Intrathoracic Impedance Monitoring in Patients With Heart Failure
Correlation With Fluid Status and Feasibility of Early Warning Preceding Hospitalization

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Background—Patients with heart failure are frequently hospitalized for fluid overload. A reliable method for chronic monitoring of fluid status is therefore desirable. We evaluated an implantable system capable of measuring intrathoracic impedance to identify potential fluid overload before heart failure hospitalization and to determine the correlation between intrathoracic impedance and standard measures of fluid status during hospitalization.

Methods and Results—Thirty-three patients with NYHA class III and IV heart failure were implanted with a special pacemaker in the left pectoral region and a defibrillation lead in the right ventricle. Intrathoracic impedance was regularly measured and recorded between the lead and the pacemaker case. During hospitalizations, pulmonary capillary wedge pressure and fluid status were monitored. Ten patients were hospitalized for fluid overload 25 times over 20.7±8.4 months. Intrathoracic impedance decreased before each admission by an average of 12.3±5.3% (P<0.001) over an average of 18.3±10.1 days. Impedance reduction began 15.3±10.6 days (P<0.001) before the onset of worsening symptoms. There was an inverse correlation between intrathoracic impedance and pulmonary capillary wedge pressure (r=−0.61, P<0.001) and between intrathoracic impedance and net fluid loss (r=−0.70, P<0.001) during hospitalization. Automated detection of impedance decreases was 76.9% sensitive in detecting hospitalization for fluid overload, with 1.5 false-positive (threshold crossing without hospitalization) detections per patient-year of follow-up.

Conclusions—Intrathoracic impedance is inversely correlated with pulmonary capillary wedge pressure and fluid balance and decreased before the onset of patient symptoms and before hospital admission for fluid overload. Regular monitoring of impedance may provide early warning of impending decompensation and diagnostic information for titration of medication.

Key Words: heart failure • pulmonary wedge pressure • pacing

New medical and device-based therapies for heart failure improve survival and reduce hospitalization rates. However, total hospitalizations continue to rise with the growing prevalence of heart failure.1 Pulmonary congestion, resulting from elevated left atrial and left ventricular (LV) filling pressures, is the most common event requiring heart failure hospitalization.2,3 In the United States and other developed countries, heart failure is one of the most costly diseases in healthcare budgets, with 70% of the expenses going to the treatment of acute heart failure decompensation.4 Although regular monitoring of heart failure patients is recommended in management programs,5 none of these measures has shown conclusive impact on heart failure morbidity.6,7 Symptoms leading to heart failure hospitalization usually occur late in the course of decompensation. In one study, dyspnea was noted on average only 3 days before admission.2 Therefore, a reliable means of chronic fluid status monitoring in ambulatory patients is needed to detect early decompensation when appropriate intervention is possible.

One potential method of detecting developing pulmonary congestion, a sign of decompensation, is to measure intrathoracic impedance. When an electrical current is passed across the lung, accumulation of intrathoracic fluid during pulmonary congestion will form a better conductance, causing a corresponding decrease in impedance. A similar but less ideal method is to measure transthoracic impedance noninvasively.
with surface electrodes. Early studies have validated the potential usefulness of this method to reflect the amount of intrathoracic fluid in animal models and in humans with pulmonary edema. However, this method does not allow the acquisition of chronic, ambulatory data, and serial comparison of measurements is difficult because the impedance is affected by electrode placement.

In our early work in dogs, measurement of intrathoracic impedance by a modified pacemaker correlated closely with heart failure severity as reflected by the LV end-diastolic pressure. This report established the foundation of our study to evaluate intrathoracic impedance as a potentially useful clinical tool to monitor fluid status in heart failure patients. Our objectives were to assess whether a reduction in intrathoracic impedance predicts the occurrence of heart failure symptoms and admission, to assess whether changes in intrathoracic impedance correlate with changes in pulmonary capillary wedge pressure and intensive diuresis during heart failure hospitalization, and to develop an automated algorithm for early detection of transient decreases in intrathoracic impedance before heart failure hospitalization.

