderate-severe chronic obstructive lung disease (forced expiratory volume < 1.0 L/s), life expectancy < 1 year, hemodialysis, primary pulmonary hypertension, and pregnancy or breastfeeding. All patients gave their written informed consent, and the study protocol was approved by the Institutional Review Board and/or Medical Ethics Committee of each center.

### Methods

**Patients**

The MOPOMOTARO (Monitoring and Management of OptiVol Alert to Reduce Heart Failure Hospitalization) Study was a prospective observational study that was carried out at 12 medical centers. Patients with either ischemic or non-ischemic heart disease were eligible for the study. Patients with either preserved or reduced left ventricular ejection fraction (EF) were included in this study. The ICD patients with preserved EF underwent implantation for secondary prevention and the patients with hypertrophic cardiomyopathy underwent implantation for primary prevention. The CRT-D patients with EF > 35% have been improved in EF after CRT-D implantation. All patients had ICD or CRT-D with OptiVol 1.0 feature (models 7297, 7303, 7277, 7289, or C154D WK; Medtronic). Devices were implanted in the pectoral region, preferably on the left side. Patients who were having a device implanted for the first time as well as those with existing devices were included in this study. We excluded patients who were < 18 years old, scheduled for or had undergone cardiac surgery in the last 90 days, and those who were listed for heart transplantation. Further exclusion criteria were moderate-severe chronic obstructive lung disease (forced expiratory volume < 1.0 L/s), life expectancy < 1 year, hemodialysis, primary pulmonary hypertension, and pregnancy or breastfeeding. All patients gave their written informed consent, and the study protocol was approved by the Institutional Review Board and/or Medical Ethics Committee of each center.

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OptiVol (Medtronic, Minneapolis, MN, USA) alert, which is a fluid status algorithm calculated from ITI trends, was designed to diagnose impending fluid accumulation before HF symptoms. Whether it is possible to diagnose worsening HF with current technology is a controversial issue. Therefore, we conducted a multicenter trial to test whether the OptiVol alert can diagnose early stages of HF, which we defined as an increase in brain natriuretic peptide (BNP). We also assessed retrospectively whether additional analysis of ITI trends may improve the diagnostic accuracy of this method.

### Endpoints

The primary endpoint was serum BNP at OptiVol alert in comparison with that at baseline. BNP was expressed as a logarithmic function. We defined increased log BNP as an increase by 0.4 points compared with that at baseline, because this increase would indicate that BNP had more than doubled. The secondary endpoints included the potential changes in other laboratory and echocardiographic parameters between OptiVol alert and baseline. We retrospectively analyzed what parameters could predict an increasing log BNP.

### Statistical Analysis

Continuous data are expressed as mean±SD, and categorical data are expressed as the percentage. BNP data were also log transformed because the distribution of plasma BNP did not

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**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>195</td>
</tr>
<tr>
<td>Male</td>
<td>149 (76.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.3±11.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.61±0.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.8±12.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>113.9±20.3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68.0±10.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.9±10.6</td>
</tr>
</tbody>
</table>

**Heart disease type**

- Ischemic: 55 (28.2)
- Non-ischemic: 140 (71.8)

**NYHA I/II/III/IV**

- 66 (34.0)/98 (50.3)/31 (16.0)/0 (0)

**Ejection fraction (%)**

- 44.3±14.3

**Serum BNP (pg/ml)**

- 254±275

**Log BNP**

- 2.2±0.5

**Serum BUN (mg/dl)**

- 22.3±10.9

**Serum creatinine (mg/dl)**

- 1.17±0.75

**Cardiothoracic ratio on chest X-ray (%)**

- 54.7±6.8

**Medications**

- ACEI or ARB: 146 (74.8)
- β-blocker: 171 (87.7)
- Diuretics: 147 (75.4)
- Anti-arrhythmic drugs: 111 (56.9)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure.
appear to be normal (ie, the data were skewed). The change in the measured value between baseline and OptiVol alert or during regular examination for each factor was evaluated using paired t-test. The optimal cut-off was determined using a receiver operating characteristic (ROC) curve produced by plotting the sensitivity and specificity of the ITI ratio (ratio of ITI at OptiVol alert to that at baseline) vs. log BNP. P<0.05 was considered statistically significant. All statistical analysis was performed using SPSS (SPSS version 21; IBM, Chicago, IL, USA).

