

Marquette University

e-Publications@Marquette

Exercise Science Faculty Research and
Publications

Exercise Science, Department of

2-2017

Cardio-Protection Afforded by **B**-Blockade Is Maintained During Resistance Exercise

Alexander V. Ng

Marquette University, alexander.ng@marquette.edu

Jason M. Conviser

University of Wisconsin

Shawn S. Rockey

University of Wyoming

D. Paul Thomas

University of Wyoming

Follow this and additional works at: https://epublications.marquette.edu/exsci_fac

Recommended Citation

Ng, Alexander V.; Conviser, Jason M.; Rockey, Shawn S.; and Thomas, D. Paul, "Cardio-Protection Afforded by B-Blockade Is Maintained During Resistance Exercise" (2017). *Exercise Science Faculty Research and Publications*. 105.

https://epublications.marquette.edu/exsci_fac/105

Cardio-Protection Afforded by β -Blockade Is Maintained During Resistance Exercise

Jason M. Conviser

*Department of Kinesiology, University of Wisconsin
JMC Healthcare Associates
Milwaukee, WI*

Alexander V. Ng

*Program in Exercise Science, Marquette University
Milwaukee, WI*

Shawn S. Rockey

*Division of Kinesiology and Health, University of Wyoming
Laramie, WY*

D. Paul Thomas

*Division of Kinesiology and Health, University of Wyoming
Laramie, WY*

Abstract

Objectives: Whether or not the cardio-protective effect of β -adrenergic blockade is retained during resistance exercise has not been systematically evaluated. Therefore the purpose of this study was to measure selected cardiorespiratory responses to isometric exercise involving hand-gripping, single-leg extension, or double-leg dead-lift, under placebo (control), β_1 -selective (atenolol), and non-selective (propranolol) adrenergic blockade conditions.

Design: Eleven young male adults were evaluated in a randomized, double-blinded, repeated measures study design and performed all three exercise modalities at 30% of maximal voluntary contraction under placebo, atenolol and propranolol conditions.

Methods: Heart rate, systolic and diastolic blood pressure, rate-pressure product, oxygen uptake, cardiac output, stroke volume and total peripheral resistance were directly measured or calculated at rest and during the third minute of each of the three exercise modes.

Results: Irrespective of drug condition, a graded pressor response was observed going from rest to exercise so that rest < handgrip < leg extension < dead-lift for heart rate, systolic and diastolic blood pressures, rate-pressure product and oxygen uptake ($p < 0.05$ for all). Cardiac output only increased with the dead-lift mode of exercise ($p < 0.01$). Importantly β -adrenergic blockade with either atenolol or propranolol similarly attenuated the rise in heart rate, and systolic blood pressure; thus rate-pressure product demonstrated a mode-of-exercise by drug interaction effect ($p < 0.001$) with the greatest reductions seen with the dead-lift procedure.

Conclusions: The findings indicate that cardio-protection afforded by selective or non-selective β -blockade at rest is preserved during isometric exercise and even enhanced once heart rate increases above 100 beats min^{-1} .

Keywords: Rate-pressure product; Myocardial oxygen consumption; Pressor response; Isometric muscle contractions

1. Introduction

The hemodynamic response to static or resistance exercise differs considerably from that to dynamic exercise. Increases in heart rate, stroke volume, and skeletal muscle blood flow are the hallmarks of dynamic exercise, while an increase in blood pressure is the signature of isometric-like muscular contractions, the so-called "pressor" response.¹

It is recognized that both types of exercise can increase the heart's requirement for oxygen (MvVO_2). The principal factors affecting MvVO_2 are heart rate (HR) and blood pressure, so that the product of HR and systolic blood pressure (SBP), or rate pressure product (RPP)

Journal of Science and Medicine in Sport, Vol. 20, No. 2 (February 2017): pg. 196-201. [DOI](#). This article is © Sports Medicine Australia, published by Elsevier Ltd. and permission has been granted for this version to appear in [e-Publications@Marquette](mailto:Publications@Marquette). Sports Medicine Australia, published by Elsevier Ltd. does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Sports Medicine Australia, published by Elsevier Ltd..

correlates strongly with $\dot{V}O_2$ measured during exercise whether it be dynamic, static or a combination of both.² Beta-adrenergic blockade that lowers $\dot{V}O_2$ through its effects on both HR and blood pressure is a common pharmacological intervention for a variety of populations including individuals with angina, arrhythmias, hypertension, and migraines as well as post-myocardial infarction patients.^{3, 4 and 5} However the response to static exercise involving muscle mass of different sizes while simultaneously undergoing selective β_1 - or non-selective β_1, β_2 -adrenergic blockade has not been systematically characterized.

