Anti-hypertensive treatment effect on exercise blood pressure and exercise capacity in older adults

Short title: Anti-hypertensives and exercise BP

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Abstract

Background

An exaggerated blood pressure (BP) response to exercise and low exercise capacity are risk factors for cardiovascular disease (CVD). The effect of pharmacological anti-hypertensive treatment on exercise BP in older adults is largely unknown. This study investigates these effects accounting for differences in exercise capacity.

Methods

Participants enrolled in the Southall and Brent Revisited (SABRE) study undertook a 6-min stepper test with expired gas analysis and BP measured throughout exercise. Participants were stratified by anti-hypertensive treatment status and resting BP control. Exercise systolic and diastolic BP (exSBP & exDBP) were compared between groups using potential outcome means (95% CIs) adjusted for exercise capacity. Exercise capacity was also compared by group.

Results

In total, 659 participants were included (mean age±SD: 73±6.6years, 57% male). 31% of normotensive and 23% of hypertensive older adults with controlled resting BP had an exaggerated exercise BP. ExSBP was similar between normotensive and treated/controlled individuals (mean(95%CI): 180(176,184)mmHg versus 177(173,181)mmHg, respectively) but was higher in treated/uncontrolled and untreated/uncontrolled individuals (mean(95%CI): 194(190,197)mmHg, $p<0.001$ & 199(194,204)mmHg, $p<0.001$, respectively); these differences persisted after adjustment for exercise capacity and other confounders.

Exercise capacity was lower in treated versus normotensive individuals (mean(95%CI) normotensive: 16.7(16.0,17.4)ml/kg/min); treated/controlled: 15.5(14.8,16.1)ml/kg/min, p=0.009; treated/uncontrolled: 15.1(14.5,15.7)ml/min/kg, p=0.001) but was not reduced in untreated/uncontrolled individuals (mean(95%CI): 17.0(16.1,17.8)ml/min/kg, p=0.621).

Conclusion

Irrespective of resting BP control and despite performing less exercise, anti-hypertensive treatment does not fully mitigate an exaggerated BP response to exercise suggesting residual CVD risk in older adults.

Key words

Antihypertensive Agents, Blood Pressure, Exercise Tolerance, Exercise, Risk Factors, Cardiovascular Diseases

Introduction

Hypertension carries an elevated risk of cardiovascular disease (CVD)[1] and all-cause mortality[2] that is not fully mitigated by pharmacological treatment, even with blood pressure (BP) control at rest.[3] An exaggerated BP response to exercise (exercise hypertension) is a risk factor for CVD independent of resting clinic BP and may be indicative of uncontrolled BP not detected by standard clinic BP measures.[4-6] In hypertensive individuals, an exaggerated exercise BP has been attributed to underlying dysregulation of sympathetic nerve signalling (a hyper-sensitive metabo-reflex response).[7-10] This is important because current anti-hypertensive treatments do not target mechanisms that would potentially desensitize the metabo-reflex and, while anti-hypertensive treatment may effectively reduce resting BP, comprehensive physiological studies suggest they may be variously effective at addressing exercise BP.[11] The effect of pharmacological anti-hypertensive treatment on exercise BP has not previously been described in large observational, population-based study samples. Understanding this further is clinically relevant as we are missing an important aspect of hypertension control and mitigation of CVD risk.

Aerobic exercise capacity is a measure of global cardiorespiratory function. Reduced exercise capacity is a well described risk factor for subsequent CVD morbidity and mortality.[12-14] The relationship between aerobic fitness and incident hypertension is well established,[13,15-17] however, aside from the specific effects of β-blockers, the effect of anti-hypertensive treatment (mono- or combined) on aerobic capacity, with or without BP control at rest, is largely unexplored. Thus, even with BP control at rest, if exercise BP is exaggerated and exercise capacity impaired, this would indicate that older

adults are not benefiting from optimal CVD risk mitigation even when prescribed treatment and this is going undetected by resting BP measurements.

Therefore, this study aims to determine if anti-hypertensive treatment mitigates an exaggerated exercise BP response in older adults independently of resting blood pressure control and the amount of exercise achieved (exercise capacity). We also aim to determine the effect of treatment and BP control on measures on aerobic exercise capacity as indicators of excess CVD risk in older adults and explore the effects of different classes of anti-hypertensive agents.

Methods

Participants

Participants for this analysis were drawn from a tri-ethnic cohort study of older adults resident in West London, UK: the Southall and Brent Revisited (SABRE) study.[18] Data presented in this study were collected at the 25-30 year follow-up visit (2015–2018).[19] Participants were excluded from undertaking exercise tests according to co-morbidity contraindications given in the American College of Sports Medicine (ACSM) guidelines.[20]

All procedures were in accordance with the principles of the Helsinki declaration, all participants gave written informed consent and the study was approved by the National Research Ethics Service (NRES) Committee London—North Fulham.

