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Single subject design: Use of time series analyses in a small cohort to understand adherence with a prescribed fluid restriction

Carolyn Miller Reilly, RN, PhD [a,*], Melinda Higgins, PhD [a], Andrew Smith, MD [b], Steven D. Culler, PhD [c], Sandra B. Dunbar, RN, PhD [a]

[a] Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA 30322, USA
[b] Emory University School of Medicine, Atlanta, GA 30322, USA
[c] Emory School of Public Health, Atlanta, GA 30322, USA

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ABSTRACT

Purpose: This paper presents a secondary in-depth analysis of five persons with heart failure randomized to receive an education and behavioral intervention on fluid restriction as part of a larger study.
Methods: Using a single subject analysis design, time series analyses models were constructed for each of the five patients for a period of 180 days to determine correlations between daily measures of patient reported fluid intake, thoracic impedance, and weights, and relationships between patient reported outcomes of symptom burden and health related quality of life over time.
Results: Negative relationships were observed between fluid intake and thoracic impedance, and between impedance and weight, while positive correlations were observed between daily fluid intake and weight.
Conclusions: By constructing time series analyses of daily measures of fluid congestion, trends and patterns of fluid congestion emerged which could be used to guide individualized patient care or future research endeavors. Employment of such a specialized analysis technique allows for the elucidation of clinically relevant findings potentially disguised when only evaluating aggregate outcomes of larger studies.

1. Time series analysis of adherence with a prescribed fluid restriction

Although the translation of research to practice relies heavily on the gold-standard of the randomized clinical trial (RCT) (Portney & Watkins, 2009), other research designs offer valuable information to describe a phenomena or population, pilot interventions and instruments, and justify effect and sample sizes of subsequent studies. By design, RCTs require control groups and large numbers of comparable participants, often collecting data at two or three time points. Group averages and generalizations are calculated, and differences between groups are used to demonstrate the superiority of one intervention over another. A hindrance to the RCT is the loss of variability of individual subjects through the averaging of results (Portney & Watkins, 2009). Further, most large RCTs are limited in the ability to contribute information about individual behaviors and physiologic phenomena that might be monitored on a daily basis.

A single-subject design provides an alternative or additional approach to RCTs allowing for the evaluation of effects on treatment based upon responses of individual subjects under controlled experimental conditions (Portney & Watkins, 2009). Single-subject designs require the same attention to design and control as RCTs are guided by a research hypothesis with predicted expected relationships between independent and dependent variables and use stringent statistical methods that can provide meaningful results. Further, as there are multiple measurement points within each subject's data, analyses for statistical differences and correlations are possible for each patient. The purposes of this article are to describe the usefulness and structure of a single-subject analysis design and present its applicability in evaluating an intervention to improve adherence with a commonly prescribed treatment in persons with heart failure (HF). The hypothesis of this secondary analysis was that by analyzing the time series analyses of daily measures of fluid congestion, trends and patterns of fluid congestion would emerge which could serve to guide future research endeavors and individualized patient care. Further, correlations could be drawn between objective and patient reported outcomes of symptom burden and health related quality of life (HRQOL).

The authors declare no conflicts of interest.

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* Corresponding author at: Nell Hodgson Woodruff School of Nursing, Emory University, 1520 Clifton Rd, NE #366, Atlanta, GA 30322. Tel.: +1 404 727 9658; fax: +1 404 727 9382.
E-mail address: cmill02@emory.edu (C.M. Reilly).

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2. Background

Over 650,000 persons in the United States (US) are diagnosed with HF every year (Go et al., 2013; Mefferd, Nichols, Pakiz, & Rock, 2007), creating both a personal and society burden due to high health resource utilization and associated costs (Bonow et al., 2005; DeFrances & Podgornik, 2006). Multiple non-pharmacological treatments for persons with HF are recommended by the Heart Failure Society of America (HFSA) (Lindenfeld et al., 2010), American Heart Association (AHA)/American College of Cardiology (ACCF) (Yancy et al., 2013a, 2013b), and European Society of Cardiology (ESC) (McMurray et al., 2012), including prescribing a low sodium diet, daily monitoring of weight for possible fluid retention, abstaining from alcohol and tobacco, avoiding non-steroidal anti-inflammatory medications that contribute to sodium and fluid retention, participating in moderate physical activity, losing weight as indicated, and following a prescribed fluid restriction (FR) in selected subjects in addition to medical management. Although several studies have confirmed the importance of most of these self-care measures in reducing costs and preventing hospitalizations (Costantini et al., 2001; Krumholz et al., 2002; Lucas et al., 2000; Rich et al., 1995; West, Miller, & Parker, 1997), improving overall HF self-care (Jaarsma et al., 1999), HRQOL (Kutzleb & Reiner, 2006), and decreasing mortality (Grancelli et al., 2003), similar outcomes have not been observed with a prescribed FR.

The 2009 direct and indirect costs in the US for persons with HF hospitalized with fluid volume overload are estimated to be $37.2 billion (Lloyd-Jones et al., 2009; Thom et al., 2006). Further, HF is recognized as the most common primary discharge diagnosis of hospitalizations in those over age 65 (DeFrances & Podgornik, 2006), and the most costly Medicare diagnosis (Bonow et al., 2005). Most alarming is that approximately 50% of these patients are readmitted within 6 months following hospital discharge indicating the chronicity of the illness and burden on the healthcare system (Aghababian, 2003; Desai & Stevenson, 2012; Krumholz et al., 1997; Rich et al., 1995; Schell, 2014). In general, most patients are readmitted for fluid volume overload, profound depression of cardiac output, or signs and symptoms of both syndromes (Jessup et al., 2009). Often, these admissions are related to lack of adherence with medications and recommended self-care measures (Aghababian, 2003; Jessup et al., 2009; Krumholz et al., 1997; Michaelsen, Konig, & Thimme, 1988; Neily et al., 2009; Rich et al., 1995; Tsuyuki et al., 2001; Vinson, Rich, Sperry, Shah, & McNamara, 1990).

