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Project Title: Identification of whole body impedance cardiography-derived hemodynamic parameters associated with outcomes in heart failure patients with reduced ejection fraction

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Summary (250 words max single spaced):
Heart failure (HF) affects over 600,000 Canadians and causes over 45,000 hospitalizations annually. Patients with new-onset HF are referred to an outpatient HF clinic where they are categorized into risk groups based heavily on subjective symptoms and occurrence of poor outcomes, which impacts management and follow-up. Regardless, mortality remains high in chronic HF, with approximately 32% and 64% of patients succumbing to their illness by 1 year and 5 years, respectively. Thus, earlier identification of high-risk HF patients is warranted to prevent poor outcomes, including death.
Non-Invasive Cardiac System (NICaS) is a validated technology, which uses whole body impedance cardiography to measure hemodynamic parameters. In this study, we evaluated whether hemodynamic parameters measured at rest and post-exercise by NICaS could be used to predict outcomes in patients HF with reduced ejection fraction (HFrEF). A cohort of 65 HFrEF patients was recruited and NICaS-derived parameters were taken at rest and after up to 12 minutes of exercise on a mounted ergometer. At 6-month follow-up, subjects who experienced poor outcomes, including HF hospitalizations and death, demonstrated lower resting cardiac power index (CPI) when supine and lower resting stroke index (SI) when seated. In addition, patients with poor outcomes demonstrated increased augmentation of Granov-Goor Index (GGI), a surrogate marker of ejection systolic time. Thus, resting and/or exercise-augmented NICaS-derived hemodynamic measurements demonstrate potential to identify high-risk HF patients in the HF clinic. Early identification of high-risk patients may enable early intervention and optimal follow-up to prevent unplanned hospitalization and mortality.

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Identification of whole body impedance cardiography-derived hemodynamic parameters associated with outcomes in heart failure patients with reduced ejection fraction

Introduction & Background

Heart failure (HF) remains a significant cause of morbidity and mortality, with an estimated 64.3 million affected worldwide[1]. In Canada, over 600,000 patients live with HF, with over 45,000 hospitalizations as a result of new HF diagnoses and acute exacerbations per year[2]. Approximately 13%, 32%, and 64% of patients hospitalized with new onset HF experience mortality at 30-days, 1 year and 5 years, respectively[3]. Even among patients with stable chronic heart failure, mortality remains significantly high[4].

HF is defined as symptoms and/or signs of cardiogenic pulmonary or systemic congestion caused by structural and/or functional cardiac abnormalities corroborated with elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) levels[5]. Symptoms include impaired exercise capacity, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue[5]. Severity of symptoms can be categorized by the New York Heart Association (NYHA) Functional Classification System[6]. Given significantly high mortality and morbidity, patients with a new diagnosis of HF can be referred to an outpatient HF clinic where they are categorized into high, intermediate, and low-risk groups and followed every 1-4 weeks, 1-6 months, and 6-12 months, respectively[7]. After follow-up, low-risk patients can be discharged from HF clinic if they meet at least two of the following: Stable NYHA I or II for 6-12 months, on optimal therapies, stable adherence to optimal HF therapy, reversible causes of HF fully controlled, access to a general practitioner with expertise in HF management, primary care provider with access to urgent specialist reassessment, no hospitalization for >1 year, or left ventricular ejection fraction (LVEF) >35% on more than one recent measurement[7]. Patients who experience NYHA IIIb or IV symptoms, HF hospitalization or frequent symptomatic hypotension remain high-risk and require frequent follow-up[7]. Since risk-stratification affects follow-up and management, an ideal risk-stratification system would provide earlier identification of high-risk HF patients before they experience poor outcomes. Such a system could help reduce morbidity and mortality while being managed in HF clinic and after discharge.

Although HF is characterized by the heart's inability to maintain adequate cardiac output (CO) sufficient for the body's metabolic needs[8], there remain no universal quantifiable hemodynamic criteria that consistently either define HF or predict outcomes at intermediate terms. A lower peak-exercise to resting heart rate (HR) ratio was associated with increased risk of poor outcomes in patients with HF[9]. Chronic HF patients with blunted exercise-augmented CO were shown to have significantly reduced 1-year survival rates[10]. Thus, hemodynamic changes in response to exercise may have potential to predict outcomes in HF. Conventionally, hemodynamic parameters are measured by cardiac catheterization, magnetic resonance (MR) imaging or echocardiography[11,12]. However, each of these methods have inherent limitations. Catheterization is a costly and invasive procedure that requires sedation and is associated with complications, such as bleeding, thrombosis, and embolism[13]. MR is another costly procedure with use limited by claustrophobia, contraindication in patients with metallic implants, and lack of MR-compatible ergometers[14]. Echocardiography is relatively inexpensive, but subject to poor echo window, technical challenges associated with motion artifacts. In addition, echocardiography assumes the left ventricular outflow tract is circular, not oval[14]. Given the limitations of current day clinical practice, hemodynamic measurements among HF patients have remained limited to clinical research only. Thus, incorporating an alternative, non-invasive, cost-effective, and validated technology to monitor hemodynamic parameters in an outpatient setting might improve identification and management of high-risk patients.

Non-Invasive Cardiac System (NICaS®, NI Medical, Petach Tikva, Israel) uses whole body impedance cardiography to analyze hemodynamic parameters[15]. NICaS has been extensively validated against various conventional methods, including thermodilution, to measure CO and is approved by the Food and Drug Administration (FDA, USA) for non-invasive hemodynamic monitoring[16]. Using two dual-polar impedance

electrodes applied in a left wrist-right ankle or wrist-wrist configuration, NICaS sends an electrical current through the body to detect fluctuations in impedance, with electricity transmitting faster through blood compared with other bodily tissues[15]. A proprietary algorithm allows NICaS to convert this signal into an arterial trace and calculate CO, as well as stroke index (SI), stroke volume (SV), cardiac index (CI), cardiac power index (CPI), Granov-Goor index (GGI), total peripheral vascular resistance (TPR), TPR index (TPRI) and total body water (TBW)[15]. NICaS also records electrocardiography (ECG), hence providing HR. To date, NICaS has been used to reliably monitor patients hospitalized for acute decompensated HF (ADHF)[17] and assess the hemodynamic effects of vasodilators and diuretics in ADHF[15]. This technology was recently used to assess post-exercise changes in hemodynamic parameters in patients with myocardial ischemia[18]. Despite offering a portable, safe, and simple approach to monitor patients, it remains unknown whether NICaS parameters taken at rest and post-exercise could be used in the prognostication of HF.