Therefore the purpose of this study was to measure the hemodynamic and metabolic responses to static exercise involving three different-sized muscle masses under placebo (control), and β -adrenergic blockade conditions. In this manner we sought to determine whether the cardio-protective effect of β -blockade is preserved during static exercise. We also sought to ascertain whether difference in responses observed were muscle-mass and/or cardio-selective vs. non-selective blockade dependent.

2. Methods

Eleven male volunteers ranging in age from 19 to 28 yr, with a height of 175 ± 3 cm, and a body mass of 71 ± 2 kg served as participants for the study. All participants were non-smokers, were not taking any medications, and while active, had not engaged in training for competitive sports, or in a regimen of strength training for six months prior to the start of the study. Signed informed consent for all procedures was obtained in accordance with standards established by the University of Wisconsin-Madison Human Subjects Committee.

Subjects reported to the laboratory at the same time of day for each test, having been given written and verbal reminders not to participate in any form of exercise or to consume stimulants or alcohol within the previous 24 h. On the initial visit to the laboratory (Visit 1, [Fig. 1](#)), oxygen consumption ($\dot{V}O_2$) and electrocardiographic patterns (EKG; CM5 lead configuration) were measured on subjects while they performed a graded cycle ergometer test to volitional fatigue. The test protocol included 3 min of warm-up at 75 W followed by an initial

workload of 100 W for 2 min. The resistance was subsequently increased by 50 W every 2 min until the point of exhaustion which was defined as inability to hold the required cadence of 60 ± 10 revolutions per minute (RPM) at the highest workload attained. This cycle test also elicited a $\dot{V}O_{2\max}$ of 49 ± 2 ml $\text{kg}^{-1} \text{min}^{-1}$ from the eleven participants. Individual final workload achieved on the incremental cycle ergometer test was used to determine the submaximal constant workload which was set at 65% of the previously attained maximal workload. Two days later subjects returned to the laboratory (Visit 2) and following a warm-up consisting of pedaling at 75 W for 3 min, cycled at a resistance corresponding to 65% of individual maximal workload until a steady-state was achieved, as indicated by less than a 5 beats min^{-1} increase in HR during a 60 s period. Subsequently all subjects repeated the submaximal constant workload test under placebo (Visits 3a to 6a), propranolol (Visits 3b to 6b) and atenolol (Visits 3c to 6c) conditions (see Fig. 1).

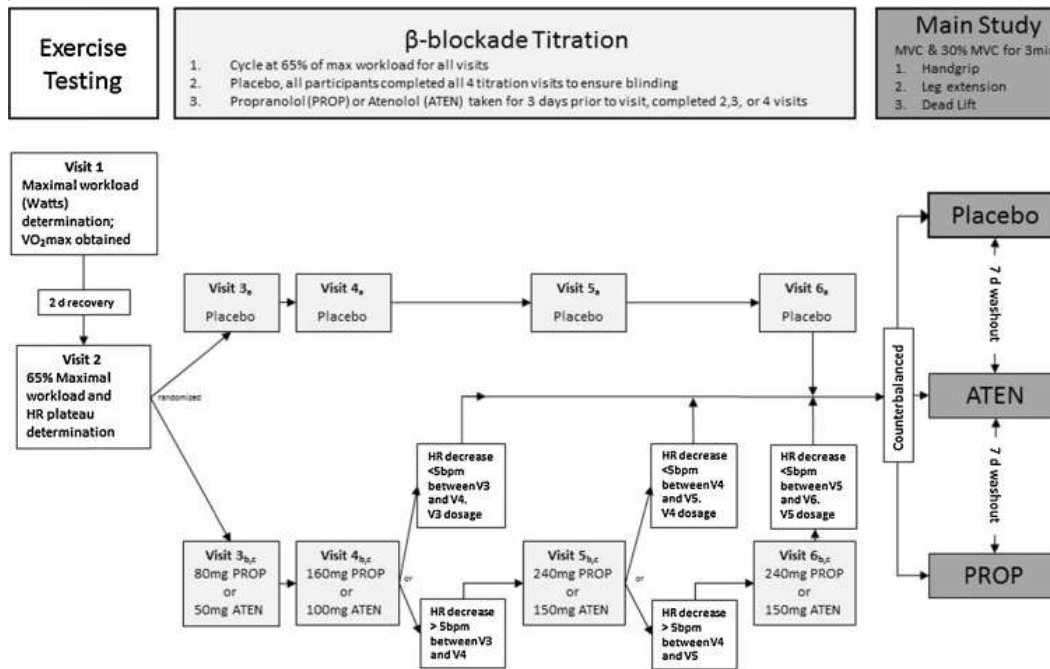


Fig. 1. Protocol schematic of exercise testing, β -blockade titration algorithm, and main study. During the titration phase, all participants took part in four visits while on placebo regardless of lack of change in HR plateau between visits in an effort to blind them from their treatment.

