Changing the time under tension: effects of different forms of concurrent training on inflammatory and cardiometabolic disease indicators

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Certificate of Original Authorship

I, Nicholas Allen, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

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Abbreviations

ANOVA	Analysis of variance
AT	Aerobic training
BFR	Blood flow restriction
BMI	Body mass index
CAD	Coronary artery disease
CCL2	Chemokine (C-C motif) ligand 2
CET	Concurrent exercise training
CRL	Control group
CRP	C-reactive protein
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
GIP	Gastric inhibitory polypeptide
GLP	Glucagon-like peptide
GLUT	Glucose transporter
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HIIT	High-intensity interval training
HOMA-IR	Homeostasis model for assessment of insulin resistance
HSD	Honestly significant difference
HR	Heart rate
HRR	Heart rate reserve
ICAM	Intercellular adhesion molecule
IL	Interleukin
IQR	Interquartile range
IRS	Insulin receptor substrate
LDL	Low-density lipoprotein
MCP-1	Monocyte chemoattractant protein 1
MI	Myocardial infarction
MMP	Matrix metalloproteinase
mRNA	Messenger ribonucleic acid
NAFLD	Non-alcoholic fatty liver disease
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PPO	Peak power output
RA	Receptor antagonist
RM	Repetition maximum
RT	Resistance training
SAA	Serum amyloid A
SAT	Subcutaneous adipose tissue
SE	Stimulus exposure
TBFM	Total-body fat mass
TBLM	Total-body lean mass
TNFα	Tumour necrosis factor α
T2DM	Type 2 diabetes mellitus

TUT	Time-under-tension
VAT	Visceral adipose tissue
VCAM	Vascular cell adhesion molecule
VO2peak	Peak oxygen consumption
VL	Vastus lateralis
vWF	von Willebrand Factor

Table of Contents

List of Figures

List of Tables

Abstract

This thesis examines the effects of different forms of concurrent exercise training (CET) on physiological biomarkers related to cardiometabolic disease risk. Specifically, a modification of CET to emphasise muscle time-under-tension (TUT) during the resistance component is examined as a potential alternative for a population of sedentary older adults. The present thesis seeks to compare conventional CET methods to a modified version (i.e. TUT) on blood-based biomarkers related to systemic inflammation, glucose homeostasis, and cardiovascular disease (CVD) risk. Secondary outcomes include whole-body and regional tissue composition, ultrasound-derived muscular thickness, and physical fitness measures. Further, a greater understanding of the relationship between training stimuli and key functional outcomes is explored.

Data derived from the present investigation is presented within three distinct studies. Firstly, study 1 explored the effect of CET versus TUT on biomarkers related to T2DM, namely inflammatory cytokines (IL-6 and TNFα) and markers of glucose homeostasis, alongside body composition and physical capacity measures. Study 2 describes the effect of these training modalities on CVD-related parameters, including blood-based measures of platelet activity and endothelial function, as well as region-specific fat mass and physical fitness. Finally, study 3 examines the relationship between selected predictor variables (aerobic capacity, muscular strength, and whole-body lean and fat mass) and key prognostic disease indicators (IL-6, TNFα and insulin resistance). A secondary aim of study 3 is to assess the dose-specific response of CET and TUT by quantifying the relationship between overall training volumes and the associated changes in the abovementioned biomarkers.

Thirty-eight sedentary adults completed either 10 weeks of 3 sessions/week of traditional CET or TUT-based concurrent training. Based on baseline characteristics (age, sex, body mass index and fitness) participants were stratified and randomly assigned into CET (n=13), TUT (n=12), or a sedentary control (CRL; n=13). CET involved 30-40 min of resistance training using a 1.5-1.5s tempo, followed by 15-20 min of moderate-intensity endurance training. In contrast, TUT performed the same repetition-volume with a 3-3s tempo, entailing twice the time-under-tension with a reduced mechanical load (resistance lifted). The aerobic component was identical across both groups, comprising non-load-bearing modalities (cycling and rowing). During the intervention period, a control group (CRL) was instructed to maintain habitual lifestyle behaviours. Prior to and following the training intervention, participants underwent testing sessions comprising a venous blood sample for measurement of cardiometabolic disease indicators. Also, a dual-energy x-ray absorptiometry (DEXA) scan provided measures of total-body lean mass (TBLM), fat mass (TBFM) and visceral and subcutaneous adipose tissue mass (VAT and SAT). Other measures included muscle ultrasound of *m. vastus lateralis* thickness, and assessment of maximal strength and endurance capacity. Pre- to post-intervention changes in these health-related parameters were analysed using a mixed-design analysis of variance (ANOVA) for detection of main effects and group x time interactions. In the presence of significant effects, post hoc tests using Tukey's HSD correction located the source of significance at an α-level of 0.05. Moreover, Pearson's correlations were used to quantify relationships between primary outcome variables, and subsequently linear regressions were used to investigate the relationship of the changes in relevant predictors to the variance of individual changes in key disease biomarkers.

