UNIVERSITY OF MANITOBA | MAX RADY COLLEGE OF MEDICINE Rady Faculty of Health Sciences

Bachelor of Science in Medicine Degree Program
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Project Title: Heart Failure Hemodynamic Prognostic evaluation and outcome (HF-HOPE)

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Summary (250 words max single spaced):
Heart failure (HF) is one of the leading causes of morbidity and mortality worldwide. Although HF is defined as impaired cardiac ability in maintaining physiologically required cardiac output, it is rarely objectively measured. To hemodynamically characterize and identify outcome associated marker in HF patients with preserved ejection fraction (HFpEF), we conducted this study using a whole-body impedance cardiography based Non-Invasive Cardiac System (NICaS). NICaS is fast, non-invasive, cost-effective, validated and approved by the FDA (USA). Forty-two clinically stable HFpEF patients were were evaluated at rest (supine and sitting position), and after exercising on a mounted bike (25 watts, for up to 12 minutes or limited by symptom). Their electronic patient records were reviewed to identify outcome at 6 months (unplanned hospital admission due to HF/arrhythmias, listing for heart transplantation or palliative care, and all-cause death). There was strong relationship between resting and post-exercise hemodynamic parameters, suggesting that resting parameters may be sufficient to characterize these patients. No relationship to age or NYHA class was identified. Twelve participants had high CO (cardiac index >3.8L/min/m2, CO>8L/min). Thirty-three participants had 6-months follow-up; no patient experienced adverse outcomes; 19 had medication changes and 6 were discharged from HF clinic due to clinical improvement. Covid-19 adversely influenced our ability to recruit these patients. Although, we could hemodynamically characterize HFpEF patients, smaller study cohort and shorter follow up were our limitations. Incorporating such measurements in routine clinical care will provide objective measurable parameters, and may provide clinically relevant details.

Student Signature

Primary Supervisor Signature

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Introduction:

Heart failure is one of the leading causes of morbidity and mortality worldwide. The National Health and Nutritional Examination Survey from 2011-2014 stated that heart failure (HF) affects more than 23 million people worldwide[1,2]. In Canada, more than 600,000 patients are reported to have chronic heart failure. Additionally, more than 45,000 new patients are diagnosed with HF each year[3,4]. Despite developing guidelines, standardizing therapeutic and procedural interventions, availability of heart transplantation or mechanical circulatory support, and establishing heart failure subspecialty services, only modest improvement in overall mortality – morbidity has been achieved[5]. Moreover, direct and indirect cost associated with HF management remains significantly high[6].

Heart failure is defined as "a complex clinical syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress"[7]. This definition aptly describes heart failure physiology, though it's implications in clinical practice remains challenging, as there are no established quantifiable hemodynamic criteria defining heart failure in an individual patient. Although, NT-pro-brain natriuretic peptide helps diagnosing new onset heart failure, their utility in prognosticating chronic stable heart failure patients in an outpatient setting remains unknown[8].

Multiple studies and international guidelines have characterized HF based upon left ventricular ejection fraction, including preserved ejection fraction (>40%) (HFpEF) and HF with reduced ejection fraction (HFrEF). Despite subgrouping of HF based upon ejection fraction alone, the main underlying hemodynamic abnormalities are (1) failure of exercise-augment cardiac output (CO), (2) abnormally high systemic vascular resistance (likely compensatory response to low cardiac output state), and (3) either resting or exercise induced pulmonary congestion, a response to abnormally elevated left ventricular end-diastolic pressure, or diastolic dysfunction. Although HF is being defined as impaired cardiac ability in maintaining physiologically required cardiac output to meet the body's metabolic demand, such objectively measurable parameters have not been reported and are not routinely measured. Rather, these patients are subjectively assessed for their symptoms[9–11]. Such limitations in objectively describing hemodynamic parameters may reside in our inability in measuring them in routine clinical practice. In the current day practice, acceptable methods for hemodynamic parameters evaluation are (1) cardiac catheterization, (2) magnetic resonance (MR) imaging, and (3) echocardiography. Despite being accepted as standard of care (mainly catheterization and MR), each of these methods has inherent limitations. Cardiac catheterization: costly, invasive, requires special facility, difficult to repeat the study at multiple time points and associated with plausibly higher complication risk, especially in patients being treated with anticoagulation or difficult vascular access; MR: requires special facility, associated with significant cost, limited by claustrophobia, contraindication in patients with metallic implants including pacemakers, and lack of MR-compatible ergometer, and echocardiography: relatively unreliable method among all 3, challenged by poor echo window, motion artefact, and assumption that the left-ventricular outflow tract is circular, not oval, as such assumption challenges precisely calculated stroke volume and hence cardiac output. With such limitations, hemodynamic measurements (at rest