Anthropometrics

Height was measured barefoot using a stadiometer (Seca 217; Seca, Hamburg, Germany). Weight was measured using digital bio-impedance scales (BC-418; Tanita, IL, USA).

Blood samples

Non–fasting blood samples were obtained in the morning of the clinic visit. Participants were permitted to take a light breakfast before clinic attendance. HbA1c was measured in stored blood samples and total cholesterol was measured from fresh samples. Both were processed using the Cobas c automated analyser (Roche Diagnostics, Burgess Hill, UK).

Questionnaires

Information on ethnicity, physical activity, history of cardiovascular disease (CVD), heart failure, hypertension and medication use were obtained by questionnaire. If a diagnosis of arterial hypertension was self-reported, this had previously been established by the participants healthcare team. Diabetes was defined as self-reported physician diagnosis, reported use of glucose-lowering medication or an elevated measurement of HbA_{1c} above the guideline cut-off value for diagnosis of type 2 diabetes (T2DM; ≥48 mmol/mol [>6.5%]).

Resting blood pressure

Resting systolic and diastolic blood pressure (SBP and DBP) and heart rate were measured during the morning of the clinic visit in the seated position (MIT Elite Plus, Omron, The Netherlands) according to European Society of Hypertension (ESH) / European Society of Cardiology (ESC) 2013 guidelines.[21] In short, BP was measured in both arms with an appropriate cuff size, with a minimum of three subsequent measures in the arm with the higher BP. Clinic BP was estimated as the average of the final 2 readings. Resting pulse pressure (PP) and mean arterial pressure (MAP) were calculated from the final reading. MAP was calculated as: DBP + ⅓SBP.

Blood pressure treatment and control

Uncontrolled resting BP was defined as having either SBP ≥140mmHg or DBP ≥90mmHg.[22] Participants considered pharmacologically 'treated' for hypertension included participants who self-reported a hypertension diagnosis and use of medication as treatment or self-reporting use of mono- or combined anti-hypertensive therapy in the list of medication provided. We stratified participants into one of four categories based on resting BP control and treatment status: normotensive (untreated/controlled), treated/controlled, treated/uncontrolled and untreated/uncontrolled. Participants were considered 'untreated' if they reported taking an anti-hypertensive medication and also reported that this was for a condition other than hypertension. Participants who reported that they had previously been diagnosed with hypertension but had never taken any medication and had controlled resting blood pressure measured during the study visit were excluded from all analysis. Participants who reported taking antihypertensive medication but did not report which agent they were taking were excluded from analyses investigating number of agents and antihypertensive class.

Aerobic exercise capacity

A sub-maximal, self-paced, 6-minute stepper test (6MST) was performed in those participants who did not meet exclusion criteria according to ACSM guidelines.[20] This has previously been validated in this age-group against walking pace and sub-maximal oxygen consumption achieved in the 6 minute walk test.[23] A portable expired gas analysis system including a Polar heart rate monitor (K4B2; COSMED, Rome, Italy) was used to measure breath-by-breath whole-body oxygen consumption ($\dot{V}O_2$) and heart rate during the 6MST. Exercise capacity was defined using 2 variables: (1) the number of steps achieved during the tests and (2) the highest $\dot{V}O_2$ of a rolling 60s average during

exercise. Metabolic equivalents (METs) achieved during exercise were calculated by dividing the highest achieved $\dot{V}O_2$ (ml/min) by 3.5.

Sub-maximal exercise blood pressure

Exercise blood pressure was measured during the second, fourth and sixth minute of the sub-maximal exercise test using a specialist motion-tolerant blood pressure monitor (Tango M2 Stress Test Monitor, SunTech Medical, USA). Exercise BP outcomes are defined as the highest values measured during the exercise test: highest exercise SBP (exSBP) and highest exercise DBP (exDBP). ExSBP was also considered adjusted for METs achieved during the 6MST to give exSBP in mmHg/MET. Exercise PP (exPP) and MAP (exMAP) were determined for each measurement during exercise and the final values defined as the greatest value calculated. We categorised participants as having an exaggerated BP response to exercise if their exercise BP was above guideline thresholds for exercise hypertension (for men: exSBP≥210mmHg or exDBP≥110mmHg; for women: exSBP≥190mmHg or exDBP≥110mmHg).[24]

Statistical methods

Statistical analysis was carried out in STATA 17 (StataCorp College Station, TX, USA). Categorical data are presented as frequency (%). Continuous data were examined for normality; normally distributed sample data are summarised as means±SD and skewed data as medians (interquartile range). Comparison of participant characteristics in the treated versus untreated group was done using an unpaired Student's *t* test for continuous data and χ^2 test for categorical data.

