High-Intensity Small Muscle Mass Training in Patients with Heart Failure: Rationale and Design of a Randomized Controlled Trial

CLINICAL TRIAL PROTOCOL

TITLE

High-intensity Small Muscle Mass Training in Patients With Heart Failure: Rationale and Design of a Randomized Controlled Trial

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ABSTRACT

Objective. Small muscle mass training localized to the quadriceps femoris muscle group has been proposed as an intervention to reverse heart failure-related skeletal muscle impairments. Although this training paradigm has demonstrated efficacy in heart failure, it remains to be evaluated in a conventional clinical context. Hence, the aim of this proposed study is to determine the effects of integrating high-intensity small muscle mass training (HISMT) isolated to the knee extensor muscles within a standard heart failure rehabilitation program.

Methods. This single-blind, randomized controlled trial will aim to recruit 70 participants with heart failure. Participants will be randomized to either (i) standard training: combination of upper and lower extremity cardiovascular and resistance-based exercises, or (ii) high-intensity small muscle mass training plus modified standard training: bilateral knee extensor high-intensity small muscle mass training and a modified version of the standard training, so that the total volume of work will be similar to standard training alone. The training interventions will be undertaken twice weekly for 12 weeks in an outpatient clinical setting. Outcome measurements will be performed at baseline and after the 12-week intervention period. The primary outcome will be exercise capacity (6-Minute Walk Test), with secondary

outcomes being physical performance measures, muscle strength, and health-related quality of life. Data will be analyzed using the intention-to-treat principle.

Impact. This study will address a gap in the literature regarding the efficacy of small muscle training under routine clinical conditions for individuals with heart failure. The findings will also provide insight into the effects of high-intensity small muscle mass training within a heart failure rehabilitation program, thus enabling the optimization of exercise prescription for this patient population.

BACKGROUND

Progressive symptoms such as dyspnea, fatigue and exercise intolerance are a typical sequela of heart failure, which can limit participation in physical and social activities, and result in a decreased quality of life (QoL).[1] Although this symptom burden is due to a complex interplay of factors, skeletal muscle impairments play a considerable role in limiting exercise performance.[2] As such, these heart failure-related skeletal muscle alterations have become an important therapeutic focus, with exercise training being the only intervention thus far shown to consistently reverse or mitigate these abnormalities.[3] Despite these findings, the optimal exercise prescription in heart failure remains elusive, which has implications for clinical practice and guideline recommendations and, most importantly, patient outcomes.

Whole-body exercise training, though proven to be beneficial in heart failure,[4] results in recruitment of a large muscle mass and can therefore tax the already compromised cardiac system. Considering this, studies have examined the effects of small muscle mass training, localized to the quadriceps femoris muscle group, as an alternate or supplementary exercise training method for individuals with heart failure.[5,6] By restricting exercise to a single muscle group (approximately 2 kg of working muscle per leg),[7] the central circulation is not excessively burdened, thereby permitting a near-maximal intensity training protocol that has the scope to augment training-induced improvements in skeletal muscle function.

The application of localized knee extensor small muscle mass training in heart failure is supported by a recent literature review that found improvements in whole-body exercise capacity, quadriceps muscle strength and health-related QoL for those with reduced ejection fraction (HFrEF).[8] However, the identified shortcomings of the available evidence that comprised this review, which was based on 13 small-scale studies in a select population with

heart failure (n = 218, HFrEF), limited the generalisability of the findings.[8] Moreover, the knee extensor training was not undertaken as part of a "real-world" heart failure rehabilitation program, but rather as a singular intervention or combined with whole-body cycle ergometer training.

Whilst the preliminary evidence for small muscle training in heart failure suggests effectiveness, it is imperative that this training paradigm is also examined under routine clinical practice conditions, with heterogenous heart failure populations in a conventional rehabilitation context, to verify its broad clinical application. This randomized controlled trial will therefore aim to evaluate whether the addition of knee extensor high-intensity small muscle mass training (HISMT) to a heart failure rehabilitation program results in a greater improvement in exercise capacity, physical performance, muscle strength and health-related QoL.

