

ORIGINAL PAPER

Association of Impedance Cardiography Parameters With Changes in Functional and Quality-of-Life Measures in Patients With Chronic Heart Failure

Assessment and prognosis of chronic heart failure is often difficult due to a lack of objective and easily obtainable parameters that accurately reflect disease status. This study was conducted to determine whether impedance cardiography (ICG) parameters were associated with changes in functional and quality-of-life measures in chronic heart failure patients. Retrospective chart review identified 64 patients (73% male, aged 73±13 years) with paired ICG measurements followed for 180±113 days. Outcome measures were changes in New York Heart Association class, 6-minute walk distance, patient visual analog scale score, and Minnesota Living with Heart Failure Questionnaire score. Measures of ICG, heart rate and blood pressure, left ventricular ejection fraction, and B-type natriuretic peptide levels were assessed for their association with outcome measures. From baseline to final evaluation, there were significant changes ($p<0.05$) in New York Heart Association class (from 3.2±0.5 to 3.0±0.6), 6-minute walk distance (from 668±380 m to 874±390 m), patient visual analog scale score (from 49±10 to 64±20), Minnesota Living with Heart Failure Questionnaire score (from 54±22 to 39±22), and ICG parameters of stroke index (from 38±9 to 41±8), left ventricular ejection time (from 273±42 to 291±33), and systolic time ratio (from 0.56±0.2 to 0.52±0.2). Changes in multivariate ICG parameters were significantly correlated to changes in New York Heart Association class (R, 0.80), 6-minute walk distance (R, 0.94), patient visual analog scale score (R, 0.69), and Minnesota Living with Heart Failure Questionnaire score (R, 0.67). ICG provides objective data that reflects changes in chronic heart failure disease status and treatment effectiveness. (CHF. 2004;10(2 suppl 2):22–27) ©2004 CHF, Inc.

Heat failure (HF) is a multifaceted disorder with progression characterized hemodynamically by worsening cardiac output and elevated filling pressures, and an associated reduction in functional capacity and increase in symptoms.¹ More than \$50 billion is spent each year in the United States on HF care, the most significant component of which is related to hospital admissions for acutely decompensated HF.² Physician assessment, prognosis, and treatment of HF are often hampered by the subjective nature of the physical examination.^{3–5} Chronic HF functional and quality-of-life status can be monitored through the use of well validated measures,^{6–9} but these are not employed routinely outside the HF specialist setting.

Studies have demonstrated the association of invasive hemodynamics with

patient outcomes,^{10–20} but the results have been debated.^{21,22} Utilization of invasive hemodynamics to tailor therapy has been shown to improve outcomes,^{23–25} but serial invasive hemodynamic monitoring is neither practical nor cost-effective for routine monitoring of HF in outpatients.

Noninvasive impedance cardiography (ICG) provides hemodynamic parameters that may be useful in objective assessment and monitoring of chronic HF. ICG cardiac output has been validated compared with invasive hemodynamic methods in both chronic²⁶ and acutely decompensated²⁷ HF. The purpose of this study was to evaluate whether changes in ICG parameters correlated with changes in functional outcome measures in chronic HF patients treated in an outpatient HF clinic.

Methods

Subjects. Patients in this study were enrolled from a comprehensive outpatient HF program that included education, pharmacologic optimization, implantable device therapy, and behavior modification. Patients were treated by a single HF specialist physician with the goal of improving and extending life while decreasing need for hospitalization. Patient visits were scheduled as medically necessary. All patients with at least two visits at least 3 months apart and with paired ICG measurements were eligible for inclusion. Variables other than ICG were not always collected on visits when ICG measurements were performed, but the lack of availability of other variables did not exclude any patient from the study.