Outcomes (exSBP, exDBP and exercise capacity measures) were compared between normotensive participants and each of three hypertensive groups (treated/controlled,

treated/uncontrolled and untreated/uncontrolled) using potential outcome means (POMs). POMs were estimated using an augmented inverse probability weighted (AIPW) estimator with a linear outcome model and logit treatment model. AIPW is a statistical approach that combines propensity-based inverse probability weighting (where the contribution of an individual's data is weighted by the propensity score) and regression adjustment. AIPW has the advantage that it is 'doubly robust', i.e., only one of the inverse probability weighting or regression adjustment need be correctly specified to obtain an unbiased effect estimator.[25]

Average treatment effects (ATE) were estimated for treatment with any anti-hypertensive agent (alone or in combination) and for treatment with 1, 2 or ≥3 agents versus untreated using AIPW. Estimates were adjusted for: 1) age, sex & ethnicity (model 1); 2) model 1 plus presence of cardiovascular disease (CVD) (model 2), type-2 Diabetes Mellitus (T2DM), total cholesterol and years of education; 3) model 2 with exclusion of participants prescribed β-blockers because of the well described effects of β-blockers on exercise capacity and exercise heart rate (model 3). Auxiliary covariates clinic BP (resting values for the specified outcome) and exercise capacity (steps completed, as a measure of the volume of exercise performed) were specified in the outcome models of model 2 and model 3. Histograms of propensity scores for all models were examined for appropriate overlapping.

Results

Participant characteristics

In total, 659 participants who attended the SABRE visit 3 clinic completed the 6MST with exercise blood pressure measurements (mean age±SD: 73±6.6years, 57% male). The

flow chart presented in Appendix 1 describes steps leading to inclusion of the final study sample). There were 166 (25%) normotensive individuals, 187 (28%) treated hypertensive individuals with controlled resting BP, 204 (31%) treated hypertensive individuals with uncontrolled resting BP and 103 (15%) hypertensive individuals who were not treated and had uncontrolled resting BP (table 1). Participants on antihypertensive treatment included a higher proportion of men and participants of South Asian or African Caribbean origin, they were generally older with a higher BMI and had greater prevalence of T2DM and CVD. Treated participants achieved fewer steps and a lower $\dot{V}O_2$ compared to those not on treatment (table 1). Nine participants reported taking antihypertensive medication but did not report which agent they were taking. A small proportion of individuals (n=11) were considered 'untreated' despite taking one of the stated medications for a condition other than hypertension.

Exaggerated exercise BP, defined as an exSBP or exDBP above the cut-offs for diagnosis of exercise hypertension was observed in 31% of normotensive, 23% of treated-controlled, 43% of treated-uncontrolled and 64% of untreated-uncontrolled individuals (table 1).

[Table 1]

Exercise BP and exercise capacity in normotensive versus hypertensive individuals stratified by treatment and resting BP control

Sub-maximal exercise blood pressure

ExSBP was similar between the normotensive and the treated hypertensive group with controlled resting BP (mean(95%CI): 180(176,184)mmHg, blue bars versus 177(173,181)mmHg, p=0.266, orange bars; figure 1a) but was higher in both hypertensive groups with uncontrolled resting BP, regardless of treatment (mean(95%CI)

for treated/uncontrolled: 194(190,197)mmHg, p<0.001, grey bars and for untreated/uncontrolled: (199(194,204)mmHg, p<0.001, yellow bars; figure 1a). These differences persisted after adjustment for the amount of exercise performed (steps completed) and other confounders as well as after exclusion of participants taking β-blockers (models 1-3).

ExDBP was lower in treated/controlled hypertensive versus normotensive individuals and similar in treated/uncontrolled hypertensive versus normotensive individuals (mean(95%CI) normotensive: 91(89,93)mmHg, blue bars versus treated/controlled: 88(86,90)mmHg, p=0.047, orange bars and treated/uncontrolled: 90(88,93)mmHg, p=0.650 grey bars; figure 1b). ExDBP was higher in untreated/uncontrolled hypertensive versus normotensive individuals (mean(95%CI): 100(97,103)mmHg, p<0.001; figure 1b). These differences persisted after adjustment for confounders and exclusion of participants taking β-blockers (model 3).

[Figure 1]

Change in systolic blood pressure with exercise corrected for METs (ΔSBP/METs) was similar in groups with controlled resting BP (mean(95%CI) normotensive: 11.9(11.0,12.9), blue bars versus treated/controlled: 11.8(10.9,12.8), p=0.885, orange bars, figure 2a). In hypertensive individuals with uncontrolled resting BP, the change in BP with exercise was smaller than the normotensive individuals for both groups (mean(95%CI) treated/uncontrolled: 10.1(9.3,10.9), p=0.004, grey bars and untreated/uncontrolled: 10.4(9.4,11.5), p=0.034, yellow bars, figure 2a).

