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Delayed systolic blood pressure recovery following exercise as a mechanism of masked uncontrolled hypertension in chronic kidney disease

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ORIGINAL ARTICLE

ABSTRACT

Background. Among people treated for hypertension, the presence of elevated blood pressure (BP) out of the clinic but normal BP in the clinic is called masked uncontrolled hypertension (MUCH). What causes MUCH remains unknown. The purpose of this study was to answer the question of whether patients with MUCH have an increased hemodynamic reactivity to exercise and delayed hemodynamic recovery following exercise.

Methods. Four groups were compared: controlled hypertension (CH, $n = 58$), MUCH ($n = 34$) and uncontrolled hypertension (UCH, $n = 12$), all of which had chronic kidney disease (CKD), and a group of healthy normal volunteers who did not have hypertension or CKD ($n = 16$). All participants underwent assessment of 24-h ambulatory BP monitoring, BP measurement during a graded symptom-limited exercise using a cycle ergometer and BP recovery over 7 min following exercise.

Results. Exercise-induced increase in systolic BP was similar among the four groups. When compared with healthy controls, recovery of systolic BP following termination of exercise was blunted among the CKD groups in unadjusted ($P < 0.0001$) and adjusted ($P < 0.001$) models. During recovery, the healthy control group had 5.9% decline in systolic BP per minute. In contrast, MUCH had only 3.3% per minute reduction and the UCH group had 0.3% reduction per minute. A test of linear trend was significant ($P = 0.002$, adjusted model).

Conclusion. Because there was no impairment in the heart rate recovery among groups, we speculate that the parasympathetic pathway appears intact among treated hypertensives with CKD. However, the failure to withdraw sympathetic tone upon termination of exercise causes ongoing vasoconstriction and delayed systolic BP recovery providing a biological basis for MUCH. Delayed recovery from exercise-induced hypertension in those with poorly controlled BP provides potentially a new target to assure round-the-clock BP control.

Keywords: ambulatory blood pressure monitoring, chronic kidney disease, exercise, recovery, systolic blood pressure

INTRODUCTION

It has long been recognized that both heart rate and systolic blood pressure increase with physical activity and are risk factors for the future development of hypertension [1–4]. This activity-induced change in heart rate and systolic BP are important determinants of myocardial oxygen demand and, in those with obstructive coronary artery disease, may trigger myocardial ischemia. It is also well recognized that masked hypertension and masked uncontrolled hypertension (MUCH) is associated with increased cardiovascular risk [5–9]. Whether this elevated cardiovascular risk is due to a more robust vascular reactivity is unknown. If those with MUCH have an increased systolic BP and heart rate response to exercise, it may shed light on the pathophysiology of MUCH.

During rest, following a bout of physical activity, withdrawal of sympathetic tone and increase in parasympathetic activity allows BP and heart rate to return to baseline. The diagnosis of MUCH requires measurement of ambulatory BP—the diagnosis is made among treated hypertensives when ambulatory BP is elevated but clinic BP is normal [10]. It is therefore possible that MUCH is associated with a more persistent sympathetic tone and delayed recovery of systolic BP following a bout of exercise. This has not been previously reported, but if this notion is correct it would contribute to our understanding of the pathophysiology of MUCH and its association with increased cardiovascular risk.

In this study, we test the hypothesis that patients with MUCH have an exercise-induced hypertensive response that has an intermediate phenotype, i.e. the hypertensive response in MUCH is more than those with controlled hypertension (CH) but less than those with uncontrolled hypertension (UCH).

Furthermore, we test the notion of whether those with MUCH have recovery of BP and heart rate after a bout of exercise that is slower than those with CH and better than those with UCH. Accordingly, the overarching aim of this study was to answer the question of whether patients with MUCH have an increased hemodynamic reactivity to exercise and delayed hemodynamic recovery following exercise.

MATERIALS AND METHODS

Participants

This is a prospective study of chronic kidney disease (CKD) patients Stages 2–4 [estimated glomerular filtration rate (GFR) defined using the modification of diet in renal disease equation <90 mL/min/1.73 m^2 but >15 mL/min/1.73 m^2]. For those with Stage 2 CKD, albuminuria (A2 or >300 mg/g creatinine) was required for inclusion in the cohort. Those with an initial clinic BP of 140/90 mmHg or less were considered eligible and studied further. Participants with recent hospitalization, use of home oxygen, inability to ride a stationary bicycle due to disability or a recent cardiovascular event were excluded. Detailed inclusion and exclusion criteria have been previously published [11]. The study was approved by the Institutional Review Board of Indiana University and the Research and Development Committee of the Roudebush Veterans Administration Medical Center, Indianapolis. All study participants provided written informed consent.

