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Original article

An improved algorithm calculated from intrathoracic impedance can precisely diagnose preclinical heart failure events: Sub-analysis of a multicenter MOMOTARO (Monitoring and Management of OptiVol Alert to Reduce Heart Failure Hospitalization) trial study

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ABSTRACT

Background: Ambulatory measurement of intrathoracic impedance (ITI) with an implanted device has potential to assess fluid accumulation in patients with heart failure (HF), but it has failed to reduce HF-related hospitalization because of a high false-positive rate.
Objective: We aimed to examine whether a modified algorithm (OptiVol 2.0) could reduce false-positive HF events documented in our multicenter trial (MOMOTARO).
Methods: The MOMOTARO trial assessed the potential that fluid index could predict fluid accumulation and therefore HF. The MOMOTARO trial assessed whether HF events could be detected based on fluid accumulation as assessed by fluid index. We re-analyzed raw data of ITI trends of the threshold-crossing events with the modified algorithm.
Results: The study consisted of 195 patients who had been implanted with a high-energy device. During a mean follow-up period of 658 ± 165 days, there were 154 primary HF events detected by the previous algorithm (OptiVol 1.0). With the previous algorithm, there was no significant difference in log concentration of brain natriuretic peptide (BNP) between baseline and alert ($p = 0.21$). Among 150 alerts of the previous algorithm, only 37 reached the threshold by the modified algorithm, and log BNP was significantly higher in these 37 events compared with the baseline value (2.40 ± 0.46 vs. 2.27 ± 0.52, $p < 0.01$).
Conclusion: Our simulation study demonstrates that fluid index calculated with the modified algorithm reduces the number of false-positive threshold-crossing HF events and is promising for accurate diagnosis of fluid accumulation in patients.

Introduction

Heart failure (HF) is associated with frequent hospitalizations and has become one of the largest medical problems worldwide [1]. Identifying patients at risk for hospitalization would be extremely helpful for reducing HF-related hospitalization. Symptoms such as exertional dyspnea or fatigue are unspecific, and daily measurement of body weight is not sensitive enough to predict

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clinical deterioration [2–4]. Intrathoracic electrical impedance (ITI) is another potentially interesting biomarker that can be measured safely by an implantable device. This measure has potential to diagnose worsening HF before symptoms of HF appear [5], but whether it can reduce HF hospitalization remains a controversial issue. A previous study demonstrated the low sensitivity (60%) and positive predictive value (60%) of this system for predicting the deterioration of HF [6]. Conraads et al. reported a positive predictive value of 38.1% for this approach [7]. A diagnostic outcome trial for HF (DOT-HF) indicated that the use of OptiVol alert (Medtronic, Dublin, Ireland) to measure ITI with an audible patient alert did not improve outcome in HF patients [8]. It increased HF hospitalizations and outpatient visits because of a high frequency of false-positive alerts. In a previous multicenter trial called MOMOTARO (Monitoring and Management of OptiVol Alert to Reduce Heart Failure Hospitalization), we also found a high frequency of alert events that were not associated with an increase in the concentration of serum brain natriuretic peptide (BNP) level compared with the baseline value [9]. We reduced the false-positive alerts by adding a criterion specifying that the alert be triggered only when ITI decreases by $\geq$4% from baseline.

The previous OptiVol algorithm (OptiVol 1.0) that is used to calculate fluid index has been modified and is now referred to as OptiVol 2.0, which improves the ability to track ITI changes. The modified algorithm added the following improvements: the calculation of reference impedance and fluid index, temporal accumulation limit. Thus, in patients with high day-to-day variability in ITI values, the modified algorithm accumulates fluid index information less aggressively than the previous algorithm, especially for the initial period of an event. This improvement is expected to reduce the false-positive alerts for more precise diagnosis of worsening HF. However, it is unknown whether OptiVol 2.0 could reduce false-positive alerts that were detected by the previous algorithm. To resolve this clinical issue, we conducted a simulation in which raw ITI data for all alert events detected by the previous algorithm in the MOMOTARO trial were re-analyzed with OptiVol 2.0. We examined whether OptiVol 2.0 could indeed reduce the false-positive alerts in comparison with BNP levels and other laboratory and echocardiographic parameters of HF.