**Methods**

**Patients**

We recruited 34 patients with NYHA functional class III or IV heart failure and a history of significant heart failure–related events in the prior 12 months. These events were defined as 2 heart failure hospitalizations with a history of responding to in-hospital medical therapies, 1 heart failure hospitalization requiring inotropic therapy, or 1 heart failure hospitalization with a history of responding to in-hospital medical therapies plus an emergency room visit, unscheduled clinic visit, or change in medication as a result of worsening heart failure symptoms. Patients were excluded if they met any of the following conditions: chronic primary pulmonary diseases, unstable angina, Q-wave myocardial infarction within the last 3 weeks, cardiac surgery within the previous 3 months, pericardial effusion or cachexia with serum albumin < 2.8 g/dL, inability to tolerate temporary placement of a Swan-Ganz catheter, contraindication for a pacemaker implantation, dependency on a pacemaker, use of an implantable cardioverter-defibrillator, anticipated noncompliance with the follow-up schedule, inability to communicate on the telephone, and use of anticoagulation therapy that could not be withheld for the implantation procedure. All enrolled patients were on optimal pharmacological therapy with an average of 2.7±1.7 heart failure hospitalizations within the prior 12 months.

**Device Implantation**

The device implantation was similar to that of a conventional pacemaker. An implantable cardioverter-defibrillator lead was implanted in the right ventricular (RV) apex (model 6943 or 6945, Medtronic, Inc). A pacemaker with 2 sensors, activity and minute ventilation, was placed in the left pectoral region (model KSP401, Medtronic; Figure 1). This device was modified to accept an implantable cardioverter-defibrillator lead and to measure impedance between the implantable cardioverter-defibrillator lead and the device case, with a resolution of 0.4 Ω and a range of 0 to 107 Ω. The pacemaker was programmed to provide ventricular rate support when indicated.

**Study Design**

This observational study had a prospectively defined end point of heart failure hospitalizations resulting from volume overload.

After successful device implantation, patients entered the chronic follow-up phase, which lasted up to 2 years. Patients were seen monthly by a physician through the first year and as needed for disease management during the second year. The heart failure nurse assessed medication compliance and symptoms by weekly telephone contact for the first year.

Intrathoracic impedance was measured automatically every 6 hours and later retrieved by a blinded study monitor for analyses. When patients were hospitalized for worsening heart failure, they were transferred to the cardiac care unit (CCU) and entered into the acute phase of the study. Intravenous diuretics and other anti–heart failure medications were given, and a Swan-Ganz catheter was inserted for hemodynamic monitoring. Systemic blood pressure, pulse, and fluid input/output were monitored closely and recorded. Pulmonary capillary wedge pressure was measured every 2 hours when possible, and intrathoracic impedance was measured every 30 minutes. When patients were discharged, they returned to the chronic follow-up phase. Neither the patients nor their physicians had access to the impedance data. A committee reviewed each hospital admission to verify if it resulted from worsening heart failure. The ethics committee of each institution approved the study protocol, and all patients gave written informed consent.

**Measurement of Intrathoracic Impedance**

The minute ventilation sensor was used to measure intrathoracic impedance. This sensor, which has been described previously, has been used to measure patient respiration in rate-response pacemakers. For our study, we tested 3 stimulation/measurement pathways: (1) RV lead ring electrode to device case/RV coil electrode to device case, (2) RV coil to device case/RV coil to device case, and (3) RV ring electrode to device case/RV tip electrode to device case. For this report, our data analysis focused on only the RV coil electrode to device case pathway. A constant current was sent through the tissue between the “stimulation” electrode pair with a measurement frequency of 16 Hz, asynchronous with the cardiac cycle. The resulting voltage (and therefore calculated intrathoracic impedance) was acquired from the “measurement” electrode pair. Patients implanted with the model 6945 lead did not have all pathways tested because this model lacks a separate ring electrode. A total of 2048 consecutive impedance measurements were collected and averaged over ~2 minutes. This 2-minute averaging was used to eliminate the effects of cardiac and respiratory cycles on the measurement.

During the chronic phase, eight “2-minute average” intrathoracic impedance values were collected during each 6-hour period (1 every...
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For this report, the data presented intrathoracic impedance data from the 3 pathways before overwriting the device memory stored up to 34 days of continuous daily readings of the temporal changes in fluid status during intensive diuresis during hospitalization. Label indicates reference baseline (initial reference impedance value when daily impedance value consistently falls below reference impedance line before admission). Magnitude and duration of impedance reduction are also shown. Days in hospital are shaded.

