

Hypertensive Response to Maximal Exercise Test in Young and Middle Age Hypertensive on Blood Pressure Lowering Medication: Monotherapy vs. Combination Therapy

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Abstract—Background: Hypertensive response during maximal exercise test provides important information on the level of blood pressure control and evaluation of treatment. Method: A single center retrospective descriptive study was conducted among 117 young (aged 20 to 40) and middle age (aged 40 to 65) hypertensive patients, who underwent treadmill stress test. Currently on maintenance frontline medication either monotherapy (Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker [ACEi/ARB], Calcium channel blocker [CCB], Diuretic - Hydrochlorothiazide [HCTZ]) or combination therapy (ARB+CCB, ARB+HCTZ), who attained a maximal exercise on treadmill stress test (TMST) with hypertensive response (systolic blood pressure: male >210 mm Hg, female >190 mm Hg, diastolic blood pressure >100 mmHg, or increase of >10 mm Hg at any time during the test), on Bruce and Modified Bruce protocol. Exaggerated blood pressure response during exercise (systolic [SBP] and diastolic [DBP]), peak exercise blood pressure (SBP and DBP), recovery period (SBP and DBP) and test for ischemia and their antihypertensive medication/s were investigated. Analysis of variance and chi-square test were used for statistical analysis. Results: Hypertensive responses on maximal exercise test were seen mostly among female population ($P < 0.000$) and middle age ($P < 0.000$) patients. Exaggerated diastolic blood pressure responses were significantly lower in patients who were taking CCB ($P < 0.004$). A longer recovery period that showed a delayed decline in SBP was observed in patients taking ARB+HCTZ ($P < 0.036$). There were no significant differences in the level of exaggerated systolic blood pressure response and during peak exercise (both systolic and diastolic) in patients using either monotherapy or combination antihypertensives. Conclusion: Calcium channel blockers provided lower exaggerated diastolic BP response during maximal exercise test in hypertensive middle age patients. Patients on combination therapy using ARB+HCTZ exhibited a longer recovery period of systolic blood pressure.

Keywords—Antihypertensive, exercise test, hypertension, hypertensive response.

I. INTRODUCTION

HYPERTENSION is a leading cause of morbidity and mortality around the globe and across all races, especially if left untreated. The end-organ complications that are brought about by this disease are sufficient enough to start intervention and lifestyle modification at the time of diagnosis. According

to Centers for Disease Control and Prevention (CDC) in 2013, the prevalence of hypertension has an exponential rise ranging from 7.3% to 65% among patients aged 18 and 60 years and above, respectively [3]. There are numerous diagnostic exams to evaluate a hypertensive patient both in the clinics and in-patient basis; one of these modalities is the treadmill exercise test.

In today's treatment for hypertension, there have been multiple studies and trials done and currently ongoing, about the different antihypertensive regimen. There are advantages and disadvantages of the different classes of each drug, mainly based on their pharmacodynamics and pharmacokinetics. In recent years, combination therapy emerged which improved patient's compliance and most importantly, took advantage of the synergistic effect of drugs from two different classes.

Treadmill stress test is one of the most widely used diagnostic tools to evaluate patients suspected of having or at risk for develop cardiovascular disease. Froelicher and Myers identified four major clinical uses of exercise testing in clinical practice relating to diagnosis, prognosis, functional assessment, and therapeutic prescription [1]. Also, masked hypertension can be exposed due to the blood pressure response during light exercise [2]. Another important clinical application of exercise test in patients with hypertension can be found in the assessment of antihypertensive treatment efficacy in such patients.