In this study, we aimed to characterize NICaS parameters obtained at rest and post-exercise in patients with stable HF with reduced ejection fraction (HFrEF; LVEF ≤40%). We hypothesized that at least one hemodynamic parameter measured by NICaS would be associated with poor outcomes in HFrEF patients. We identified resting and exercise-augmented NICaS-derived parameters associated with risk of adverse health outcomes in patients with HFrEF.

Materials & Methods

Study design, ethics, and subjects

The Heart Failure HemOdynamic Prognostic Evaluation and OutcomE (HF-HOPE) study is a single center, prospective, pragmatic clinical study conducted at St. Boniface General Hospital (SBGH). This study was approved by the University of Manitoba Research Ethics Board (REB: HS23206). A cohort of 65 patients aged 18 or over with confirmed diagnosis of HFrEF stable over the last 3 months was recruited. Exclusion criteria included recent worsening of clinical state (increased dose of diuretics or unplanned hospital admission due to HF or arrhythmia over the last 3 months), and cancer or terminal illness with an anticipated lifespan of less than 1 year. After written, informed consent was obtained, the study participants were brought to the Albrechsten Research Centre for assessment.

Baseline measurements

Blood pressure was measured in seated position using an automatic blood pressure monitor. We measured height (meter) required for the calculation of body mass index (BMI). Body composition parameters, including weight (kg), BMI, skeletal muscle mass (SMM, kg), and percent body fat (PBF, %) were measured using InBody 750 Body Composition Analyzer (InBody Canada, Ottawa, Canada).

NICaS-derived measurements and exercise

In this study, a wrist-wrist configuration was used, with electrodes applied to the palmar surface of each wrist and centred over the radial artery. Once applied, NICaS calculated hemodynamic parameters within 30 seconds, updating each of these parameters every 20 seconds. Hemodynamic parameters were recorded after at least five consistent values were measured. Obtained parameters included HR (beats/min; bpm), SV, (ml), SI, (ml/m^2), CO, (l/min), CI, (l/min/m^2), CPI, (W/m^2), GGI, TPR (dn*s/cm^5), TPRI (din*s/cm^5*m^2), and TBW (%). NICaS measurements were obtained at rest, both in supine and seated position. Each study participant exercised on a mounted ergometer at 25 watts in a seated position for up to 12 minutes or until limited by symptoms. The distance achieved during exercise was recorded and another set of post-exercise NICaS measurements were taken in seated position. Post-exercise measurements were taken immediately after exercise (1-3 minutes after completion of exercise). Each NICaS measurement comprised the average of at least five replicates after removal of replicates containing motion artifacts. The study participants continued their routine medications.

Data collection and outcomes
Patient demographics, including age, LVEF, NYHA class, etiology of HF, medications, and comorbidities, were collected from the Heart Failure Database at St. Boniface Hospital. At 6 months and 12 months after baseline hemodynamic assessment, clinical outcomes were abstracted by review of electronic patient records. Poor outcomes comprised the composite outcome of HF exacerbation presenting to emergency department (ED), HF hospitalization, new arrhythmia, referral for implantable device, adjustment of existing implantable device parameters, referral for heart transplant, referral for palliative care, and all-cause death. Implantable devices included implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy defibrillators (CRT-Ds), CRT-pacemaker (CRT-Ps), and permanent pacemakers (PPMs). Favourable outcomes included ≥5% increase in LVEF, improvement in NYHA class, and discharge from HF clinic due to clinical improvement. When a subject experienced both poor and favourable outcomes by 6-month follow-up, they were categorized based on the outcome that occurred first chronologically.

Statistical analysis
Statistical analyses were performed using GraphPad Prism Software (GraphPad, San Diego, CA, USA). Categorical variables were expressed as number of subjects and proportion and analyzed using Chi-squared tests. Continuous variables were expressed as mean±standard deviation (SD) and analyzed using either 2-tailed t-tests or 2-way ANOVAs with post-hoc Tukey tests for multiple comparisons. A 2-tailed $p < 0.05$ was considered statistically significant.

Results

Subject recruitment and patient demographics
A cohort of 65 HFrEF patients were enrolled in the study and medical records were accessed for 57 patients for which 6 months had elapsed since enrolment (Table 1). The mean age, BMI, SMM, and PBF of study participants was 63.25 years, 31.13 kg/m^2, 32.69 kg, and 33.78%, respectively (Table 1). Males comprised a significantly higher proportion of the study subset compared with females (82.46% vs. 17.54%, $p<0.0001$, Table 1). NYHA class II/III were greater represented in the study subset compared with NYHA I and IV (40.35% and 36.84% vs. 19.30% and 3.51%, $p=0.0002$, Table 1). Cardiovascular risk factors thought to contribute to HF included hypertension (HTN), ischemic/coronary artery disease (CAD), and dilated (57.89%, 45.61%, and 24.56%, respectively, Table 1). Medications included beta-blockers, diuretics, mineralocorticoid receptor antagonists (MRA), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and angiotensin converting enzyme inhibitors (ACEI), used in 87.72%, 82.46%, 59.65%, 57.89%, and 52.63% of subjects, respectively (Table 1). Comorbidities represented in the study subset included HTN, type 2 diabetes, dyslipidemia, chronic kidney disease, and prior smoking history (57.89%, 42.11%, 40.35%, 40.35%, 40.35%, and 31.58%, respectively, Table 1).

Outcomes at 6-month and 12-month follow-up
To date, 6-month follow-up was completed for 57 of the 65 enrolled subjects (Table 2). Poor outcomes occurred in 31.58% of subjects at 6 months post-assessment (Table 2). Poor outcomes included referral for implantable device (10.53%), all-cause death (7.02%), HF hospitalization (5.26%), new arrhythmia (3.51%), HF exacerbation in ED (1.75%), and referral for palliative care (1.75%, Table 2). There were no referrals for heart transplant at 6 months post-assessment (Table 2). Favourable outcomes occurred in 29.82% of subjects at 6 months post-assessment (Table 2). Favourable outcomes included ≥5% improvement in LVEF (19.30%), discharge due to clinical improvement (7.02%), and improvement in NYHA class (5.26%, Table 2).

To date, 12-month follow-up was completed for 34 of the 65 enrolled subjects (Table 2). New poor outcomes occurred in 11.76% of subjects (Table 2). Outcomes included HF hospitalization (5.88%), referral

for implantable device (2.94%), and all-cause death (2.94%). New favourable outcomes occurred in 7 subjects from 7-12 months post-assessment (Table 2). These subjects experienced ≥5% improvement in LVEF (11.76%) and discharge due to clinical improvement (11.76%, Table 2).

