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Single Subject Design: Use of Time Series Analyses in a Small Cohort to Understand Adherence with a Prescribed Fluid Restriction

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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

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allows for the elucidation of clinically relevant findings potentially disguised when only evaluating aggregate outcomes of larger studies.

Keywords

Heart failure; single study design; time series analyses; fluid restriction; Research design; fluid therapy; electric impedance; self-care

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 and 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 and 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 and 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 is possible for each patient. The purpose of this article is 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).

Background

Over 650,000 persons in the United States (US) are diagnosed with HF every year (Mefferd, Nichols et al. 2007, Go, Mozaffarian et al. 2013), creating both a personal and society burden due to high health resource utilization and associated costs (Bonow, Bennett et al. 2005, DeFrances and Podgornik 2006). Multiple non-pharmacological treatments for persons with HF are recommended by the Heart Failure Society of America (HFSA) (Lindenfeld, Albert et al. 2010), American Heart Association (AHA)/ American College of

Cardiology (ACCF) (Yancy, Jessup et al. 2013), and European Society of Cardiology (ESC) (McMurray, Adamopoulos 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 (Rich, Beckham et al. 1995, West, Miller et al. 1997, Lucas, Johnson et al. 2000, Costantini, Huck et al. 2001, Krumholz, Amatruda et al. 2002), improving overall HF self-care (Jaarsma, Halfens et al. 1999), HRQOL (Kutzleb and Reiner 2006), and decreasing mortality (Grancelli, Varini 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 (Thom, Haase et al. 2006, Lloyd-Jones, Adams et al. 2009). Further, HF is recognized as the most common primary discharge diagnosis of hospitalizations in those over age 65 (DeFrances and Podgornik 2006), and the most costly Medicare diagnosis (Bonow, Bennett 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 (Rich, Beckham et al. 1995, Krumholz, Parent et al. 1997, Aghababian 2003, Desai and Stevenson 2012, 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, Abraham et al. 2009). Often, these admissions are related to lack of adherence with medications and recommended self-care measures (Michaelsen, Konig et al. 1988, Vinson, Rich et al. 1990, Rich, Beckham et al. 1995, Krumholz, Parent et al. 1997, Tsuyuki, McKelvie et al. 2001, Aghababian 2003, Jessup, Abraham et al. 2009, Neily, Toto et al. 2009).

Fluid Management and Restriction in HF

Management of volume status is a core principal of HF management (Yancy, Jessup et al. 2013), 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, Jessup et al. 2013). 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, Albert et al. 2010, McMurray, Adamopoulos 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 et al. 2010, Nieuwenhuis, van der Wal et al. 2011, Nieuwenhuis, Jaarsma et al. 2012).

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 et al. 2001, Yu, Wang et al. 2002).

Decreasing intrathoracic impedance has been demonstrated to directly correlate with worsening HF, predicting hospitalizations (Yu, Lau et al. 2002, Wang, Yu et al. 2003) even prior to patients first noticing symptoms (Wang, Yu et al. 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 systems devices including thoracic impedance measurement may be useful in preventing hospitalizations and emergency department visits (Vollmann, Nagele et al. 2007, Andriulli, Coles et al. 2008, Singla, Kumar et al. 2012, Nichols, Trentham-Dietz et al. 2013).

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, Thompson 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 et al. 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.

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.

Setting and Sample

Institutional Review Board approval, including HIPAA waiver for eligibility screening, was granted for the screening, consent, and enrollment of eligible participants from a large Center for Heart Failure Therapy (CHFT) in the Southeast US. NYHA class II to IV outpatients were recruited meeting inclusion criteria of: presence of an IIM device; hospitalization for HF exacerbation within the previous 6 months; ability to read, write, and speak English; prescribed daily diuretics, angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers if ACEI- intolerant, and beta-blockers (or documented contraindication) (Yancy, Jessup et al. 2013); prescribed FR of 1.5 to 2 liters per day; and telephone access. Patients were excluded for residence greater than 100 miles from the enrolling center; physical or mental impairments that would limit ability to complete study procedures; uncontrolled medical conditions such as renal failure (defined as serum creatinine greater than 2.0mg/dl), anemia (defined as a hemoglobin less than 10gm/dl), or documented, uncontrolled hypothyroidism that could cause HF exacerbations.