Figure 2. A, Operation of algorithm for detecting decreases in impedance over time. Differences between measured impedance (bottom; ○) and reference impedance (solid line) are accumulated over time to produce fluid index (top). Threshold is then applied to fluid index to detect sustained decreases in impedance. B, Example of impedance reduction before heart failure hospitalization (arrow) for fluid overload and impedance increase during intensive diuresis during hospitalization. Use of loop diuretics, β-blockers, and ACE inhibitors was consistent with current heart failure management guidelines (the Table).4 There were 25 adjudicated heart failure hospitalizations in 10 patients. The hospitalized and nonhospitalized patients differed only with respect to prior history of ischemic heart disease (the Table). Twenty-four of the hospitalizations in 9 patients occurred ≥1 month after implantation. Admission records with the date of self-reported admission were stored in the device every 30 minutes during hospitalization.

Statistical Analysis

To determine the correlation between intrathoracic impedance and pulmonary capillary wedge pressure during hospitalization, four 30-minute intrathoracic impedance measurements were averaged and compared with each raw pulmonary capillary wedge pressure measurement, collected every 2 hours when possible.

To determine the correlation between the change in intrathoracic impedance and the net fluid loss during hospitalization, we used the impedance and fluid status at the time of admission to the CCU as the baseline. The trend of changes in impedance relative to the baseline (averaged every hour) was then compared with the net fluid input/output in the CCU (recorded hourly).

Fisher’s exact test and 2-sample t tests were used to compare baseline characteristics between patients who were hospitalized during the study period and those who were not. One- or 2-sample t tests were used for all other comparisons. Pearson’s correlation was used to quantify the linear relationship between intrathoracic impedance and pulmonary capillary wedge pressure or net fluid input/output balance. All data were expressed as mean±SD. A value of P<0.05 was considered statistically significant.

Detection Algorithm

An automated algorithm for detection of transient decreases in impedance before heart failure admission was developed on a randomly selected portion of the available data (development data set) and then validated on the remaining data (validation data set). The algorithm is similar to one previously reported.15 On days when the measured impedance was less than the reference impedance, the difference between the measured impedance and the reference impedance was accumulated to produce the output of the algorithm, the “fluid index” (Figure 2A, top). If the measured impedance was consistently greater than the reference impedance, the fluid index was set to 0. Finally, the fluid index was compared with a threshold (Figure 2A, top) to detect a sustained transient decrease in impedance.

Performance of the detection algorithm was evaluated on the validation data set, with hospitalization for fluid overload as the end point. Sensitivity was defined as the percentage of all hospitalizations in which the fluid index exceeded the threshold at any point in the 30-day window preceding hospital admission. False-positive detections were defined as any occasion in which the fluid index exceeded the threshold and the extent of the suprathermal fluid index was entirely outside the 30-day window preceding each hospital admission. The number of false-positive detections per patient-year was computed as the total number of false-positive detections divided by the total duration of patient follow-up. Detection performance curves were constructed by plotting the sensitivity and false-positive rate as a function of the detection threshold. Finally, the “early warning” was defined as the number of days between the initial threshold crossing and hospital admission.

Results

Patients

Of 34 patients enrolled, 33 had a successful implantation procedure. The mean follow-up period was 20±8.4 months. Use of loop diuretics, β-blockers, and ACE inhibitors was consistent with current heart failure management guidelines (the Table).4 There were 25 adjudicated heart failure hospitalizations in 10 patients. The hospitalized and nonhospitalized patients differed only with respect to prior history of ischemic heart disease (the Table). Twenty-four of the hospitalizations in 9 patients occurred ≥1 month after implantation. Admission records with the date of self-reported
symptom onset were available for 20 of the 24 hospitalizations. The first occurrence of worsening heart failure symptoms was 3.0/2.5 days (range, 1 to 10 days) before admission. Intrathoracic impedance started to decrease before worsening symptoms with a mean lead time of 15.3/10.6 days ($P<0.001$). The most common self-reported symptom was shortness of breath (95%). For these patients, 29% first noticed worsening symptoms within 24 hours of admission, and 67% first noticed worsening symptoms 3 days before admission.

