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

Brief title: Diagnostic precision of the improved algorithm calculated from intrathoracic impedance

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Key Words: Intrathoracic impedance; OptiVol alert; False-positive; Brain natriuretic peptide; Heart failure

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 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 ≥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 canceled and the integral of the difference between reference and ITI finally reaches the threshold. In the “spontaneous recovery” pattern, ITI is below the reference curve for several days and spontaneously recovers to baseline, but the integral of the difference between reference and ITI reaches the threshold before the recovery. In the “temporary elevation” pattern, a temporary increase in ITI is associated with an upward deviation of the reference curve. We examined whether OptiVol 2.0 could exclude these false-positive patterns.

Statistical analysis

The Statistical Product and Service Solutions Statistics package, version 20 (IBM Inc., Chicago, IL, USA), was used for all statistical analyses. Continuous data are

expressed as the mean ± standard deviation, and categorical data are expressed as the percentage. BNP data were also log transformed because the distribution pattern of plasma BNP values did not appear to be normal (i.e. the data were skewed) [10]. The change in the measured value between baseline and OptiVol alert or during regular examination for each factor was evaluated by the paired t-test, and differences with $p < 0.05$ were considered to be significant. Nonparametric χ^2 test was used to assess whether there was a reduction in any false-positive pattern, and $p < 0.05$ was considered statistically significant. Pearson's correlation was used to assess the simulation software accuracy.

Results

Patient characteristics at baseline

From April 2010 to August 2011, 200 patients in 12 institutes were enrolled in the MOMOTARO study. Five patients were excluded according to the exclusion criteria. Mean age was 66.3 ± 11.3 years, and there were 149 male patients (76.4%). Mean LVEF was 44.3 ± 14.3%, and mean BNP was 254 ± 275 mg/dl. Patient characteristics are listed in Table 1.

Threshold-crossing events by the previous algorithm

Figure 2 shows simulated fluid index trends as detected with OptiVol 1.0 and OptiVol 2.0. With OptiVol 1.0, there were three types of threshold-crossing events. Because ITI crossed the reference line in the first two types of events, the accumulated difference between reference and real ITI values reached the threshold value. With OptiVol 2.0, only the last type of event was associated with threshold crossing (Fig. 2).

During the mean follow-up period of 658 days (range: 102–731 days), there were 154 primary threshold-crossing events. We successfully simulated fluid index trends from the raw ITI data with OptiVol 2.0 for 150 (97%) of the events. There was no significant difference in log BNP between baseline and threshold-crossing events compared with data for OptiVol 1.0 (2.22 ± 0.46 vs. 2.23 ± 0.47, $p = 0.48$; Fig. 3A), and the incidence of an increase in log BNP was observed in 82 patients (55%). Among the 150 threshold-crossing events, ITI at threshold crossing was lower than that at baseline by 4% for only 46 patients (31%) with OptiVol 1.0. Of the 150 events, the threshold was crossed for only 37 (25%) with OptiVol 2.0. Among these 37 events (OptiVol 2.0 positive group), log BNP was significantly higher at threshold crossing than at baseline (2.40 ± 0.46 vs. 2.27 ± 0.52, $p = 0.009$; Fig. 3B), and the incidence of an increase in log BNP was observed in 28 of 37 events (76%). For the remaining 113 events (OptiVol 2.0 negative group), the fluid index simulated with OptiVol 2.0 did not cross the threshold

of 60. For this OptiVol 2.0 negative group, there was no significant difference in log BNP between baseline and threshold-crossing events (2.20 ± 0.44 vs. 2.18 ± 0.46, p = 0.16; Fig. 3C), and the incidence of an increase in log BNP was observed in 54 patients (48%).

In the OptiVol 2.0 positive group, ITI at threshold crossing was ≥4% lower than at stable baseline for 23 patients (62%), and the remaining 14 events were considered as false positives (38%). In the OptiVol 2.0 negative group, ITI at threshold-crossing was ≥4% lower than at stable baseline in 23 patients (20%), and the remaining 90 events were considered as false positives (80%).