Classification of groups

Four groups were compared in this report: CH, MUCH, UCH and a group of healthy normal volunteers who did not have hypertension or CKD. The latter also were Veterans, all >50 years of age, non-smokers, had no diabetes mellitus and did not have pre-existing cardiovascular disease. The diagnostic criteria for the diagnosis of hypertension have been previously published [11]. Briefly, thresholds of BP to define hypertension were $\geq$140/90 in the clinic and $\geq$135/85 mmHg using daytime ambulatory BP. MUCH was diagnosed in those who had controlled clinic BP ($<$140/90 mmHg on average of three clinic visits by oscillometric BP measurement) but elevated ambulatory BP. CH required BP below the thresholds and UCH above the thresholds both in the clinic and outside. White coat hypertension was not studied.

Protocol for exercise and BP measurements

Participants were familiarized with the instruments and procedures were generally carried out in a fasting state in the morning. Subjects mounted an electronically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). Following measurement of three baseline blood pressures at 1 min intervals (Tango M2, Suntech), a ramped symptom-limited maximal test was performed. Exercise was started at 20 W/min and was increased by 20 W/min every 3 min. Every minute after the onset of exercise we monitored the auscultatory BP and the subjective feeling of shortness of breath and exercise intensity using the Borg scale. All participants were instructed to stop exercise immediately if they experienced dizziness or chest pain. The reason for stopping the exercise was recorded.

After the end of exercise, subjects were transferred to a flat bed and monitored for another 7 min. During this time, BP and heart rate were measured.

Blood pressure was recorded with an automated auscultatory device with EKG gating (Tango M2, Suntech). Exercise bike was electronically braked to give a consistent work-rate at a cadence of >30 r.p.m. Participants were asked to pedal at $\sim$60 r.p.m.

Data analysis

Baseline characteristics among groups were compared using one-way ANOVA for continuous variables and χ^2 test for discrete variables. Hemodynamic variables during exercise (BP and heart rate) were regressed over exercise intensity to calculate slopes for each individual. Box plots over groups were created to display results. Given the negative exponential rate of recovery following the termination of exercise, natural logs of BP and heart rate were regressed over time to calculate recovery slopes and plotted in a similar fashion as above.

A linear mixed model was used to estimate slopes of hemodynamic response and exercise relationship (as shown Table 2) [12]. In this model, the outcome was either BP (systolic or diastolic) or heart rate. The predictor variables were the group classification (normal, CH, MUCH, UCH) as indicator variables, exercise intensity in watts as continuous variable and interaction of the two terms. A random coefficient model was used with subject and time of exercise as random variables and covariance was modeled as unstructured; estimation algorithm was that of maximal likelihood. Multivariable adjustments were then made for the following variables: age, race, body mass index, hemoglobin, albumin, estimated GFR, natural log of the urine albumin/creatinine ratio in the overnight specimen and the number of antihypertensive medications. We also adjusted the model for interaction terms for each of these covariates with exercise intensity (two-way interactions) and group classifications (three-way interactions). Baseline presence of cardiovascular disease and diabetes mellitus are likely in the causal pathway for hemodynamic response and therefore not adjusted for in Model 2. However, Model 3 was further adjusted for diabetes mellitus and cardiovascular disease defined as past myocardial infarction, stroke or hospitalization for congestive heart failure.

A mixed model was used to model slopes of hemodynamic response and recovery relationship (as shown in Table 3). In this model, the outcome was either BP (systolic or diastolic) or heart rate. Given the negative exponential rate of recovery, each of these variables was natural log transformed prior to model fitting. The predictor variables were the group classification (normal controls, CH, MUCH, UCH) as indicator variables, time since end of exercise in minutes as a continuous variable and interaction of the two terms. A random coefficient model was used with subject and time of exercise as random variables and covariance was modeled as unstructured with maximal likelihood estimation.

In each of the mixed models noted above, the unadjusted results are shown as Model 1. Model 2 shows multivariable adjusted results for the variables noted above. Model 3 was

further adjusted for diabetes and cardiovascular disease. Each of these variables completely interacted with recovery time and BP classification to examine not only the influence of these terms on the intercepts but also the slopes.

To examine the influence of systolic BP recovery after exercise in relation to β-blocker use, a similar mixed model was used. β-Blocker term was interacted with the group classification × recovery time term. Marginal means were calculated per minute of recovery among users and non-users of β-blockers (as shown in Figure 4). A similar model was used to estimate marginal means of systolic BP recovery in relationship to ischemia (see Figure 5). All analyses were carried out using Stata 14.1 (Stata Corp, College Station, TX, USA).

RESULTS

Table 1 shows the baseline characteristics of the study sample. Of the 21 healthy subjects evaluated in this study, 4 were found to have masked hypertension and 1 hypertension and therefore excluded from the control group; the table shows the 16 truly normotensive controls. Age, sex, weight and body mass index were well matched but as expected there were more blacks among those with CKD. Mean estimated GFR averaged 33–35 mL/min/1.73 m^2 in those with CKD. The median urinary albumin/creatinine ratio was <0.01, 0.02, 0.04 and 0.22 g/g in controls, CH, MUCH and UCH groups, respectively.

Figure 1 shows the mean observed hemodynamic responses among groups during exercise (top row) and recovery (bottom row). The hemodynamic response during exercise (Figure 1A–C) is plotted against exercise intensity which was ramped every 3 min, whereas the recovery (Figure 1D–F) is plotted as minutes elapsed after the end of exercise.