and/or exercise-augmented changes) only remain limited to research studies. What is required, is an alternative, non-invasive, cost-effective, validated technology that is fast (not compromising the outpatient clinic flow), and can be used in an outpatient / mobile setting to monitor hemodynamic parameters in an outpatient setting might improve identification and management of high-risk patients.

Total-body impedance based technologies: A solution may be a non-invasive cardiac system (NICaS) that incorporates the whole-body impedance cardiography. Obtained cardiovascular parameters include stroke volume (SV), stroke index (SI), cardiac output (CO), cardiac index (CI), total peripheral vascular resistance, body water content, cardiac power index (CPI), a marker of myocardial contractility, and Granov Goor Index (GGI), a surrogate marker of ejection systolic time. This technology is based on two independent principles. The first principle is that electrical conductance of the blood is higher than that of the surrounding tissue structures. Consequently, with each arterial systolic expansion (pulsation), an increase in the electrical conductance (or reduction in the electrical resistance) of the body can be measured. The second principle, the Granov Goor Index (GGI), is based on the systolic time intervals, which, similarly to left ventricle ejection fraction, can assess cardiac function, or cardiac power index (CPI). A reduction in GGI is a marker of worsening cardiac muscle strength. A series of publications have verified NICaS derived hemodynamic parameters with those obtained invasively in the catheter laboratory using the Fick formula, thermo-dilution, trans-thoracic echocardiography, and other non-invasive technologies[12–14].

Hypothesis:
We hypothesis that NICaS derived resting and exercise-augmented hemodynamic parameters in patients with heart failure with preserved ejection fraction (HFpEF) will identify patients at higher risk for recurrent hospital admission due to heart failure or arrhythmias, listing for heart transplantation or palliative care, and death irrespective of underlying etiology.

Methods:
Participants: Patients with a known diagnosis of HF, irrespective of etiology, >18 years of age, with stable clinical state for 3 months, capable of providing written informed consent, and have no cancer, terminal illness, or any comorbidities with a life expectancy of <12 months were recruited.

NICaS: Hemodynamic parameter measurements require application of 2 dual-polar impedance electrodes in wrist-wrist configuration. Once applied, the NICaS system records and updates hemodynamic parameters every 20 seconds; once, consistent 5 recordings were made, the hemodynamic parameter values were recorded.

Assessment: NICaS evaluated each patient at rest and after exercise on a mounted bike. Initial hemodynamic measurements were performed in supine position at rest, followed by sitting position. Subsequently each study participant exercised on a mounted exercise-bike at 25 Watts for upto 12 minutes or till they experienced subjective symptoms of tiredness and could no longer exercise. Exercise time was documented and once again NICaS derived hemodynamic

parameters were recorded at the peak exercise. Motion artefact affected NICaS measurement; hence we waited to obtain steady state tracing to obtain the hemodynamic parameters.

Follow-up: These patients were followed to identify repeat hospital admission for heart failure, arrhythmia, listing for transplantation or palliative care, and death at 6-months. Follow up data acquisition will be obtained by reviewing Electronic Patient Records (EPR).

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 paired t-tests; $p < 0.05$ was considered statistically significant.

Results:
Forty-two patients were recruited from the heart failure clinic at St. Boniface Hospital. All patients had one of either a cardiac echocardiogram (echo), cardiac MR, multigated acquisition scan (MUGA), or myocardial perfusion scan (MIBI) scan to evaluate their left ventricular ejection fraction (LVEF) to confirm an LVEF of $\geq$40%. Patient demographics are described in table 1 and table 2, with follow-up data in table 3.