ΔDBP/METs was similar between normotensive and treated/controlled individuals (mean(95%CI) normotensive: 3.5(3.0,4.1), blue bars versus treated/controlled:

3.5(3.0,4.1), p=0.927, orange bars and treated/uncontrolled: 90(88,93), p=0.650 grey bars; figure 2b). In hypertensive individuals with uncontrolled resting BP, ΔDBP/METs was only lower than the normotensive values in the treated group (mean(95%CI) treated/uncontrolled: 2.2(1.6,2.7), p=0.001 grey bars; untreated/uncontrolled: 3.2(2.4,3.9), yellow bars, p=0.419, figure 2b).

[Figure 2]

Exercise capacity

The number of steps achieved during the 6MST was lower in both treated hypertensive groups versus normotensive individuals (mean(95%CI) normotensive: 217(205,229)steps, blue bars versus treated/controlled: 204(193,215)steps, p=0.118 orange bars and treated/uncontrolled: 195(184,205), p=0.005 grey bars; figure 1c) but was similar between normotensive and untreated/uncontrolled hypertensive individuals (mean(95%CI) for untreated/uncontrolled: 220(205,234), p=0.781 yellow bars; figure 1c). These differences were attenuated towards the null with adjustment for confounders and exclusion of participants prescribed β-blockers (figure 1c, model 3).

Highest achieved $\dot{V}O_2$ was lower in both treated hypertensive groups versus the normotensive group regardless of BP control at rest (mean(95%CI) for normotensive: 16.7(16.0,17.4), blue bars versus treated/controlled: 15.5(14.8,16.1), p=0.009 orange bars and treated/uncontrolled: 15.1(14.5,15.7), p=0.001 grey bars; figure 1d) but was similar in untreated hypertensive versus normotensive individuals (mean(95%CI) for untreated/uncontrolled: 17.0(16.1,17.8), p=0.621 yellow bars; figure 1d). These differences persisted after adjustment for confounders and exclusion of participants taking β-blockers (figure 1d, model 3).

Untreated versus treated individuals overall

ExSBP was slightly lower in individuals treated with any anti-hypertensive agent (monotherapy or combination), however, this effect was attenuated towards the null after adjustment for resting blood pressure, the amount of exercise performed and other co-variates (table 2). When participants prescribed a β-blocker were excluded, the treatment group had a 3mmHg higher exSBP compared to the untreated group. ExDBP and exMAP were lower in treated versus untreated participants, these effects persisted after further adjustment (table 2). ExPP was larger in treated versus untreated participants, this effect was as much as 7.6mmHg when individuals prescribed a β-blocker were excluded (table 2). Exercise capacity (steps achieved and highest measured $\dot{V}O_2$) was lower in treated individuals, these effects persisted after adjustment for confounding factors and exclusion of participants prescribed β-blockers (table 2).

Untreated individuals versus individuals treated with 1, 2 or ≥3 anti-hypertensive agents

There was a progressive increase in treatment effect as the number of anti-hypertensive agents prescribed increased from 1 to ≥3. Prescription of ≥3 anti-hypertensive agents provided the greatest effect on exercise blood pressure with a 12.6mmHg exSBP lowering effect and an 8.7mmHg exDBP lowering effect on mean values (table 2, model 1). The effect size on exSBP was attenuated by half after adjustment for resting BP, CVD, T2DM and exercise performed (table 2, model 2) and attenuated by nearly 3 times when participants prescribed β-blockers were excluded from the analysis (table 2, model 3). Prescription of ≥3 anti-hypertensive agents was associated with the greatest reduction in exercise capacity; even after adjustment for confounders individuals prescribed ≥3 agents, on average, achieved 44 fewer steps and a peak $\dot{V}O_2$ of 3.0 ml/kg/min less during the

exercise test. This effect size was partially attenuated when participants prescribed β-blockers were excluded (table 2, model 3).

[Table 2]

Untreated individuals versus individuals treated with specific classes of anti-hypertensive treatment agent

When compared to all untreated individuals, exSBP was lower in individuals prescribed angiotensin II receptor blockers (ARBs) (orange bars), α-blockers (yellow bars), β-blockers (blue bars) and diuretics (green bars) but was similar in individuals prescribed angiotensin converting enzyme inhibitors (ACEi, purples bars) and calcium channel blockers (CCBs, grey bars) (figure 2a). The confidence intervals were wide for the estimated effect sizes; only in individuals prescribed ARBs and diuretics did the 95%CI not include the null (figure 2a). ExDBP was lower in participants prescribed any treatment agent compared to untreated participants. Again, 95% confidence intervals were wide for these estimates, however, the effects for ACEi, CCBs, and α-blockers did not include the null (figure 2a).