The slopes of hemodynamic response during exercise are shown in Figure 2. Since β-blockers can be reasonably expected to influence hemodynamic responses during exercise, data in the bottom graphs are dichotomized by β-blocker use. The slopes of hemodynamic recovery after exercise are shown in Figure 3. Data were log transformed to reflect the exponential nature of the recovery. The bottom three graphs are stratified by β-blocker use.

Table 2 shows the slopes of hemodynamic changes during exercise compared with the control group using a mixed model. Model 1 shows the unadjusted results. Model 2 shows multivariate adjusted results for the variables noted in the materials and methods section. For the outcome of systolic BP, the overall interaction effect of hypertension classification × exercise intensity was not significant (P = 0.31 in unadjusted model, P = 0.12 in adjusted model). Thus, systolic BP response was similar among groups, as were other hemodynamic responses. Model 3 was further adjusted for diabetes and cardiovascular disease. The overall interaction effect of hypertension classification × exercise intensity remained non-significant (P = 0.08).

To investigate the independent effect of β-blocker use on hemodynamic response to exercise, Model 1 was further adjusted for β-blocker use. No statistical significance was found between the use of β-blocker and BP response to exercise (P-values systolic BP = 0.33 and diastolic BP = 0.10). Resting heart rate was lower among users of β-blockers (P = 0.02); however, the increment in heart rate was not influenced by β-blocker use

Table 1. Clinical characteristics of the study sample

Clinical characteristic	Control	Controlled hypertension	Masked uncontrolled hypertension	Uncontrolled hypertension	P-value
Number of participants	16	58	34	12	
Age (years)	66.5 ± 6.6	71 ± 9.4	69.1 ± 10.2	68.2 ± 12.4	0.38
Male sex	15 (93.8%)	58 (100%)	34 (100%)	12 (100%)	0.09
Whites	15 (93.8%)	49 (84.5%)	22 (64.7%)	8 (66.7%)	0.01
Blacks	1 (6.3%)	9 (15.5%)	12 (35.3%)	3 (25%)	
Asians	0 (0%)	0 (0%)	0 (0%)	1 (8.3%)	
Weight (kg)	85.4 ± 15.7	91.4 ± 18.8	88.5 ± 15.1	83.7 ± 21.1	0.42
Body mass index (kg/m^2)	27.5 ± 3.9	30.2 ± 5.2	28.8 ± 4.6	28.9 ± 6	0.25
Waist circumference (cm)	102.1 ± 11.1	110.6 ± 13.8	106.5 ± 12.0	103.6 ± 14.1	0.07
Hip circumference (cm)	102.6 ± 6.7	106.6 ± 10.8	103.4 ± 8.7	100.2 ± 11.9	0.13
Waist–hip ratio	0.99 ± 0.07	1.04 ± 0.06	1.03 ± 0.06	1.03 ± 0.08	0.16
Current tobacco use	0 (0%)	9 (15.5%)	12 (35.3%)	2 (16.7%)	0.02
Diabetes mellitus	0 (0%)	35 (60.3%)	20 (58.8%)	9 (75%)	<0.0001
Myocardial infarction	0 (0%)	17 (29.3%)	8 (23.5%)	4 (33.3%)	0.09
Stroke	0 (0%)	5 (8.6%)	4 (11.8%)	1 (8.3%)	0.58
Congestive heart failure	0 (0%)	8 (13.8%)	5 (14.7%)	4 (33.3%)	0.1
Systolic BP (mmHg)	116.6 ± 9.6	113.9 ± 11.6	126.5 ± 7.8	152.1 ± 14.9	<0.0001
Diastolic BP (mmHg)	68.3 ± 7.7	59.9 ± 8.1	64.1 ± 8.7	71.7 ± 18.2	<0.001
Pulse rate	65.3 ± 7.9	66.2 ± 11.4	64.4 ± 11.3	62.6 ± 11.9	0.73
Number of BP medications	0.1 ± 0.3	2.6 ± 1.5	2.7 ± 1.6	2.5 ± 1.9	<0.0001
β-Blocker use	0 (0%)	37 (63.8%)	22 (64.7%)	9 (75%)	<0.0001
ACE inhibitor or ARB use	0 (0%)	34 (58.6%)	15 (44.1%)	5 (41.7%)	<0.001
Estimated GFR (mL/min/1.73 m^2)	78.3 ± 17.7	35 ± 11.4	34.9 ± 13.8	33.2 ± 14.9	<0.0001
Log urinary albumin/creatinine ratio (g/g)	−5.7 ± 0.6	−3.6 ± 1.8	−2.7 ± 2.5	−2 ± 2.5	<0.0001
Serum albumin (g/dL)	3.9 ± 0.4	3.8 ± 0.3	3.8 ± 0.3	3.9 ± 0.6	0.75
Hemoglobin (g/dL)	14.8 ± 1.3	13.4 ± 1.6	13.3 ± 1.8	13.3 ± 2.1	0.03

Data are presented as mean ± standard deviation, or *n* (%).