Median age was 64 and 71% of participants were male. The body mass index (BMI), LVEF, New York Heart Association functional classification (NYHA), and comorbidities are also listed in table 1. All of the parameters measured by the NICaS system are also listed in table 2 with the media, mean, and standard error of mean listed. The parameters of most interest were CO, CI, heart rate (HR), SV, SI and CPI. In each of these parameters there was no significant difference between the supine and sitting results, therefore, the sitting and post-exercise results were used to prove correlation (figure 1).

The r values comparing resting and exercise-augmented hemodynamics for HR, SI, SV, CI, CO and CPI were 0.91, 0.45, 0.61, 0.77, 0.77, 0.76, respectively. All parameters except for SV and SI had strong r values of over 0.7, however, all r values were significant ($p<0.05$). There was no significant trend in HR, CO, CI, SV, SI, or CPI across age or NYHA classes. Overall in HR, SI, SV, CI, CO, and CPI there was a significant augmentation between pre- and post-exercise values (figure 2).

There was a subset of twelve participants that were assessed who met the criteria to be classified as high output based on a CI above 3.8, CO above 8.0, or both. The mean age of this group was 54 ± 14.98 years. There were no significant differences in HR, CO, CI, SV, SI, or CPI when at rest, but there was a significant difference in their SV post exercise values ($p<0.05$); however, the absolute value of the augmentation was not significant.

Thirty-three participants had their six-month follow-up at the time of writing this report (table 3). Of the 33, no one had any new hospital admissions, arrhythmias, or were listed for heart transplantation or palliative care, and no one experienced death irrespective of underlying etiology. Only one person was referred for a pacemaker. Nine participants had no alterations to their care, and 19 had only alterations to their medications made at the time of their clinic visit. Seven participants had an improvement in their LVEF and six were clinically discharged from the heart failure clinic to be managed by their family doctor. There was no significant difference in the HR, CO, CI, SV, SI, or CPI of the participants who were discharged to those who were not.

Discussion:
Heart failure patients require close monitoring under specialist clinic or with a physician with expertise in managing these high-risk patients. At the time of clinic visit, their symptoms are assessed in many ways, such as New York Heart Association (NYHA) class, heart imaging to assess progression of ventricular contractility and any other associated structural anomalies, and blood work, including but not limited to BNP measurement.

Given the HF is associated with hemodynamic abnormalities, objective documentation of such parameters may provide precise, and objective parameters that can eliminate subjective aspect of their assessment. To meet our objectives, here we evaluated stable HFpEF patients using the NICaS system in an outpatient clinic setting. As other validation studies have demonstrated, the NICaS system is reliable and can reproduce similar results as other more invasive modalities[15]. Especially with current COVID times, when various investigational tools were not easily accessible, availability and incorporating such technologies might provide clinically relevant hemodynamic information.

We were able to assess 42 patients to make our baseline and had the six-month follow-up information of 33 of them. Even very young patients were followed in the HF clinic with their diagnosis of HFpEF. However, as anticipated, these patients were noted to have significant comorbidities, mainly obesity. Other significant comorbidities included chronic kidney disease, hypertension and diabetes. Fair proportion of these patients were noted to be in atrial fibrillation, again a marker of likely stiff/noncompliant ventricle that result in left atrial dilatation eventually resulting in rhythm abnormality due to progressive scaring in atrial wall. In contrast to HFrEF, where myocardial insult is the primary pathophysiology, HFpEF is likely to be a systemic disease process and heart is one of the organs involved. Hence, till date no really effective therapies have been identified improving outcomes in this patient cohort.

While being supine, the study participants were noted to have preserved cardiac output and other hemodynamic parameters, however, these parameters markedly changed with postural change from supine to sitting. Although these are striking hemodynamic alterations, clinical significance of these changes remains unclear at this stage. Interestingly, CPI and GGI described these ventricles to demonstrate preserved contractility, however, NICaS parameters associated with diastolic functional assessment remains unknown.