The β_1 -selective (atenolol, (ATEN)) or non-selective β -blocker (propranolol, (PROP)) as well as a placebo pill were randomly administered in a double-blind fashion and doses of the two β -blockers were individually titrated according to each individual's HR response to the submaximal workload (see below). Initially all subjects took either placebo, PROP (80 mg), or ATEN (50 mg) for a period of three days, and reductions in HR caused by non-selective or selective blockade during the constant workload test were measured. Three days later subjects returned to repeat the same cycle ergometer test with doses of the two β -blockers increased to 160 mg and 100 mg, respectively. If no further reduction in HR was observed with the higher dose in a particular subject, the initial dosage of either PROP or ATEN was used for that subject. However if the higher dose caused a further reduction in HR (>5 beats min^{-1}) a higher dose of PROP (240 mg) and ATEN (150 mg) was administered for three days and the test repeated a second time. This routine was repeated until the individual HR response to the 65% maximal workload test decreased less than 5 beats min^{-1} from the previous test. As anticipated, placebo administration did not affect HR response to the 65% workload test (Fig. 1).

Completion of the titration experiments indicated that, for PROP, four of the 11 subjects achieved complete blockade taking 80 mg day^{-1} , four achieved it with 160 mg day^{-1} , with the remaining three requiring 240 mg day^{-1} . For ATEN, three of the subjects demonstrated a HR plateau with the lowest dose (50 mg day^{-1}), 6 subjects required the intermediate dose (100 mg day^{-1}), and two subjects required 150 mg day^{-1} (Fig. 2). As also shown in Fig. 2, titration of the mean HR response of all 11 subjects to PROP resulted in a significant 20 beats min^{-1} reduction in HR (143 to 123 beats min^{-1}) going from the un-medicated state to 80 mg day^{-1} ($p < 0.005$), while treatments of 160 and 240 mg day^{-1} did not result in further significant decreases in HR. For ATEN, mean HR reductions were observed going from the un-medicated state to 50 mg day^{-1} (142 to 119 beats min^{-1} , $p < 0.005$), and from 50 to 100 mg day^{-1} (119 to 110 beats min^{-1} ; $p < 0.05$), but not from 100 to 150 mg day^{-1} . During the main study (see below) a seven day wash-out period was employed between each of the three experimental

sessions to ensure that all β -blockers were completely metabolized prior to commencement of the subsequent experimental session.

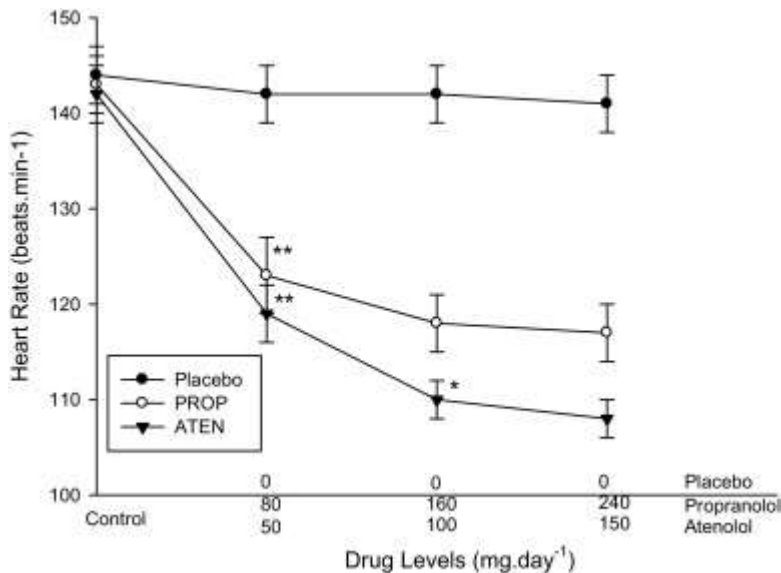


Fig. 2. Mean titration curves ($n = 11$ subjects) in response to placebo, propranolol (PROP) and atenolol (ATEN) β -blockade while cycling on an ergometer at 65% individual maximal workload. For PROP, 80 mg day⁻¹ resulted in a significant HR reduction from the un-medicated state (**, $p < 0.005$), with no further reduction in HR seen with 160 or 240 mg day⁻¹. For ATEN, 50 mg day⁻¹ resulted in a significant HR reduction from the un-medicated state (**, $p < 0.005$), with a further reduction (*, $p < 0.05$) seen going from 50 to 100 mg day⁻¹, but not from 100 to 150 mg day⁻¹.