Overall, training loads showed the between-group difference in volume-load was not significantly different ($p=0.080$), although when incorporating total lifting time-under-tension, TUT showed a greater overall stimulus exposure (SE) ($p=0.003$). The key findings from this training intervention are that IL-6 showed a significant group x time interaction ($p=0.017$), whereby CET showed the greatest reduction of all groups ($p=0.021$). In contrast, only TUT significantly decreased TNFα ($p=0.016$), without any significant changes in any other inflammatory markers ($p>0.05$). Whilst all groups reduced plasma glucose ($p<0.05$), there were no significant changes in HOMA-IR or other glucose regulatory markers ($p>0.05$). Further, CVD-related markers of inflammatory and platelet activity showed no significant changes following training ($p>0.05$). CRP was unchanged ($p>0.05$), while MCP-1 increased in CRL ($p=0.015$), without significant change in CET and TUT ($p>0.05$). Exercise-induced reductions were only evident for p-selectin, which decreased in CET ($p=0.009$).

Whole-body lean and fat mass were improved most by CET, as it was the only group to show a decrease in TBFM ($p=0.027$) and an increase in TBLM ($p<0.001$). In contrast, regional measures showed TUT provided the greatest reduction in SAT ($p=0.030$) and CET preferentially decreased VAT ($p=0.049$). Further, thickness of *m. vastus lateralis* showed a significant group x time interaction ($p=0.002$), decreasing in CRL ($p=0.028$) and increasing in CET ($p=0.003$). Physical fitness parameters showed a mode-specific response whereby CET preferentially increased quadriceps strength ($p=0.001$) and TUT provided the greatest increase in VO_{2peak} ($p<0.001$). Both CET and TUT increased peak power output ($p<0.05$).

Linear regression analyses revealed that the change in IL-6 was explained by the change in strength and TBLM (y = 0.355 – (0.035 x strength) + (0.774 x TBLM)). In contrast, for HOMA-IR no predictors were significant in a linear regression model, and no significant correlations were present with any variable. The cumulative volume-load showed that the change in IL-6 was significantly and negatively correlated with total volume-load (r = -0.387, p=0.011). The change in TNFα was negatively correlated with total volume-load (r = -0.396, p = 0.018). However, when controlling for strength changes, these correlations were no longer significant. Moreover, in a linear regression equation volume-load was significantly associated with strength (y = 3.24 + (0.137 x volume-load); p = 0.023) and VO_{2peak} (y = 0.925 + (0.013 x volume-load); p = 0.022). Conversely, volume-load did not significantly explain TBLM (y = 0.431 + (0.002 x volume-load); p = 0.072) or TBFM changes (y = 0.002 – (0.004 x volume-load); p = 0.076).

The present findings suggest that modifying the resistance component through novel modalities such as TUT may have small, yet relevant consequences that can aid the tailoring of exercise stimuli to individual needs. Specifically, although CET was superior to reduce IL-6, TUT showed greater decreases in TNFα. By comparison, traditional CET was superior to increase TBLM and muscular strength and decrease TBFM, while TUT preferentially decreased VAT and increased VO_{2peak}. For individuals seeking to enhance body composition, physical capacity, and cardiometabolic disease indicators, conventional CET strategies may be most appropriate, although TUT does provide some distinct benefit. Importantly, increased muscular strength seems to be an important predictor of a decreased inflammatory milieu, and greater training volumes are associated with larger strength gains, recognising the standardisation of the aerobic component. Such

findings provide evidence for practitioners to tailor the exercise training stimuli from concurrent training to better suit the specific demands of sedentary, aged populations.

The present findings will assist exercise professionals and individuals in the prescription of CET for older adults. In particular, the safety and efficacy shown in the current studies reiterates the importance of CET modalities to offset age-related increases in cardiometabolic risk. More specifically, conventional CET strategies incorporating higher RT loads may provide superior strength adaptations, while prolonged TUT techniques may enhance endurance parameters. Mode-specific adaptations further show that traditional CET can confer enhancements in body composition, alongside an anti-inflammatory effect. Future research should investigate the role of these training strategies to manage existing cardiometabolic diseases, and elucidate the long-term effects of CET, particularly with regards to injury rates, training adherence, and sustainability