Interestingly, we wished to evaluate not only resting but also exercise-augmented hemodynamic parameters in this patient cohort with intention to mimic their symptoms and identify limiting hemodynamic parameters. However, as described in figure 1, there is a strong correlation between resting and exercise-augmented hemodynamic parameters. Based upon these findings, one can anticipate that just obtaining resting values may suffice. Measuring such parameters simplifies the whole process, as one may not require an exercise bike and measurements can be obtained in less than 15 minutes without compromising the patient flow in a clinic setting.

With exercise, we noted that patients with HFpEF were able to augment CI, SI and CPI, but again, given the small study cohort, we were unable find a significant difference in parameters between the patients with different NYHA class. While HR, SI, SV, CI, CO and CPI all significantly augmented, the heart rate did not rise as much as we would expect. This outcome was likely due to the medications the participants were taking – namely rate control medications such as metoprolol and carvedilol which were prescribed to many. Additionally, in all parameters, there was quite a large amount of variability, resulting in some ambiguity in the

individual augmentations. Nevertheless, that the participants could augment is a sign in their favour in their heart failure outlook.

None of the study participants encountered any adverse outcomes during our study follow up period. This is very reassuring and describes that such event rate is relatively low in patients with HFpEF, in comparison to the HFrEF[16]. Most participants only had medication changes made to their management or nothing done at all – simply a check-in to track progress and stability. This would point to likely needing a longer follow-up period to see more meaningful outcomes for participants and a larger sample size of individuals to hopefully see a wider range of outcomes, even at the six-month mark. Further, it would be prudent to have a more equal ratio of women to men and have more people of colour as participants to ensure that is the data is representative of the population and that the results could be generalized for most if not all.

While not all of r values for the correlations done in figure 1 are strong, all of them were considered significant and which points to the reliability and the opportunity to use NICaS as an outpatient tool to assess patients where they are at and their exercise potential while only needing to take resting, sitting values. All of these parameters would be of use; however, CPI is a known prognostic factor and CO and CI would be useful in discussing exercise tolerance with patients. Unfortunately, none of the assessed hemodynamic parameter were found to be prognostic factors of significance.

There were no discernable pattern to the twelve high output patients – all were a mix of ages, genders, BMI's, NYHA classes and comorbidities, with the only thing tying them together being their abnormally high output. Interestingly, even though the absolute value of the augmentation was not significant, meaning that their likely dilated ventricle was maintaining its ejection fraction and was able to augment as much as those that were not while also not augmenting its CPI.

Conclusions:
In this project, we could evaluate stable HFpEF patients form the HF clinic and objectively evaluate their hemodynamic parameters. Given significant correlation between resting and exercise-augmented hemodynamic parameters, resting hemodynamic assessment may suffice. Recruiting larger number of study participants and following them longer term may provide prognostically valuable hemodynamic parameters.

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.

Future plan:
We aim to continue recruiting study participants to further describe the hemodynamic parameters and hopefully find a prognostic marker.

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Table 1. Demographics of HFpEF patients