Relation to signs of HF

We compared HF-related parameters between baseline and threshold-crossing events. HF-related parameters included body weight, dimension of the inferior vena cava, E-wave velocity, early-to-late ventricular filling velocities ratio, and the pressure gradient of tricuspid regurgitation. We also measured red blood cell count, hemoglobin, hematocrit, serum albumin, blood urea nitrogen, total protein, and creatinine (Table 2). There were no significant differences in any of these parameters between baseline and threshold-crossing events in the OptiVol 2.0 negative group. In the OptiVol 2.0 positive group, the dimensions of the inferior vena cava and the E-wave velocity were

significantly higher. In contrast, red blood cell count, hemoglobin, hematocrit, total protein, albumin, blood urea nitrogen, and creatinine levels were significantly lower compared with the baseline values. The changes in HF-related parameters indicate fluid retention at the threshold-crossing events detected by OptiVol 2.0.

OptiVol 2.0 and the three false-positive ITI trends

In the previous study, we identified three typical ITI trends that were often associated with false-positive determinations based on OptiVol 1.0. The "cross to reference" pattern was found in 56 threshold-crossing events in OptiVol 1.0 without an increase in BNP. After analysis with OptiVol 2.0, only 5 (9%) of these 56 events showed threshold crossing (91% reduction, $p < 0.001$; Fig. 4A). The "spontaneous recovery" pattern was observed in 59 threshold-crossing events in OptiVol 1.0 without an increase in BNP. After analysis with OptiVol 2.0, only 7 (12%) of 59 events showed threshold crossing (88% reduction, $p = 0.003$; Fig. 4B). The third pattern of "temporary elevation" was found in 27 threshold-crossing events in OptiVol 1.0, but after the analysis with OptiVol 2.0 10 (37%) of the 27 events showed threshold crossing, and OptiVol 2.0 did not reduce the false-positive alerts in this ITI pattern (63% reduction, $p = 0.14$; Fig. 4C).

Reproducibility of the simulation

The simulation with OptiVol 2.0 was performed again with the raw ITI data

from a randomly selected set of 50 patients. The calculated fluid index values from the simulation showed strong correlation with the real fluid index values (R = 0.997 ± 0.001, range: 0.964–1.000, $p < 0.001$).

Discussion

New findings

Although remote monitoring of ITI trends by an implantable device is expected to facilitate early diagnosis of HF before symptoms appear, a high frequency of false-positive alerts limits the clinical application of this system. In this simulation study, we demonstrated a significant reduction in threshold-crossing events, from 150 to 37 events (75% reduction), with the modified algorithm. These 37 events were also associated with an increase in log BNP compared with the baseline value and changes in laboratory and echocardiographic parameters, supporting the determination of fluid accumulation at the threshold-crossing events. This modified algorithm was able to discriminate false-positive events associated with the two typical ITI trends “cross to reference”and “spontaneous recovery”. To our knowledge, this is the first study to demonstrate that the modified OptiVol 2.0 algorithm can reduce false-positive events and may improve the diagnostic potential of this system for early-stage HF.

Comparison to previous study

The practicality of remote monitoring of ITI remains controversial because of the high false-positive alert rate. Several previous studies have examined the issue of false alerts. Van Veldhuisen et al. demonstrated that remote ITI monitoring with the alert function increased hospitalizations and outpatient visits owing to false-positive alerts [8]. Ypenburg et al. reported that only 33% of the alerts were associated with HF-related events in patients with implantable cardioverter defibrillators [11]. Then, the modified OptiVol 2.0 algorithm was developed to reduce false-positive alerts. Actually, Sarkar et al. reported that the modified algorithm reduces unexplained detections by 30% [12]. Our simulation study also demonstrated considerable reduction in threshold-crossing events compared with the previous algorithm, and that the remaining threshold-crossing events by the modified algorithm were associated with increases in BNP and signs of HF indicated by HF parameters. The positive predictive value obtained with OptiVol 2.0 (76%) was substantially greater than that for OptiVol 1.0 (55%). Therefore, the modified algorithm appears to be superior to the previous algorithm for the diagnosis of early-stage HF. In other words, the modified OptiVol 2.0 algorithm might select only true HF-related events.