Results

Patient Characteristics
From April 2010 to August 2011, 200 patients in 12 institutes were enrolled in this study. Five out of 200 patients were subsequently excluded according to the exclusion criteria. Mean patient age was 66.3±11.3 years, and there were 149 male patients (76.4%). Mean left ventricular EF was 44.3±14.3%, mean BNP was 254±275 mg/dl (range, 4–1,558 pg/ml; mean log BNP, 2.2±0.5), mean serum blood urea nitrogen was 22.3±10.9 mg/dl and mean serum creatinine was 1.17±0.75 mg/dl. Patient characteristics are listed in Table 1.

Primary Endpoints
During the follow-up period (mean, 658±165 days), there were 154 primary OptiVol alert events. There was no significant difference in log BNP between baseline and OptiVol alert (2.21±0.45 vs. 2.24±0.46, P=0.21; Figure 1) and in BNP between baseline and OptiVol alert (258±260 pg/ml vs. 280±293 pg/ml, P=0.18).

False-Positive OptiVol Alerts
The poor predictive potential of OptiVol alerts resulted from many false-positive events. We found 3 false-positive alert patterns for ITI trends. These false-positive patterns were defined based on ITI patterns from the raw data. The first was “cross to reference” (57 of 154 events), in which the ITI trend crossed the reference line without a decrease in ITI compared with baseline (Figure 2A). The second was “spontaneous recovery” (62 of 154 events), in which the ITI trend was below the reference curve for several days but spontaneously recovered to baseline (Figure 2B). The third was “temporary elevation” (28 of 154 events), in which a temporary increase in ITI was associated with an upward deviation of the reference curve, followed by a spontaneous return to baseline.
by a decrease in the ITI trend toward baseline (Figure 2C). All 3 patterns can cause an OptiVol alert based on the algorithm of this monitoring device, whereas the actual ITI value at the time of the alert was similar to the baseline level. Of the 154 OptiVol alert events, 109 (71%) had at least 1 of these 3 characteristics. For these events, there was no difference in log BNP between OptiVol alert and baseline (2.22±0.46 vs. 2.21±0.46, P=0.56) or in BNP (267±276 pg/ml vs. 254±245 pg/ml, P=0.46). In these patients, mean ∆log BNP (log BNP at OptiVol alert–log BNP at baseline) was –0.01±0.22. In contrast, 45 OptiVol alerts did not have any characteristics of a false positive. In these events, the log BNP at OptiVol alert was significantly higher than that at baseline (baseline vs. OptiVol alert: 2.21±0.46 vs. 2.33±0.49, P=0.002), as was BNP (260±240 pg/ml vs. 365±393 pg/ml, P=0.007). In these patients, mean ∆log BNP was 0.11±0.23. Thus, we referred to these 3 ITI patterns as false-positive patterns, but it was not perfect, and there were some exceptions. Representative case of both false and true OptiVol alert events are shown in Figure 3.

New ITI Parameter to Predict HF Events
We calculated the ratio of ITI at OptiVol alert to that at baseline. We named this the “ITI ratio” and tested it as a new potential parameter to detect HF. OptiVol alert data were not available for 6 of the 154 primary alert events, because we could not directly access the OptiVol data in these instances. In 148 primary OptiVol alert events, there was a significant relationship between ITI ratio and difference in log BNP (r=–0.36, P=0.000006; Figure 4). This suggests that a change in ITI reflects a change in BNP. Therefore, we hypothesized that the magnitude of the decrease of ITI at OptiVol alert might predict
an increase in BNP.