METHODS

Study Design

This study is designed as a randomized, controlled, single-blind clinical trial with a two-armed parallel design. Figure illustrates the flow of the study from recruitment and screening for eligibility to follow-up assessment and data analysis.

Participants

Seventy participants with heart failure will be recruited from the cohort of patients who are referred to the Gold Coast Hospital and Health Service and The Prince Charles Hospital heart failure exercise-based rehabilitation programs. Inclusion criteria are: age over 18 years, a confirmed diagnosis of heart failure as per the National Heart Foundation of Australia and

Cardiac Society of Australia and New Zealand heart failure guidelines,[4] clinically stable and deemed suitable to participate in an exercise program, and New York Heart Association functional classification I to III.

Participants will be excluded if they have comorbid disease or physical, cognitive or behavioural factors that significantly impact exercise performance, as well as contraindications to exercise testing or training as per the Heart Failure Association and European Association for Cardiovascular Prevention and Rehabilitation position paper.[9]

Randomization and Blinding

Following the baseline assessments, participants will be randomized using random sequence generation and allocation concealment in a 1:1 ratio to either (i) standard training (n = 35), or (ii) HISMT plus modified standard training (n = 35) (Fig.). As the heart failure inclusion criteria is non-selective, a sub-group analysis will be performed if an adequate number of participants with preserved ejection fraction (HFpEF) are recruited. This study will also comprise blinded outcome assessors and data analysis.

Training Protocol

(i) Standard Training (Control Group)

Participants will complete the standard heart failure rehabilitation program provided by the Gold Coast Hospital and Health Service and The Prince Charles Hospital. The heart failure exercise-based rehabilitation programs comprise twice-weekly exercise sessions for 12 weeks, during which a combination of upper- and lower-extremity aerobic and resistance exercises are performed (as specified in Table). The aerobic training entails 4 separate exercises of up to 6-minute duration each, with the use of training modes such as treadmill,

stationary bicycle, rower and arm ergometer. Resistance-based training modalities include free weights, resistance machines and resistance bands, as well as body-weight exercises.

The training sessions begin with a 10- to 15-minute warm-up of low-intensity aerobic exercise and conclude with a 15-minute cool-down consisting of a low-intensity aerobic exercise and static upper and lower body stretches. After each training session, the exercise prescription is reviewed by a physical therapist and progressed based on the person's tolerance of their set program and clinical parameters.

Initial Exercise Prescription: aerobic exercise prescription is based on factors including the baseline exercise capacity assessment of the 6-Minute Walk Test (6MWT), as well as the individual's cardiac condition and co-morbidities. Walking speed on a treadmill is initially prescribed at approximately 80% of the speed achieved during the 6MWT.[10] Baseline exercise prescription for other aerobic training modalities is prescribed using the initial exercise capacity measure, in addition to a target intensity range of 11 to 13 as assessed by the Borg Rating of Perceived Exertion (scores of 6-20) scale.[11]

Resistance exercise training is also prescribed with consideration of the person's cardiac history and co-morbidities, as well as strength measurements such as quadriceps maximal voluntary isometric contraction and hand grip strength conducted during baseline assessments. These exercises are prescribed as per the recommended protocol for individuals with heart failure, such as 8 to 15 repetitions, 1 to 3 sets, and 4 to 8 different exercises for the major muscle groups.[12] The resistance training intensity is monitored with the Borg Rating of Perceived Exertion scale (scores of 6-20), with a target range of 11 to 13 during the initial

sessions.

Training Progression: the intensity and/or duration of the individual exercises are increased after each session for those who can tolerate further increments, with the aim to achieve a target intensity range of 12 to 14 on the Borg Rating of Perceived Exertion scale (scores of 6-20). However, participants showing signs and symptoms of intolerance to their set exercise program require a careful evaluation and potential reduction in the training intensity and/or duration.

(ii) HISMT Plus Modified Standard Training (Intervention Group)

Participants will undertake knee extensor HISMT during the twice-weekly exercise sessions, with the training load increased as tolerated over the 12-week period. During each session, they will also undertake a modified version of the standard training so that the total volume of work is similar to standard training alone. The modified standard training will entail the substitution of lower limb resistance exercises in the standard training with the HISMT protocol as detailed in Table and below.