Demographics and characteristics of subjects categorized by poor outcomes at 6 months
Subjects followed at 6 months were categorized into patients with poor outcomes by 6 months (wPO, n=18) and patients with no poor outcomes by 6 months (nPO, n=39). Diastolic blood pressure (DBP) was significantly lower in the wPO subset compared with the nPO subset (68.11 vs. 76.15, p=0.0303, Table 1). The wPO subset had a greater proportion of NYHA class III subjects compared with the nPO subset (55.56% vs. 28.21%, p=0.0466, Table 1). The wPO subset also had a greater proportion of NYHA class IV subjects compared with the nPO subset (11.11% vs. 0.00%, p=0.0341, Table 1). There were no significant differences between the groups in age, body composition, sex, LVEF, HF etiologies, medications, implantable devices, and comorbidities (Table 1).

Demographics and characteristics of subjects categorized by improved LVEF at 6 months
Subjects followed at 6 months were also categorized into patients with improved LVEF by 6 months (iLVEF, n=11) and patients with no improvement in LVEF by 6 months (nLVEF, n=46). DBP was significantly higher in the iLVEF subset compared with the nLVEF subset (81.91 vs. 71.63, p=0.0183, Table 1). There were no significant differences between the groups in age, body composition, sex, LVEF, NYHA class, HF etiologies, medications, implantable devices, and comorbidities (Table 1).

NICaS parameters associated with poor outcomes at 6 months
NICaS-derived parameters were compared between the wPO and nPO groups at rest and post-exercise (Table 3). For the resting supine parameters, CPI was low in the wPO subset compared with the nPO subset (0.50 vs. 0.60, p=0.0371, Table 3). For the resting seated parameters, SI was significantly decreased in the wPO subset compared with the nPO subset (32.06 vs. 37.28, p=0.0322, Table 3). None of the NICaS-derived parameters were statistically significant between the nPO and wPO subsets post-exercise (Table 3).

Since worse NYHA classes III and IV, were greater represented in the wPO group compared with the nPO group, we compared NICaS parameters between subjects classified as NYHA I/II and NYHA III/IV at baseline assessment (Data not shown). Resting supine HR was significantly higher in NYHA III/IV patients compared with NYHA I/II patients (83.77 vs. 72.50, p=0.0291). Resting supine SI, SV, and GGI were significantly lower in NYHA III/IV patients (33.48 vs. 41.64, 71.63 vs. 84.07, and 9.80 vs. 11.52, respectively) with p-values of 0.0009, 0.0388, and 0.0266, respectively. The age of the NYHA III/IV group was significantly higher than the age of the NYHA I/II group (68.65 vs. 59.09, p=0.0180). No other resting and post-exercise hemodynamic parameters were significantly different between the groups (Data not shown).

NICaS parameters associated with improved LVEF at 6 months
NICaS-derived parameters were compared between the iLVEF and nLVEF groups at rest and post-exercise (Table 4). There were no statistically significant differences in parameters between the iLVEF and nLVEF subsets at rest and post-exercise (Table 4).

Changes in NICaS parameters from rest to post-exercise associated with poor outcomes at 6 months
Differences between resting (seated) and post-exercise (seated) NICaS-derived parameters were analyzed for both the wPO and nPO subsets (Figure 1). In the nPO group, CI and CPI increased significantly from rest to post-exercise (p values of 0.0356 and 0.0447, respectively, Figure 1C, D). The wPO group showed similar increases in CI and CPI, but these were not statistically significant (Figure 1C, D). GGI significantly increased in the wPO group from rest to post-exercise (p=0.0141, Figure 1E). There was a slight increase in GGI from rest to post-exercise in the nPO group, but not to a statistically significant extent (Figure 1E). In the nPO group, TPR decreased significantly in from rest to post-exercise (p=0.0475, Figure 1H). The

wPO group showed a similar decrease in TPR, but this was not statistically significant (Figure 1H). In the wPO group, TPRI decreased significantly from rest to post-exercise (p=0.0324, Figure 1I). A similar decrease was shown in the nPO group, but not to a statistically significant extent (Figure 1I).

Changes in NICaS parameters from rest to post-exercise associated with improved LVEF at 6 months
Differences between resting (seated) and post-exercise (seated) NICaS-derived parameters were analyzed for both the iLVEF and nLVEF subsets (Figure 2). In the nLVEF group, CO, CI and CPI increased significantly from rest to post-exercise (p values of 0.0104, 0.0025 and 0.0272, respectively, Figure 2C, D). The iLVEF group showed similar increases in CO, CI, and CPI, but these were not statistically significant (Figure 2B, C, D). GGI significantly increased in the nLVEF group from rest to post-exercise (p=0.0211), but remained relatively similar from rest to post-exercise in the iLVEF group (Figure 2E). SI significantly increased from rest to post-exercise in the nLVEF (p=0.0205), but stayed relatively similar from rest to post-exercise in the iLVEF group (Figure 2G). In the nLVEF group, TPR and TPRI decreased significantly in from rest to post-exercise (p values of 0.0048 and 0.0044, respectively, Figure 2H, I). The iLVEF group showed similar decreases in TPR and TPRI, but these were not statistically significant (Figure 2H, I).

GGI ratio in subjects categorized by poor outcomes and improved LVEF at 6 months
Since GGI increased significantly post-exercise in the wPO group (Figure 1E) and the nLVEF group (Figure 2E), while the nPO and iLVEF groups remained relatively unchanged post-exercise, we analyzed whether a marker of augmentation in GGI could be used to predict outcomes. GGI ratio was calculated by dividing the post-exercise GGI with the resting GGI for each subject and used to quantify augmentation of GGI from rest to post-exercise. The mean GGI ratio of all subjects followed at 6 months was 1.26±0.36, with a median of 1.19. As depicted in Figure 3A, the GGI ratio was significantly higher in the wPO group (1.44±0.36) compared with the nPO group (1.16±0.33) with a p-value of 0.0090. The augmentation ratios between the wPO and nPO groups for HR, SI, SV, CI, CO, CPI, TPR, TPRI, and TBW were not statistically significant (p-values of 0.6084, 0.1092, 0.1114, 0.1224, 0.1948, 0.2027, 0.1970, 1962, and 0.5368, respectively).

As depicted in Figure 3B, the GGI ratio was significantly higher in the nLVEF group (1.30±0.33) compared with the iLVEF group (1.03±0.31) with a p-value of 0.0248. The augmentation ratios between the iLVEF and nLVEF groups for HR, SI, SV, CI, CO, CPI, TPR, TPRI, and TBW were not statistically significant (p-values of 0.2001, 0.0665, 0.0665, 0.1909, 0.1913, 0.1880, 0.2384, 0.2374, and 0.730, respectively).