Net fluid input/output was documented for 6 patients during 17 hospitalizations, and pulmonary capillary wedge pressure recordings (27.7±8.6 mm Hg on CCU admission) were available from 5 patients with 14 hospitalizations. One patient was hospitalized for dehydration. Eight patients died with a mean follow-up duration of 9.0±7.5 months: 3 of sudden cardiac deaths, 2 of intractable heart failure, and 3 of noncardiac causes.

**Impedance Data Before Hospitalization**

After the implantation procedure, intrathoracic impedance first decreased and then recovered. This stabilization period was typically 4 weeks. This may be attributed to the postimplantation swelling around the device pocket because the device case is used in the impedance measurement pathway. The impedances averaged over the first 150 days after implantation for all patients who were not hospitalized during this period demonstrate the initial decline and the subsequent gradual increase to a relatively steady state (Figure 3, left). In contrast, for those patients with hospitalizations, the averaged intrathoracic impedance for the 31 days leading up to hospitalizations decreased substantially (Figure 3, right).

In all 24 heart failure hospitalizations that occurred ≥1 month after implantation (required for the reference impedance to be established), the daily intrathoracic impedance was consistently below the reference impedance for an average of 18.3±10.1 days (range, 3 to 42 days) leading up to hospital admission. During this time, impedance decreased by 12.3±5.3% ($P<0.001$) from the reference baseline to the impedance measured on the day before hospitalization (Figure 4). For the 1 patient hospitalized for dehydration, impedance actually increased 8% over the 3 days before admission.

**Impedance Data During Hospitalization**

Of 24 hospitalizations, 17 were admitted to the CCU. Because of a lack of a CCU bed or a delay in the emergency room staff contacting the study team, the other 7 were admitted to and treated in the general medical ward. Pulmonary capillary wedge pressure monitoring was started within an average of 12.5 hours (range, 1 to 36 hours) after presentation to the emergency room. Patients were treated
with intravenous furosemide during all 17 CCU admissions and with vasodilators in 12 of the 17 admissions. Intravenous diuretic therapy over 3.2±1.8 days resulted in a significant 17.1±9.4% increase in intrathoracic impedance from 62.0±9.8 Ω, measured at the first 2-hour pulmonary capillary wedge pressure measurement, to 72.0±7.9 Ω (P<0.001), just before Swan-Ganz catheter removal. During this same period, the pulmonary capillary wedge pressure decreased 45.1±21.7% from 27.7±8.6 to 15.2±5.1 mm Hg (P<0.001), and the patients lost an average of 5.2±2.6 L fluid. Figure 5A shows sequential measurements of the intrathoracic impedance, pulmonary capillary wedge pressure, and net fluid loss in a single patient who was hospitalized for 4 days. The increase in impedance during this period of diuretic therapy was strongly correlated with both the pulmonary capillary wedge pressure (r = −0.91, P<0.001) and net fluid loss (r = −0.94, P<0.001). After all available hospitalization events were pooled, good correlations between intrathoracic impedance and pulmonary capillary wedge pressure (r = −0.61, P<0.001; Figure 5B) and between intrathoracic impedance and net fluid loss (r = −0.70, P<0.001) remained. In addition, the intrathoracic impedance value on admission into the CCU correlated very closely with the overall amount of fluid loss that occurred during hospitalization (r = 0.86, P<0.001; Figure 5C).

Algorithm Performance
The algorithm development data set included 6.2 patient-years of monitoring from 7 patients, with 11 hospitalizations from 4 patients. The algorithm validation data set included 22.6 patient-years of monitoring from 26 patients, with 13 hospitalizations from 8 patients (3 hospitalized patients contributed separate hospitalization events to both the development and validation data sets). Figure 6 shows 2 threshold-crossing occasions from 1 patient in the validation dataset. In the left panels, the fluid index crossed the nominal threshold of 60 Ω · d on day 35 on the scale (not relative to implantation date). On day 69, the patient presented for a monthly follow-up in which the physician noted excess fluid accumulation by routine patient history and physical examination. The physician then prescribed a 50% increase in the patient’s furosemide dose for 3 days (shaded region 1), which resulted in an abrupt increase in impedance and a reset of the fluid index. This threshold crossing was classified as a false-positive event because no hospitalization occurred within 30 days of the threshold crossing. More than 1 year later, the patient was hospitalized for fluid overload (Figure 6, right). Preceding hospital admission on day 29 (not relative to implantation date), the impedance rapidly decreased and remained below the reference impedance for ~12 days. The fluid index crossed the nominal threshold of 60 Ω · d on day 22. This event therefore contributed to algorithm sensitivity with an early warning of 7 days.