Single Subject Design

The two core elements of 1) repeated measurement and 2) distinct design phases distinguish single-subject designs from case studies (Portney and Watkins 2009). In a single-subject design, biobehavioral actions and responses are collected serially, if not daily. With these repeated measures, trends, patterns, and variability in the individual subject data can be observed offering an opportunity to revise clinical instructions or use the data to provide feedback to subjects to modify personal behavior (Portney and Watkins 2009). While the main symptom and outcome results of the parent study have been presented elsewhere (Reilly, Higgins et al. 2014), this article will focus on a subset analysis that was undertaken in five subjects whose daily analysis of reported fluid intake, thoracic impedance, and weights provides a unique picture of volume status and self-care management. These five participants were selected to best represent the patients participating in the study based upon the quality of their data and not their adherence with the intervention. Thus this paper attempts to highlight the diversity in various levels of fluid congestion and patient reported outcomes of symptom burden and HRQOL; these subjects best demonstrate the relationships between their data and outcomes. As with all single-subject designs, these five subjects served as their own controls providing nearly 180 days each of robust data with which

clinical decisions for single subjects could be made. Each of these subjects was in the EBI group of the parent study and thus all received an intervention to foster their adherence with their fluid restriction prescription.

Intervention

Upon consent, subjects were randomized to either the attention control (AC) group or the EBI group using computer generated randomization schema. Every effort was made to schedule the first home visit for both groups within 2 weeks of enrollment. Key to this first visit was an hour education session that focused on information about HF, prescribed medications, need for daily weights, signs and symptoms of HF exacerbation that require medical attention, and 2000mg per day sodium restriction. Both groups were provided the education via a calendar/ educational booklet that included the Daily Weight and Fluid Log requiring daily journaling of weight, perception of health, and in the FR groups, a measure of daily fluid intake. Pre and post test administration was undertaken to evaluate the knowledge level of the participants at baseline, intervention learning, and assure comparability with regard to knowledge of disease state and treatments.

While both AC and EBI subjects received the brief education as described, the intervention subjects also received the focused EBI with strategies to promote adherence to their prescribed FR. This included fluid measurement and management approaches, direction on how to keep track of daily fluid intake, provision with a 2 liter pitcher and measuring cups and spoons, and brainstorming thirst management strategies with the subject. To prevent diffusion of the intervention since the same researcher made home visits to both AC and EBI subjects, the education session and the additional EBI session were taught from curriculum and scripts developed by the investigator but validated by experts in HF and behavior change principles. Fidelity to the intervention was documented through checklists that key elements of the EBI were provided to the EBI group only.

Variables and Measures

Most of the measures utilized in this study are used widely, having demonstrated accuracy or sound psychometric properties in HF such as the *EuroQOL (EQ-5D)*. These variables and measures are defined, grouped according to the domains assessed below.

Self-Care Behaviors—Subject monitoring of daily weights for increased fluid retention is a mainstay of education for persons with HF (Hunt 2005), and therefore all EBI patients were instructed to keep a *Daily Weight and Fluid Log*. Patients are often instructed to call their physician or take extra diuretic for weight gain of 2 to 3 pounds in one day. A log of weights has also been suggested to help patients view the trend in weight against symptoms. Recording fluid intake has been suggested in the renal population as helpful in maintaining adherence to a FR (O'Neill and Glaskow 1991, Welch and Davis 2000, Pryer 2005), though has previously not been used in persons with heart failure.

Physiologic Measures of Fluid Congestion—Fluid congestion was assessed with four different measures allowing for posthoc evaluation of timing and correlation of changes. The two daily measures were patient reported *daily weights* and daily measures of

IIM data obtained from one of three Medtronic pacemaker/ defibrillators (InSync Sentry™, Concerto™, or Virtuoso™) inserted prior to this study. Each of these devices has the OptiVol Fluid Status Monitoring feature providing thoracic impedance data. These devices store clinical information for up to 14 months and data can be either downloaded at clinical visits, or uploaded remotely by the patient via telephone transmission. In this study, the uploaded patient data was obtained from the Medtronic central repository for the 6 month study period.