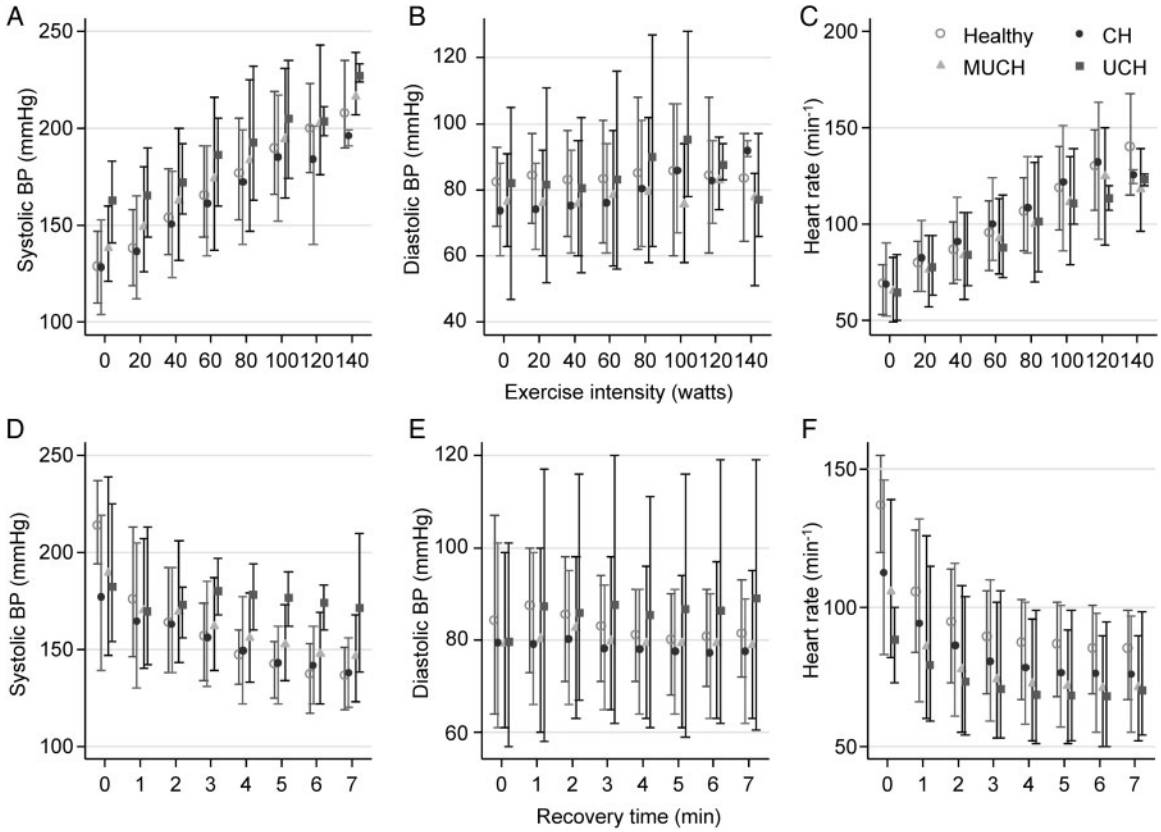

FIGURE 1: Mean hemodynamic responses by blood pressure (BP) classification status. (**A–C**) Response during exercise as a function of stationary bicycle exercise measured in watts. The baseline measurement is a mean of three at rest when exercise intensity is zero. Hemodynamic responses are an average of three measurements at each level of exercise. Each level of exercise was maintained for 3 min before being escalated to the next level. The I bars are 10th and 90th percentile of values at that level. After exercise, the participant was immediately placed supine in bed. (**D–F**) The changes following termination of exercise. Time zero reflects the response just before rest in that individual following which measurements were made at each of the seven minutes. The first plotted value in (D) does not match the last plotted value of (A) because participants terminated exercise at varying times. The last value prior to rest is what is plotted in (D). CH, controlled hypertension; MUCH, masked uncontrolled hypertension; UCH, uncontrolled hypertension.

($P = 0.19$ for slope differences compared with β-blocker nonusers).

When compared with healthy controls, unadjusted models showed that recovery of systolic BP ($P < 0.0001$) and heart rate ($P = 0.02$), but not diastolic BP ($P = 0.11$), was blunted among the CKD groups (Table 3). Multivariable adjustments did not remove the statistical significance of systolic BP recovery ($P < 0.001$), did not change the statistical significance of diastolic BP recovery ($P = 0.11$) and removed the significance of heart rate recovery ($P = 0.22$). The coefficients in Table 3 noted are approximately the percent change per minute of recovery. Thus, the control group has 5.9% decline in systolic BP per minute. In contrast, CH and MUCH groups had only 3.3% per minute reduction and the UCH group had 0.3% reduction per minute. Thus, the UCH group had no notable change in systolic BP recovery over the 7 min of recovery. A test of linear trend was highly significant ($P < 0.0001$) in unadjusted model and significant ($P < 0.001$) in the adjusted models (Models 2 and 3). Thus, systolic BP recovery followed the trend healthy>CH>MUCH>UCH. In comparison, diastolic BP recovery was similar among groups ($P > 0.10$ for each of the three models). Heart rate recovery was different among groups in the unadjusted model ($P = 0.02$) but was similar following adjustments ($P = 0.22$, Model 2 and $P = 0.29$, Model 3).