Discussion

This single-center study examined the hemodynamic parameters at rest and post-exercise measured non-invasively by NICaS in stable HFrEF patients. Main findings of the study include the characterization of baseline characteristics of HFrEF patients that experienced poor outcomes by 6-month follow-up and patients that experienced improvement in LVEF by 6-month follow-up. We then identified NICaS-derived hemodynamic parameters associated with poor outcomes by 6-month follow-up, including supine CPI, seated SI, and GGI ratio, a marker describing augmentation of GGI from rest to post-exercise.

We compared baseline characteristics of the cohort categorized by poor outcomes and improvement in LVEF. Low DBP was observed in patients with poor outcomes, as well as among patients with unchanged LVEF at 6 months post-enrolment. These findings suggest that a lower DBP may be associated with poor outcomes or lack of improvement in HFrEF patients. This aligns with recent studies, which showed that low DBP values <60 mmHg are associated with significant risk of adverse outcomes, such as HF hospitalization and death, in HF with preserved ejection fraction (HFpEF) patients treated for hypertension[19,20]. Furthermore, DBP ≤77 mmHg predicted HF readmission in patients with acute decompensated HFpEF[21]. Although published findings are reported among patients with HFpEF, diastolic dysfunction is also a major pathological abnormality observed in patients with HFrEF[22]. Diastolic

dysfunction can be caused by hypertension, ischemia, tachycardia, atrial fibrillation, and age-related cardiac changes[23]. However, hypertension, ischemia, arrhythmias and age were not significantly different between HFrEF patients with and without poor outcomes in this study.

The subset with poor outcomes had a greater proportion of NYHA class III and IV patients compared with the subset that did not experience poor outcomes at 6 months. This aligns with a study that showed that increased NYHA class was associated with mortality in HF patients undergoing prophylactic ICD implantation[24]. Furthermore, patients with worsening NYHA class demonstrated increased mortality over a 10 year span[25]. However, in a previous study of several clinical trials, mortality could not reliably be predicted by NYHA class[26]. Since NYHA class is based on patient-reported symptoms and limitations in physical activity, it is highly subjective[27]. Furthermore, NYHA class may be difficult to assess in patients who are non-verbal or patients with cognitive impairments and may not be a reliable method to categorize patients for prognostic purposes[27]. In our study, worse NYHA classes demonstrated higher supine HR and lower supine SI, SV, and GGI. Although increased age may be a contributing factor to the differences seen in the worse NYHA group, normal age-related hemodynamic changes are not well defined[28]. Notwithstanding, it may be of future interest to assess whether supine HR, SI, SV, and GGI measured by NICaS could be used as an objective measure to characterize symptom severity.

We compared NICaS-derived parameters between those with poor outcomes and those who did not experience poor outcomes. Low resting supine cardiac power index (CPI) was observed in patients with poor outcomes. Resting CPI is measured in watts per square meter (W/m^2) using the following formula: cardiac index ($L/min/m^2$) x mean arterial pressure divided by 451[29]. Normal CPI ranges from 0.5-0.7 W/m^2[29]. Our findings align with a previous study, which demonstrated the association between diminished CPI (<0.44 W/m^2) and increased risk of adverse outcomes in HF patients[29]. However, a recent study in HF patients with non-ischemic dilated cardiomyopathy showed that the prognostic value of resting CPI depended on mean arterial pressure, which was a stronger predictor of adverse outcomes[30]. In our study, patients experiencing worse outcomes at 6-month follow-up were noted to have lower resting seated SI. Similar findings were reported by a study that demonstrated that lower resting SI <35 ml/m^2 was associated with decreased survival in patients with acute decompensated HF[31]. However, low SI was only weakly associated with increased risk of mortality in another study[32].

Since HF is associated with impaired exercise capacity, driven by impaired exercise-augmented cardiac output, we characterized changes in NICaS-derived hemodynamic parameters from rest to post-exercise. In order to fulfill the metabolic demand of the muscles and vital organs during exercise, CO increases as a result of increased SV and HR, while TPR decreases as a result of metabolic vasodilation in muscle vasculature[33]. As expected, CI and CPI increased post-exercise in all categories of HFrEF patients enrolled in the study, though only statistically significant in patients who maintained a clinically stable state (no poor outcomes) and those with no improvement in LVEF at 6-month follow-up. This result is as expected since CI and CPI are derived from CO, which has been shown to increase from rest to peak exercise in stable HF patients[34]. Furthermore, TPR and TPRI decreased as expected in all categories of HFrEF patients enrolled in the study.

In our study, GGI significantly increased post-exercise in patients with poor outcomes, while remaining relatively unchanged post-exercise in patients without poor outcomes at 6 months. Similarly, GGI increased post-exercise in patients with no improvement in LVEF and remained relatively unchanged in patients with improvement in LVEF at 6 months. Due to the apparent difference in augmentation of GGI upon exercise between groups categorized by poor outcomes and groups categorized by improvement in LVEF, we established GGI ratio as a marker to quantify the change in GGI from rest to post-exercise. We found that GGI ratio was significantly higher in patients who experienced poor outcomes and patients with unimproved LVEF compared with patients with no poor outcomes and patients with improved LVEF, respectively. This suggests that increased augmentation of GGI may be associated with poor outcomes or

lack of improvement in LVEF by 6 months. These groups of patients may require significant augmentation in GGI in order to meet the metabolic demands of exercise. Conversely, it may also suggest that patients with clinically stable HF or patients with improved LVEF in 6 months do not require significant augmentation in GGI in order to meet the metabolic demands of exercise. GGI is a proprietary parameter based on heart rate and bioimpedance variations during systolic peak time of the cardiac cycle. As a surrogate marker of ejection systolic time, it can be used as a measure of cardiac function[35,36]. One study characterized low GGI as an early biomarker to predict heart failure in cancer patients after chemotherapy, with GGI <8.3 described as a cut-off to detect patients with significantly elevated NT-proBNP levels[37]. However, very few studies have evaluated GGI as an important prognostic marker in HF to date. Our study is the first to identify increased augmentation of GGI post-exercise as a potential prognostic marker associated with poor outcomes in HFrEF.

The findings of this study have potential implications for the management of HFrEF patients in outpatient HF clinics. HF clinics were designed to reduce post-discharge re-hospitalization, morbidity, and mortality after acute decompensated HF[38]. Patient education, medication management, and monitoring of symptoms in HF clinics has been shown to reduce the risk of post-discharge mortality by approximately 50%[39]. One limitation of current day management is that it is guided by a subjective description of symptoms, which may not always align with the severity of disease pathology. Non-invasive hemodynamic monitoring, which takes the same amount of time as an ECG, could provide objective measurable units to describe clinically useful information without subjective variation. Another obstacle in current HF management is that risk-stratification is affected by a retrospective account of health outcomes[7]. Thus, a patient may only be deemed high-risk and managed accordingly once already experiencing a poor outcome, such as re-hospitalization due to acute decompensated HF. Instead, hemodynamic parameters associated with poor outcomes, such as increased GGI ratio, can be used to proactively identify high-risk HF patients that require adjustment in their management and/or continued care in the HF clinic.