Measured at baseline and three months were **Brain Natriuretic Peptide (BNP)** and the **Congestion Score (CS)**. The commonly measured BNP is a 32-amino acid peptide secreted predominantly from the ventricles in response to ventricular dilation (Greenberg, Daniels et al. 1996), and recognized as a 'measure' of congestion (Lucas, Johnson et al. 2000). The CS is a clinician assessment tool calculated by assigning a value of 1 for the presence of typical HF signs of orthopnea, jugular venous distention, peripheral edema, increase in weight, and/or the need to adjust diuretic doses. Scores were summed for a total possible score of 0-5 quantifying the degree of fluid retention (Lucas, Johnson et al. 2000, Shah, Claise et al. 2005). The CS has previously been associated with two-year survival (Lucas, Johnson et al. 2000), and guided the clinical assessment of HF patients (Shah and O'Connor C 2000, Binanay, Califf et al. 2005).

Patient Reported Outcomes—Patient reported outcomes were measured at baseline, 3 and 6 months with the **Heart Failure Symptom Survey (HFSS)**, **Thirst Distress Scale (TDS)**, and the **EQ-5D**. The **HFSS** consists of 12 physical symptoms (e.g.: shortness of breath at rest, irregular heart beat) and two psychological symptoms (i.e.: depression and cognitive impairment) (Hertzog, Pozehl et al. 2010), for which participants rate the symptom severity, frequency, interference with physical activity and enjoyment of life during the past seven days on a scale of 0 (no symptom/ interference) to 10 (very frequent or severe/ great deal of interference). Items are summed along the four subscales with higher results indicating worse symptom experience and interference. Previous psychometric evaluation revealed excellent content validity index coefficients ranging from 0.90 to 1.00 (Hertzog, Pozehl et al. 2010), and good internal consistency across the four symptom dimensions with Cronbach alpha coefficients of .80, .87, .88 and .88 when tested with 138 HF subjects (Pozehl, Duncan et al. 2007). Originally developed to assess the thirst in patients requiring hemodialysis, thirst was assessed using the 6-item **TDS** for which participants rated items using a 5-point scale from 1 (strongly disagree) to 5 (strongly agree) for a composite score ranging from 5-30 (Welch 2002). In the renal patients, inter-item correlations of the six items was found to range between .43 and .68, with Cronbach's alpha of .78 (Welch 2002), a goodness-of-fit index of .94, and a relative chi-square of 4.52 representing good data-model fit (Aroian and Norris 2001).

As a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning, measures of HRQOL focus on the impact health status has on quality of life. The **EQ-5D** is a self-administered, validated, multi-attribute, preference-based measure of health status (Calvert, Freemantle et al. 2005). The EQ-5D has been used in a wide range of health conditions and treatments including HF (Calvert, Freemantle et al. 2005, Almenar-Pertejo, Almenar et al. 2006), providing a simple descriptive profile and a

single index value for health status. Patients were asked to rate the severity of their illness on five health dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each dimension comprises three levels (no problems, some/moderate problems/extreme problems), providing a unique EQ-5D health state index by combining 1 level from each of the 5 dimensions. In addition, a visual acuity scale was provided generating a self-rating of HRQOL

Analysis

All data analyses were completed with SPSS statistical software version 21 and the time series plots produced using customized code developed in MATLAB R2011a. NYHA functional class routinely measured by study criteria and confirmed by the attending physician provider was considered as a covariate.

Time series analyses models were constructed for a period of 0-180 days to determine correlations between the patient reported fluid intake, thoracic impedance, and daily weights in the five subjects selected for their unique graphs. Individual subjects served as their own controls. Overlaid on these individual profiles is a line showing the smoothed trend for each set of measures over a period of 28 days. The three y-axes are standardized for fluid and impedance, but scaled for daily weight given the significant differences in patient size between subjects. For each individual, bivariate cross-correlations were then calculated for observed relationships between patient reported fluid intake, thoracic impedance, and daily weights, two variables at a time, and a determination made for lead and lag times between variables. Because fluid effects of intake, impedance, and weight changes within the body are individual and do not happen simultaneously, the best possible fit per correlation was selected based upon these lead and lag times. A negative lag indicates that measure 2 was shifted before measure 1 by the number of days given; a positive lag for measure 2 is the number of days after measure 1. For every patient, events of fluid intake alterations, changes in impedance, and weight variability do not happen simultaneously, but usually sequentially and vary in the timing.