Figure 4 shows that β-blocker significantly blunted the recovery in systolic BP ($P = 0.004$ for β-blocker × systolic BP recovery interaction). This was not the case for either diastolic BP ($P = 0.5$) or heart rate ($P = 0.17$). To investigate further the reason for delayed systolic BP recovery, the reasons for stopping exercise were explored. Participants who exercised to exhaustion served as a comparator group to those who stopped exercising because of leg pain, leg fatigue or shortness of breath. Those who experienced shortness of breath were not tired or exhausted but had to stop because of the unpleasant sensation due to dyspnea. For these analyses, for the sake of convenience we classify these two groups as absence or presence of ischemia.

Figure 5 shows that ischemia significantly impaired the recovery of systolic BP after exercise in both the adjusted ($P = 0.006$) and unadjusted models ($P = 0.007$). Exercise was terminated due to ischemia for only 3 (19%) in the healthy controls group, but in 21 (36%) in CH, 13 (38%) in MUCH and 6 (50%) in UCH. Exercise was terminated because of exhaustion in 29 (50%) in CH, 19 (56%) in MUCH, 5 (42%) in UCH and 12 (75%) in controls. In the remaining 12 participants, exercise

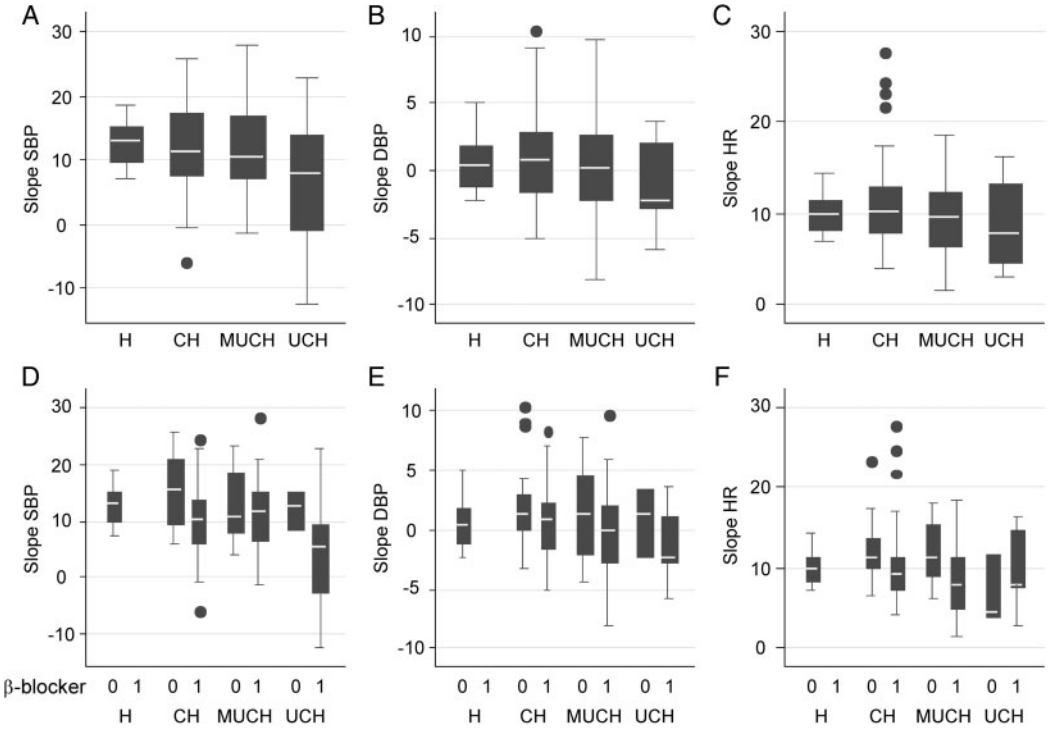

FIGURE 2: Box plots of hemodynamic slopes during exercise by blood pressure (BP) classification status. SBP, systolic BP; DBP, diastolic BP; HR, heart rate; H, healthy controls; CH, controlled hypertension; MUCH, masked uncontrolled hypertension; UCH, uncontrolled hypertension. (**A**–**C**) Overall exercise response. (**D**–**F**) Exercise responses stratified by β-blocker use where 0 represents no β-blocker use and 1 represents the prescription of the drug. No healthy volunteers were on β-blockers. The box represents 25th and 75th percentiles, the clear horizontal bar in the box is the median. The error bars are upper and lower adjacent values and dots the values that lies outside these ranges. Since exercise was incremented by 20 W every 3 min, data shown are changes in each of the hemodynamic parameter per 20 W. Thus, BP changes are mmHg per 20 W increment in exercise. HR changes are beats per minute change per 20 W increment in exercise.