From our experience, patients in the HF clinic at SBGH were generally amenable to undergoing exercise and assessment with NICaS technology. The software used to monitor NICaS-derived hemodynamic parameters was easy to use and had a simplistic user interface (Figure 4A). The process of testing was simple and could generally be completed within 30-45 minutes (10 minutes for assessment at rest and ~20-35 additional minutes to evaluate with exercise). Some obstacles included motion artifacts that occurred during movement or while patients were unsteady or speaking. Since NICaS is prone to motion artifacts, such technology may not be ideal for patients who are unable to sit still, such as patients with tremors or spasticity. The need to bring patients to a separate facility posed another obstacle for conducting exercise testing since some patients experienced significant exertional dyspnea or mobility issues. To ensure these patients were represented in the study, we transported them to the research facility using wheelchairs. If NICaS were to be implemented in the HF clinic, it might be useful to have a separate room that contains a mounted ergometer and NICaS equipment in order to make testing more accessible for HF patients with severe functional limitations. The clinic room used for the assessment of subjects in this study is depicted in Figure 4 B. For HF clinics in which exercise testing is not feasible and for patients unable to exercise on a mounted ergometer, resting parameters seem to be sufficient in providing clinically useful information. Resting NICaS-derived hemodynamic parameters associated with poor outcomes, such as supine CPI and seated SI, may be used to identify high-risk patients without subjecting patients to exercise.

Future research is necessary to support GGI ratio, supine CPI, and seated SI as parameters associated with poor outcomes in HFrEF patients. Although we have enrolled 65 patients into the study, 6 months and 12 months since enrolment had only elapsed to allow us to follow 57 and 34 patients in this analysis. The outcomes of the remaining patients will be included in future analyses. Furthermore, we aim to recruit additional subjects to increase the power of this study to determine whether the parameters associated with poor outcomes in this study continue to predict poor outcomes at 6-month and 12-month follow-up. In

addition, we aim to establish reliable cut-off values for GGI ratio, resting supine CPI and seated SI, which can be used for risk-stratification of patients in the HF clinic.

Another avenue we aim to explore is whether the pattern of post-exercise augmentation of NICaS-derived parameters seen in the HFrEF patients of this study is similar in HFpEF patients. Furthermore, we aim to assess whether that parameters associated with poor outcomes in HFrEF patients also correlate with poor outcomes in HFpEF patients.

Impact of COVID-19

The COVID-19 pandemic significantly affected HF clinical practice during this study. For example, virtual clinic visits were used to reduce the spread of COVID-19 in the HF clinic. Moreover, many HF patients and their accompanying relatives who presented to in-person clinics were hesitant to spend additional time in the hospital. These factors significantly hampered our ability to recruit study participants.

Conclusions

Low resting supine CPI and low resting seated SI, measured non-invasively by NICaS, identified high-risk HFrEF patients experiencing poor outcomes. Additionally, GGI ratio, a measure of augmentation in GGI post-exercise, demonstrates potential to predict poor outcomes in HFrEF patients at 6-month follow-up. Results of this study provide rationale for incorporating resting and/or exercise-augmented NICaS-derived measurements when evaluating stable HFrEF patients to identify high-risk individuals before they experience poor outcomes. Early identification of high-risk patients may enable early intervention and optimal follow-up to prevent unplanned hospitalization and mortality.

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Figures, Figure Legends, and Tables

Table 1. Baseline characteristics of HFrEF patients and subgroups that were followed after 6 months