False positive ITI trends corrected by modified OptiVol 2.0 algorithm

In our previous study, we identified three ITI trends that were often associated with false-positive alerts with the previous algorithm. We found that the modified algorithm substantially reduced the threshold-crossing events associated with the “cross to reference” and “spontaneous recovery” patterns. However, the modified algorithm could not reduce the number of the threshold-crossing events for the “temporary elevation” pattern. For this pattern, ITI shows a gradual reduction to baseline level after a relatively long period of increase, which is associated with an increase in the reference curve. This ITI trend is often observed in patients experiencing dehydration or with increasing doses of diuretics [13]. In this situation, it is important to consider the change in ITI values from baseline. If the values do not decrease by ≥4% compared with baseline, these threshold-crossing events may be false-positives.

Clinical implication of modified OptiVol 2.0 algorithm

It is difficult to diagnose impending HF before symptoms appear in clinical settings. Stevenson et al. reported that physical examination often fails to detect elevated LV filling pressures in patients with chronic HF [14]. Monitoring body weight and symptoms with telephone interviews also failed to reduce HF hospitalization. Yu et al. retrospectively analyzed the temporal relationship between ITI decrease and clinical symptoms related to HF. They found that the time interval between the start of ITI

decrease and HF-related symptoms was significantly longer than that between HF-related symptoms and HF hospitalization (15.3 ± 10.6 vs. 3.0 ± 2.5 days, $p < 0.001$) [5]. In our study, log BNP values in the OptiVol 2.0 positive group were significantly higher at OptiVol alert than that at baseline. On the other hand, patients in the OptiVol 2.0 negative group were not associated with HF-related symptoms or clinical signs of HF deterioration. Therefore, the modified algorithm may be effective in selecting patients with early-stage HF.

Study limitations

This study has several limitations. First, this study is a simulation, and a prospective clinical study is required to conclude whether the modified algorithm reduces false-positive events. However, the modified algorithm was able to reduce the false-positive events in the same ITI trends compared with the previous algorithm for the same raw ITI data. Second, it is also important to reduce false-negative events for the accurate diagnosis of HF, but our study did not examine whether the modified algorithm reduced false-negative events because we did not retain the raw ITI data for patients with HF hospitalization without threshold-crossing events. Finally, ITI is affected by many factors other than fluid retention, such as pocket infection, pneumonia, and anemia. The

diagnostic potential of the new algorithm has not been determined under these pathological conditions.

Conclusions

ITI monitoring with the modified OptiVol 2.0 algorithm may represent a new and promising way to detect impending HF with increased reliability compared with the previous OptiVol 1.0 algorithm. Device-based diagnostics could be helpful as an adjunct tool.

Acknowledgments

We thank Yoshimasa Tsushima, MD; Hiroshi Kawamura, MD; Hiroshi Tasaka, MD; Kohei Miyaji, MD; Satoshi Kawata, MD; Shigeki Hiramatsu, MD; Akihiro Hayashida, MD; Keisuke Okawa, MD; Chisato Suezawa, MD; Kenji Takagaki, MD; Toshiaki Yamanaka, MD; Yusuke Kawai, MD; Hiroki Oe, MD; Hisanori Toh, MD; Toru Miyoshi, MD; Masayuki Doi, MD; Hiromi Matsubara, MD; Kazufumi Nakamura, MD; and Tohru Ohe, MD, for the MOMOTARO investigators. We thank Nobuhisa Watanabe and Yasuharu Tanabe for the echocardiography. We thank Yuki Takenaka for the medical engineering work. We thank Yuko Kobayashi, Kaoru Akazawa, Miyuki

Fujiwara, and Masayo Ohmori for assistance with the manuscript.

Funding and Disclosures

This study was supported financially by Medtronic. None of the authors had any additional relationships with industry.

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Tables

Table 1 Patient characteristics at baseline

Data given as mean ± SD.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Secondary endpoints at baseline and each OptiVol alert

Data given as mean ± SD.

Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; E/A ratio, early-to-late ventricular filling velocities; Hb, hemoglobin; Ht, hematocrit; IVC (E), dimension of the inferior vena cava at expiration; IVC (I), dimension of the inferior vena cava at inspiration; RBC, red blood cells; TP, total protein; TRPG, pressure gradient of tricuspid regurgitation.

Figure legends

Figure 1 Intrathoracic impedance **trends associated with false-positive events.** (A) "cross to reference," (B) "spontaneous recovery," and (C) "temporary elevation" patterns.