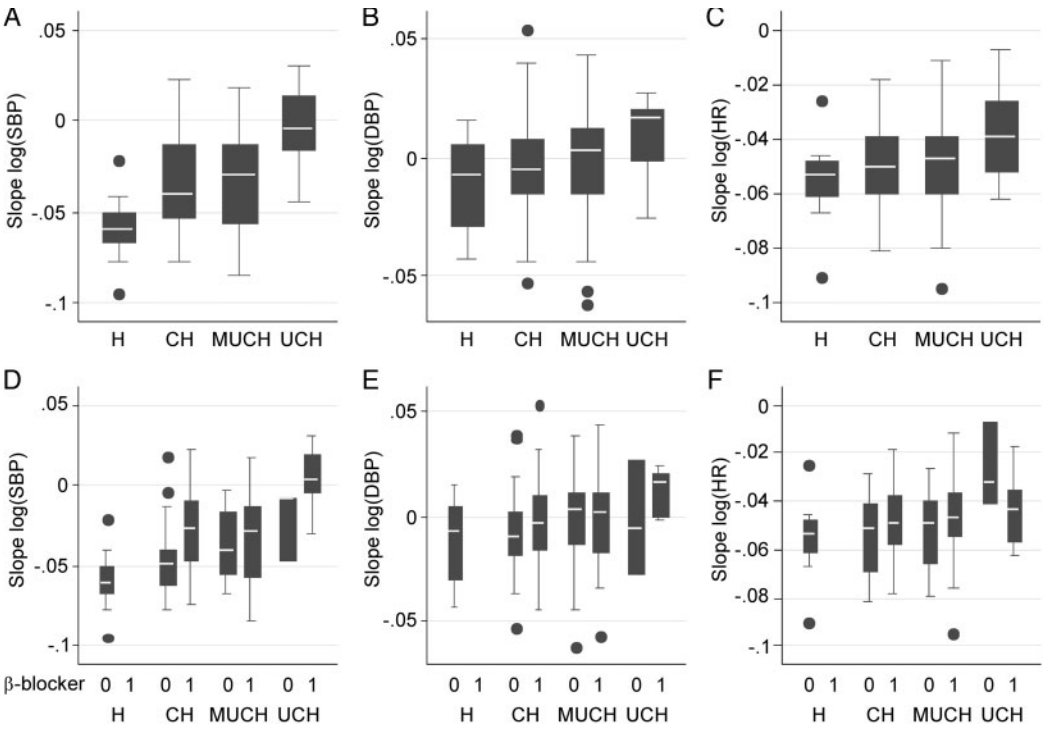

FIGURE 3: Box plots of hemodynamic recovery slopes by blood pressure (BP) classification status. SBP, systolic BP; DBP, diastolic BP; HR, heart rate; H, healthy controls; CH, controlled hypertension; MUCH, masked uncontrolled hypertension; UCH, uncontrolled hypertension. (**A**–**C**) Overall recovery response. (**D**–**F**) Responses stratified by β-blocker use. 0 represents no β-blocker use and 1 represents the prescription of the drug.

Table 2. Mixed model derived slope estimates during exercise

Variable	Model 1		Model 2		Model 3	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Healthy controls						
Systolic BP	4.27 ± 1.5	<0.01				
Diastolic BP	0.01 ± 0.6	0.99				
Heart rate	5.7 ± 0.88	<0.0001				
Controlled hypertension						
Systolic BP	3.25 ± 0.93	<0.001	2.84 ± 1.35	0.03	2.93 ± 1.35	0.03
Diastolic BP	0.77 ± 0.35	0.03	0.51 ± 0.45	0.26	0.49 ± 0.45	0.27
Heart rate	7.99 ± 0.53	<0.0001	8.16 ± 0.73	<0.0001	8.03 ± 0.74	<0.0001
Masked uncontrolled hypertension						
Systolic BP	6.09 ± 1.18	<0.0001	6.24 ± 1.61	<0.001	6.44 ± 1.64	<0.0001
Diastolic BP	0.26 ± 0.45	0.56	0.72 ± 0.55	0.19	0.79 ± 0.55	0.15
Heart rate	6.13 ± 0.68	<0.0001	6.18 ± 0.9	<0.0001	6.25 ± 0.91	<0.0001
Uncontrolled hypertension						
Systolic BP	3.86 ± 2.05	0.06	2.14 ± 4.01	0.59		
Diastolic BP	0.01 ± 0.78	0.99	−0.4 ± 1.36	0.77		
Heart rate	7.66 ± 1.17	<0.0001	7.79 ± 2.15	<0.001		

The P-values test the hypothesis of slopes within group being 0 and ± are standard errors of estimates. Healthy controls do not have adjusted information because they were not on antihypertensive agents and they did not have albuminuria, covariates that were adjusted for in other groups. Nonetheless, if adjustments were made, the coefficients became unstable. Model 2 is multivariate adjusted for the following variables: age, race, body mass index, hemoglobin, serum albumin, estimated glomerular filtration rate, log of urinary albumin/creatinine ratio and the number of blood pressure (BP) medications. Model 3 is further adjusted for diabetes mellitus and cardiovascular disease (myocardial infarction, stroke or congestive heart failure). Model 3 does not have estimates shown for uncontrolled hypertension due to them being unstable. The unit for estimates for BP are mmHg/20 watts exercise and fr heart rate b.p.m/20 watts exercise.