The performance curve of the algorithm designed to detect heart failure hospitalization on the validation data set is shown in Figure 7. Lower detection thresholds lead to higher sensitivity but also higher false-positive rate. The performance at the upper right end of the curve corresponds to a threshold of 20 Ω · d, and the threshold increases by 10 Ω · d for each point thereafter. The suggested nominal operating threshold is 60 Ω · d near the “knee” of the curve. At this threshold, the sensitivity was 76.9%, the false-positive rate was 1.5 false-positives per patient-year, and the early warning was 13.4±6.2 days (range, 5 to 22 days). One of 3 hospitalization events in the validation data set that was not detected at the nominal threshold occurred 48 days after implantation.
impedance predated the onset of symptoms by an average of 15 days and therefore could potentially serve as a “warning window” for early intervention. We also showed a correlation between the intrathoracic impedance values recorded by the implanted system, the pulmonary capillary wedge pressure, and the input/output fluid balance documented during intravenous diuretic therapy in the CCU. Finally, an automated algorithm detected changes in impedance preceding hospital admission with 76.9% sensitivity and only 1.5 false-positive (threshold crossing without hospitalization) detections per patient-year of monitoring.

Use of Externally Measured Transthoracic Impedance for Heart Failure Patients

Thoracic impedance refers to the hindrance to flow of the current carried by ions across the chest. It is related to the total amount of intrathoracic fluid. Therefore, thoracic impedance is related to the total volume of fluid in the electric field of interest. With the lack of technology to measure intrathoracic impedance, early studies envisaged measuring transthoracic impedance across the chest noninvasively by means of an external electrode system in animal models. In the canine, induction of pulmonary edema by alloxan or sucrose infusion resulted in a small decrease in transthoracic impedance of 2 to 5 Ω. In the study in which the Minnesota Impedance Cardiograph measured the transthoracic impedance in dogs, it decreased in proportion to the amount of pulmonary extravascular volume measured by radioactive tracer and increased with phlebotomy. Subsequently, human studies were performed to validate and to confirm the feasibility of measuring transthoracic impedance using surface electrodes. The noninvasive monitoring of transthoracic impedance was found useful in early case reports in which improvement of pulmonary congestion in heart failure was associated with an increase in transthoracic impedance as measured by the Minnesota Impedance Cardiograph. Other studies have shown that a reduction in transthoracic impedance closely correlated to positive fluid balance during vascular and cardiac surgery. These data suggest the useful role of impedance measurements in monitoring fluid status during chest surgery. Patients with LV failure were found to have lower transthoracic impedance than normal patients, which was gradually increased to normal range when heart failure was resolved.

In the emergency room setting, measurement of transthoracic impedance has been suggested to provide additional information for possible earlier diagnosis of fluid overload compared with clinical and radiographic information. Newer systems such as those developed by CardioDynamics use a similar technique with an external spot electrode system. However, this system was developed to measure cardiac output rather than intrathoracic fluid status, and like other methods of measuring transthoracic impedance, it requires exact repetition of electrode placement to ensure accurate comparisons over time. Continuous noninvasive monitoring of transthoracic impedance is possible only when the patient is in the clinic or during hospitalization, so ambulatory data are not available on how impedance varies with progressive thoracic fluid accumulation in the process of...
heart failure decompensation. Sequential clinic measurements on the same patient may not be as reliable because variations in transthoracic impedance measurement, without changes in patient fluid status, could be introduced by slight differences in placement of external electrodes or changes in skin-electrode contact. Because skin contact is the major contributor to noninvasive transthoracic impedance, any change in this component may cause significant changes in the total impedance measured. Respiratory movement of the chest wall may also affect transthoracic impedance measured noninvasively. As a result, the accuracy of using transthoracic impedance to detect pulmonary fluid accumulation has been questioned. In a recent study, a new external device was used to measure transthoracic impedance by automatically calculating skin electrode impedance and subtracting it from the transthoracic impedance. This method claimed to be more sensitive than conventional measurement of transthoracic impedance to detect pulmonary fluid accumulation, although its role remained limited to nonambulatory use.