2.1. Fluid management and restriction in HF

Management of volume status is a core principal of HF management (Yancy et al., 2013a, 2013b), with the prescription of diuretics, sodium restriction, and careful monitoring of fluid status via patient measurement of daily weights and symptoms. Daily FRs were common prior to the advent of modern-day medications, and remain a recommendation from the ACC/AHA for the most compromised stage D HF patients with persistent recurrent fluid retention despite sodium restriction and high-dose diuretics (Yancy et al., 2013a, 2013b). Similarly, a FR of 1.5 to 2 liters per day for patients with severe hyponatremia or continued fluid congestion despite high diuretic dosage and dietary sodium restriction is supported by the Heart Failure Society of America (HFSA) and the European Society of Cardiology (ESC) (Lindenfeld et al., 2010; McMurray et al., 2012). Of note, these guidelines suggest no clinical benefit in routine FR in all patients with mild to moderate symptoms, yet FRs are still prescribed as observed in several studies with 37–89% of patients reporting a prescribed FR (Linhares, Aliti, Castro, & Rabelo, 2010; Nieuwenhuis, Jaarsma, van Veldhuisen, Postmus, & van der Wal, 2012; Nieuwenhuis, van der Wal, & Jaarsma, 2011).

2.2. Intrathoracic impedance measurement

Invasive hemodynamic monitoring of persons in acute HF has long been standard procedure in intensive care units and cardiac catheterization laboratories, but routine invasive hemodynamic monitoring in persons with chronic HF is limited due to obvious issues of risk of infection and complications from the presence of an invasive line, patient discomfort, and inability to assess filling pressures during usual daily activities (Adamson, 2005). Over the past 10 years, remarkable strides have been made in the development and testing of implantable hemodynamic monitoring systems to provide meaningful information on volume status. Newer biventricular pacemakers and internal cardioverter defibrillators (ICDs) have fluid status monitoring capacity with intrathoracic impedance measurement (IIM). With this technology, small electrical impulses measured in Ohms, are generated by the device multiple times a day and detected by the lead wire of the pacemaker or ICD. Because electricity is readily conducted through fluid, the impedance (or resistance) to this flow of current is found to be decreased during thoracic fluid accumulation that occurs in acute decompensated HF. Conversely, an increase in intrathoracic impedance indicates a reduction in fluid congestion (Yu, Lau, & Tang, 2001; Yu, Wang, & Chau, 2002).

Decreasing intrathoracic impedance has been demonstrated to directly correlate with worsening HF, predicting hospitalizations (Wang, Yu, & Chau, 2003; Yu, Lau, & Tang, 2002) even prior to patients first noticing symptoms (Wang, Yu, & Chau, 2004). With this early detection of fluid volume overload, prompt interventions can be undertaken to prevent HF exacerbations. Recent clinical trials have demonstrated that early intervention guided by these implantable hemodynamic monitoring system devices including thoracic impedance measurement may be useful in preventing hospitalizations and emergency department visits (Andriulli, Coles, & Hettrick, 2008; Maines, Catanzariti, Cemin, Vaccarini, & Vergara, 2007; Singla, Kumar, & Bardia, 2012; Vollmann et al., 2007).

Because these devices provide an excellent objective and timely measure of fluid volume status in the outpatient and home setting, adherence to prescribed FRs, sodium restricted diets, and prescribed diuretic medications can be directly assessed using this physiologic measure. Rathman described case studies of HF patients for whom the daily trending of the thoracic impedance was able to be used as a teaching instrument regarding their adherence with medications and dietary restrictions of sodium and fluid (Rathman, 2007). Most recently, thoracic impedance was demonstrated as superior in detecting acute decompensation than daily weight monitoring by the patient (Thomson et al., 2009), and demonstrated significant correlations with B-type natriuretic peptide (BNP) elevations and alterations of diastolic filling as described by Doppler transmittal flow pattern (Wernli, Hampton, Trentham-Dietz, & Newcomb, 2011), yet, correlations between patient reported and physiologically measured adherence with prescribed pharmacologic therapy and lifestyle modifications have not been undertaken. A better understanding of patterns of adherence with prescribed therapies through the direct physiological measures of volume status could assist in the development of future interventions and self-management strategies in this fragile population.

3. Methods

In this pilot study, we used a randomized controlled approach with longitudinal follow up to ascertain if an educational and behavioral intervention (EBI) improved adherence with a prescribed FR in comparison to an attention control (AC) group. A comprehensive set of outcomes were examined for trends in effects and to determine effect size for use in planning a future study including adherence with FR (daily fluid log), physiologic measures of fluid congestion (thoracic impedance/IIM, daily weights, BNP, and the congestion score), and patient reported outcomes of symptom burden (heart failure symptoms and thirst distress) and HRQOL at baseline, 3 and 6 months. All assessments, data collection, and delivery of intervention were by a PhD-prepared RN with over 20 years of cardiovascular nursing experience.