Results

Three tables of data have been constructed to support understanding of the time series analysis plots presented (Figures 1-5). The amount of patient reported fluid intake, thoracic impedance, and daily weights are presented in Table 1, correlations by subject between physiologic and patient reported outcomes in Table 2, and a final table of individual results by subjects and time for the physiologic measures, subject reported symptom burden, and HRQOL in Table 3. As previously described, these subjects were assigned to the EBI group and thus were asked to measure and record their daily fluid intake as a strategy to improve adherence.

By examining each of the time series analyses plots that represent 180 days in a subject's lives, we can identify relationships between patient reported fluid intake, thoracic impedance, and daily weights. In Figure 1, by closely examining days 100 to 120, we can see that Patient A's reported fluid intake increased over the previous 100 days from a mean

of 1850ml to a peak of nearly 2100ml that corresponded to a decrease in thoracic impedance (marker of increased fluid congestion), and a later increase in weight. As presented in Table 1, the relationship between reported fluid intake days 100 to 120 trended toward significance and the correlation between thoracic impedance and weight with a lag of 10 days was significant at $p < .05$. Clinically, this represented a nearly 10 pound weight gain. Because the timing of this significant change corresponded with a clinical assessment and completion of patient reported outcome measures (HFSS, Thirst Distress and EQ-5D), we were able to align changes in these outcomes with the time series analysis including a worsening total congestion score from 3 at baseline to 5 at the 3 month measurement, a slight increase in the mean frequency of assessed symptoms ($M = .65$ to $.67$), and accompanying decrease in the subject's reported HRQOL from the visual acuity scale rating ($M = .85$ to $.78$).

In Figure 2, increases in fluid intake appear to coincide with decreases in impedance indicating greater fluid congestion. Of note, less variability in the reported amount of fluid consumed can be observed with the subject appearing to vacillate mostly between a very low 900 and 1400ml/ day. During the first 20 days of the study, Subject B reported consistently drinking 900ml, while during days 20-40, the subject increased to 1400-1800ml/ day. This corresponded to a decrease in thoracic impedance and a subsequent increase in weight of 5 pounds that was statistically significant. Similar patterns between fluid intake and impedance changes for days 70-100 and 120-150 can be observed however the relationships with weight increases were not consistent.

Subject C displayed an interesting graph in Figure 3. Unfortunately, this subject did not appear to understand all instructions and failed to record weight and fluid intake as prescribed until a reminder call at day 40. At another reminder call on day 60 in that the 3 month visit was scheduled with the subject, there is a significant drop in fluid intake that corresponds to an increase in impedance (indicating less fluid congestion) and a drop in weight. Later, between days 120-140, the subject reported a slight increase in fluid intake that corresponded with impedance decline and weight gain, both of which were significantly related (Table 2).

As pictured in Figure 4, subject D rarely recorded deviating from 1950ml of fluid intake a day, and was very self-aware of their diet, weight, and symptoms. The time series depicts very tight impedance varying only between 72 and 82 Ohms and weight fluctuating between 132 and 138 pounds over the course of 180 days. This resulted in only correlations between impedance and weight which were significant in the expected direction of decreases in impedance reflected in weight gain. Clinically, this subject reported improvements from the baseline to 3 and 6 month assessments in HF symptom severity and frequency, and her congestion score was concordant and decreased from 3 at baseline to just 1 at 3 months.

Finally, in Subject E (Figure 5), we can observe that impedance is continually low, while their fluid intake appears relatively stable at 1999 ml/ day (SD 243 ml), but whose weight climbs over the course of the 180 days from 136 to 144 pounds. There were no associated increases in subject reported frequency and severity of HF symptoms and no clinical signs or symptoms of worsening HF as assessed by the CS and BNP. This gradual weight increase was attributed to actual weight gain and not fluid retention over time. In this patient, the

weight gain brought the patient from a low BMI to a normal indicating improved health perhaps related to his HF stability during these three months.