A pooled data of 46,314 individuals with a mean follow up of 15 years were analyzed in a meta-analysis done by Schultz et al., and they demonstrated that a hypertensive response to exercise (HRE) at moderate exercise, independent of office blood pressure (BP), predicts cardiovascular (CV) outcomes [16]. Moreover, each 10 mm Hg systolic BP increase during moderate intensity exercise was accompanied by a 4% increase in CV events and mortality (95% CI, 1.01–1.07, $p = 0.02$) [16]. A study done by Sieira et al. defined hypertensive response to exercise as systolic blood pressure of ≥ 210 mm Hg in men and ≥ 190 mm Hg in women [4]. Hence, blood pressure exaggeration predicts the future development of cardiovascular morbidity and mortality, independent of resting BP in apparently healthy, normotensive individuals.

Recovery time is also evaluated in patients who undergo exercise test. Parasympathetic nervous system reactivation is considered responsible for the fall of heart rate immediately after exercise at this phase. The difference between peak

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exercise heart rate and 1 minute after was the definition of abnormal heart rate recovery by Cole et al. in 1999 [6]. On the other hand, systolic blood pressure recovery time (SBPRT) has a range of 5 to 7 minutes and was determined statistically by age, gender and intensity of exercise [7].

Antihypertensive medications are the cornerstone for the management of hypertension, along with other means like exercise and diet modification. According to Joint National Committee (JNC) 8, the initial drugs of choice for hypertension are ACE inhibitors (ACEi), Angiotensin receptor blockers (ARB), Thiazide diuretics and Calcium channel blockers (CCB) [8]. The choice should be individualized per patient depending on the clinical profile. Nowadays, the benefit of combination antihypertensive through its synergistic effect and minimizing the adverse reaction of a single drug at maximal dosage is being taken advantage. There were multiple trials that already exhibited the efficacy of blood pressure reduction of these combination therapies over a single agent, including effects on the central BP and aortic pulse pressure [9]-[11]. However, there are only few studies about the effects of different pharmacological classes of antihypertensives on exercise test, including combination therapy.

II. METHODS

3387 exercise tests were performed at the Treadmill Stress Test in the Cardiovascular Laboratory of The Medical City from September 2015 to August 2016. A total of 117 patients were selected with the following inclusion criteria: young and middle age adults (aged 20 to 65), who were hypertensive on maintenance frontline medication either monotherapy (ACEi/ARB, CCB, diuretic [HCTZ]) or combination therapy (ARB + CCB, ARB + HCTZ), attained maximal exercise on treadmill stress test (TMST) with hypertensive response (SBP: male ≥ 210 mm Hg, female ≥ 190 mm Hg [4], diastolic blood pressure ≥ 100 -105 mm Hg or increase of ≥ 10 mm Hg at any time during the test) [4], on Bruce and Modified Bruce protocol. Criteria for exclusion were: aged over 65 years old, had submaximal exercise, does not have hypertension, hypertensive but not on any antihypertensive drugs, taking a beta blocker, post-MI, suffering from angina, reason for termination of exercise test was due to angina, and arrhythmia as indication to do the test. Written informed consent was obtained after they received a detailed explanation of the aim and how the procedure will be done, as well as a brief interview and physical examination. Anthropometric measurements were also recorded. A baseline characteristic of the study population is presented in Table I.

Baseline BP measurement. A well-trained nurse took resting BP, using a Kenz sphygmomanometer, in a seated position after the subjects had been resting for 5 minutes. After the initial resting BP was taken, an initial pretest 12-lead electrocardiogram (ECG) was recorded. Then, the patients were asked to hyperventilate and another ECG tracing was recorded.

Exercise testing and assessment of BP response. A graded uninterrupted symptom-limited maximum exercise test

was performed on an electrical treadmill stress test machine (GE Marquette, T2100, USA). On a Bruce protocol, there were six stages with progressive increase in inclination and speed every three minutes as follows: stage 1 – 1.7 mph, stage 2 – 2.5 mph, stage 3 – 3.4 mph, stage 4 – 4.2 mph, stage 5 – 5 mph, stage 6 – 5.5 mph. These are equivalent to 3.4 METS, 4.6 METS, 7.0 METS, 10.1 METS, 13.4 METS, 17.2 METS, 20.3 METS, respectively. Blood pressure was taken and recorded every 2 minutes. For the Modified Bruce protocol, there were stage 0 and $\frac{1}{2}$ prior to stage 1. Both have 1.7 mph speed with corresponding 2.3 METS and 3.4 METS, respectively. Hypertensive response by regimen is presented in Table II.