Methods

The design and main results of the MOMOTARO study have been published [9]. The MOMOTARO study was a prospective observational study that was carried out in 12 medical centers to study whether the OptiVol alert can diagnose early stages of HF, which we defined as an increase in BNP.

Patients included in this study

Data from the 195 MOMOTARO HF patients with either preserved or reduced left ventricular ejection fraction (LVEF) were included in this study. All of these patients had undergone cardioverter defibrillator implantation or cardiac resynchronization therapy with cardioverter defibrillator implantation for the purpose of monitoring ITI. All implanted devices used the previous algorithm (OptiVol 1.0; Model 7297, 7303, 7277, 7289, or C154DWK). Data for patients who had a device implanted for the first time during the initial trial as well as those with existing devices were included in this study. For the former cases, there was at least a one-month waiting period to allow postoperative clinical stabilization, resolution of pocket edema, and automatic calibration of the impedance reference. 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.

Analysis and storage of ITI data

Fluid status monitoring with OptiVol was based on calculations of the average daily ITI values measured between the right ventricular defibrillation electrode and the device case. Temporal changes in ITI values were compared with the reference impedance, which was derived from a moving average algorithm, to assess fluid status. When daily impedance values consistently fell below the reference, the differences were accumulated to generate the OptiVol fluid index. When this index exceeded a threshold of 60, the OptiVol alert was sent to the analysis center (Okayama University). The audible patient alert was turned off for the trial. All device-based diagnostic information, including fluid index, heart rate, heart rate variability, and patient's activity, was also sent by a wireless remote monitoring system (Medtronic CareLink network).

Primary and secondary endpoints

Whenever a threshold-crossing event was noted on the remote monitoring system, the protocol required patient-physician contact within 3 days. Patients underwent clinical evaluation, laboratory tests, chest X-ray, 12-lead electrocardiogram, and echocardiography in an outpatient clinic. The primary endpoint was serum log BNP levels at the OptiVol alert in comparison with those at baseline. The secondary endpoints included the other laboratory and echocardiographic parameters between OptiVol alert and baseline. If the patient showed decompensated HF, they were treated according to a standardized treatment protocol.

Simulation of fluid index with modified algorithm

The OptiVol 2.0 index was calculated from the raw ITI data collected in the MOMOTARO study by a calculation algorithm with use of Microsoft Excel 2010 software. We examined if the calculated OptiVol 2.0 index values in a simulation reached threshold at the same frequency as the OptiVol 1.0 alert events. Then, the OptiVol 1.0 alert events from the MOMOTARO study were divided into two groups—those for which the calculated OptiVol 2.0 index also reached threshold (OptiVol 2.0 positive group), and those for which the calculated OptiVol 2.0 index did not reach the threshold (OptiVol 2.0 negative group). We then compared the changes in log BNP values and of laboratory and echocardiographic parameters at threshold-crossing events in the two groups.

We also analyzed the reproducibility of the OptiVol 2.0 simulation with data from 50 randomly selected patients. We compared the fluid index values between the original (OptiVol 1.0) and simulated (OptiVol 2.0) data.

ITI trends associated with false-positive events

In the previous study, we found three ITI trends that were likely associated with false-positive threshold-crossing events based on the previous algorithm (OptiVol 1.0) (Fig. 1), namely "cross to reference" (Fig. 1A), "spontaneous recovery" (Fig. 1B), and "temporary elevation" (Fig. 1C) patterns in relation to the reference line [9]. In the "cross to reference" pattern, the ITI crosses the reference line several times, but the accumulated fluid index is not

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