Exercise capacity was lower in all individuals prescribed an anti-hypertensive treatment compared to those who were untreated. Estimated effects of each agent were a reduction capacity by ~25-40steps and a reduction in measured $\dot{V}O_2$ by ~1-4ml/kg/min. Estimated effects for ACEi on steps completed and measured $\dot{V}O_2$ were small and 95% confidence intervals included the null. Although the effect size was large (28 less steps than untreated individuals), the confidence interval for the effect of α-blockers on steps completed also included the null.

[Figure 2]

Sensitivity Analyses

Two sensitivity analyses were performed and the results are provided in Appendices 2 and 3. First, the analysis was repeated with exclusion of individuals (n=11) considered 'untreated' despite taking one of the stated medications for a condition other than hypertension (Appendix 2). Second, analysis was repeated with exclusion of individuals with heart failure or who failed to report information about heart failure (Appendix 3). A similar pattern of results was observed with exclusion of each condition.

Discussion

Anti-hypertensive treatment controls exercise systolic BP to levels observed in normotensive individuals only if resting blood pressure is also controlled. 32% of normotensive and 24% of hypertensive older adults with controlled resting BP still had an exaggerated exercise BP. Being on treatment is associated with a lower exercise capacity. Treatment with ≥3 anti-hypertensive agents provided the greatest exSBP control (~9mmHg lower than in untreated individuals). Together these findings suggest that, even with anti-hypertensive treatment and resting BP control, there remains an excess risk of CVD in hypertensive older adults.

This study presents novel insight into the exercise blood pressure response in older adults in the presence, or absence, of pharmacological treatment for hypertension. Despite BP control at rest, 24% of treated/controlled hypertensive individuals still had an exercise BP above the cut-off for exercise hypertension. Worryingly, we also observed 32% of normotensive (untreated) older adults with an exaggerated exercise BP. This highlights the importance of out-of-clinic or exercise measures in guidance of treatment and mitigation of excess CVD risk even where resting BP is controlled.[4-6] Previous work

described an elevated exSBP response in treated hypertensive individuals despite BP control at rest.[11] Our findings are in line with this, however, a limitation of our study is that we used a self-paced exercise test, where others have used incremental workload tests. This may explain why we observed a smaller proportion of treated/controlled hypertensive individuals with an exaggerated exercise BP. However, we also present average exSBP values by BP group adjusted for the exercise performed (steps completed) and show, overall, a similar exSBP between normotensive and treated/controlled hypertensive individuals suggesting some reduction in exercise BP in treated individuals with resting BP control. A potential explanation for elevated exercise BP in the presence of controlled resting BP in some individuals could be the presence of hyper-sensitivity of afferent SNA[7-10] which would elicit an exaggerated exercise BP response irrespective of resting BP. As current pharmacological treatment options do not target this mechanism is could remain unchecked in some individuals. These findings highlight the importance of undertaking 'out-of-clinic' or exercise BP measures, however, in order to provide robust clinical recommendations, future work is necessary to establish the specific pathophysiological mechanisms underpinning these differences in older adults. it remains challenging to offer apposite clinical recommendations based on these findings.

In treated individuals with uncontrolled resting BP, exercise SBP was elevated to levels similar to that of untreated hypertensive individuals, even after adjustment for the lower exercise capacity. Nearly half of treated/uncontrolled hypertensive individuals (43%) were above the cut-off for exercise hypertension. One explanation for the lack of both resting and exercise BP control is that this group of treated patients were not compliant with prescribed medication, however, the lower exDBP and exMAP in treated compared to untreated indicates this is unlikely to be the complete explanation. On average exDBP

was only elevated in untreated hypertensive individuals, suggesting anti-hypertensive treatment effectively reduced exDBP. Treated individuals had ~4mmHg lower exDBP than untreated, even after adjustment for resting diastolic BP. We hypothesize that this difference could be attributable to vasodilation and lower peripheral resistance resulting from anti-hypertensive treatment.

Aerobic exercise capacity is reduced in both treatment groups indicating increased risk of CVD even with BP control at rest.[12,14] This is aligned with a previously described strong negative association between hypertension and fitness [17,26] and may be explained by the negative vascular consequences of hypertension, such as microvascular rarefaction and endothelial dysfunction. However, it is interesting that in the untreated hypertensive group exercise capacity was similar to levels observed in the normotensive group, even after adjustment for presence of diagnosed CVD or T2DM. This could be attributed to more extreme (pre-clinical) vascular dysfunction in the treated group related to a longer duration of hypertension such that anti-hypertensive treatment only partially reverses vascular remodelling.[27] It is also plausible that the action of some anti-hypertensive agents may blunt aerobic capacity. Mechanisms for this include blunting augmentation of cardiac output, a known effect of β-blocker therapy, or blunting of peripheral vasoconstriction which may limit the capacity to redistribute blood to exercising muscles. It is important to recognise a reduction in exercise capacity because it indicates elevated CVD risk which is undetected by resting or exercise/ambulatory BP measurements. It is also important to consider adjustment for the difference in exercise capacity to account for the potential that reduced exertion in our treated-controlled group may have provided a lower stimulus, therefore lower exercise BP.[28] Furthermore, improving aerobic exercise capacity is a potential treatment target. Because this analysis

is cross-sectional, we cannot be sure if reductions in exercise capacity were present before or after initiation of treatment. Further work is necessary to better describe the effect of treatment on aerobic exercise capacity and to better understand the safety of exercise training as a therapeutic target in older adults with hypertension.