To test the feasibility of using ITI ratio as a predictor of worsening HF, we collected data from the 148 primary OptiVol alert events and the primary 102 periodic outpatient clinic visits. The area under the ROC curve with respect to ITI ratio for predicting increase in log BNP ≥0.4 was significantly larger than that with respect to the OptiVol alert (0.81 vs. 0.64, P=0.0078; Figure 5). On ROC analysis, ITI ratio=0.96 could predict the events leading to HF when there is an increase in log BNP ≥0.4, with a sensitivity of 75% and specificity of 88%.

Forty-nine OptiVol alert events had ITI ratio ≤0.96, and for these alerts log BNP was significantly higher at OptiVol alert than at baseline (baseline vs. OptiVol alert: 2.19±0.49 vs. 2.31±0.47, P=0.004; Figure 6A), as was BNP (249±260 pg/ml vs. 326±342 pg/ml, P=0.03). In 99 OptiVol alert events in which ITI ratio was >0.96, there was no increase in log BNP between baseline and OptiVol alert (baseline vs. OptiVol alert: 2.21±0.44 vs. 2.18±0.46, P=0.20; Figure 6B) nor in BNP (258±262 pg/ml vs. 252±266 pg/ml, P=0.73).

**Secondary Endpoints**

We also analyzed the 154 primary OptiVol alert events for secondary endpoints including body weight, dimension of inferior vena cava, early-to-late ventricular filling velocities (E/A ratio), and the pressure gradient of tricuspid regurgitation (TRPG). We also measured the number of red blood cells, hemoglobin, total protein, and albumin (Table 2). At OptiVol alert with ITI ratio ≤0.96, we found that the dimension of the inferior vena cava, E/A ratio, and TRPG had significantly increased, whereas red blood cells, hemoglobin, total protein, and albumin were all significantly lower than at baseline. At OptiVol alert with ITI ratio >0.96, however, there were no significant differences in any of these parameters between OptiVol alert and baseline. Therefore, the parameters associated with fluid retention were also changed only at OptiVol alert with ITI ratio ≤0.96.

Increase in body weight is another sign of developing HF, but there was no statistically significant difference in body weight between baseline and alert, even for ITI ratio ≤0.96 (Table 2).

During follow-up, there were 11 deaths and 23 HF hospitalizations. At the time of HF hospitalization, ITI was decreased approximately 10% compared with that at baseline (63.4±8.8 Ω vs. 70.0±7.4 Ω, P=0.001). For patients who underwent HF hospitalization, ITI ratio was ≤0.96 on 12.8±12.7 days before hospitalization. Thus, if we focused on ITI ratio as well as on OptiVol alert, we could detect the state of fluid retention before HF hospitalization.
A decrease in ITI is one way to diagnose lung congestion. 5

ITI Trends: New Therapeutic Target to Reduce HF

Decreased ITI at OptiVol alert, we may be able to differentiate HF events accurately. At this level of BNP increase, most of the patients did not require hospitalization (data not shown). If we focus on the OptiVol index to predict increased BNP, such as OptiVol alert, ITI ratio, and ITI ratio independent of the OptiVol index. Recent ICD and CRT-D have the alert triggered by the OptiVol alert, but not by ITI ratio. It was not known whether ITI ratio independent of OptiVol index was useful to predict increased BNP. In this study, ITI ratio was more useful to predict increased BNP than the OptiVol alert.

Discussion

Only the OptiVol alerts with ITI ratio ≤0.96 were associated with an increase in log BNP and significant changes in E/A ratio, TRPG, dimension of the inferior vena cava, and red blood cells, hemoglobin, total protein, and albumin, which are indicative of fluid retention. These parameters did not change in the OptiVol alerts with ITI ratio >0.96. Therefore, at the time of OptiVol alert, there should be additional analysis of ITI trend to diagnose HF events accurately. Only when ITI ratio is ≤0.96 can we predict fluid retention that may cause early stage HF (with modest sensitivity and high specificity), even when it is not associated with noticeable physical symptoms.