HISMT Protocol: will consist of bilateral, dynamic, localized knee extension exercises against a resistive load using a knee extensor machine, with the training load increased as tolerated over the 12-week intervention period. This protocol will be undertaken as 3 sets separated by 90 seconds of passive recovery. Each set will consist of up to 25 repetitions, with a concentric-eccentric contraction tempo of 1:2. This 1:2 movement tempo is consonant with previous findings that a combination of slower eccentric movements with faster concentric movements is more effective for muscle hypertrophy.[13] The number of repetitions and sets are based on a laboratory-based study conducted by the authors that evaluated the

efficacy of two types of 12-week knee extensor HISMT protocols (ie, concentric-only HISMT and concentric-eccentric HISMT) for individuals with HFrEF.

Perceived levels of quadriceps muscle fatigue (using the Borg Category-Ratio scale[11]) and knee pain (using a 0-10 integer numerical rating scale; 0 = no pain, 10 = worst pain imaginable[14]) will be ascertained prior to commencing the HISMT protocol and following completion of each set. Participants will be monitored for adverse responses relating to the HISMT during the session, as well as any carry-over from the previous training session.

Calculation of Initial HISMT Load: estimations of knee extensor 1-repetition maximum will be based on previous research that suggested 5-repetition maximum is equivalent to ~80% 1-repetition maximum[15] and calculated using the baseline assessment of knee extensor 5-repetition maximum measurement as described in the outcome measures section. From this calculation, the initial knee extensor HISMT load will be set to 30% of the estimated 1-repetition maximum.

The knee extensor HISMT protocol will be implemented as follows:

- The aim is to achieve quadriceps muscle fatigue at the end of each set, as determined by a rating of ≥7 on the Borg Category-Ratio scale (scores of 0-10), with the object of inducing an adequate mechanical stimulus to facilitate strength and hypertrophy-based adaptations.[16]
- Any provocation of adverse signs or symptoms, or musculoskeletal pain during the HISMT protocol will involve termination of the set.
- Participants will be monitored for partial repetitions (ie, not achieving full knee extension), poor technique due to muscle fatigue, or not understanding the instructions.

- Cueing and correction will be provided as necessary to ensure correct repetitions.

Training Progression: the HISMT load will be progressed by 5-10% after every fourth session as tolerated. However, if the participant is achieving 25 repetitions for all 3 sets, with a rating of muscle fatigue <7 on the Borg Category-Ratio scale and experiences no adverse signs or symptoms, the training load will be progressed at the next session.

Outcome Measures

The outcome measures will be completed at baseline and immediately following the 12-week exercise training period. These will be undertaken by an independent assessor who will be blinded to the participants' group allocation. The outcome measures include:

Primary Outcome Measure

Exercise Capacity:

(i) *6-Minute Walk Test (6MWT):* is an established measurement of functional capacity for individuals with heart failure.[17] The 6MWT will be performed as per European Respiratory Society/American Thoracic Society technical standards.[18] Two tests will be performed to account for a learning effect, with a 15 to 30 minute rest period between them, and the best-of-two 6MWT results recorded in meters.

Secondary Outcome Measures

Physical Performance:

(ii) *Timed "Up & Go" Test (TUG):* is a composite measure of lower limb function and muscle strength, mobility, balance and falls risk.[19] The TUG test will be performed in

accordance with the published protocol.[20] Participants will perform 2 trials, with the fastest time to complete the test recorded in seconds.[21]

(iii) *30-Second Chair Stand Test*: measures the maximum number of repetitive transitions from a sitting to standing position in a 30-second period. The test will be conducted as per standard protocol using a chair with a floor-to-seat height of 44-46 cm.[22] The 30-Second Chair Stand Test will be performed twice, with a 5-minute rest interval between trials, and the best score recorded. A modified version of the test will be permitted and noted for participants requiring use of their upper limbs to assist and replicated at both the pre- and post-intervention assessments.

