Making a Splash?
– Intrathoracic Impedance and the Prediction of Arrhythmic Events –

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Over the past decade, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) device platforms have been expanded to include a host of new integrated device-based diagnostic capabilities. Parameters such as a sustained drop in intrathoracic impedance, reduced heart rate variability, high resting heart rate, decreased patient activity, prolonged periods of atrial fibrillation (AF), and reduced biventricular pacing percentage are all measurements that correlate with an increased risk of heart failure (HF) hospitalization and potential mortality.1-4

These diagnostics are attractive to clinicians as independent and “objective” indicators of patient status, are readily accessible during routine device interrogation, and also appear to precede the clinical symptoms and signs that classically portend HF decompensation.5 Although potentially useful in predicting HF exacerbation, the role of these device diagnostics in anticipating clinically significant arrhythmias remains unclear. Given the increased mortality noted after both appropriate and inappropriate ICD shocks, a means to identify at-risk periods for patients a priori would be of considerable value.

In this issue of the Journal, Sekiguchi et al focus on one device-based diagnostic of particular interest, intrathoracic impedance, and its association with cardiac arrhythmia.6 They performed a post-hoc analysis of the Concerto-AT study, a multicenter, non-randomized trial evaluating the efficacy of atrial cardioversion in patients receiving CRT. For each patient, they obtained data regarding intrathoracic impedance, as well as a derived quantity, the OptiVol fluid index threshold crossing (TC).

The OptiVol fluid index is a proprietary algorithm for computing intrathoracic impedance incorporated into Medtronic ICD and CRT platforms.7 The fluid index is calculated as the cumulative difference between mean daily impedance, with a reference that is based on an average of the patient’s previous 4 mean daily impedance values. The proof-of-concept investigation of the OptiVol fluid index was conducted by Yu et al in the Medtronic Impedance Diagnostics in Heart Failure Patients Trial (MIDHeFT).8 Based on receiver-operator characteristics from MIDHeFT, a nominal OptiVol threshold was established of 60 ohm-days, which demonstrated 77% sensitivity in predicting subsequent HF hospitalization in that study.

More recent investigations, however, have suggested sensitivity is dynamic, and may be as low as 21%.9 In any event, Sekiguchi et al used the more conventional 60 ohm-days threshold in their analysis of arrhythmia.

The majority of the 282 patients included in this study were male (71%), and nearly all demonstrated NYHA class III HF symptoms (93%). The patients demonstrated accepted indications for CRT, with a mean QRS duration of 157.0±23.4 ms, mean left ventricular ejection fraction of 23.3±6.8%, and a median age of 68.3 years. Slightly more than half demonstrated ischemic cardiomyopathy (56%). Because Concerto-AT sought to determine the effect of atrial cardioversion, a significant portion of patients (40%), demonstrated a history of atrial arrhythmia, including atrial tachycardia, atrial flutter, and AF. Importantly, 18% also had a history of sustained ventricular tachycardia (VT) and 10% had a history of ventricular fibrillation (VF) at baseline.

Sekiguchi et al grouped all patients into 2 cohorts: patients with at least 1 fluid index TC (TC[+] group, n=145) and those no fluid index TCs (TC[−], n=137). They found no significant differences in the baseline characteristics of these 2 cohorts. Over a mean follow-up of 10.0±3.2 months, a total of 4,725 arrhythmic events occurred, which included 3,521 atrial events in 90 patients and 1,204 ventricular events in 70 patients. A statistically significant association was observed between fluid index TCs (ie, TC[+]) and both atrial and ventricular arrhythmic events, occurring significantly more often in patients in the TC[+] group than in the TC[−] group (3,241 vs. 1,484 total arrhythmic events; 753 vs. 451 VT/VF events).

In multivariate analysis, baseline NYHA class, female sex, and age were also found to be statistically significantly correlated with arrhythmic events. This should be interpreted cautiously, however, as only small numbers of patients had higher baseline NYHA class (7%) and there was only minimal risk associated with age and atrial arrhythmia (RR=1.01).