Differentiation of False-Positive OptiVol Alert Events

There have been several reports that OptiVol alerts do not predict impending HF hospitalization. 13-15 These reports were due to a high percentage of false-positive alerts. In this study, we also found that two-thirds of OptiVol alerts are false positives, with log BNP not changing between baseline and alert. We focused on analyzing ITI itself. Previous studies demonstrated that ITI is inversely correlated with (1) left ventricular end diastolic pressure in a canine HF model; 23 (2) pulmonary artery wedge pressure; 24 and (3) right ventricular pressure. 24 The present study suggests that a decrease ≥4% in ITI ratio at alert can indicate an increase in log BNP ≥4 with reasonable accuracy. At this level of BNP increase, most of the patients did not require hospitalization (data not shown). If we focus on decreased ITI at OptiVol alert, we may be able to differentiate between false-positive and accurate OptiVol alert events.

ITI Trends: New Therapeutic Target to Reduce HF Hospitalization

A decrease in ITI is 1 way to diagnose lung congestion. 5,24 This study showed that ITI ratio ≤0.96 at the time of OptiVol alert can predict increase in log brain natriuretic peptide (BNP) ≥0.4. Lüthje et al reported that natriuretic peptide-proBNP is increased at the time of OptiVol alerts as compared with times without HF symptoms and that a change in ITI is negatively correlated with a change in N-terminal-proBNP. 25 Similarly, in this study, ITI ratio ≤0.96 at the time of OptiVol alert was associated with an increase in TRPG, dimension of the inferior vena cava, and E/A ratio and was also correlated with a reduction in the number of red blood cells, hemoglobin, total protein, and albumin, all of which relate to fluid retention. ICD and CRT-D, which have remote monitoring systems, are commonly implanted in patients with an especially high risk of HF. Therefore, if we could administer drugs at the time of OptiVol alert with decreased ITI ratio, we might reduce HF hospitalizations. We have a number of indexes to predict increased BNP, such as OptiVol alert, ITI ratio, and ITI ratio independent of the OptiVol index. Recent ICD and CRT-D have the alert triggered by the OptiVol alert, but not by ITI ratio. It was not known whether ITI ratio independent of OptiVol index was useful to predict increased BNP. In this study, ITI ratio was more useful to predict increased BNP than the OptiVol alert.

Self-Adjusting Running Average Algorithm

Three types of false positive were produced, possibly because of the self-adjusting running average algorithm used by this device. The cross to reference pattern occurred when the ITI trend crossed the reference line several times without a decrease in ITI, but the area under the reference line reached the threshold for an alert. In the spontaneous recovery pattern, the ITI trend was below the reference curve for several days, and the area under the reference curve reached the threshold, but the ITI spontaneously recovered to the baseline level. In the temporary elevation pattern, ITI increased and was associated with an upward deviation of the reference curve, followed by a decrease in the ITI trend toward baseline. This usually occurred during transient dehydration. An important point for each of these false positives is that the final ITI was the same as that at baseline.

Selection of Threshold for OptiVol Alerts

In this study, we used a nominal threshold for OptiVol alerts (60 Ω), given that 2 prospective double-blind clinical trials have shown a reasonable sensitivity of this threshold for predicting HF hospitalizations. 5,16 We observed, however, that two-thirds of alert events were not associated with decreased ITI. Other studies reported that a higher threshold can increase the specificity and decrease the number of false-positive signals. 25,26 In the current study, however, OptiVol alert was set to occur at a nominal threshold of 60 Ω, and these alerts might have influenced the incidence of subsequent HF events. We encountered several decompensated HF events before the fluid index reached the nominal threshold in this study. A subsequent prospective study is required to test whether a higher threshold can improve the accuracy for predicting HF events.

