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Accurate monitoring of intravascular fluid volume: A novel application of intrathoracic impedance measures for the guidance of volume reduction therapy

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ABSTRACT

Background: A significant proportion of patients admitted for acute decompensated heart failure (ADHF) that undergo volume reduction therapy are discharged with unchanged or increased bodyweight suggesting that the endpoints for these therapies are not optimally defined. We aimed to identify vectors that can help monitor changes in intravascular fluid volume, that in turn may more accurately guide volume reduction therapy.
Methods: Data from six different impedance vectors and corresponding changes in intravascular volume derived from changes in hematocrit were obtained from 132 clinical congestion events in 56 unique patients enrolled in a multisite trial of early detection of clinical congestion events (DEFEAT PE). Mixed effects regression models were used to determine the relation between changes in impedance derived from six different vectors and changes in intravascular plasma volume.
Results: Changes in impedance were negatively associated with changes in plasma volume. Two vectors, the right atrial ring to left ventricular ring and the left ventricular ring to the right ventricular ring, were most closely associated with changes in intravascular plasma volume.
Conclusion: Impedance vectors derived from a multivector monitoring system reflect changes in intravascular plasma volume. Two of these vectors most closely track changes in plasma volume and may be used to more accurately guide and optimize volume reduction therapy.

1. Introduction

Heart failure (HF) is a leading cause of morbidity and mortality in the US and significantly contributes to national health care costs [1]. Due to the progressive and unstable natural history of HF, many patients develop recurrent episodes of acute decompensated heart failure (ADHF) requiring frequent hospital admissions [2]. The health care costs associated with heart failure are mainly due to these events and are expected to increase by 120% by 2030 [1]. ADHF and refractory congestive heart failure (CHF) are considered the end product of a vicious cycle of reduced cardiac output, impaired salt and water renal excretion and consequent neurohormonal activation. It often results in volume overload, body water redistribution and concomitant high cardiac filling pressures [3]. In the US, approximately 90% of all heart failure related admissions are due to symptoms of pulmonary congestion and fluid overload that are in turn associated with HF progression and increased mortality [4]. Estimation of total body water and redistribution of extra and intravascular volumes is crucial for assessment and treatment of these patients and has been the focus of research and care innovations [5,6].

Although intrathoracic impedance monitoring has been extensively studied as a means for early detection of clinical congestion events resulting from the above mechanisms, there has been little attention given to its role in monitoring or guiding volume reduction therapies.Many implantable defibrillator systems and biventricular pacing devices have incorporated intrathoracic impedance measurement in their monitoring capabilities [7–10]. Therefore, a large number

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of patients with ADHF could benefit from more accurate direction of volume reduction therapies. Strategies to effectively use this information should be developed.

It has been reported in the literature that as many as 50% of ADHF admitted patients treated with diuretics are discharged with unchanged or increased body weight compared to admission despite clinical improvement [11]. This suggests that clinical endpoints used to direct and terminate diuretic therapy might be inappropriate. One explanation for this observation is that effective volume reduction therapy ideally targets decreased extravascular volume without significant reduction in intravascular volume that elicits activation of neurohormonal mechanisms that promote fluid retention and a net increase in total body water. Therefore, effective volume monitoring must reflect not only total intrathoracic volume but must isolate the intravascular from the extravascular fluid compartment [12].

Recently developed volume monitoring algorithms have used the multiple impedance vectors that can be derived across different leads of pacing systems in an effort to more accurately detect volume changes [13]. It is possible that among these, specific vectors or their combinations more accurately report changes in plasma volume rather than extravascular or total intrathoracic fluid volume.

We therefore aimed to examine the relationship between different impedance vectors to changes in plasma volume and thus identify vectors that most accurately report changes in the intravascular compartment. Identification of vectors that specifically isolate the intravascular volume compartment will contribute to significant advances in the direction of volume reduction therapies and address an important unmet need in the treatment of acute decompensated heart failure.

2. Methods

2.1. Patient sample

The study sample was derived from participants in the pivotal trial (DEFEAT PE; ClinicalTrials.gov, NCT00916929) of a multivector algorithm for prevention of clinical volume overload events sponsored by St. Jude Medical. All subjects had heart failure with standard indications for either an ICD or CRTD device and were required to have at least one episode of decompensated congestive heart failure within six months of study enrollment. The participants in this sub-study were those who were admitted to a hospital for decompensated heart failure events for whom serial hematocrit data were available along with impedance vector data encompassing the time period of volume reduction therapy. Patients who received blood transfusions, had episodes of active bleeding during an admission or who had a history of a lead dislodgment were excluded from the analysis.