Study strengths and limitations

This prospective observational study uses a population-based sample representative of older adults living in the UK. A limitation of the study is that we are unable to determine compliance with medication among participants, and treatment optimisation is via primary care. There may also be factors that influence a participant's decision to seek treatment which we were unable to control for and contribute to residual bias. We believe our sample fairly well represents the population; 53% of treated older adults had uncontrolled resting BP, although these rates are higher than reported in the Health Survey for England,[29] they are slightly fewer than previously reported in another UK cohort.[2] Our assessment of resting blood pressure (therefore categorisation of control at rest) was based on measurements made in the morning as part of the research visit and although trained research staff took care to measure blood pressure at the same time of day under the same resting conditions in all participants, we cannot be certain there was no 'white-coat' effect in some participants who would then have been stratified incorrectly into the hypertensive-untreated group. Furthermore, BP control is presently based on in-clinic measurements only and we cannot confirm 'true' BP control without home or ambulatory BP measurements.

As we used a sub-maximal, self-paced exercise test, we cannot be sure of the factors which limited exertion and therefore exercise capacity. However, this type of exercise captures a more representative measure at a self-assigned intensity which would be

carried out in the participants 'real-world' exercise session. We also provided standardized test instructions to try and align exertion. We used thresholds for exaggerated exercise BP that have been established for maximal tests [30,31] because cut-off values for sub-maximal exercise hypertension have not previously been defined.[4,32] It is possible that these thresholds are too high; lowering thresholds would increase the proportion of participants assigned exercise hypertension but is unlikely to change the pattern of our results. Previous large studies that have assessed exercise BP in a similar age group during treadmill exercise, suggest peak values for SBP of 196(160-234)mmHg in men and 185(154-220)mmHg in women and for DBP 84(70-100)mmHg and 83(70-96)mmHg for men and women, respectively.[31] Despite the different exercise mode undertaken here, we describe a similar range of mean exercise SBP and DBP values (exSBP:~177-199mmHg and, exDBP: ~88-100mmHg). A direct comparison of blood pressure during different modes of exercise would be a useful future research objective.

Conclusion

These data suggest that exSBP is unsatisfactorily controlled; even when resting BP is normal, an exaggerated exercise BP is present in 23% of treated individuals and 31% of normotensive individuals. This highlights the importance of measuring ambulatory or exercise BP in order to optimize treatment and mitigate CVD risk. In additions, the reduced exercise capacity in treated hypertensive older adults is a concerning CVD risk factor that should be explicitly addressed in further research.

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Tables

	Normotensive (n=166)	Treated/ controlled (n=187)	Treated/ uncontrolled (n=204)	Untreated/ uncontrolled (n=102)
Sex male, n(%)	74(45%)	112(60%)	130(64%)	56(55%)
Ethnicity E;SA;AFC(%)	60;23;17	42;31;27	29;46;25	49;29;22
Age (years)	71±6.5	73±6.7	75±6.3	72±6.4
BMI (kg/m^2)	26.6±4.3	28.8±4.6	28.1±4.2	27.0±3.8
Resting HR (bpm)	68±10	68±13	65±11	66±11
T2DM n(%)	19(11%)	57(31%)	69(34%)	11(11%)
CVD n(%) (n=652)	6(4%)	31(17%)	40(20%)	1(1.04)
Hypertension duration, median [RANGE] years	-	17.5[2-63]	18[1-52]	6[4-47]
Physical activity level (MJ/week)	6.1±4.5	5.6±3.4	5.9±3.6	6.3±3.9
Steps achieved	217±80	204±76	195±75	220±75
$\dot{V}O_2$ achieved (ml/kg/min)	16.7±4.5	15.5±4.0	15.1±4.1	17.0±3.9
Resting SBP (mmHg)	126±9	128±9	152±10	153±11
Resting DBP (mmHg)	74±7	73±8	81±8	86±7
Resting MAP	116±10	115±10	132±9	137±9
Resting PP	52±8	55±9	71±11	66±11
Exercise SBP (mmHg)	180±27	177±28	194±26	199±25
Exercise DBP (mmHg)	91±14	88±15	90±16	100±16
ΔSBP on exercise (mmHg)	55±25	50±26	43±24	47±23
Exercise ΔSBP/METs (mmHg/MET)	12.0±5.8	11.8±6.2	10.1±5.6	10.4±4.9
Exaggerated exBP n(%)	52(31%)	43(23%)	87(43%)	65(64%)
Treatment				
Number of anti-hypertensive agents (% by category 1-5)		39, 40, 15, 3, 0.5	46, 30, 15, 6, 0.5	
Treated (did not report class)		4	5	
Treated (not for BP)	8			3
ACE inhibitor		66	61	
ARB		51	60	
(ACEi or ARB)		*115*	*118*	
CCB	1	94	100	
α-Blocker	7	30	34	2
β-Blocker		47	61	1
Diuretic		48	47	