Table 3. Mixed model derived slope estimates during recovery

Variable	Model 1		Model 2		Model 3	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Healthy controls						
Systolic BP	−0.059 ± 0.006	<0.0001				
Diastolic BP	−0.012 ± 0.005	0.06				
Heart rate	−0.055 ± 0.004	<0.0001				
Controlled hypertension						
Systolic BP	−0.033 ± 0.003	<0.0001	−0.036 ± 0.003	<0.0001	−0.036 ± 0.003	<0.0001
Diastolic BP	−0.003 ± 0.003	0.27	−0.006 ± 0.003	0.06	−0.006 ± 0.003	0.05
Heart rate	−0.05 ± 0.002	<0.0001	−0.05 ± 0.002	<0.0001	−0.05 ± 0.002	<0.0001
Masked uncontrolled hypertension						
Systolic BP	−0.033 ± 0.004	<0.0001	−0.037 ± 0.004	<0.0001	−0.037 ± 0.004	<0.0001
Diastolic BP	−0.001 ± 0.004	0.7	−0.003 ± 0.004	0.34	−0.003 ± 0.004	0.34
Heart rate	−0.048 ± 0.003	<0.0001	−0.049 ± 0.003	<0.0001	−0.049 ± 0.003	<0.0001
Uncontrolled hypertension						
Systolic BP	−0.003 ± 0.007	0.7	−0.005 ± 0.007	0.53	−0.006 ± 0.007	0.43
Diastolic BP	0.01 ± 0.006	0.12	0.012 ± 0.006	0.07	0.01 ± 0.006	0.1
Heart rate	−0.037 ± 0.005	<0.0001	−0.039 ± 0.005	<0.0001	−0.04 ± 0.005	<0.0001

The P-values test the hypothesis of slopes within group being 0 and ± are standard errors of estimates. Healthy controls do not have adjusted information because they were not on antihypertensive agents and they did not have albuminuria, covariates that were adjusted for in other groups. Nonetheless, if adjustments were made, the coefficients became unstable. Models 2 and 3 are as described in the legend of Table 2. BP, blood pressure.

was stopped due to arthritic pain or discomfort from the seat of the cycle with distribution as follows: 8 (14%) in CH, 2 (6%) in MUCH, 1 (8%) in UCH and 1 (6%) in the control group. Data shown are after dropping the 12 participants who stopped the exercise early due to miscellaneous reasons. Including the 12 participants in the third category did not significantly alter the statistical significance of the results.

DISCUSSION

The hypothesis tested in this report was that heightened BP reactivity to exercise is an important cause that underscores the pathophysiology of masked hypertension. Accordingly, those with MUCH were compared with three other groups: CH, UCH and healthy controls. We did not find any differences among groups in pressor or chronotropic response to exercise. Numerically, the systolic BP–exercise relationship was nearly twice in those with MUCH as in CH. However, the statistical significance was marginal (P = 0.07) and disappeared after multivariable adjustments. Even small differences were not seen in heart rate response or diastolic BP among groups. Furthermore, pressor or chronotropic responses in the groups with CKD were similar to age-matched controls without CKD or hypertension. Perhaps a larger study may be able to detect smaller differences but the results of this study suggest that exercise-induced

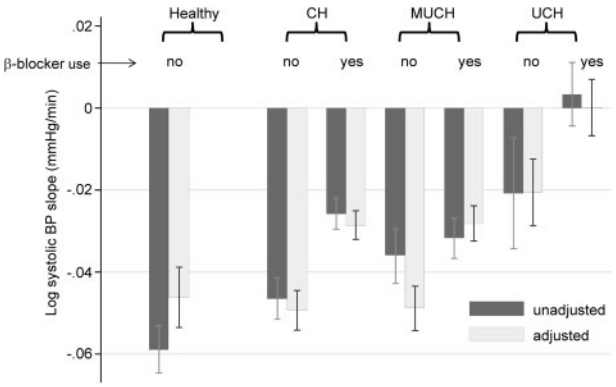

FIGURE 4: Effect of β-blocker use on systolic blood pressure (BP) recovery. The slope estimates from mixed model are plotted for healthy controls, controlled hypertension (CH), masked uncontrolled hypertension (MUCH) and uncontrolled hypertension (UCH). The I bars indicate standard error of the mean. β-Blocker use is indicated as no or yes across the groups. No healthy participant was on any antihypertensives so the slope estimates are absent. β-Blocker use significantly impaired the recovery of systolic BP after exercise in both the adjusted (P = 0.004) and unadjusted models (P = 0.004).