Variable	All n=57	Poor outcomes			Improved ejection fraction		
		wPO n=18	nPO n=39	P-value	iLVEF n=11	nLVEF n=46	P-value
Age, yr	64.50±15.04	65.06±13.51	61.97±15.92	ns	56.18±18.14	64.57±14.09	ns
BMI, kg/m^2	31.13±6.97	31.91±9.52	30.77±5.53	ns	31.82±5.69	30.96±7.29	ns
SMM, kg	32.69±7.22	31.75±7.51	33.17±7.23	ns	34.34±7.03	32.19±7.36	ns
PBF, %	33.78±9.75	33.03±11.98	34.15±8.77	ns	33.31±5.56	33.92±10.80	ns
SBP, mmHg	120.84±20.08	114.22±12.15	123.90±20.25	ns	126.64±19.21	119.46±20.24	ns
DBP, mmHg	73.61±13.14	68.11±12.15	76.15±12.94	0.0303	81.91±13.52	71.63±12.38	0.0183
Sex, n (%)	****						
Male	47 (82.46%)	15 (83.33%)	32 (82.05%)	ns	10 (90.91%)	37 (80.43%)	ns
Female	10 (17.54%)	3 (16.67%)	7 (17.95%)	ns	1 (9.09%)	9 (19.57%)	ns
LVEF, n (%)							
<20%	11 (19.30%)	5 (27.78%)	6 (15.38%)	ns	3 (27.27%)	8 (17.39%)	ns
20-29.9%	24 (42.11%)	9 (50.00%)	15 (28.46%)	ns	4 (36.36%)	20 (43.48%)	ns
30-40%	22 (38.60%)	4 (22.22%)	18 (46.15%)	ns	4 (36.36%)	18 (39.13%)	ns
NYHA class, n (%)	***						
I	11 (19.30%)	2 (11.11%)	9 (23.08%)	ns	3 (27.27%)	8 (17.39%)	ns
II	23 (40.35%)	4 (22.22%)	19 (48.72%)	ns	4 (36.36%)	19 (41.30%)	ns
III	21 (36.84%)	10 (55.56%)	11 (28.21%)	0.0466	4 (36.36%)	17 (36.96%)	ns
IV	2 (3.51%)	2 (11.11%)	0 (0.00%)	0.0341	0 (0.00%)	2 (4.35%)	ns
HF etiology, n (%)							
Ischemic/CAD	26 (45.61%)	10 (55.56%)	16 (41.03%)	ns	4 (36.36%)	22 (47.83%)	ns
Valve disease	10 (17.54%)	2 (11.11%)	7 (17.95%)	ns	3 (27.27%)	7 (15.22%)	ns
Dilated	14 (24.56%)	5 (27.78%)	9 (23.08%)	ns	3 (27.27%)	11 (23.91%)	ns
Systemic HTN	33 (57.89%)	11 (61.11%)	22 (56.41%)	ns	5 (45.45%)	28 (60.87%)	ns
Cardiac arrest	5 (8.77%)	2 (11.11%)	3 (7.69%)	ns	1 (9.09%)	4 (8.70%)	ns
Idiopathic	8 (14.04%)	1 (5.56%)	7 (17.95%)	ns	2 (18.18%)	6 (13.04%)	ns
Other	8 (14.04%)	0 (0.00%)	8 (20.51%)	-	3 (27.27%)	5 (10.87%)	-
Medications, n (%)							
ARNI	13 (22.81%)	3 (16.67%)	10 (25.64%)	ns	2 (18.18%)	11 (23.91%)	ns
MRA	34 (59.65%)	12 (66.67%)	22 (56.41%)	ns	7 (63.64%)	27 (58.70%)	ns
Beta blocker	50 (87.72%)	14 (77.78%)	36 (92.31%)	ns	9 (81.82%)	41 (89.13%)	ns
SGLT2i	33 (57.89%)	13 (72.22%)	20 (51.28%)	ns	6 (54.55%)	27 (57.17%)	ns
ACE inhibitor	30 (52.63%)	10 (55.56%)	20 (51.28%)	ns	6 (54.55%)	24 (52.17%)	ns
ARB	5 (8.77%)	1 (5.56%)	4 (10.26%)	ns	1 (9.09%)	4 (8.70%)	ns
Diuretics	47 (82.46%)	16 (88.89%)	31 (79.49%)	ns	9 (81.82%)	38 (82.61%)	ns
ICD/CRT/PPM, n (%)	24 (42.11%)	8 (44.44%)	16 (41.03%)	ns	2 (18.18%)	22 (47.83%)	ns
Comorbidities, n (%)							
Hypertension	33 (57.89%)	10 (55.56%)	23 (40.35%)	ns	5 (45.45%)	28 (60.87%)	ns
T2D	24 (42.11%)	9 (50.00%)	15 (38.46%)	ns	4 (36.36%)	20 (43.48%)	ns
CKD	23 (40.35%)	5 (27.78%)	18 (46.15%)	ns	3 (27.27%)	20 (43.48%)	ns
Liver disease	3 (5.26%)	0 (0.00%)	3 (7.69%)	ns	0 (0.00%)	3 (6.52%)	ns
CVD	6 (10.53%)	2 (11.11%)	4 (10.26%)	ns	0 (0.00%)	6 (13.04%)	ns
TIA	4 (7.02%)	2 (11.11%)	2 (5.13%)	ns	0 (0.00%)	4 (8.70%)	ns
Dyslipidemia	23 (40.35%)	6 (33.33%)	17 (43.59%)	ns	4 (36.36%)	19 (41.30%)	ns
Smoking, Current	10 (17.54%)	4 (22.22%)	6 (15.38%)	ns	0 (0.00%)	10 (21.74%)	ns
Smoking, Previous	18 (31.58%)	6 (33.33%)	12 (30.77%)	ns	4 (36.36%)	14 (30.43%)	ns
Arrhythmia	23 (40.35%)	9 (50.00%)	14 (35.90%)	ns	3 (27.27%)	20 (43.48%)	ns

BMI=body mass index, BP=blood pressure, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, HTN=hypertension, CAD=coronary artery disease, ARNI=angiotensin receptor-neprilysin inhibition, MRA=mineralocorticoid receptor antagonist, SGLT2i= sodium-glucose cotransporter 2 inhibitor, ACE=Angiotensin converting enzyme, ARB=angiotensin receptor blocker, ICD=implantable cardioverter defibrillator, CRT=cardiac resynchronization therapy, PPM=permanent pacemaker, T2D=type 2 diabetes, CKD=chronic kidney disease, CVD=cardiovascular disease, TIA=transient ischemic attack. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Table 2. Outcomes for HFrEF patients followed at 6-months and 12-months post-assessment

Outcome	0-6 months n=57	7-12 months n=34
Poor outcomes, total # of patients	**18 (31.58%)**	**4 (11.76%)**
HF exacerbation in ED	1 (1.75%)	0 (0.00%)
HF hospitalization	3 (5.26%)	2 (5.88%)
New arrhythmia	2 (3.51%)	0 (0.00%)
Referral for implantable device	6 (10.53%)	1 (2.94%)
Adjustment/repair of existing device	2 (3.51%)	0 (0.00%)
Referral for heart transplant	0 (0.00%)	0 (0.00%)
Referral for palliative care	1 (1.75%)	0 (0.00%)
All-cause death	4 (7.02%)	1 (2.94%)
Favourable outcomes, total # of patients	**17 (29.82%)**	**7 (20.59%)**
≥5% improvement in LVEF	11 (19.39%)	4 (11.76%)
Improvement in NYHA class	3 (5.26%)	0 (0.00%)
Discharge due to clinical improvement	4 (7.02%)	4 (11.76%)

LVEF=left ventricular ejection fraction, NYHA=NewYork Heart Association, HF=heart failure, ED=emergency department

Table 3. NICaS-derived hemodynamic parameters in patients with poor outcomes at 6-months follow up (wPO, n=18) and no poor outcomes at 6-months follow-up (nPO, n=39)

	Rest (Supine)		Rest (Seated)		Post-exercise (Seated)	
	wPO	**nPO**	**wPO**	**nPO**	**wPO**	**nPO**
HR (bpm)	81.35±23.20	75.14±16.42	81.39±21.66	77.00±15.40	88.94±22.39	84.48±21.58
SI (mL/m^2)	34.93±9.89	39.87±8.59	32.06±8.37*	37.28±8.33*	39.11±10.53	41.22±8.66
SV (mL)	71.88±23.38	82.28±20.66	67.35±22.03	77.04±20.71	81.99±28.53	85.07±17.31
CI (L/min/m^2)	2.72±0.68	2.93±0.66	2.60±0.77	2.84±0.75	3.41±1.05	3.46±1.12
CO (L/min)	5.61±1.69	6.04±1.56	5.39±1.87	5.87±1.89	7.17±2.81	7.12±2.27
CPI (W/m^2)	0.50±0.15*	0.60±0.15*	0.48±0.16	0.58±0.17	0.63±0.26	0.70±0.23
GGI	10.08±3.05	11.16±2.68	8.90±2.43	10.66±3.81	12.65±4.10	11.66±3.43
TPR (dn*s/cm^5)	1284.24±429.51	1301.78±403.15	1397.22±549.64	1362.28±417.33	1029.38±387.10	1102.19±308.32
TPRI (dn*s/cm^5*m^2)	2611.00±877.92	2637.89±709.15	2818.50±1033.65	2758.36±771.14	2066.94±64.06	2290.52±706.17
TBW (L)	50.46±9.07	50.05±7.03	52.30±9.85	52.67±8.12	51.93±9.33	50.31±8.98