While every plot does not reveal such dynamic relationships, most indicate a negative relationship between weight and impedance, positive correlation between weight and daily fluid intake, and a negative association between fluid intake and thoracic impedance.

Discussion

The time series analysis presented clearly demonstrates a relationship between patient reported fluid intake, thoracic impedance, and daily weights. As demonstrated, fluid intake and impedance are sequentially related such that increased fluid intake is closely followed by increases in fluid congestion measured by thoracic impedance. This extends previous research where acute decreases in thoracic impedance have been shown to be sensitive to worsening HF (Vollmann, Nagele et al. 2007, Andriulli, Coles et al. 2008), and predict HF hospitalization (Singla, Kumar et al. 2012, Nichols, Trentham-Dietz et al. 2013). These time series analyses suggest that a precursor to the increases in thoracic impedance may be associated with increased fluid intake. Of note, we found weight gain to be a slower indicator of worsening fluid congestion occurring at several times 9-10-days following the initiation of fluid congestion.

While no cause and effect relationship can be determined from this limited analysis, some possible explanations exist that could hold implications for directing nursing interventions and subject instruction. Foremost, the parent-study found that overall, subjects struggled with adherence with their prescribed fluid restriction despite strategies to foster education and provide behavioral strategies. Perhaps one explanation for this was that subjects did not observe for themselves immediate responses to adhering with the fluid restriction. The subjects were not privy to the thoracic impedance results and only had their self-measured amount of fluid intake and daily weights with which to gauge success and failure. As noted from the time series analyses presented here, this relationship lagged by days and may not have been apparent to even the most astute subject.

Secondly, thirst is a profound symptom that subjects struggle to control and may influence the ability of patients to adhere with a prescribed FR. Adherence with a prescribed FR has been described as causing profound thirst, "which is one of the most agonizing and troublesome symptoms experienced by patients with moderate to severe HF" (Holst, Stromberg et al. 2003). As a subjective symptom or sensation of dryness in the mouth and throat with an associated desire for fluids (Greenleaf 1992, Porth and Erickson 1992), thirst has a physiological etiology in the HF patient. Due to low cardiac output, the renin-angiotensin-aldosterone axis is activated triggering the thirst center in the hypothalamus (Hansen 1998), and the sensation of dry mouth due to lack of saliva, or xerostomia, is induced by diuretics (Braunwald 1992). In our study, we believe continued suffering with this symptom without observable improvements in health may have limited adherence with the fluid restriction. While subjects can readily observe the effects of taking an extra diuretic with increased urinary output and decreased weight, at this time, they are unable to observe

the variability in their impedance values and its relationship to fluid intake and weight we were able to observe retrospectively through these time series analyses.

A possible implication of this secondary analysis could be the future development of a subject notification system whereby a handheld or telephonic device reads the thoracic impedance data daily and provides the patient with immediate data regarding their level of fluid congestion. With daily measurement, a patient could titrate their fluid and sodium intake, and diuretic dosage based upon the thoracic impedance readings and provider guidelines. Previous research has suggested that HF hospitalizations were predicted by a drop in thoracic impedance by an average of $12.3 \pm 5.3\%$ ($p < 0.001$) over an average of 18.3 ± 10.1 days prior to the hospitalizations (Singla, Kumar et al. 2012). Further, the authors found that impedance reduction began 15.3 ± 10.6 days ($p < 0.001$) before the onset of worsening symptoms. Thus, by initiating self-management prior to the presentation of symptoms, a highly motivated subject could decrease the development of symptoms, decrease health care utilization, and possibly improve HRQOL and mortality. However, this level of self-regulation would require significant self-efficacy and patient education by providers.