	Demographic	Number of subjects (N=42)	Proportion of subjects (95% CI)
Age	<30 years old	2	4.76% (0.46-16.65%)
	30-49 years old	8	19.05% (9.72-33.56%)
	50-69 years old	15	35.71% (22.94-50.88%)
	>70 years old	17	40.48% (27.02-55.53%)
Sex	Male	30	71.43% (56.32-82.94%)
	Female	12	28.57% (17.06-43.68%)
BMI	Underweight: <18.5 kg/m^2	0	0% (0-9.99%)
	Normal weight: 18.5–24.9 kg/m^2	4	9.52% (3.21-22.62%)
	Overweight: 25–29.9 kg/m^2	19	45.24% (31.22-60.06%)
	Obesity: ≥30 kg/m^2	19	45.24% (31.22-60.06%)
LVEF	40-49%	19	45.24% (31.22-60.06%)
	50-60%	16	38.10% (24.97-53.22%)
	>60%	7	16.67% (8.00-30.92%)
NYHA class	I	13	30.95% (18.98-46.11%)
	II	11	26.19% (15.16-41.21%)
	III	18	42.86% (29.11-57.81%)
	IV	0	0% (0-9.99%)
Comorbidities	Hypertension	21	50.00% (35.53-64.47%)
	Type 2 diabetes	9	21.43% (11.49-36.15%)
	Type 1 Diabetes	1	2.38% (0.01-13.44%)
	Chronic kidney disease	10	23.81% (13.31-38.70%)
	Liver disease	2	4.76% (0.46-16.65%)
	Cardiovascular disease	3	7.14% (1.77-19.70%)
	Peripheral vascular disease	3	7.14% (1.77-19.70%)
	Transient ischemic attack	4	9.52% (3.21-22.62%)
	Dyslipidemia	16	38.10% (24.97-53.22%)
	Smoking (Current)	6	14.29% (6.33-28.22%)
	Smoking (Previous)	17	40.48% (27.02-55.53%)
	Atrial fibrillation	17	40.48% (27.02-55.53%)
	Ventricular fibrillation	2	4.76% (0.46-16.65%)
	Supraventricular tachycardia	0	0% (0-9.99%)
	Ventricular tachycardia	5	11.90% (4.73-25.46%)
	Atrial flutter	3	7.14% (1.77-19.70%)
	Bradyarrhythmia	1	2.38% (0.01-13.44%)
	Asthma	3	7.14% (1.77-19.70%)
	Chronic obstructive pulmonary disease	5	11.90% (4.73-25.46%)
	Obstructive sleep apnea	6	14.29% (6.33-28.22%)
	Drug abuse	4	9.52% (3.21-22.62%)
	Alcohol abuse	5	11.90% (4.73-25.46%)
	Arthritis	6	14.29% (6.33-28.22%)
	Gout	4	9.52% (3.21-22.62%)
	Hypothyroidism	3	7.14% (1.77-19.70%)
	Cancer (cured)	4	9.52% (3.21-22.62%)

	Hemochromatosis	0	0% (0-9.99%)
	Depression	9	21.43% (11.49-36.15%)
	Morbid obesity	8	19.05% (9.72-33.56%)

Table 2. Demographic and hemodynamic parameters

Hemodynamic parameter	**Rest (supine)**	**Rest (sitting)**	**Post exercise (sitting)**
HR (bpm)	71.81±15.95	76.17±23.11	80.34±15.10
SI (mL/beat)	43.72±9.013	36.39±8.789	42.36±8.450
SV (mL)	89.47±18.88	74.68±19.28	86.90±19.79
CI (L/min/m^2)	3.141±1.023	3.288±3.3333	3.393±0.9552
CO (L/min)	6.391±1.856	5.687±2.401	6.965±2.012
CPI (W/m^2)	0.6593±0.2462	0.5824±0.3256	0.7137±0.2336
GGI	12.12±2.629	9.754±2.962	12.64±4.310
TPR (mmHg*min/L)	1259±424.7	1459±453.9	1162±333.0
TPRI (dn*s/cm^5*m^2)	2612±920.6	2993±952.7	2391±738.3
TBW (L)	47.71±9.020	49.57±11.28	49.68±10.58

SD=Standard Deviation, 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

Table 3. Outcomes for HFpEF patients followed at 6-months

	Outcome	**Number of subjects (N=33)**	**Proportion of subjects (95% CI)**
Poor outcomes	Death	0	0% (0-12.39%)
	Referral to palliative care	0	0% (0-12.39%)
	Referral for heart transplant	0	0% (0-12.39%)
	Hospitalizations	0	0% (0-12.39%)
	New arrhythmia	0	0% (0-12.39%)
	Referral or implantation of implantable device	1	3.03% (0.01-16.65%)
	Decline in NYHA class	0	0% (0-12.39%)
	Decline in LVEF	0	0% (0-12.39%)
Neutral outcomes	Medication changes	19	57.58% (40.79-7278%)
	No changes	9	27.27% (14.90-44.39%)
Favourable outcomes	Improvement in NYHA class	0	0% (0-12.39%)
	Discharge due to clinical improvement	6	18.18% (8.23-34.77%)
	Discharged to pacemaker clinic	1	3.03% (0.01-16.65%)
	Improvement in LVEF	7	21.21% (10.38-38.05%)

