

Editorial

Bioimpedance: Has Its Time Finally Come?DANIEL BURKHOFF, MD, PHD^{A,B}*New York, New York*

Bioimpedance, the measurement of the frequency-dependent resistance to the flow of low energy electrical currents between two electrodes on or within the body, has been investigated for various medical applications for over 50 years. Applications in cardiology date back to at least 1966¹ and have included attempts to estimate stroke volume, cardiac output, cardiac contractility and lung fluid volume. The interest in lung fluid volume relates directly the goal of providing an objective, actionable measure of volume status in patients with heart failure to guide adjustments of medical therapies, predominantly diuretic doses. This is feasible since when salt and water content increase in the lungs, electrical currents pass more easily through the tissue and bioimpedance is therefore decreased. Despite prior advances in electrode technology, electric circuitry, signal processing algorithms and attempts to optimize the number and location of electrodes the accuracy, reproducibility and clinical utility of information retrievable from bioimpedance devices continue to be challenged.²

However, in this issue of the *Journal*, Shochat and colleagues report rather remarkable results of a study designed to test whether periodic assessment of lung volume status by a new bioimpedance device, can reduce hospitalizations and mortality in patients with heart failure.³ The study employed a device manufactured by RSMM Ltd (Tel Aviv) who supplied the devices for the study. In contrast to traditional bioimpedance devices that measure the total impedance between one or more pairs of electrodes placed on the body surface (generally on the same side of the body), the RSMM approach measures impedance across the chest (anterior to posterior, with the electrical currents transmitted through the lung) and with the thoracic wall impedance subtracted from the total impedance.⁴ This latter calculation allows for estimation of the impedance of the lung tissue itself, which

normally accounts for only a relatively small portion of the total impedance. By isolating net lung impedance (LI) in this manner, theory suggests that this approach should yield greater sensitivity and specificity in detecting changes in lung fluid content. Because of this important differentiating technological feature, the results of this study should not be extrapolated to other bioimpedance systems. The present study randomized 256 patients from two hospitals to either standard of care (SOC, the Control group) or SOC plus monthly net LI measurement-guided medication adjustments (the Active group), predominantly changes in diuretic doses. All patients were seen in the clinic once per month, and more often if they had a change in medications. All patients underwent bioimpedance measurements but the results were made available to the treating physicians only for the active group. Adjustments in medications were protocolized to enhance uniformity of how the bioimpedance results were used in the Active group. The mean duration of follow up was 48 months.

The time course of changes in net LI prior to, during and following heart failure admissions paralleled what has been reported for invasively measured pulmonary artery pressure, starting to decrease (signifying increased lung fluid) ~ 3 weeks prior to a hospitalization.⁵ Net LI measurements also showed that most patients were discharged from hospital prior to complete return of volume status to baseline values.

The main findings of the study were a reduction in the rate of acute heart failure (AHF) hospitalizations at one year from 1.23 to 0.52 events/pt.yr (hazard ratio 0.51, $P < .001$) and a reduction in acute heart failure hospitalizations during the entire follow up period from 0.94 to 0.41 events/pt.yr (hazard ratio 0.63, $P < .001$). All-cause hospitalizations were also reduced, but this appeared entirely due to reductions in AHF and cardiac hospitalizations since the rate of non-cardiac hospitalizations, which accounted for ~1/3 of all hospitalizations in the Control group, were not reduced. Remarkably, total mortality, heart failure-related mortality and cardiac mortality were all decreased in the Active group compared to controls. A host of other secondary endpoints were also favorably impacted in the Active group. There was a NYHA functional class-dependence of the rates of hospitalizations (increasing with NYHA class), but the impact of monitoring was present in all classes.