Table 2. Secondary Endpoints vs. Presence of ITI Ratio ≤0.96

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=154)</th>
<th>P-value</th>
<th>ITI ratio ≤0.96 (n=49)</th>
<th>P-value</th>
<th>ITI ratio &gt;0.96 (n=99)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVC (E) (mm)</td>
<td>14.3±5.4</td>
<td>0.009</td>
<td>13.7±4.8</td>
<td>0.002</td>
<td>14.4±5.5</td>
<td>0.296</td>
</tr>
<tr>
<td>IVC (l) (mm)</td>
<td>5.3±3.5</td>
<td>0.010</td>
<td>4.5±4.6</td>
<td>0.001</td>
<td>5.6±5.5</td>
<td>0.847</td>
</tr>
<tr>
<td>E wave (cm/s)</td>
<td>68.1±29.9</td>
<td>0.005</td>
<td>63.7±26.7</td>
<td>0.00007</td>
<td>70.3±31.9</td>
<td>0.535</td>
</tr>
<tr>
<td>E/A</td>
<td>1.02±0.62</td>
<td>0.028</td>
<td>0.83±0.52</td>
<td>0.002</td>
<td>1.06±0.86</td>
<td>0.427</td>
</tr>
<tr>
<td>TRPG (mmHg)</td>
<td>25.3±8.5</td>
<td>0.004</td>
<td>24.2±7.5</td>
<td>0.002</td>
<td>25.6±8.5</td>
<td>0.129</td>
</tr>
<tr>
<td>RBC (10^6/μl)</td>
<td>4.16±0.60</td>
<td>0.004</td>
<td>4.02±0.60</td>
<td>0.000001</td>
<td>4.21±0.54</td>
<td>0.845</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.1±1.8</td>
<td>0.033</td>
<td>12.6±1.7</td>
<td>0.000003</td>
<td>13.2±1.7</td>
<td>0.763</td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>7.1±0.5</td>
<td>0.016</td>
<td>7.1±0.5</td>
<td>0.007</td>
<td>7.1±0.6</td>
<td>0.361</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>4.2±0.4</td>
<td>0.0497</td>
<td>4.2±0.3</td>
<td>0.001</td>
<td>4.2±0.4</td>
<td>0.794</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.2±13.2</td>
<td>0.062</td>
<td>58.1±12.5</td>
<td>0.234</td>
<td>61.2±13.6</td>
<td>0.220</td>
</tr>
</tbody>
</table>

Data given as mean±SD. Raw data for ITI were not available for 8 OptiVol alert events. Alb, albumin; Hb, hemoglobin; ITI ratio, ratio of intra-thoracic impedance at alert to that at baseline; IVC (E), dimension of the inferior vena cava at expiration; IVC (l), dimension of the inferior vena cava at inspiration; RBC, red blood cells; TP, total protein; TRPG, pressure gradient of tricuspid regurgitation.
Remote Monitoring
We followed all patients by remote monitoring. There have been many studies on the advantages of remote monitoring, such as reduction of workload associated with device follow-up, early detection of arrhythmic or adverse events, and improvement of prognosis. OptiVol alert with decreased ITI is also useful for remote monitoring. We can receive notification of OptiVol alert with decreased ITI, even though patients are at home and do not have any symptoms. We can also receive notification for various parameters associated with HF, such as heart rate, heart rate variability, arrhythmic events, and activity by remote monitoring. If we could combine various parameters, we may predict early stage HF more precisely.

Study Limitations
There are several limitations in this study. First, this study was unable to validate multimodal HF detection algorithms of devices because of the relatively small sample size. For example, the Cardiac Compass (Medtronic) can provide data on the activity, arrhythmic events and electrophysiology of the individual. These data might improve the diagnostic potential of HF, but we were able to establish a new ITI parameter, ITI ratio, for detecting subclinical increases in BNP, and this provides the rationale for further testing. Second, this study included HF patients with both reduced EF and preserved EF. CRT-D was implanted in the patients with reduced EF, and ICD was more likely to be used in those patients with preserved EF. In both the patients with preserved EF and with reduced EF, however, ITI ratio was correlated with the difference in log BNP. Trends in ITI before HF events and the optimal cut-off point of the ITI ratio may be different between patients with preserved EF and with reduced EF. Thirdly, it is difficult to know whether baseline truly represents the dry impedance in these patients. In this study, we measured baseline ITI when patient condition was stable and they were without symptomatic HF.

Conclusions
Use of an implantable diagnostic tool to measure fluid index did not diagnose the worsening of HF (increase in BNP). Decrease in ITI as compared with baseline, however, may be a useful marker of worsening of HF.

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Disclosures
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