HR=Heart Rate, SI=Stroke Index, SV=Stroke Volume, CI=Cardiac Index, CO=Cardiac Output, CPI=Cardiac Power Index, GGI=Granov-Goor Index, TPR=Total Peripheral Resistance, TPRI=TPR Index, TBW=Total Body Water, *p<0.05 between wPO and nPO

Table 4. NICaS-derived hemodynamic parameters in patients with improved LVEF (iLVEF, n=11) and no improvement in LVEF (nLVEF, n=46) at 6 months

	Rest (Supine)		Rest (Seated)		Post-exercise (Seated)	
	iLVEF	**nLVEF**	**iLVEF**	**nLVEF**	**iLVEF**	**nLVEF**
HR (bpm)	79.20±10.73	75.20±20.08	82.45±9.06	76.44±18.87	92.40±18.65	83.15±22.17
SI (mL/m^2)	37.86±8.51	39.44±8.85	35.00±8.04	36.61±8.30	36.52±6.57	41.61±9.35
SV (mL)	80.23±23.35	81.06±20.62	74.52±23.14	75.80±20.29	78.30±19.97	88.03±21.09
CI (L/min/m^2)	2.96±0.61	2.88±0.67	2.88±0.75	2.77±0.74	3.34±0.68	3.51±1.18
CO (L/min)	6.25±1.75	5.92±1.57	6.14±2.17	5.71±1.78	7.11±1.79	7.27±2.63
CPI (W/m^2)	0.63±0.14	0.56±0.16	0.61±0.16	0.54±0.17	0.71±0.18	0.67±0.26
GGI	11.38±3.15	10.84±2.75	9.94±2.85	10.34±3.66	10.32±2.67	12.74±3.80
TPR (dn*s/cm^5)	1324.00±438.84	1278.22±414.01	1388.73±495.78	1349.12±446.09	1146.00±304.65	1048.76±354.28
TPRI (dn*s/cm^5*m^2)	2711.70±749.81	2593.85±778.13	2839.18±856.23	2727.58±831.99	2407.20±607.42	2151.00±723.83
TBW (L)	48.31±7.82	50.42±7.82	52.26±10.02	52.24±8.64	50.64±10.88	50.90±8.95

HR=Heart Rate, SI=Stroke Index, SV=Stroke Volume, CI=Cardiac Index, CO=Cardiac Output, CPI=Cardiac Power Index, GGI=Granov-Goor Index, TPR=Total Peripheral Resistance, TPRI=TPR Index, TBW=Total Body Water

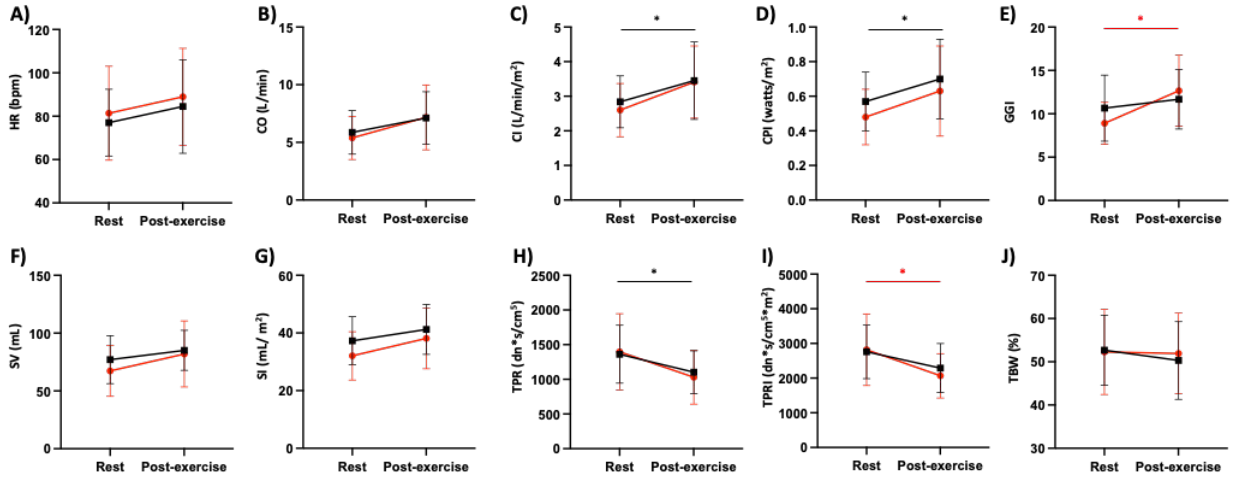

Figure 1. NICaS hemodynamic parameters at rest and post-exercise in subjects with poor outcomes (wPO, n=18, red circle) and no poor outcomes (nPO, n=39, black square) by 6-month follow-up. Heart rate (HR; A), Cardiac Output (CO; B), Cardiac Index (CI; C), Cardiac Power Index (CPI; D), Granov-Goor Index (GGI; E), Stroke Volume (SV; F), Stroke Index (SI; G), Total Peripheral Resistance (TPR; H), TPR Index (TPRI; I), and Total Body Water (TBW; J) were measured while seated at rest and after up to 12 minutes of exercise at 25 watts on a mounted ergometer. Comparing parameters at rest and post-exercise for the wPO subset (red) and the nPO subset (black): $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