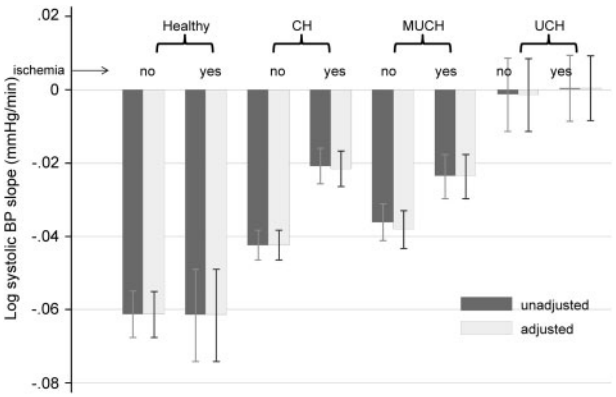

FIGURE 5: Effect of ischemia as reason for stopping exercise on systolic blood pressure (BP) recovery. The slope estimates from mixed model are plotted for healthy controls, controlled hypertension (CH), masked uncontrolled hypertension (MUCH) and uncontrolled hypertension (UCH). The I bars indicate standard error of the mean. Ischemia is indicated as no or yes across the groups. In contrast to exhaustion or maximal exercise, ischemia was defined as leg pain, leg fatigue or shortness of breath as the reason for stopping exercise. Ischemia significantly impaired the recovery of systolic BP after exercise in both the adjusted (P = 0.006) and unadjusted models (P = 0.007).

changes in BP are not important in the pathophysiology of MUCH in CKD.

The major finding of this study was that systolic BP recovery after termination of exercise was delayed; this is important and requires an explanation. The normal response to termination of exercise is an increase in parasympathetic tone and a reduction in sympathetic tone. This allows the heart rate and BP to return to baseline. There was no impairment in the heart rate recovery among groups, thus the parasympathetic pathway appears intact among treated hypertensives with CKD. The failure to withdraw sympathetic tone would cause ongoing vasoconstriction and delayed systolic BP recovery. CKD is a state of sympathetic hyperactivity [13, 14] and ischemia can further trigger sympathetic activation [15, 16]. Consistent with this hypothesis is the observation that β-blocker use that is associated with heightened vasoconstriction was associated with a further impairment in systolic BP recovery (Figure 4). Furthermore, in those participants who stopped not because of exhaustion due to maximal exercise but due to leg pain or shortness of breath proxies for impaired peripheral oxygenation; there was also impairment in systolic BP recovery. A highly significant linear relationship was noted among the progressively increasing hypertension categories (moving from healthy, CH, MUCH and to UCH) and delayed systolic BP recovery. This suggests that withdrawal of sympathetic tone may be important for the pathophysiology of MUCH.

Endothelial function was not directly measured so it is difficult to exclude this as a cause of the delayed systolic BP recovery. It is possible that endothelial dysfunction can cause failure of vasorelaxation after the termination of exercise; but this is less likely the explanation for the observations. One would expect that if endothelial dysfunction was the sole explanation of these findings, the systolic BP response during exercise should have been steeper in those with CKD. This was however not the case. Future studies will examine the role of endothelial dysfunction and its relationship with delayed systolic BP recovery since endothelial function is known to be impaired during sympathetic activation [17].

The study was relatively small and predominantly performed in older men. Whether our findings translate to younger people and women remains to be seen. There is at least some evidence that an elevated post-exercise BP is a predictor of the future development of hypertension [18]. Nearly all participants with hypertension were treated. Whether our results apply to those with untreated hypertension will require future studies. There are several strengths of our study. We used 24-h ambulatory blood pressure monitoring to diagnose out-of-office hypertension. This is the gold-standard against which other methods are measured and it provides the most accurate classification based on out-of-office BP control. A formal exercise testing protocol was used for all participants and one physician performed all the measurements. This likely increases the precision of the results, especially as it relates to uncovering the pathophysiology of MUCH.

In summary, although we did not find increased hemodynamic reactivity among those with MUCH and CKD, the delayed systolic BP recovery following exercise related to the hypertension categories among those with CKD is a novel discovery. The delayed systolic BP recovery had a graded relationship with increasing severity of hypertension even after multivariable adjustment. In those who had UCH, systolic BP remained elevated persistently over the 7 min of recovery. This suggests that whereas the stationary component of hypertension may be important for target organ damage among those with hypertension, more attention should be paid to understand the mechanisms and methods to mitigate the delayed recovery from exercise-induced hypertension in those with poorly

controlled BP. This may provide strategies to better diagnose and manage hypertension. The occurrence of delayed systolic recovery following exercise in MUCH provides further evidence for a biological basis for MUCH.

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CONFLICT OF INTEREST STATEMENT

R.A. has consulted for several pharmaceutical companies that make antihypertensive drugs including Merck, Takeda, Novartis, Daiichi Sankyo, Abbvie, Bayer, and Johnson and Johnson.

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