In further analysis of intrathoracic impedance change and time course of subsequent arrhythmia, Sekiguchi et al found that ventricular arrhythmic events (VT or VF) were more likely within 1 month of a fluid index TC>1 month after a TC. The same was not seen for atrial arrhythmic events, which were more likely to occur >1 month after a TC. Only 16% of the TC[+] patients demonstrated subsequent ventricular arrhythmia.

Overall, the results of Sekiguchi et al mirror the work by Jhanjee et al with respect to an increased incidence of atrial
arrhythmias in patients with TC(+). Although Jhanjee et al further speculated that atrial arrhythmias might lead to increased pulmonary congestion and thus lead to a TC, a similar “preceding” arrhythmic event analysis was not performed in this study, and thus cannot be confirmed.

There is conflicting data regarding the relationship between intrathoracic impedance and subsequent ventricular arrhythmia in the literature leading up to Sekiguchi et al’s study. In a study of 121 patients by Moore et al, a novel measure, ΔTI, calculated as the sum of the daily differences between the averaged daily and referenced impedance, did decline prior to VT/VF episodes, but no association with OptiVol fluid index was found. Ip et al, on the other hand, found an association between VT/VF and TCs of 15, 30, and 45 ohm-days, but not at the 60 ohm-days threshold that was used by Sekiguchi et al. In light of Moore and Ip’s work, it is difficult to comment conclusively on the value of intrathoracic impedance change and prediction of ventricular arrhythmia, although a general association does appear plausible.

Perhaps some of the difficulty may lie in the underlying pathophysiology. Returning to first principles, impedance is assessed through delivery of alternating current between the pulse generator and the right ventricular coil of the ICD lead. Because blood and fluid are highly conductive, intrathoracic impedance will drop with pulmonary edema or any other phenomenon that increases the conductivity of the thorax, including pneumonia and pleural effusion. Conversely, emphysematous air trapping can falsely increase impedance.

Importantly, advanced HF patients may demonstrate hypertrophy of pulmonary lymphatics, leading to relatively minor or slowly changing pulmonary congestion, which might lead to relatively small changes in impedance, and could be missed entirely by the OptiVol algorithm, because it automatically resets to a value of zero when the daily impedance is sustained above the reference impedance. All of these barriers limit the role of intrathoracic impedance assessment in HF prediction, leaving aside the more complicated pathobiology of HF exacerbation and increased ventricular arrhythmia risk, which remains to be elucidated. It is perhaps too much to hope that a simple measure of impedance difference might reliably predict the changing milieu of arrhythmia.

From an electrophysiologic perspective, however, Sekiguchi et al provide an excellent discussion of the limitations to their study. Chief among these is lack of access to stored ECGs in order to determine the veracity of arrhythmic characterization, and also a lack of information regarding antitachycardia pacing episodes or direct current shock therapies delivered. These data would be particularly helpful in gauging the overall clinical impact of TC assessment. Device programming for arrhythmia detection and treatment delivery was also left to the discretion of clinicians, and would certainly need to be standardized in any future investigations.

Data from the recent PARTNERS HF Trial suggest that an algorithm combining a suite of device-based diagnostics might perform better than a single diagnostic in predicting HF exacerbation. The ongoing randomized trials of the Diagnostic Trial in Heart Failure (DOT-HF) in Europe and the Prospective, Randomized Evaluation of Cardiac Compass with OptiVol in the EarlyDetection of Decompensation Events for Heart Failure (PRECEDE-HF) in North America will no doubt shed light on this question with even more robustness.

The work done by Sekiguchi et al confirms there is likely a role for intrathoracic impedance in arrhythmia prognostication, although it lacks specificity to stand by itself as a clinically practical prediction tool. Taken together, their study findings perhaps best demonstrate that intrathoracic impedance may only be among the “first into the pool” of device-based diagnostic tools that cardiologists might use in the longitudinal management of HF patients, with more sophisticated and comprehensive assessments still in the pipeline.

Disclosures
Conflict of Interest: Dr Upadhyay reports no disclosures. Dr Singh is a consultant and receives lecture fees from Biotronik, Boston Scientific, Medtronic, Sorin Group, and St. Jude Medical, and is also a consultant for CardioInsight Inc, Thoratec Inc, and Biosense Webster.

References