Kris Vijayaraghavan, MD; Sue Crum, RN; Sangita Cherukuri, BS; Leslie Barnett-Avery, PA-C
From the Arizona Heart Hospital, Phoenix, AZ

Address for correspondence: Kris Vijayaraghavan, MD, Arizona Heart Hospital, 1930 East Thomas Road, Phoenix, AZ 85016
E-mail: kvijay@azheart.com

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|--|---------|
| Age (years) | 73.1±13 |
| Male gender (n [%]) | 47 (73) |
| Ischemic heart disease (n [%]) | 48 (76) |
| Mean NYHA class | 3.2±0.5 |
| LVEF (%) | 25±10 |
| Creatinine (mg/dL) | 1.6±1.1 |
| NYHA=New York Heart Association class; LVEF=left ventricular ejection fraction | |

| PHARMACOLOGIC AGENT | BASELINE | | FINAL | |
|--|----------|----|-------|----|
| | N | % | N | % |
| ACE inhibitor | 32 | 50 | 31 | 48 |
| ARB | 13 | 20 | 11 | 17 |
| Digitalis | 35 | 55 | 59 | 92 |
| β Blocker | 46 | 72 | 57 | 89 |
| Diuretic | 52 | 81 | 59 | 92 |
| ACE=angiotensin converting enzyme; ARB=angiotensin II receptor blocker | | | | |

Data Collection. All variables were obtained on physician order and were available to the treating physician. Functional measures included New York Heart Association (NYHA) classification and 6-minute walk distance (6MW) in meters. Additional patient-assessed qualitative measures included a quality-of-life assessment using a visual analog scale (VAS) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. Vital signs included heart rate (HR), systolic blood pressure, and diastolic blood pressure. Diagnostic testing of left ventricular ejection fraction (LVEF) was performed with transthoracic echocardiography. B-type natriuretic peptide (BNP) levels (BNP Triage, Biosite, San Diego, CA) and ICG noninvasive hemodynamic variables (BioZ ICG Monitor, CardioDynamics, San Diego, CA) were obtained. To obtain ICG parameters, patients were in a supine position and sensors were placed on both sides of the neck and lower thorax. After approximately 3 minutes, the measurements were recorded on the hemodynamic status report. All measures were repeated as necessary during subsequent visits to the clinic.

Database Creation and Statistical Analysis. A retrospective chart review was conducted for all enrolled patients.

All available variables from the patient records were recorded in a database (MS Excel, Microsoft Corp, Redmond, WA) and were analyzed with statistical analysis software (SAS, SAS Institute, Cary, NC). Measured variables were expressed as mean ± standard deviation. Individual variable differences from baseline to final were determined using the paired Student *t* test with significance at $p < 0.05$. To compare changes in variables to each other, predictive measures were grouped in four categories: vital signs, LVEF, BNP, and ICG. Linear regression models were created to examine the association of the changes in predictive measures from baseline to final to changes in functional (NYHA, 6MW) or qualitative (VAS, MLHFQ) outcome measures. Each outcome measure was modeled with its baseline value as a covariate to evaluate the change in the predictive measure while adjusting for the initial value of the outcome measure. Univariate and multivariate models were created with quadratic fits to adjust for nonlinear relationships. The baseline for each end point was then fit and quadratic terms for the variable(s) in each category grouping were added. The R^2 and adjusted R^2 for each model were calculated as indicators of the adequacy of the models. The *p* values were calculated using the Fisher exact test, with $p < 0.05$ considered statistically significant.

Results

Patient Characteristics. Sixty-four patients (73% male, aged 73.1±13 years) were enrolled in the study, with a mean observational time of 180±113 days. Baseline patient characteristics are summarized in Table I. NYHA class II accounted for five patients (8%), with 47 patients (73%) in class III, and 12 patients (19%) in class IV.

Treatment. Table II displays the changes in pharmacologic treatment. Compared with baseline and at final measurement, there were significantly more patients taking β blockers (89% vs. 72%), digitalis (92% vs. 55%), and diuretics (92% vs. 81%). In addition, during the study period, 15 patients (23%) received biventricular pacemakers, 12 (19%) received automatic implantable cardioverter-defibrillators, and two (3%) received dual chamber pacemakers.

Hospitalizations and Deaths. Thirty-one patients (48%) were hospitalized during the study period, with 10 (16%) primarily for the exacerbation of HF. Eight patients (13%) died during the study, with five deaths specifically attributed to HF.