Shochat and colleagues discuss several of the limitations of the study. First and foremost, this was a single blind study

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and it is unclear how much effort and rigor was placed on ensuring that hospitalization decisions were not influenced by group assignment. Naturally, the mortality results are independent of this limitation. Second, hospitalizations and mortality events were classified as heart failure-, cardiac- and non-cardiac-related by the unblinded investigators, not by an independent blinded adjudication committee as is usually the case. In fact, the study appeared to lack the usual pre-defined definitions of what constituted a heart failure hospitalization. Further related to this point, the authors report that the “vast majority” of the hospitalizations for heart failure were either patient self-referrals or family physician-referrals to the emergency department (ED). The authors further report that patients referred to the ED with known HF are usually admitted to the medical wards even if their symptoms improve following treatment in the ED. This is not standard of care in centers in many hospitals. Additionally, it is uncertain whether such admissions would qualify as *heart failure hospitalizations* if typical, rigorous clinical trial definitions were applied. Third, the study included patients with NYHA functional class II, III and IV at baseline, with nearly half of the patients in NYHA II. Yet, the rate of heart failure hospitalizations in the Control group (1.23 events/pt.yr during the first year and 0.94 events/pt.yr during the entire follow up period) were substantially higher than the rate of heart failure hospitalizations in the control group of the CHAMPION study (0.68 events/pt.yr) despite the fact that CHAMPION enrolled only NYHA III patients at baseline.⁶ This high rate of hospitalizations was also present even though both groups of patients were seen in the clinic at least monthly and thus receiving a high degree of attention from medical professionals. Fourth, the study spanned a total of 8 years, during which period medical therapies and standard clinical practices, including criteria for hospital admission may have evolved. Again, all of these limitations concerning hospitalizations do not apply to the all-important mortality findings. Finally, since the most common change in medications was an increase in diuretic dose, it would have been interesting to report the rate of adverse events and hospitalizations for worsening renal function, metabolic abnormalities (e.g., hypokalemia), arrhythmias and hypotension. It would also have been of interest to know if hospitalizations related to such events were classified as being heart failure-related, cardiac-related, or non-cardiac-related.

Despite its limitations, the results of this study raise several interesting questions and encourage further investigation. First, other monitoring approaches to reduce AHF hospitalizations rely on daily home recording or automatically generated alerts during continuous monitoring. The present results based on monthly measurements would seem to suggest that such intense monitoring may not be required. I would caution against prematurely accepting this premise, and note that the apparent time course of change in net LI prior to a hospitalization (Fig. 3 of the paper) is derived from a linear mixed effects regression model of all available data from all patients; it is therefore unknown if more frequent monitoring could have had a further impact on results.

Second, the monitoring device studied is a relatively simple (from the patients’ perspective) noninvasive bioimpedance test; there are presumably no adverse events associated with its use. On the other hand, patients were seen in the clinic on a monthly basis, which is significantly more frequent than is typical standard of care. There was no mention of the number of missed visits, which must have been present especially in a trial that ran for such a long time. Nevertheless, presumed reduced costs and reduced adverse events in comparison to an invasive, chronically implanted device that employs a centralized data monitoring center for generating alerts for out of bound values could be offset by the increased level of clinical care provided. Directly related to this is that most currently investigated monitoring devices for heart failure involve home-based versus office-based measurements. Since office-based measurements can be performed by trained personnel, there is the potential for tests to be performed more uniformly which can reduce test variability and increase reliability of results.

With the growing heart failure population, the correlation between repeated bouts of heart failure exacerbations due to fluid overload and disease progression and the socioeconomic implications of repeated hospitalizations to treat those exacerbations, there is a justifiable emphasis on validating approaches to reduce exacerbations by maintaining an acceptable fluid balance. Prior studies using various noninvasive approaches, including weight, bioimpedance, and nurse home visits have reported variable successes. Invasive bioimpedance measurements between the electrode tip of an ICD lead and the ICD can have also had variable success. Prior studies using chronically implanted invasive pressure monitors in the pulmonary artery were the first to demonstrate a substantial reduction in heart failure hospitalizations during long term use.^{5,6} The findings of Shochat and colleagues provide further support for the concept that hospitalizations for AHF exacerbations can be reduced through enhanced monitoring strategies. Their findings concerning mortality are particularly important. These encouraging results deserve to be confirmed with a multi-center study designed to overcome the limitations inherent in the current study.

Disclosures

DB is a consultant to Sensible Medical, Corvia Medical, IMPULSE Dynamics, Heartware International and Cardiac Implants LLC.

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