Another observation from this time series analysis is that each subject had their own unique targets for fluid intake and the level of thoracic impedance that was clinically significant. Typically, patients are instructed to follow a fluid restriction of 1.5 to 2.5 liters per day. In subject B, we observed greater fluid congestion and lower impedance when the subject ingested greater than their usual 950cc per day, while other subjects were able to drink greater amounts with no adverse results. Similarly, the level for which thoracic impedance is indicative of fluid congestion varies from person to person. Typically, clinically significant congestion is believed to be present at or below the factory preset level of 60 Ohms, but this target is determined by the physician based upon the individual patient trends (Singla, Kumar et al. 2012, Calip, Boudreau et al. 2013). In the five patients presented, impedance levels varied from a low of 60 Ohms to a high of 94 Ohms and none were hospitalized for HF. Yet as each time series analysis presents, their individual ranges varied with subject B ranging from 78-94 Ohms compared with subject E who ranged from 60-67.75 Ohms. These patients would each require 2 different targets for which the thoracic impedance measure is considered significant for fluid congestion and warrants treatment.

Limitations from this and similar single-case studies is the lack of generalizability to large groups of subjects. Further, the presentation of these particular 5 cases assumes selection bias in presenting the most interesting and explainable patient graphs rather than those that were less revealing or did not demonstrate logical relationships. However, as with any research, patients choose to adhere with the intervention while others do not. These particular patients were selected for inclusion in this secondary analysis for this very demonstrable reason.

As fully explained in the parent study findings (Reilly, Higgins et al. 2014), patient adherence with a prescribed FR remained difficult for patients even when provided with in-depth education and behavioral strategies. Those receiving the intervention consumed less fluid, which trended toward significance ($p = .08$). No differences in clinical measures of

congestion were observed but EBI patients trended to have less HF symptom frequency ($p = .13$) and severity ($p = .06$), and significantly increased symptoms of thirst ($p < .01$) across time. While important, these aggregated findings do not allow for the in-depth analysis of patterns and trends established by analyzing daily patient data, in both patients that are adherent and non-adherent.

By analyses of single-cases using time series analysis, we are able to further elucidate that in patients who are adherent with a fluid restriction, less fluid congestion occurred and improved outcomes were observed holding important implications for personalized or tailored interventions. As suggested, the amount of fluid restriction could be individualized based upon patient stability, and immediate fluid congestion measures such as IIM (rather than daily weights) could be used by the patient to better titrate fluid and sodium intake, and possibly diuretic dosage in collaboration with their healthcare provider.

Conclusion

The time series analyses constructed for each of these five subjects adds more depth and understanding than that gleaned through analysis of the parent RCT. By looking at each subject as a single-subject design, both the clinical and statistical significance that fluid intake is directly correlated with thoracic impedance and daily weights (as measures of physiologic fluid congestion) can be appreciated. This relationship was not observed in the parent study as many of the participants did not adhere with their fluid restriction or failed to accurately record their fluid intake. Analysis of the data by subject with 180 days of data allowed for the evaluation of effects of the fluid restriction based upon responses of individual subjects and holds implications for future nursing interventions in select subjects. Thus use of a secondary single-subject analyses design is a worthy addition to the armamentarium of the nurse researcher and findings from this secondary analysis using this technique may hold promise for clinical practice.

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Figure 1.
Subject A Time Series Analysis Plot of fluid intake, thoracic impedance, and weight over 180 days.

Figure 2.
Subject B Time Series Analysis Plot of fluid intake, thoracic impedance, and weight over 180 days.

Figure 3. Subject C Time Series Analysis Plot of fluid intake, thoracic impedance, and weight over 180 days.

Figure 4.
Subject D Time Series Analysis Plot of fluid intake, thoracic impedance, and weight over 180 days.

Figure 5.
Subject E Time Series Analysis Plot of fluid intake, thoracic impedance, and weight over 180 days.

Table 1

Descriptive Statistics of Daily Clinical Measures

	Subject	Valid	Missing	Mean	SD	Minimum	Maximum
Reported fluid intake (mL)	A	114	67	1887.44	266.168	946	2366
	B	160	21	1217.00	272.010	473	1893
	C	135	46	2303.79	341.063	1301	3708
	D	151	30	1995.36	182.332	1500	2500
	E	152	29	1999.34	243.315	1440	2700
Thoracic Impedance	A	181	0	79.7666	2.96104	69.75	87.00
	B	181	0	85.4986	2.76140	78.25	93.50
	C	181	0	79.9820	3.93233	71.50	91.25
	D	181	0	77.6064	2.26693	72.75	83.75
	E	181	0	64.1022	1.54647	60.00	67.75
Daily weight	A	125	56	265.29	5.059	251	275
	B	173	8	173.69	2.002	170	179
	C	135	46	203.64	2.454	197	209
	D	165	16	134.32	.803	132	136
	E	156	25	140.22	2.200	136	144