2.2. Estimation of percent plasma volume change

Percent change in plasma volume (ppchange) at any two points during a hospitalization was determined by using a formula that has been successfully used in clinical hemodialysis and ultrafiltration [14].

$$\text{Percent change in plasma volume} = (100/(100-\text{Hctpre})) * (100(\text{Hctpre}-\text{Hctpost})/\text{Hctpost}).$$

Where Hctpre is the first hematocrit measurement and Hctpost is a subsequent measure.

For this study, we chose two hematocrit values that were separated by the greatest time interval during volume reduction therapy.

Positive values of percent plasma volume change represent an increase in plasma volume from the time when the first hematocrit sample was drawn to the time of the repeated measurement.

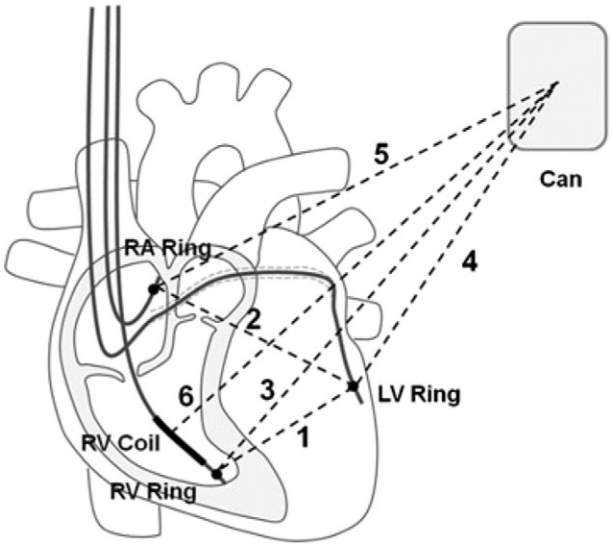

Fig. 1. Diagram of CRDT impedance vectors. Electrode configurations used for measuring impedance: (1) LVr–RVr, (2) LVr–RAr, (3) RVr–can, (4) LVr–can, (5) RAr–can, and (6) RVc–can. LV: left ventricle, RA: right atrium, RV: right ventricle, c: coil electrode, r: ring electrode. Modified from Binkley et al. [15].

2.3. Analysis of impedance vectors

The CRTD device measures impedances obtained from six independent vectors formed by the following electrode configurations (Fig. 1): (1) LVr–RVr, LV ring electrode to RV ring electrode;(2) LVr–RAr, LV ring electrode to right atrium (RA) ring electrode; (3) RVr–Can, RVring electrode to device can;(4) LVr–Can, LV ring electrode to device can; (5) RAr–Can,RA ring electrode to device can; and (6) RVc–Can, RV coil electrode to device can. Impedance measurements were recorded every 2 h[15]. The ICD device only measures impedance vectors for configurations: (3) RVr–Can, RVring electrode to device can, (5) RAr–Can, RA ring electrode to device can; and (6) RVc-Can, RV coil electrode to device can.

Impedance data from each vector obtained at times that most closely corresponded to acquisition of the hematocrits were selected for analysis. Therefore impedance measurements corresponding to the first and second of two hematocrit measures were analyzed for each of the six vectors. If the available impedance data were more than 2 h from a corresponding hematocrit, the observation was not included in the analysis. The change in impedance for each vector was calculated by subtracting the post-hematocrit related impedance (PostImp) from the pre-hematocrit related impedance (PreImp) values as follows:

$$\text{Impedance vector difference} : \text{PostImp} - \text{PreImp}.$$

Therefore, positive values of impedance difference represent an increase in impedance overtime, while negative values represent a decrease of impedance.

2.4. Statistical analysis

Changes in impedance and percent plasma volume were represented by the mean and standard deviation. The association between changes in impedance and plasma volume was analyzed using mixed linear models to account for inter-subject variability in measures and the different number of measurements made on each participant. Sequential models were constructed consisting of the mixed effects model with random intercept (defined by the patient identification number) and the mixed effecfs model with both random intercept and coefficient relating change in impedance and change in plasma volume. Models were constructed for each of the six impedance vectors. The likelihood ratio test was used to