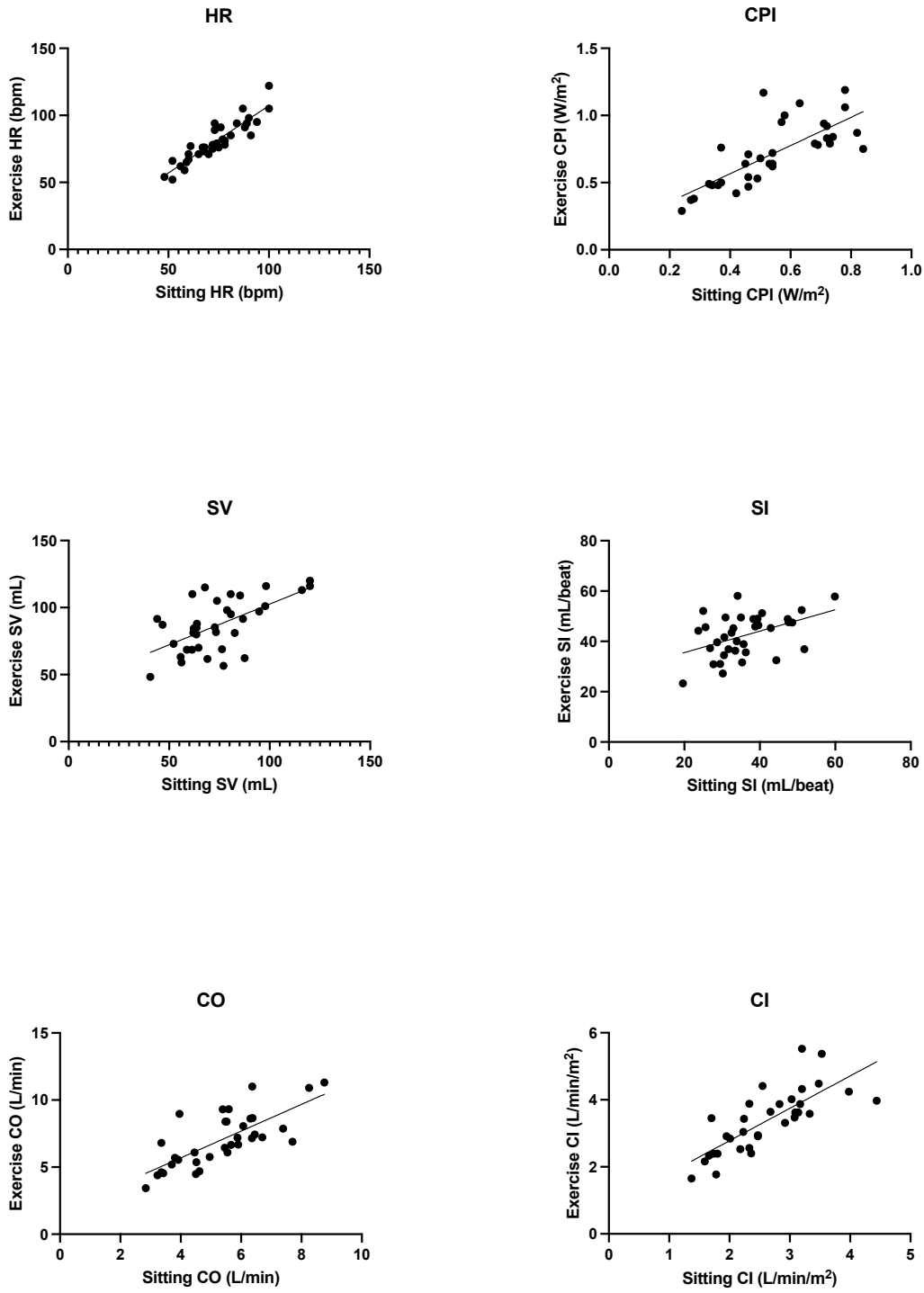

Figure 1: Correlation of post-exercise and resting HR, CPI, SV, SI, CO and CI. The r values are 0.91, 0.76, 0.61, 0.45, 0.74 and 0.77, respectively.