Table 2

Correlations by Subject and Time Frame

Subject	Time Frame	Measure 1	Measure 2	Correlation $r=$	P values $p=$	Number of days
A	Days 100-120	Fluid	Impedance (–1 day)	0.44	.07	18
A	Days 100-120	Fluid	Weight		NS	
A	Days 100-120	Impedance	Weight (–10 days)	.52	.02	21
B	Days 20-40	Fluid	Impedance (+4 day)	0.47	.03	21
B	Days 20-40	Fluid	Weight (+1 day)	0.61	< .01	21
B	Days 20-40	Impedance	Weight (+9 days)	.42	.07	20
B	Days 70-100	Fluid	Impedance (–4 day)	0.35	.05	31
B	Days 70-100	Fluid	Weight (–1 day)	0.45	.01	30
B	Days 70-100	Impedance	Weight (+3 days)	.34	.07	30
B	Days 120-150	Fluid	Impedance (+4 day)	0.39	.04	29
B	Days 120-150	Fluid	Weight		NS	
B	Days 120-150	Impedance	Weight (+2 days)	.38	.04	31
C	Days 70-90	Fluid	Impedance (0 day)	.40	.08	20
C	Days 70-90	Fluid	Weight (–3 day)	.49	.03	19
C	Days 70-90	Impedance	Weight (–2 days)	.90	< .01	20
C	Days 120-140	Fluid	Impedance (–1 day)	0.62	< .01	21
C	Days 120-140	Fluid	Weight (–3 days)	0.55	.01	21
C	Days 120-140	Impedance	Weight (–2 days)	.87	< .01	21
D	Days 80-130	Fluid	Impedance		NS	
D	Days 80-130	Fluid	Weight		NS	
D	Days 80-130	Impedance	Weight (0 days)	.40	< .01	46
D	Days 130-180	Fluid	Impedance		NS	
D	Days 130-180	Fluid	Weight		NS	
D	Days 130-180	Impedance	Weight (0 days)	.36	.01	49
E	Days 20-40	Fluid	Impedance		NS	
E	Days 20-40	Fluid	Weight (+2 day)	0.40	< .09	19
E	Days 20-40	Impedance	Weight (–1 days)	.47	.03	21

Bivariate cross-correlations presented between Measure 1 and Measure 2 were evaluated for the best fit for each patient during the prescribed period. In many instances, there were noted lead and lag times between variables (indicated as the number of days in parenthesis). A negative lag indicates that measure 2 was shifted before measure 1 by the number of days given; a positive lag for measure 2 is the number of days after measure 1.

Table 3

Individual Patient Reported Outcomes and Clinical Measures by Subject and Time

Subject	Time Frame	Congestion Score	BNP	HFSS Frequency	HFSS Severity	TDS	EQ-5D Index	EQ-5D VAS
A	BL	3	59	87	65	23	.44	.85
A	3m	5	36	52	67	24	.44	.78
A	6m	NA	NA	*	*	*	*	*
B	BL	2	*	39	20	7	.85	.5
B	3m	1	48	16	16	13	.78	.64
B	6m	NA	NA	26	25	16	.78	.6
C	BL	0	34	19	16	9	1	.6
C	3m	0	31	11	3	6	1	.60
C	6m	NA	NA	0	0	13	1	.65
D	BL	3	52	30	35	7	.82	.75
D	3m	1	175	18	15	7	.82	.55
D	6m	NA	NA	13	2	12	.82	.60
E	BL	0	26	16	9	16	1	.80
E	3m	0	31	5	8	15	1	.90
E	6m	NA	NA	8	9	21	1	.80

BNP: B-type natriuretic peptide; HFSS: Heart Failure Symptom Survey; TDS: Thirst Distress Scale

* Data missing; NA not assessed at this time point; BL= baseline; 3m= 3 months; 6m= 6months