Frequency of Comparison Variables. In the 64 enrolled patients with paired ICG measurements, NYHA class data was available for 56 (88%), 6MW data for 39 (61%), VAS score data for 30 (47%), and MLHFQ score data for 44 (69%). Paired measurements of vital signs, LVEF, and BNP were available with NYHA data in 56, 35, and 36 patients, 6MW with 39, 24, and 28 patients, VAS with 30, 19, and 23 patients, and MLHFQ data in 44, 24, and 30 patients, respectively.

Baseline to Final Variable Changes. Significant group changes occurred in functional measures of NYHA class (from 3.2±0.5 to 3.0±0.6; $p < 0.01$) and 6MW (from 667.7±380 m to 874.2±390 m; $p < 0.001$) and qualitative measures of VAS (from 49±10 to 64±20; $p < 0.01$) and MLHFQ score (54.4±22 to 39.3±22; $p < 0.0001$). ICG

Table III. Predictor Measure Association With Outcome Measures

| OUTCOME MEASURE | PREDICTOR MEASURE | R | R ² | N | P Value |
|-----------------|-------------------|------|----------------|----|---------|
| NYHA | Vitals | 0.68 | 0.46 | 56 | <0.001 |
| | LVEF | 0.59 | 0.35 | 35 | 0.0002 |
| | BNP | 0.61 | 0.37 | 36 | 0.0003 |
| | ICG | 0.80 | 0.64 | 55 | 0.0001 |
| 6MW | Vitals | 0.79 | 0.63 | 39 | 0.0795 |
| | LVEF | 0.73 | 0.55 | 24 | 0.4429 |
| | BNP | 0.82 | 0.69 | 28 | 0.8425 |
| | ICG | 0.94 | 0.89 | 39 | 0.0016 |
| VAS | Vitals | 0.42 | 0.17 | 30 | <0.001 |
| | LVEF | 0.22 | 0.05 | 19 | 0.0045 |
| | BNP | 0.33 | 0.11 | 23 | <0.001 |
| | ICG | 0.69 | 0.48 | 30 | <0.001 |
| MLHFQ | Vitals | 0.46 | 0.21 | 44 | 0.0333 |
| | LVEF | 0.47 | 0.22 | 24 | 0.0688 |
| | BNP | 0.40 | 0.16 | 30 | 0.0401 |
| | ICG | 0.67 | 0.45 | 44 | 0.0090 |

NYHA=New York Heart Association class; 6MW=6-minute walk test; VAS=visual analog scale score; MLHFQ=Minnesota Living with Heart Failure Questionnaire; Vitals=heart rate and blood pressure; LVEF=left ventricular ejection fraction; BNP=B-type natriuretic peptide; ICG=impedance cardiography

parameters showing significant change between paired measurements included stroke index (from 37.6 ± 9 mL/m² to 40.9 ± 8 mL/m²; $p < 0.01$), stroke volume (from 71.2 ± 19 mL to 76.8 ± 17 mL; $p < 0.01$), left ventricular ejection time (from 273 ± 42 ms to 291 ± 33 ms; $p < 0.05$), and systolic time ratio (from 0.56 ± 0.2 to 0.52 ± 0.2 ; $p < 0.05$). HR also changed significantly (from 72.7 ± 13 to 67.4 ± 9 bpm; $p < 0.001$). No significant changes occurred with BNP (from 568 ± 338 pg/mL to 575.8 ± 375 pg/mL; $p = 0.47$) or LVEF (from $25.5 \pm 12\%$ to $29.5 \pm 13\%$; $p = 0.11$), although there were fewer baseline to end point measurements of LVEF ($n = 37$) and BNP ($n = 42$) than with ICG. ICG parameters of thoracic fluid content (from 33.9 ± 7 /kOhm to 32.4 ± 7 /kOhm; $p = 0.13$), acceleration index (from $82.7 \pm 34/100/s^2$ to $88.6 \pm 37/100/s^2$; $p = 0.14$), and systemic vascular resistance index (from 2380 ± 647 to 2267 ± 684 dyne \times s \times cm⁻⁵ \times m²; $p = 0.18$) trended toward improvement, but changes were not statistically significant.