Figure 2 Comparison of simulation analysis with OptiVol 2.0 and OptiVol 1.0. The blue-shaded area shows an event in which the fluid index threshold was crossed in OptiVol 1.0 but not OptiVol 2.0, and BNP was not different between the baseline and OptiVol 1.0 alert (246.0 vs. 257.0 pg/ml). The orange-shaded area shows an event in which the threshold was crossed in both OptiVol 1.0 and 2.0, and BNP was higher at the OptiVol alert than at baseline (246.0 vs. 487.9 pg/ml).

BNP, brain natriuretic peptide.

Figure 3 Differences in log BNP between baseline and OptiVol alerts. (A) There was no significant difference in log BNP between baseline and OptiVol 1.0 alerts (N = 150, $p = 0.48$). (B) Log BNP was significantly higher at OptiVol alerts in the OptiVol 2.0 positive group than at baseline (N = 37, 2.27 ± 0.52 vs. 2.40 ± 0.46, $p = 0.009$). (C) There was no significant difference in log BNP between baseline and OptiVol alerts in the OptiVol 2.0 negative group (N = 113, $p = 0.16$).

BNP, brain natriuretic peptide.

Figure 4 Comparison of the three types of alert events between OptiVol 2.0 and OptiVol 1.0. (A) “cross to reference,” (B) “spontaneous recovery,” and (C) “temporary elevation” patterns.

Table 1 Patient characteristics at baseline

N	195
Male, N (%)	149 (76.4)
Age, years	66.3±11.3
Height, m	1.61±0.10
Weight, kg	59.8±12.9
Systolic blood pressure, mmHg	113.9±20.3
Diastolic blood pressure, mmHg	68.0±10.6
Heart rate, bpm	69.9±10.6
Heart disease type, N (%)	
Ischemic	55 (28.2)
Nonischemic	140 (71.8)
NYHA classification I/II/III/IV, n (%)	66 (34.0) / 98 (50.3) / 31 (16.0) / 0 (0)
LVEF, %	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 in chest X-ray, %	54.7±6.8
Medications, N (%)	
ACE inhibitor or ARB	146 (74.8)
β-blocker	171 (87.7)
Diuretics	147 (75.4)
Antiarrhythmic drugs	111 (56.9)

Table 2 Secondary endpoints at baseline and each OptiVol alert

Parameter	All OptiVol 1.0 alert (N = 150)			OptiVol 2.0 positive group (N = 37)			OptiVol 2.0 negative group (N = 113)		
Measured	Baseline	OptiVol alert	p value	Baseline	OptiVol alert	p value	Baseline	OptiVol alert	p value
Body weight, kg	60.0±13.3	60.5±13.0	0.08	58.6±13.3	59.6±14.0	0.11	60.4±13.3	60.9±12.8	0.25
IVC (E), mm	14.1±5.2	15.1±5.8	0.02	13.5±4.8	15.0±6.9	0.08	14.4±5.4	15.1±5.3	0.11
IVC (I), mm	5.1±5.1	6.1±5.7	0.03	5.4±4.7	7.4±6.0	0.008	5.1±5.3	5.6±5.6	0.29
E wave, cm/s	67.6±30.1	71.0±33.2	0.01	62.5±29.9	72.4±38.9	<0.001	69.4±30.0	70.6±31.2	0.42
E/A ratio	0.96±0.72	1.05±0.77	<0.05	0.90±0.52	1.07±0.75	0.06	0.99±0.78	1.05±0.78	0.23
TRPG, mmHg	25.0±8.1	26.8±9.0	0.007	24.9±8.3	26.8±9.4	0.12	25.1±8.1	26.8±8.9	0.03
RBC, 10^6/μl	4.17±0.56	4.07±0.59	<0.001	4.09±0.61	3.87±0.64	0.001	4.20±0.54	4.14±0.55	0.07
Hb, g/dl	13.1±1.7	12.9±1.8	0.006	12.5±1.6	11.9±1.7	0.002	13.3±1.7	13.2±1.8	0.26
Ht, %	39.3±4.8	38.7±5.0	0.02	37.7±4.7	36.1±4.9	0.004	39.9±4.7	39.7±4.8	0.32
TP, g/dl	7.1±0.5	7.0±0.5	0.03	7.0±0.5	6.9±0.6	0.23	7.2±0.5	7.1±0.5	0.07
Alb, g/dl	4.2±0.4	4.2±0.4	<0.05	4.1±0.3	4.1±0.4	0.25	4.3±0.4	4.2±0.4	0.10
BUN, mg/dl	22.8±11.8	21.6±10.0	0.07	24.5±16.5	21.6±13.4	0.03	22.1±9.5	21.6±8.5	0.50
Cre, mg/dl	1.14±0.50	1.13±0.42	0.70	1.26±0.68	1.16±0.52	0.01	1.09±0.41	1.12±0.38	0.17