The main study involved three identical experimental sessions. Three days prior to each session, subjects self-administered their individually-titrated dose of one of the two β -blockers (or placebo). The last dose was taken at least 3 h, but not more than 6 h prior to arrival at the laboratory. During each visit to the laboratory subjects performed a maximal voluntary contraction (MVC) for one-arm handgrip (HG), single-leg extension (LE), and double-leg dead-lift, (DL). Based on these values, subjects subsequently maintained 30% of MVC for 3 min while performing each of the three types of static contractions. 30% MVC was chosen to allow time to collect all of the required parameters of interest (see below) and also because this intensity had been used previously in the literature to study the exercise pressor response.^{6, 7 and 8}

Hand-gripping was carried out using a calibrated Stoelting dynamometer adapted so that tension exerted during contraction was displayed on a dual beam oscilloscope (Portland, OR) and a LCD digital

Ohm multimeter (Radio Shack, Fort Worth, Texas). The left arm was supported by a small metal tray to reduce extraneous muscular effort. Single-leg extension was performed on a padded table on which strain gauges had been mounted to a steel bar secured to the legs of the table. The subject was secured by a seat belt. The angle of the knee joint was set at 70 degrees prior to full extension to facilitate tension production in this maneuver. The strain gauges were calibrated with known weights at the angle at which force was generated (70 degrees) and was linear within the range studied. The DL maneuver involved outfitting the subject with a modified parachute harness in a semi-squat position. Subject angle at the knee was set at 70 degrees, with the trunk, shoulders and back extending vertically up through the harness. The subject was connected to a wooden platform specifically designed to hold the steel bar strain gauge previously described for LE. During this maneuver the subject utilized both trunk and lower limb, but not upper limb muscles. This permitted blood pressure measurements to be made on the upper extremity. The 30% MVC force being maintained by each subject during the three minute period for HG, LE and DL under each condition (placebo, PROP, ATEN) was observed on the oscilloscope, and a digital readout provided visual reinforcement of the constant tension required.

The parameters of HR, SBP, DBP, RPP, $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), cardiac output (\dot{Q}), stroke volume (SV), and total peripheral resistance (TPR), were obtained either directly or by calculation, both at rest and during 30% MVC for the three modes of exercise. $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated using a Beckman E2 gas analyzer and a Godart Capnograph, respectively calibrated with standard gases verified by Scholander analysis, as reported previously during isometric exercise.⁶ SBP and DBP were obtained with a Puritan Bennett Infrasonde Model 04000 electronic blood pressure monitor. Measurements taken in this manner had previously been validated against intra-arterial pressures obtained under similar experimental conditions.⁹ Cardiac output (\dot{Q}) was determined using the CO_2 rebreathing technique as described by Jones and Campbell¹⁰ as employed previously during static exercise.⁷

The measured \dot{Q} was divided by the recorded HR to obtain SV. Mean arterial blood pressure (MABP) was calculated from the

measured SBP and DBP ($MABP = DBP + (SBP - DBP)/3$). This calculation then permitted the additional calculation of TPR from MABP divided by \dot{Q} .

Data were analyzed by a two-way repeated measures analysis of variance (ANOVA) for exercise and drug main effects as well as for interactions. Post-hoc contrasts to determine differences between means were carried out when appropriate, with α set at $p < 0.05$.

3. Results

Neither selective (β_1) nor non-selective ($\beta_{1,2}$)-adrenergic blockade significantly affected maximal tension development (and consequently 30% MVC) for HG, LE and DL as shown in [Table 1](#) expressed in Newtons (N). This permitted evaluation of the effects of ATEN and PROP on hemodynamic and metabolic responses to these same three modes of isometric exercise that was not compounded by differences in force development between the three treatment conditions.

Table 1. Heart rate (HR) measured at rest, and at 30% MVC (Newtons (N)) for handgrip (HG), single-leg extension (LE) and double-leg dead-lift (DL), measured under placebo, propranolol (PROP) and atenolol (ATEN) conditions.

	Condition	Parameter	Placebo ^a	PROP ^a	ATEN ^a
HG	Rest	HR (beats min ⁻¹)	65 ± 2	54 ± 2 ^b	53 ± 3 ^c
		HR (beats min ⁻¹)	77 ± 3	67 ± 4 ^b	63 ± 4 ^c
		30% MVC (N)	128	128	137
LE	Rest	HR (beats min ⁻¹)	87 ± 2	73 ± 3 ^c	72 ± 3 ^c
		30% MVC (N)	128	118	128
DL	Rest	HR (beats min ⁻¹)	115 ± 6	88 ± 3 ^c	88 ± 4 ^c
		30% MVC (N)	588	579	598

^a Within a treatment condition (placebo, PROP, ATEN) HR increased significantly going from rest to HG to LE to DL (all $p < 0.05$ or greater, except for HG to LE under PROP conditions ($p < 0.06$)).