Regression Analysis. Table III displays the full results of the univariate and multivariate regression analysis of pre-

dictor measures of vital signs, LVEF, BNP, and ICG to outcome measures of NYHA class (0.68, 0.59, 0.61, 0.80), 6MW (0.79, 0.73, 0.82, 0.94), VAS score (0.42, 0.22, 0.33, 0.69), and MLHFQ score (0.46, 0.47, 0.40, 0.67), respectively. Table IV displays the univariate ICG parameter association with outcome measures. The strongest univariate ICG parameter correlation with NYHA class was preejection period ($R = 0.71$), with 6MW were acceleration index and cardiac index ($R = 0.76$), with VAS was systemic vascular resistance index ($R = 0.50$), and with MLHFQ was cardiac index ($R = 0.50$).

Discussion

Disease prognosis has always been, and will remain, of fundamental importance to physicians.²⁸ In patients with HF, a more easily obtainable, objective evaluation of chronic HF status and prognosis would be of great value because it could increase awareness of pending decompensation and provide a feedback mechanism for short-term pharmacologic treatment decisions. This could allow more aggressive treatment strategies to prevent clinical decompensation.^{29,30}

In clinical studies of HF, functional and quality-of-life measures such as NYHA class, 6MW, VAS score, and MLHFQ score have been used and well validated. However, these measures of clinical status and outcome are not consistently used in the management of HF in the vast majority of patients. Measurement of vital signs such as HR, systolic blood pressure, and diastolic blood pressure, and ventricular function with LVEF are performed more routinely in chronic HF patients, although the value of serial LVEF measurement has been debated.^{31,32}

In previous studies, ICG hemodynamic parameters have shown diagnostic value in determination of cardiac vs. noncardiac causes of emergent dyspnea,³³ profiling of emergent HF vs. non-HF,³⁴ and determination of systolic dysfunction vs. preserved systolic function.^{35,36} Prognostic value has been shown in advanced HF in profiling survivors vs. nonsurvivors³⁷ and in association with need for hospitalization.³⁸ ICG has demonstrated value in therapeutic management with pacemaker optimization,³⁹ β blocker titration,⁴⁰ and in documenting hemodynamic stability and improvement

Table IV. Univariate Impedance Cardiography Parameter Correlations With Outcome Measures (*R* values)

| PARAMETER | NYHA (N=56) | 6MW (N=39) | VAS (N=30) | MLHFQ (N=44) |
|-----------|----------------|---------------|---------------|-----------------|
| SI | 0.65 | 0.74 | 0.37 | 0.49 |
| CI | 0.66 | 0.76 | 0.40 | 0.50 |
| SVRI | 0.61 | 0.70 | 0.50 | 0.39 |
| PEP | 0.71 | 0.68 | 0.19 | 0.41 |
| LVET | 0.66 | 0.71 | 0.22 | 0.45 |
| STR | 0.70 | 0.68 | 0.25 | 0.48 |
| ACI | 0.61 | 0.76 | 0.47 | 0.34 |
| TFC | 0.61 | 0.71 | 0.29 | 0.38 |

NYHA=New York Heart Association class; 6MW=6-minute walk test; VAS=visual analog scale; MLHFQ=Minnesota Living with Heart Failure Questionnaire; SI=stroke index, CI=cardiac index; SVRI=systemic vascular resistance index; PEP=preejection period; LVET=left ventricular ejection time; STR=systolic time ratio; ACI=acceleration index; TFC=thoracic fluid content

with intravenous nesiritide administration.^{41,42} This evidence, along with familiarity of invasive hemodynamic parameters and positive anecdotal experiences with ICG, has prompted some comprehensive HF management programs to incorporate ICG measurements into their care pathways for both chronic and acute HF.⁴³

In our study, significant changes in pharmacologic and device therapy occurred from baseline to final measurement. These therapies were instituted because of their proven ability to improve outcomes, and in this population also resulted in the improvement in functional and qualitative measures. However, clinicians treating HF understand that patient response differs with each intervention—pharmacologic, device, or otherwise—which has created the need for more objective measures with which to evaluate therapeutic options.