Figure 1 ITI trends associated with false-positive events

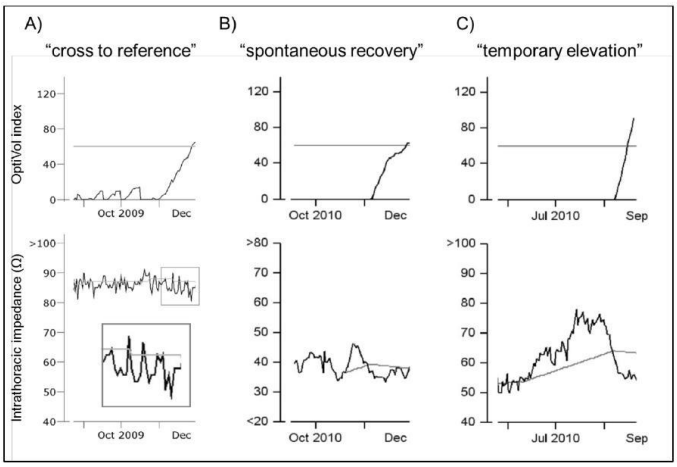

Figure 2 Comparison of simulation analysis with OptiVol 2.0 and OptiVol 1.0

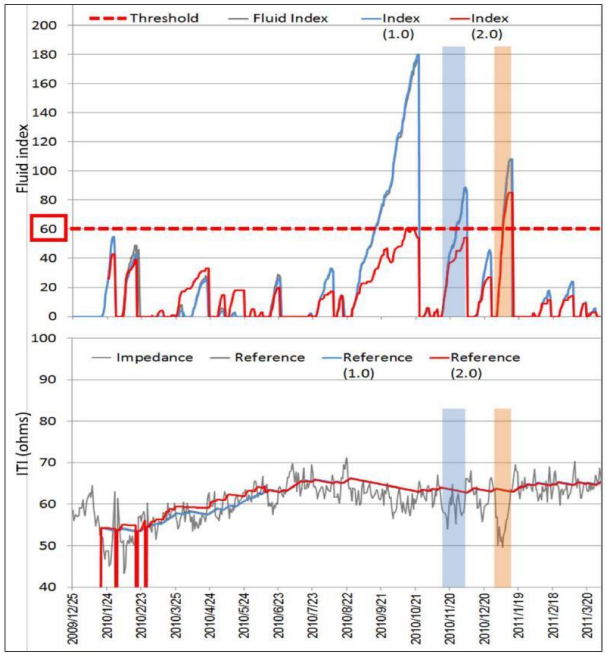

Figure 3 Differences in log BNP between baseline and OptiVol alerts

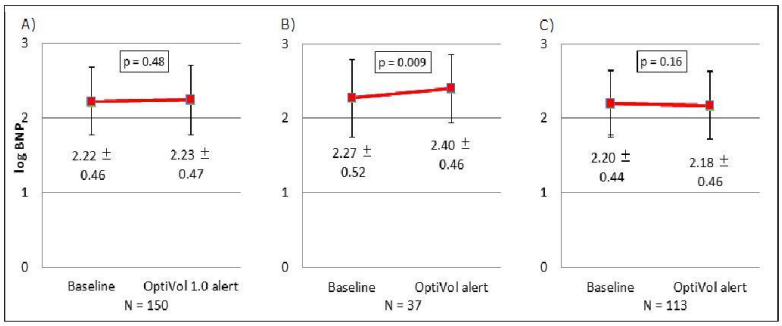

Figure 4 Comparison of the three types of alert events between OptiVol 2.0 and OptiVol 1.0