Table 1. Participant characteristics stratified by treatment and blood pressure (BP) control at rest. Exaggerated exBP was based on guideline cut-off for exaggerated BP for men and women separately (exBP ≥210/110 mmHg for men and ≥190/110mmHg for women). ACE Angiotensin converting enzyme, ARB Angiotensin receptor blocker, AFC African Caribbean, BMI body mass index, CCB Calcium channel blocker, CVD cardiovascular disease, DBP diastolic blood pressure, E European, HR heart rate, MAP mean arterial pressure, PP pulse pressure, SA South Asian, SBP systolic blood pressure, T2DM type-2 Diabetes Mellitus, $\dot{V}O_2$ Oxygen consumption.

Outcome:		*n*	**ATE Any AH treatment** ***p value***	*n*	**ATE of being on 1, 2 or >3 combined agents** 0 vs 1 (n=177)	0 vs 2 (n=137)	0 vs ≥3 (n=79)
ExSBP	M1	*659*	-2.6(-7.0,1.7) *0.235*	*650*	1.7(-3.6,7.0) *0.536*	-1.6(-7.5,4.2) *0.583*	-12.6(-19.4,-5.9) *<0.001*
	M2	*498*	0.10(-4.8,5.0) *0.968*	*493*	3.4(-2.3,9.2) *0.238*	-1.3(-7.7,5.1) *0.689*	-8.6(-14.7,-2.6) *0.005*
	M3	*417*	3.0(-1.6,7.8) *0.197*	*412*	4.0(-1.6,9.6) *0.164*	2.0(-5.4,9.3) *0.596*	-5.2(-11.3,1.0) *0.102*
ExDBP	M1	*659*	-4.7(-7.1,-2.2) *<0.001*	*650*	-2.9(-6.0,0.10) *0.058*	-5.6(-8.7,-2.6) *<0.001*	-8.7(-13.0,-4.4) *<0.001*
	M2	*498*	-4.2(-7.5,-0.79) *0.016*	*493*	-3.2(-6.9,-0.52) *0.092*	-3.7(-7.6,0.31) *0.171*	-5.6(-11.0,-0.15) *0.044*
	M3	*417*	-3.9(-7.0,-0.81) *0.014*	*412*	-3.3(-6.9,-0.28) *0.071*	-2.6(-6.9,1.7) *0.241*	-6.7(-14.2,0.78) *0.079*
ExMAP	M1	*659*	-4.3(-6.9,-1.6) *0.001*	*650*	-1.7(-4.9,1.4) *0.283*	-4.4(-7.7,-1.1) *0.009*	-10.4(-14.4,-6.5) *<0.001*
	M2	*498*	-2.9(-6.2,0.49) *0.098*	*493*	-1.0(-4.8,2.8) *0.604*	-2.9(-7.0,1.2) *0.167*	-7.1(-11.4,-2.8) *0.001*
	M3	*417*	-1.7(-4.7,1.4) *0.282*	*412*	-0.75(-4.4,2.9) *0.692*	-1.1(-5.8,3.6) *0.640*	-6.9(-11.7,-2.0) *0.006*
ExPP	M1	*659*	1.8(-2.4,5.9) *0.404*	*650*	4.7(-0.45,9.9) *0.073*	2.8(-2.8,8.3) *0.330*	-4.7(-11.6,2.3) *0.188*
	M2	*498*	4.4(-0.04,8.9) *0.052*	*493*	6.4(1.0,11.9) *0.020*	2.0(-4.0,8.0) *0.516*	1.7(-7.8,4.5) *0.598*
	M3	*417*	7.6(2.8,12.4) *0.002*	*412*	7.4(2.0,12.9) *0.007*	4.2(-2.4,10.8) *0.216*	5.9(-0.76,12.5) *0.083*
Steps achieved	M1	*659*	-13(-25,-1) *0.032*	*650*	-6(-20,8) *0.377*	-10(-25,4) *0.158*	-26(-53,0.27) *0.052*
	M2	*498*	-22(-36,-8) *0.002*	*441*	-13(-28,2.8) *0.107*	-25(-45,-6) *0.011*	-44(-75,-12) *0.007*
	M3	*417*	-14(-28,0.6) *0.060*	*372*	-8(-24,9) *0.378*	-20(-43,3.2) *0.092*	-29(-61,4) *0.087*
$\dot{V}O_2$ achieved (ml/kg/min)	M1	*587*	-1.5(-2.2,-0.78) *<0.001*	*578*	-0.85(-1.7,-0.04) *0.039*	-1.6(-2.5,-0.75) *<0.001*	-2.4(-3.7,-1.1) <0.001
	M2	*446*	-1.6(-2.4,-0.72) *<0.001*	*441*	-0.83(-1.7,0.08) *0.075*	-1.9(-3.1,-0.76) *0.001*	-3.0(-4.6,-1.4) *<0.001*
	M3	*377*	-1.2(-2.2,-0.31) *0.009*	*372*	-0.59(-1.6,0.37) *0.231*	-2.0(-3.4,-0.57) *0.006*	-2.3(-4.0,-0.56) *0.009*