The lack of a univariate change from baseline to final should not necessarily be taken as a lack of value of a measured variable. Some patients improved and others worsened during the study period. The comparison of changes in variables, therefore, provides a more useful framework for understanding their association to chronic HF status. Previous reports have demonstrated a link between NYHA and 6MW and invasive hemodynamics.⁴⁴ In this study, we demonstrated significant ICG parameter

changes from baseline to final, and univariate association with changes in functional measures (NYHA and 6MW) and quality-of-life measures (VAS score and MLHFQ score). Multivariate ICG models showed an even stronger correlation with these same measures, and were higher than multivariate vital signs and univariate LVEF and BNP.

It is unclear why different univariate ICG parameters showed the highest correlation in each outcome measure category. It may be because the parameters are measuring distinct HF characteristics and were related differently to each unique functional outcome measure. A change in one ICG parameter was not necessarily associated with a change in another, but because the multivariate association was significantly greater than the univariate association, we believe the collection of ICG parameters provides a more complete picture of HF status and should be evaluated as such.

Recently, measurements of BNP and N-terminal B-type natriuretic peptide (N-BNP) levels have emerged as an aid in the diagnosis of acute HF in the emergency department.^{45,46} Use of BNP in chronic HF is also expanding, but some have questioned the role of BNP or N-BNP levels in the medical decision-making process in such cases.⁴⁷ The primary purpose of this study was not to evaluate BNP, and BNP levels were collected in signifi-

cantly fewer study subjects than with ICG. In this study population, BNP correlation was highest with changes in 6MW, although not statistically significant. Prior studies have demonstrated a BNP association with NYHA class.^{48,49} We demonstrated that BNP changes were significantly correlated with changes in NYHA class, similar to changes in vital signs and LVEF but lower than univariate and multivariate ICG. The variation of BNP levels in patients already diagnosed with chronic HF⁵⁰ may be due in part to evaluating fewer study subjects or in the unclear determination of what constitutes a significant change in BNP, or in N-BNP level.⁵¹ We believe BNP and N-BNP do provide value in the treatment of chronic HF and acknowledge a need for refinement in sensitivity and specificity of these markers in diagnosis and prognosis of chronic HF. There is a need for development of specific interventions related to the change in levels of these neurohormonal markers.

While the use of BNP to guide medical decision making in HF is still evolving, the use of invasive monitoring of hemodynamics to aid in the reduction of filling pressures and afterload, with a resultant improvement in stroke volume and cardiac output, is more established.⁵² ICG provides non-invasive hemodynamic parameters, some of which may change as plasma neurohormone levels change.⁵³ Serial

invasive measurements of hemodynamic parameters have predicted cardiac death or transplantation,⁵⁴ and it has been suggested that serial noninvasive measurements of hemodynamics offer a promising opportunity to monitor changes in chronic HF patients.^{55,56} Previous studies have demonstrated that HF specialists are more aggressive in treatment of chronic HF than cardiologists,⁵⁷ and cardiologists more so than generalists.⁵⁸ The low cost and time to acquire ICG measurements make the technology ideal for use in a community-based cardiologist's or generalist's office, in addition to the HF specialist setting. With greater access to objective measures of chronic HF status, perhaps nonspecialists could become more aggressive in their treatment and achieve better outcomes.

This study is primarily limited by its retrospective design and small number of subjects, although statistical significance was reached in a number of comparisons. In addition, the varying sample size between ICG, vital signs, LVEF, and BNP makes it difficult to conclude that one measurement is definitively superior to the others. The multivariate ICG model utilized more parameters than other models, allowing a greater opportunity for association. The treating physician's knowledge of all variables when making treatment decisions may have created bias toward improving some variables over others.

This study compared ICG to commonly used outcome measures in HF research. Larger prospective trials such as the Prospective Evaluation

of Decompensation by Impedance Cardiography Test⁵⁹ will help determine which ICG parameters are associated with death or hospitalization, and will therefore further define ICG's prognostic role in patients with chronic HF.

In our HF population, improvements in univariate and multivariate ICG parameters significantly correlated with changes in functional and QOL measures. ICG provides objective data that may reflect changes in disease status and treatment effectiveness, which may in turn lead to better treatment plans and outcomes.

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