Relationship Between Intrathoracic Impedance and Fluid Measures During Hospitalizations

A major finding in this study was the good correlation between intrathoracic impedance and pulmonary capillary wedge pressure during hospitalization. This unique information illustrates that intrathoracic impedance correlated with the severity of heart failure as reflected by the filling pressure, which is a good indicator of the amount of pulmonary fluid accumulation. Furthermore, the close correlation between intrathoracic impedance and the total negative fluid balance illustrated that intrathoracic impedance changes occurred in parallel with the clearing of pulmonary volume overload and/or edema after intravenous diuretic therapy. Therefore, intrathoracic impedance may serve as a surrogate measure of pulmonary fluid status in heart failure patients. Continuous monitoring of impedance during acute heart failure therapy may provide quantitative information on the severity of volume overload.

Implications for Early Warning of Heart Failure Hospitalizations

With the increasing use of implantable devices in patients with heart failure, the possible role of ambulatory monitoring of intrathoracic impedance is revisited. The present study is the first to confirm the feasibility and clinical usefulness of monitoring intrathoracic impedance in ambulatory heart failure patients. Although not all patients were hospitalized for worsening heart failure during the study, those who did had significantly reduced intrathoracic impedance before admission. We saw that on average the impedance trend leading up to hospitalization for fluid overload (Figure 3B) is markedly different than the impedance trend in patients without heart failure hospitalization (Figure 3A). The decrease in impedance leading up to hospitalization was observed not only in the average trend but also in every individual prehospitalization record (Figure 4). Furthermore, this reduction occurred an average of 15 days before symptom onset.

This reduction in intrathoracic impedance before hospitalization may provide an adequate window to warn clinicians and/or patients of impending acute decompensation. The proposed detection algorithm demonstrated the feasibility of this concept by providing an early warning of hospital admissions with 76.9% sensitivity at the nominal threshold of 60 Ω · d. In the algorithm validation patient group, the average early warning was 13.4 days before admission, a significant improvement over the late and subjective occurrence of patient symptoms of fluid overload. In practice, the early warning could potentially be achieved by sending an alert to patients or physicians automatically when the fluid index of the algorithm exceeds a predetermined threshold. In this way, the development of worsening heart failure might be detected early in the preclinical stage when appropriate therapy such as increasing the dose of oral diuretics or more frequent visits to the clinic could be initiated early to abort the need for hospitalization. This intrathoracic impedance information may also offer clinicians opportunities for patient education on diet and drug compliance.

At the same 60-Ω · d threshold for detection, the algorithm produced 1.5 false-positive detections per patient-year of monitoring. As shown in Figure 6, not all false detections occurred in the absence of the need for intervention. Anecdotally, other false-positive detections were associated with diuretic changes, chest infection, and dietary noncompliance, most of which are in fact worthy of medical attention.

Conclusions

Ambulatory monitoring of intrathoracic impedance by an implantable device may be a surrogate measure of fluid overload. Automated detection of decreases in intrathoracic impedance via pacemaker and implantable cardioverter-defibrillator devices could lead to advanced warning of heart failure hospitalization resulting from volume overload. Further studies are needed to determine whether such an early warning can facilitate preemptive therapy to reduce hospital admissions.

Acknowledgment

This study was supported by a research grant from Medtronic, Inc.

Disclosure

Dr Yu has received research funding from Medtronic, Inc., served on the Speakers’ Bureau of and/or received honoraria from Medtronic, Inc., and has served as a consultant to Medtronic, Inc.

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Circulation. 2005;112:841-848; originally published online August 1, 2005; doi: 10.1161/CIRCULATIONAHA.104.492207
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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