Table 2. The average treatment effect (ATE) of anti-hypertensive medication on outcomes: exercise systolic and diastolic blood pressure (exSBP & exDBP), exercise mean arterial pressure (exMAP) and pulse pressure (exPP) and exercise capacity measures (steps and whole body oxygen consumption ($\dot{V}O_2$) achieved). ATEs and 95%CI for being on any anti-hypertensive (AH) treatment and ATE of being on 1, 2 or ≥3 concurrent treatments were estimated using an augmented inverse probability weighted estimator. Models are adjusted for the following co-variables: Model 1 (M1): age, sex

and ethnicity; Model 2 (M2): M1 co-variates plus presence of type-2 Diabetes Mellitus (T2DM), cardiovascular disease (CVD), total cholesterol, years of education & auxiliary co-variates (added to the outcome model only) resting BP (resting value for the specified outcome) and steps achieved during the exercise test (for the blood pressure outcomes only); Model 3 (M3): is the same as M2 with exclusion of all participants prescribed a β-blocker.

Figure legends

Figure 1a-d. Exercise systolic and diastolic blood pressure (SBP & DBP; a&b) and exercise capacity (steps completed and highest achieved $\dot{V}O_2$; c&d) categorised by normotension (blue bars) or hypertension (orange, grey and yellow bars). Individuals with hypertension were categorised as treated with anti-hypertensive medication with controlled resting BP (orange bars), treated with uncontrolled resting BP (grey bars) or untreated with uncontrolled resting BP (yellow bars). The effect of being in each group is summarised as a potential outcome mean (POM). Error bars are 95% confidence intervals. *indicates a $p<0.05$ for the difference between the normotensive group and each hypertensive group. Models are adjusted for the following co-variables: Model 1 (M1) is adjusted for age, sex & ethnicity; Model 2 (M2) is adjusted for the same confounders as model 1 plus presence of cardiovascular disease (CVD), type-2 Diabetes Mellitus (T2DM), total cholesterol & years of education (effects on blood pressure outcomes were also adjusted for resting BP and steps achieved); Model 3 (M3) is adjusted for the same confounders as model 2 with exclusion of participants prescribed β-blockers.

Figure 2a-b. change in systolic and diastolic blood pressure (ΔSBP & ΔDBP) from rest to exercise corrected for metabolic equivalents during exercise (METs) stratified by hypertension group. Potential outcome means (POM) for ΔSBP/MET & ΔDBP/MET are given stratified by normotension (blue bars) or hypertension (HTN) (orange, grey and yellow bars). Individuals with hypertension were categorised as treated with anti-hypertensive medication with controlled resting BP (orange bars), treated with uncontrolled resting BP (grey bars) or untreated with uncontrolled resting BP (yellow bars). Error bars are 95% confidence intervals. *indicates a $p<0.05$ for the difference

between the normotensive group and each hypertensive group. Models are adjusted for the following co-variables: Model 1 (M1) is adjusted for age, sex & ethnicity; Model 2 (M2) is adjusted for the same confounders as model 2 plus presence of cardiovascular disease (CVD), type-2 Diabetes Mellitus (T2DM), total cholesterol, years of education & number of steps performed (for outcomes ΔSBP & ΔDBP only); Model 3 (M3) is adjusted for the same confounders as model 2 with exclusion of participants prescribed β-blockers.

Figure 3a-c. Average treatment effects (ATE) of being on each class of anti-hypertensive agent (alone or in combination) versus being on no treatment. Outcomes are exercise systolic and diastolic blood pressure (exSBP and exDBP, (a)), exercise capacity (steps completed, (b) & highest achieved $\dot{V}O_2$ (c)). Co-variates included in each model were: age, sex, ethnicity, presence of type-2 Diabetes Mellitus or cardiovascular disease, total cholesterol and years of education. Effects on blood pressure outcomes were also adjusted for resting BP and steps achieved. ACEi Angiotensin converting enzyme inhibitors, ARB Angiotensin II receptor blockers, CCB calcium channel blockers.