^b $p < 0.005$ versus placebo for rest or exercise mode (HG,).

^c $p < 0.001$ versus placebo for rest or exercise mode (LE, HG, DL).

As also indicated in [Table 1](#), HR increased significantly ($p < 0.005$) going from rest to HG to LE to DL, with the single exception of HG to LE under the PROP condition ($p < 0.06$). However

there was also a significant overall drug by mode-of-exercise interaction ($p < 0.001$). The HR lowering effects of both β -blockers were most pronounced with the largest contracting muscle mass (DL). Both ATEN and PROP caused a significant and identical 24% reduction in HR during DL compared to reductions seen either at rest or during the other two modes of exercise modalities ranging from 13 to 18%.

As shown in [Fig. 3](#), Panel A, all three modes of isometric exercise incrementally increased SBP above rest so that rest < HG < LE < DL (all $p < 0.005$). Both ATEN and PROP resulted in similar overall reductions ($p < 0.05$) in SBP compared to the placebo condition. In contrast to their effects on HR, there was no interaction effect so that the resting reductions in SBP caused by both β -blockers were similar to those seen during all three exercise modes. Increases in muscle mass involvement during exercise caused incremental and significant increases in DBP under all three drug conditions, so that rest < HG < LE < DL (all $p < 0.05$). Compared to the placebo condition, while both PROP and ATEN lowered DBP at rest and during HG, LE, and DL, only the reductions seen with ATEN were significant ($p < 0.05$).