Skeletal Muscle Strength:

(iv) *Quadriceps Maximal Voluntary Isometric Contraction*: will be assessed using a hand-held dynamometer as described previously.[23] It has been shown to be a reliable and valid measure of isometric muscle strength in healthy populations[24] and is sensitive to detect changes in muscle strength for groups of people with chronic obstructive pulmonary disease.[23] Three maximal knee extension efforts will be performed on each leg, with a rest of at least 1 minute between tests. The quadriceps maximal voluntary isometric contraction will be expressed as a percentage of body weight, which is calculated by adding the best attempt for each leg (in kilograms), then dividing by the participant's body weight and multiplying by 100.

(v) *Knee Extensor 5-Repetition Maximum:* will be assessed on a knee extension chair as per previous methodology.[15] Attempts of 5 repetitions of concentric-eccentric work with progressively increasing load will be undertaken. A 5-repetition maximum will be endeavoured to be reached within 3 to 4 sets to minimise accumulative fatigue, with a 3-minute passive rest period provided between tests.

(vi) *Hand Grip Strength:* has been found to have a moderate correlation with the strength of other muscle groups and is therefore an indicator of overall muscle strength.[25] It will be assessed using a Jamar hydraulic hand dynamometer (Patterson Medical, USA) in line with the standard recommendations.[26] The average of 3 measurements for each side will be recorded in kilograms.

Health-Related QoL:

(vii) *Kansas City Cardiomyopathy Questionnaire (KCCQ-12)*: is a reliable and valid, disease-specific measure of health-related QoL for individuals with heart failure.[27] It is a 12-item, self-administered instrument that quantifies physical and social function, symptoms, self-efficacy, knowledge and QoL, with higher scores reflecting a better health status. The subjects will be provided with the questionnaire and instructed to answer the questions based on their perception of their health status as a result of their heart failure condition for the 2 weeks preceding that timepoint.

Data Analysis

Data will be analyzed using intention-to-treat principle, with the inclusion of all available measures for the participants, regardless of subsequent crossover or non-adherence to the assigned treatment intervention. Descriptive statistics will be presented as numbers and percentages for categorical variables and as means and standard deviation or median and interquartile range for continuous variables according to the normality of distribution. Continuous variables will be screened for normality of distribution using the Shapiro-Wilk test. Between-group participant characteristics will be assessed using independent t-test or a nonparametric equivalent. A one-way analysis of covariance or non-parametric equivalent will be performed to determine changes in dependent variables in response to the training

interventions. Pair-wise comparisons using Bonferroni adjustments will be applied when a significant interaction and/or main effect is detected. Wilcoxon signed rank and Mann-Whitney U tests will be performed to determine between- and within-group differences respectively for the QoL data. Statistical significance will be accepted at $P < .05$.

Sample Size and Power Calculation

The sample size was determined using GPower version 3.1 program (University of Dusseldorf, Germany) and an effect size of 0.65 based on the mean change in 6MWT measure following the concentric-eccentric HISMT intervention as part of the previously discussed laboratory-based study undertaken by the authors (unpublished data). Given the very large effect size of 1.30 for the increase in mean 6MWT distance after the HISMT intervention, a more conservative value was chosen (ie, half this effect size). Using this approach, and conventional α (0.05) and ß (0.80) values, the sample size for the study was calculated as 60 participants. As such, a total of 70 participants will be recruited into this study to account for the calculated sample size and a potential 15% drop-out rate.

ETHICS

Recruitment and Consent

All potential participants will be screened against the inclusion and exclusion criteria by the attending physical therapist. Those who meet the eligibility criteria, and are interested in participating in the study, will be contacted by a member of the research team and provided with verbal and written information regarding the study. Informed written consent will be obtained prior to participation in the study.

Research Ethics

Ethics approval, as well as ratified amendments, for this trial has been obtained from the Gold Coast Hospital and Health Service (reference no. HREC/18/QGC/20) and The Prince Charles Hospital (reference no. HREC/18/QPCH/291) Human Research Ethics Committees.