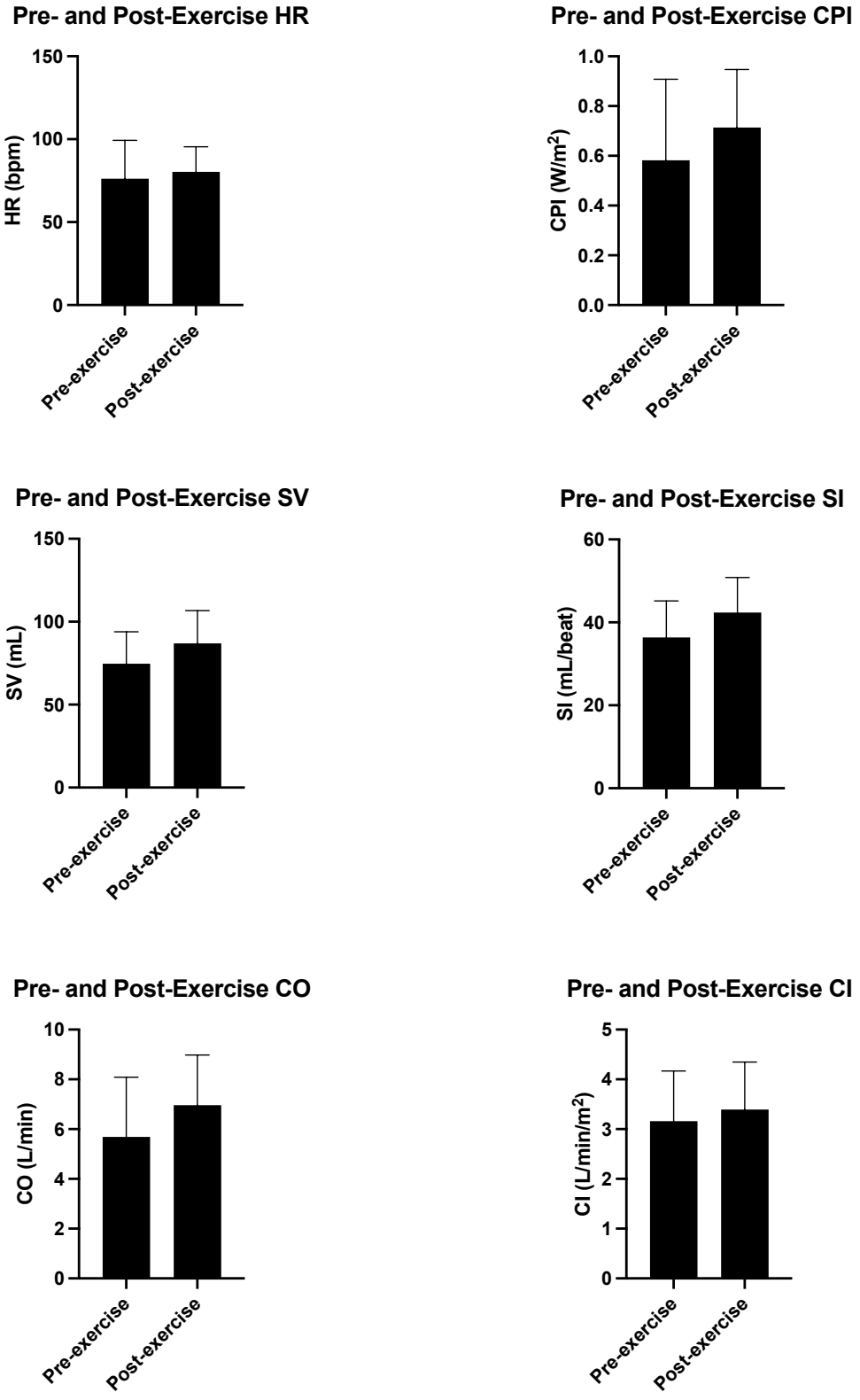

Figure 2: Pre- and post-exercise hemodynamic parameters.