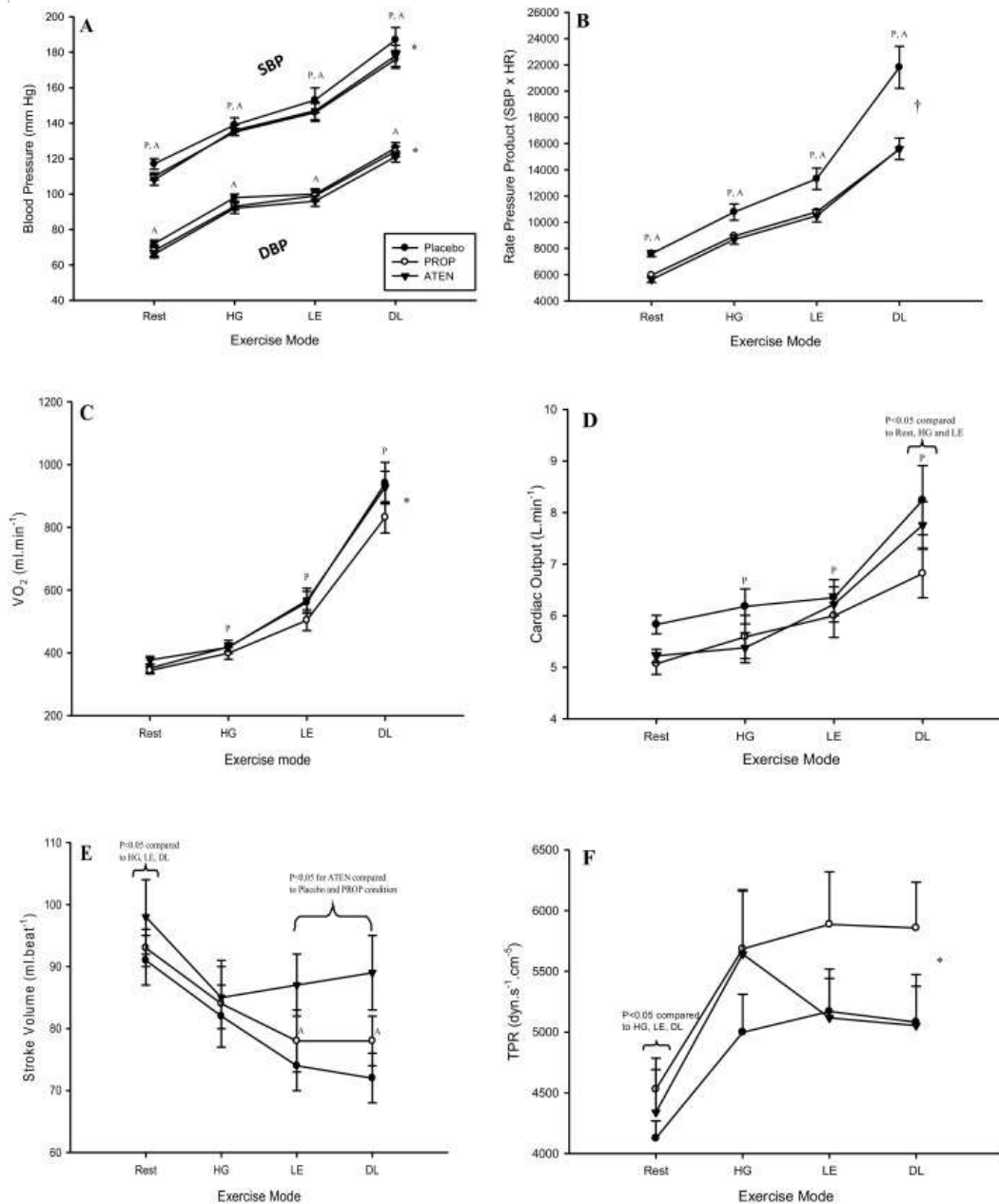


Fig. 3. Panels A–F indicate systolic and diastolic blood pressure (SBP, DBP), rate-pressure product, $\dot{V}O_2$, cardiac output, stroke volume, and total peripheral resistance at rest, and during hand-grip (HG), leg-extension (LE) and dead-lift (DL) exercise under placebo (control), propranolol (PROP) and atenolol (ATEN) conditions. A significant overall exercise main effect is indicated by * ($p < 0.05$ or greater); a significant overall exercise mode-by-drug interaction effect is indicated by † ($p < 0.001$). Significant differences in PROP or ATEN from placebo ($p < 0.05$ or greater), either at rest, or during HG, LE and DL are indicated by P (propranolol) or A (atenolol).

RPP showed a significant mode-of-exercise by drug interaction ($p < 0.001$) similar to that observed above for HR, so that the effects of either ATEN or PROP on estimated $Mv\dot{V}O_2$ were more pronounced with the largest contracting muscle mass (DL) causing a greater relative reduction in RPP compared to reductions seen at rest or employing smaller muscle masses (Fig. 3, Panel B). Again rest < HG < LE < DL (all $p < 0.05$) irrespective of drug condition, with both β -blockers causing significant RPP reductions during all three modes of exercise ($p < 0.05$), while only ATEN caused a significant reduction at rest ($p < 0.05$).

Fig. 3, Panel C also indicates that going from rest to HG exercise resulted in a significant increase in $v\dot{V}O_2$ ($p < 0.05$); each subsequent mode of exercise involving more muscle mass caused a further increment in $v\dot{V}O_2$ compared to the previous one so that rest < HG < LE < DL ($p < 0.005$ for exercise mode comparisons). PROP but not ATEN caused a significant reduction ($p < 0.005$) in $v\dot{V}O_2$ during all three exercise modes but not at rest.

Cardiac output (\dot{Q}) increased slightly above resting with HG and LE, but only the increase seen with DL was significant ($p < 0.001$, Fig. 3, Panel D). Cardiac output (\dot{Q}) during DL was also significantly higher than with either HG or LE (both $p < 0.001$). Propranolol (PROP) but not ATEN caused a significant reduction ($p < 0.01$) in \dot{Q} both at rest and during all three modes of exercise. The exercise-induced increase in \dot{Q} was achieved solely by increasing HR as SV decreased from rest to HG ($p < 0.05$), but did not decrease further going from HG to LE or to DL (Fig. 3, Panel E).

Handgrip (HG) exercise caused an increase ($p < 0.05$) in TPR above resting, with no further increment seen for LE or DL (Fig. 3, Panel F). There was also a trend ($p < 0.1$) for PROP but not ATEN to elevate TPR compared to the placebo condition but this was not significant.

4. Discussion

The main purpose of the current study was to determine whether β -adrenergic blockade altered hemodynamic and metabolic

responses to isometric exercise involving small, medium and large muscle masses, and also whether differences could be discerned between cardio-selective vs. non-selective β -blockade. The main finding from this study was that the cardio-protective effect of β -adrenergic blockade is maintained during isometric exercise involving muscle mass of contrasting sizes at least when this musculature is developing only 30% of its maximal potential force. Thus RPP as a non-invasive measure of $MvVO_2$ was significantly lower during HG, LE and DL with either PROP or ATEN with no obvious advantage of the cardio-selective vs. non-selective blocker. Furthermore this protection appears to be enhanced with the largest contracting muscle mass (i.e., DL) as indicated by the overall mode of exercise-drug interaction effect. This was presumably due to the more pronounced β -blockade effects on HR once HR rose above $100 \text{ beats min}^{-1}$, as occurred with the DL maneuver, where HR increase is thought to be primarily due to sympathetic stimulation.⁸