Confidentiality

Information will be stored during the research study in paper copy and electronic format within a secure location at the Gold Coast Hospital and Health Service and The Prince Charles Hospital sites. The electronic data will have all identifiable information removed once the relevant data has been extracted and linked. After completion of the study, a research team member blinded to treatment allocation will be provided with a copy of the non-identifiable data file for the data analysis. The study data will be kept for a minimum of 5 years following the publication of the results as per the National Health and Medical Research Council guidelines.[28]

Funding

This study is supported by the Gold Coast Health and Gold Coast Hospital Foundation Research Grant Scheme 2017-18 (grant no. RGS2017-SG0023) and The Prince Charles Hospital Foundation Innovation Grant 2018-19 (grant no. INN2018-60). These funding agencies will not play a role in the design, conduct, or reporting of this study.

DISCUSSION

Skeletal muscle alterations are well documented in heart failure and significantly contribute to the hallmark symptoms of dyspnea, fatigue and exercise intolerance.[2] Exercise training interventions, such as small muscle mass training, have been shown to be beneficial in

attenuating these heart failure-related changes.[29] A recent literature review examining isolated knee extensor small muscle mass training in HF has indicated improvements in short-term outcomes for individuals with HFrEF including exercise capacity, muscle strength and QoL.[8] However, the identified limitations of this current evidence base were the paucity of studies, as well as homogenous patient populations and rigid exercise training protocols that do not reflect standard heart failure rehabilitation programs.

This randomized controlled trial will therefore evaluate localized knee extensor HISMT in a clinical context, with the aim to determine whether combining HISMT with a traditional heart failure rehabilitation program yields superior improvements. The study will extend current knowledge relating to small muscle mass training in heart failure and provide a unique perspective on the effects of HISMT under routine clinical conditions. These results can be readily applied to everyday clinical practice and have the scope to optimize patient outcomes through the implementation of effective therapeutic exercise interventions.

The authors acknowledge that there are constraints with this study such as the lack of blinding of participants and heart failure rehabilitation therapists to the allocated intervention. These are essentially due to the nature of exercise interventions and will be mitigated by implementing a standardised protocol for exercise prescription and training progression. Strengths of this study include the adequate statistical power to evaluate the additive effects of HISMT in heart failure, as well as the rigorous study protocol that entails a random allocation process and the blinding of outcome assessors and data analysts.

AUTHOR CONTRIBUTION

All authors made a substantial contribution to the conception and design of the study. The initial draft of this manuscript was completed by M. Louis. However, all authors participated in revising the manuscript and gave their approval of the final version to be published.

Ethics Approval

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Role of the Funding Source

The grant funding will provide resources to enable this research project to be conducted.

Clinical Trial Registration

This study was registered in the Australia and New Zealand Clinical Trial Registry (ACTRN12623000055606).

Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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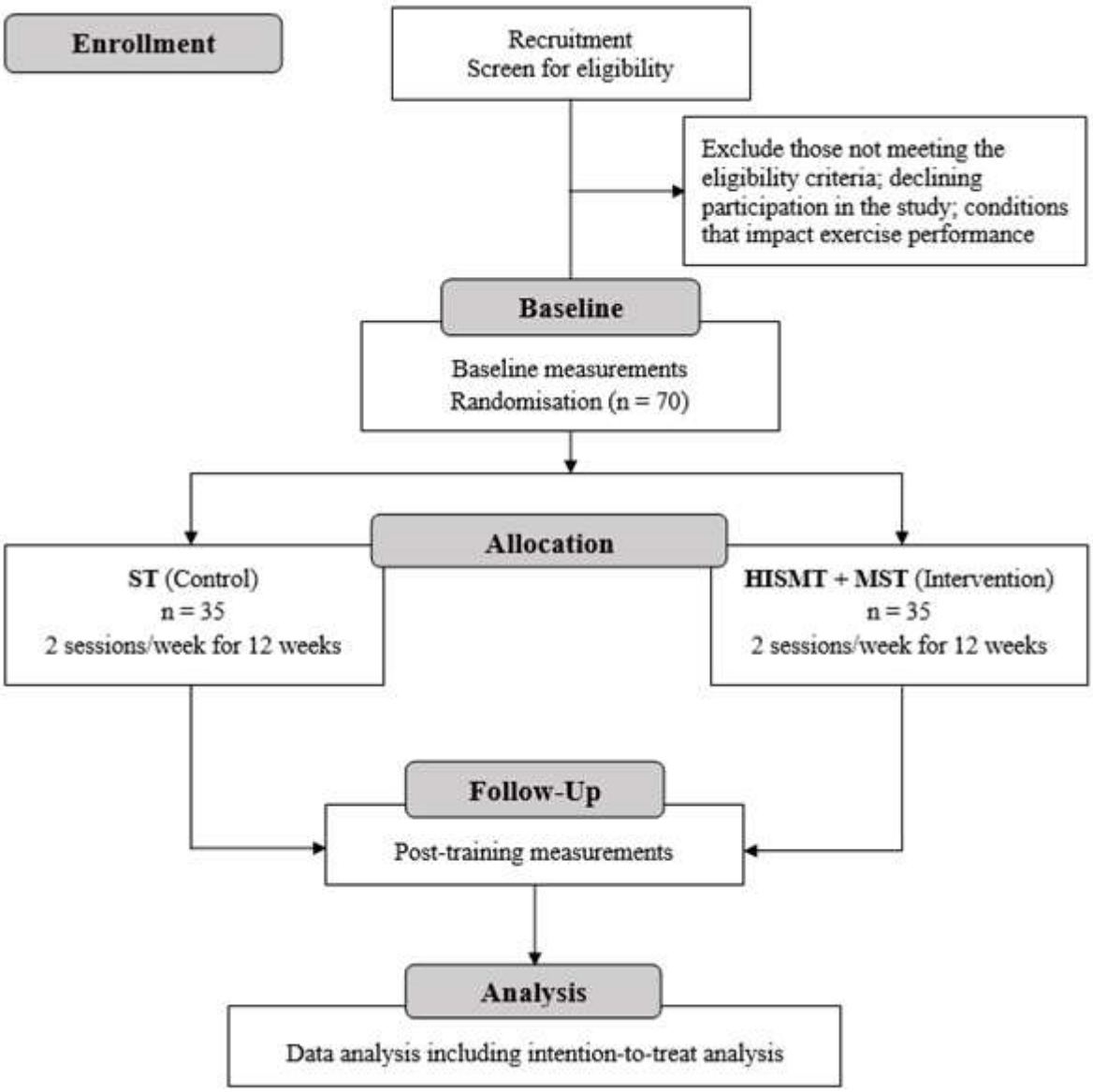

Figure 1. Study flowchart. HISMT = high-intensity small muscle mass training; MST = modified standard training; ST = standard training.

Table. Exercise Prescription and Substitution - Standard Training Versus High-intensity Small Muscle Mass Training Plus Modified Standard Training[a]

ST (Control)[b]	HISMT + MST (Intervention)[b]
1. Stationary bicycle (upright): 6 mins	1. Stationary bicycle (upright): 6 min
2. Lower limb resistance exercises[c] • Sit-to-stand: 8-15 reps, 1-3 sets • Leg press: 8-15 reps, 1-3 sets • Calf press: 8-15 reps, 1-3 sets OR • Sit-to-stand: 8-15 reps, 1-3 sets • Mini squats: 8-15 reps, 1-3 sets • Calf raises: 8-15 reps, 1-3 sets • Step ups: 8-15 reps, 1-3 sets	2. Knee extensor HISMT • 3 sets of up to 25 reps
3. Rower OR arm ergometer: 6 mins	3. Rower OR arm ergometer: 6 min
4. Treadmill: 6 min	4. Treadmill: 6 min
5. Upper limb resistance exercises[c] • Bicep curls: 8-15 reps, 1-3 sets • Seated rows: 8-15 reps, 1-3 sets • Wall push-ups: 8-15 reps, 1-3 sets	5. Upper limb resistance exercises[c] • Bicep curls: 8-15 reps, 1-3 sets • Seated rows: 8-15 reps, 1-3 sets • Wall push-ups: 8-15 reps, 1-3 sets
6. Stationary bicycle (recumbent): 6 min	6. Stationary bicycle (recumbent): 6 min

[a]HISMT = high-intensity small muscle mass training; MST = modified standard training; reps = repetitions; ST = standard training.

[b]Total volume of work performed is anticipated to be similar for both groups.

[c]Generally prescribed as 2 sets.