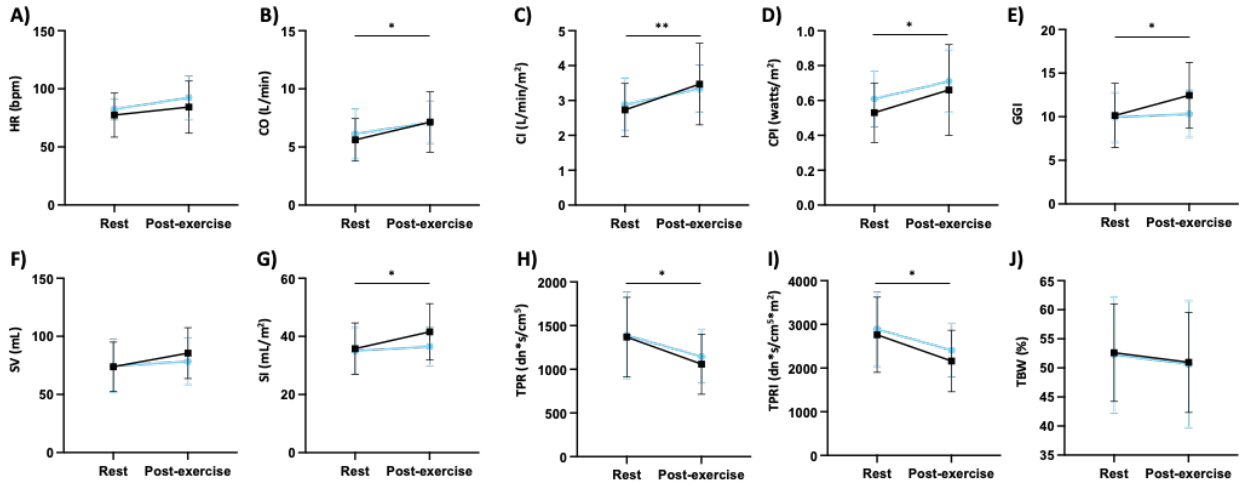

Figure 2. NICaS hemodynamic parameters at rest and post-exercise in subjects with improved LVEF (iLVEF, blue circle) and no change in LVEF (nLVEF, black square) by 6-month follow-up. Heart rate (HR; A), Cardiac Output (CO; B), Cardiac Index (CI; C), Cardiac Power Index (CPI; D), Granov-Goor Index (GGI; E), Stroke Volume (SV; F), Stroke Index (SI; G), Total Peripheral Resistance (TPR; H), TPR Index (TPRI; I), and Total Body Water (TBW; J) were measured while seated at rest and after up to 12 minutes of exercise at 25 watts on a mounted ergometer. Comparing parameters at rest and post-exercise for the iLVEF subset (blue) and the nLVEF subset (black): $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

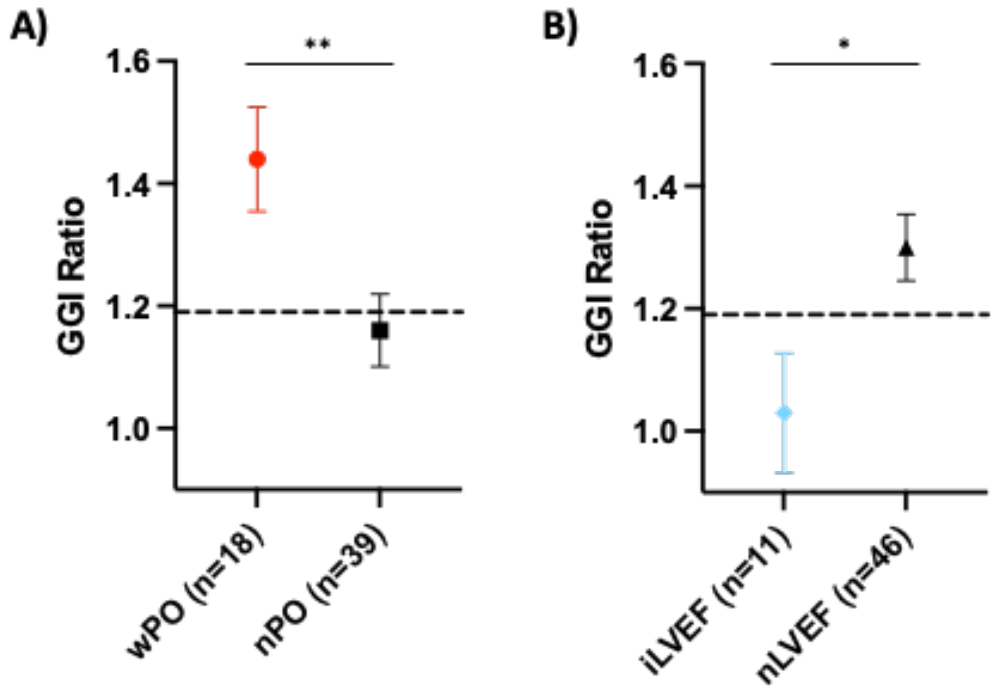

Figure 3. GGI Ratio subjects followed at 6 months for subjects categorized by poor outcomes (A) and improved LVEF (B). GGI ratio is defined as the ratio between seated GGI post-exercise and seated GGI at rest. GGI ratio for subjects with poor outcomes (wPO, red circle) and subjects with no poor outcomes (nPO, black square) (A). GGI ratio for subjects with improved LVEF (iLVEF, blue diamond) and subjects with no improvement in LVEF (nLVEF, black triangle) (B). Median of all subjects followed at 6 months (1.19, dashed line). Standard error of the mean (whiskers). $^{*}p<0.05$, $^{**}p<0.01$, $^{**}p<0.001$.

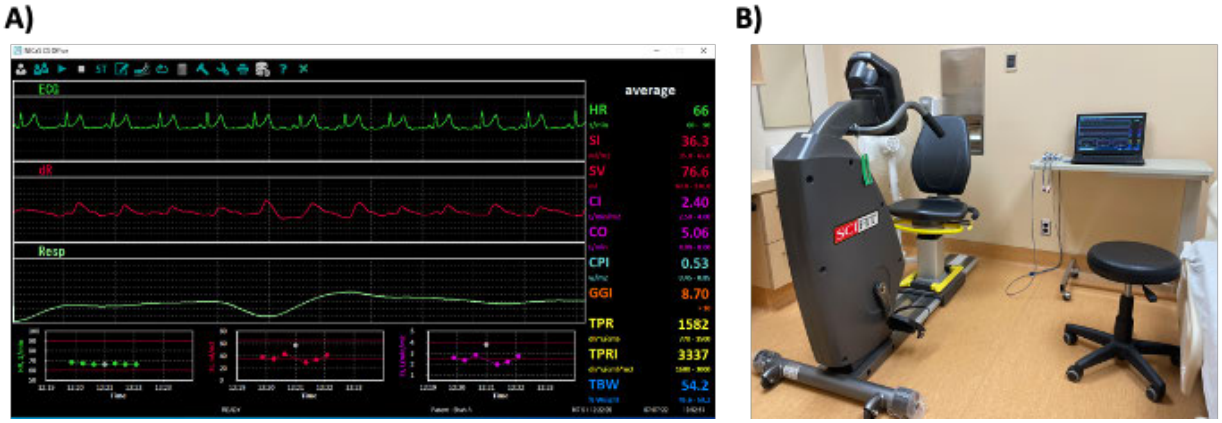

Figure 4. User interface of NICaS CS Software for the monitoring of NICaS-derived hemodynamic parameters (A) and clinical room used for the assessment exercise-augmented NICaS-derived hemodynamic parameters (B). After inputting a subject's blood pressure, height, weight, position, and orientation of electrodes, hemodynamic parameters were monitored using NICaS CS software to obtain at least five replicates with motion artifacts removed (A). Patients exercised on a mounted ergometer at 25 watts for 12 minutes, or until limited by symptoms, before post-exercise hemodynamic parameters were measured (B).