β -adrenergic blockade did not however prevent the pressor response classically seen with resistive exercise so that for both SBP and DBP there were incremental and significant increases going from rest to HG to LE to DL; pulse pressure thus remained fairly constant under placebo, PROP and ATEN conditions. While both β -adrenergic blockers had a similar lowering effect on SBP, the overall lower DBP seen with ATEN supports the tenet that selectivity of β -adrenoreceptor blockade was maintained with the doses of ATEN employed in the current study. The highest blood pressures (both SBP and DBP) were seen with the greatest amount of musculature involved (DL) under the three conditions. As TPR remained unchanged for HG, LE or DL, the increased \dot{Q} observed only with DL was achieved by an increase in HR, as SV during all three modes of exercise also remained relatively constant. The reduction in SV going from rest to HG exercise seen in the current study was also observed previously in older but not young men during hand-gripping.¹¹ This reduction in SV in response to isometric exercise was also observed previously with LE.⁷ The tendency for TPR to be higher with PROP in the current study may also explain the lower \dot{Q} observed both at rest and during HG exercise under non-selective blockade as was also seen in a previous study.¹²

The findings from the current study also add to the body of literature as to whether or not the magnitude of the pressor response to isometric exercise is dependent on the size of the contracting muscle mass and specifically how this response might be affected by both β_1 - and $\beta_{1,2}$ -blockade. Earlier studies^{13, 14 and 15} reported no significant relationship between size of actively contracting muscle mass and magnitude of the cardiovascular response to isometric contractions when percent of MVC was held constant. In contrast, more recent studies^{16, 17 and 18} reported a direct relationship, providing evidence for a greater cardiovascular response to static contractions when progressively larger muscle groups were utilized. The overall response of HR, \dot{Q} , SBP, DBP, and $\dot{V}O_2$ to the recruitment of increasing muscle mass observed in the current study would support the concept of muscle size-dependent hemodynamic and metabolic responses to isometric exercise, even though this response was modified somewhat by both β -blockers. Thus the similar reductions in HR induced by PROP and ATEN both at rest and during exercise resulted in a lower overall \dot{Q} with PROP but not ATEN. An elevated SV compensated for the reduced HR under ATEN but not PROP conditions in an attempt to maintain \dot{Q} . This difference appeared to be due to the trend towards higher overall vascular resistance with non-selective β -blockade as might be expected.

In the current study the metabolic cost of performing the various exercises as measured by $\dot{V}O_2$ was also impacted by β -adrenergic blockade. While $\dot{V}O_2$ was increased going from rest to exercise ($p < 0.05$), but more so going from HG to LE ($p < 0.005$), and from LE to DL ($p < 0.001$), PROP caused significant reductions in $\dot{V}O_2$ during all three exercise modes that may be related to the simultaneous reductions observed in \dot{Q} under non-selective blockade. This finding would again support the hypothesis that under somewhat more peripherally vasoconstricted conditions induced by non-selective β -blockade, additional reductions in blood flow delivery to working muscle could impact $\dot{V}O_2$ and rate of fatigue.^{19 and 20}

The similar force exerted under placebo, PROP and ATEN conditions for the three exercise modalities in the current study was not evaluated out to the point of task failure to assess whether non-selective blockade reduced the time that this force could be

maintained. Interestingly, in the study of Unsworth et al.²⁰ they compared maximal force (100% MVC) both before and after 3 min of sustained LE at 30% MVC under placebo, metoprolol and propranolol conditions (same recorded absolute force). The second 100% MVC contraction showed a greater reduction under propranolol compared to either metoprolol or placebo conditions, which did not differ from each other. The results from their study imply that peripheral blockade of β_2 receptors may result in additional constraints to blood flow to working muscle at least at 30% MVC.

A limitation of the current study was that we did not image or use other techniques to directly measure size of contracting muscle mass in these experiments. Nevertheless, we purposely chose muscle groups contrasting in size, consistent with those employed in previous studies.^{6 and 10}

5. Conclusion

From a clinical perspective, β_1 -selective adrenergic blockers are prescribed for cardiac patients more often than non-selective blockers. However the latter category of drugs would appear to be associated with a lower risk of thrombo-embolic events in heart-failure patients,²¹ and therefore the findings from the current study that non-selective and selective β -blockade are no different with respect to their cardio-protective effect during submaximal isometric exercise as estimated from RPP is also relevant.

Practical implications

- A class of drugs known as β -adrenergic blockers are commonly taken to lower heart rate and blood pressure.
- In this manner these drugs lower oxygen requirements of the heart thus providing cardio-protection.
- This protection is maintained during submaximal static exercise such as weight lifting.
- Earlier fatigue is a potential outcome for an individual performing resistance exercise while on a non-selective β -blocker.

Acknowledgments

Financial support for this research was provided by the University of Wisconsin-Madison. The authors wish to thank the participants for volunteering to be a part of the study and Dr. Evan Johnson for assistance with figure development. The authors do not have any financial disclosures or conflicts of interest to report.

References

- ¹ L.B. Rowell. *Human cardiovascular control*. Oxford University Press, New York (1993), pp. 302–325
- ² R.R. Nelson, F.L. Gobel, C.R. Jorgensen, *et al.* Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation*, 50 (1974), pp. 1179–1189
- ³ L. Pavia, G. Orlando, J. Myers, *et al.* The effect of beta-blockade therapy on the response to exercise training in postmyocardial infarction
- ⁴ B.B. Agbor-Etang, J.F. Setaro. Management of hypertension in patients with ischemic heart disease. *Curr Cardiol Rep*, 17 (2015), p. 119
<http://dx.doi.org/10.1007/s11886-015-0662-0>
- ⁵ P. Kokkinos, C. Chrysohoou, D. Panagiotakos, *et al.* Beta-blockade mitigates exercise blood pressure in hypertensive male patients. *J Am Coll Cardiol*, 47 (2006), pp. 794–798
- ⁶ D.R. Seals, R.A. Washburn, P.G. Hanson, *et al.* Increased cardiovascular response to static contraction of larger muscle groups. *J Appl Physiol*, 54 (1983), pp. 434–437
- ⁷ G.R. Bezucha, M.C. Lenser, P.G. Hanson, *et al.* Comparison of hemodynamic responses to static and dynamic exercise. *J Appl Physiol*, 53 (1982), pp. 1589–1593
- ⁸ F.J. Nagle, D.R. Seals, P. Hanson. Time to fatigue during isometric exercise using different muscle masses. *Int J Sports Med*, 9 (1988), pp. 313–315
- ⁹ M. Sagiv, P. Hanson, M. Besozzi, *et al.* Left ventricular responses to upright isometric handgrip and deadlift in men with coronary artery disease. *Am J Cardiol*, 55 (1985), pp. 1298–1302
- ¹⁰ N.L.C. Jones, E.J. Campbell. *Clinical exercise testing*. W.B. Saunders, Philadelphia, PA, USA (1982), pp. 130–151
- ¹¹ K. Krzeminski, G. Cybulski, A. Ziemba, *et al.* Cardiovascular and hormonal responses to static handgrip in young and older healthy men. *Eur J Appl Physiol*, 112 (2012), pp. 1315–1325
- ¹² C.E. Martin, J.A. Shaver, D.F. Leon, *et al.* Autonomic mechanisms in hemodynamic responses to isometric exercise. *J Clin Invest*, 54 (1974), pp. 104–115

- ¹³ A.R. Lind, H.L. Taylor, P.W. Humphreys, *et al.* The circulatory effects of sustained voluntary muscle contraction. *Clin Sci*, 27 (1964), pp. 229–244
- ¹⁴ U. Freyschuss. Elicitation of heart rate and blood pressure increase on muscle contraction. *J Appl Physiol*, 28 (1970), pp. 758–761
- ¹⁵ D.I. McCloskey, J.H. Mitchell. Reflex cardiovascular and respiratory responses originating in exercising muscle. *J Physiol*, 224 (1972), pp. 173–186
- ¹⁶ B. Saltin, G. Sjøgaard, F.A. Gaffney, *et al.* Potassium, lactate, and water fluxes in human quadriceps muscle during static contractions. *Circ Res*, 48 (1981), pp. I18–I24
- ¹⁷ J.H. Mitchell, D.R. Reeves, H.B. Rogers, *et al.* Autonomic blockade and cardiovascular responses to static exercise in partially curarized man. *J Physiol*, 413 (1989), pp. 433–445
- ¹⁸ D.R. Seals. Influence of muscle mass on sympathetic neural activation during isometric exercise. *J Appl Physiol*, 67 (1989), pp. 1801–1806
- ¹⁹ G. Sjøgaard, G. Savard, C. Juel. Muscle blood flow during isometric activity and its relationship to muscle fatigue. *Eur J Appl Physiol Occup Physiol*, 57 (1988), pp. 327–335
- ²⁰ K. Unsworth, A. Hicks, R. McKelvie. The effect of beta-blockade on plasma potassium concentrations and muscle excitability following static exercise. *Pflugers Arch*, 436 (1998), pp. 449–456
- ²¹ O.R. De Peuter, P.C. Souverein, O.H. Klungel, *et al.* Non-selective vs. selective beta-blocker treatment and the risk of thrombo-embolic events in patients with heart failure. *Eur J Heart Fail*, 13 (2011), pp. 220–226