Target heart rate was determined by using the equation: $220 - \text{age} \times 0.85$, based on regression equation adjusted for patient's age [12]. When the target heart rate of 85% predicted for age was achieved or when the patient wished to stop the procedure for any reason, the procedure was halted immediately.

During the recovery period, blood pressure was taken within 30 seconds of the immediate recovery (first 1 minute), then every 2 minutes for the succeeding recovery 2, 3 and 4, each with 3-minute duration.

TABLE I
BASELINE CHARACTERISTIC OF THE STUDY POPULATION

Patient Profile	Frequency / Range	Percent / Mean \pm SD
Age of Patient	32 - 65	51.0 \pm 8.07
20 - 40 y.o.	12	10.3
41 - 65 y.o.	105	89.7
Gender of Patient		
Female	66	56.4
Male	51	43.6
Comorbidities		
Diabetes Mellitus	14	12.0
Dyslipidemia	27	23.1
Therapy - Group		
Monotherapy	66	56.4
Combination Therapy	51	43.6
Therapy - Specific		
Combination - ARB + CCB	45	38.5
Mono - ARB	40	34.2
Mono - CCB	25	21.4
Mono - CCB-Dihydropidine	23	19.7
Mono - CCB-Nondihydropidine	2	1.7
Combi - ARB + HCTZ	6	5.1
Mono - ACEi	1	0.9
TOTAL	117	100.0

Values shown on the 2nd column represents number of patients. Percentage (%) and \pm SD values on the 3rd column. ACEi = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; HCTZ = Hydrochlorothiazide

Statistical analysis. To determine the differences and relationship between patient profiles with hypertensive response and clinical outcome (exercise test for ischemia) *Analysis of Variance (for numerical variable) and Chi-Square Test of Independence or Kruskal Wallis Test (for categorical variables) at 5% level of significance was used.* Data analysis

was performed using SPSS version 19 for Windows.

III. RESULT

Hypertensive response during exercise. Patients with exaggerated blood pressure response to exercise, both systolic and diastolic, were mostly seen in the middle age group (41 to 65 years old) and among females, presented in Table II. The

most common hypertensive response to maximal exercise test was exaggerated diastolic blood pressure (DBP) in which 90% were males. The female population demonstrated more exaggerated systolic blood pressure (SBP) response than the males. The hypertensive response and test outcome is shown in Table III.

TABLE II
PATIENT PROFILE VS. HYPERTENSIVE RESPONSE

Patient Profile	Hypertensive Response			P-Value
	Exaggerated SBP	Exaggerated DBP	Exaggerated Both	
Age of Patient	55.5 ± 7.11	48.8 ± 7.86	54.3 ± 6.67	
20 – 40 y.o.	1 (4%)	11 (15%)	0 (0%)	0.101
41 – 65 y.o.	24 (96%)	64 (85%)	17 (100%)	<0.000**
Gender of Patient				
Female	21 (84%)	29 (39%)	16 (94%)	<0.000**
Male	4 (16%)	46 (61%)	1 (6%)	
Comorbidities				
Diabetes Mellitus	4 (16%)	8 (11%)	2 (12%)	0.776
Dyslipidemia	7 (28%)	18 (24%)	2 (12%)	0.449
TOTAL	25 (21%)	75 (64%)	17 (15%)	

Values are shown as mean ± SD or numbers (%). P-value significant at 1% (<0.05). SBP = systolic blood pressure; DBP = diastolic blood pressure

TABLE III
HYPERTENSIVE RESPONSE AND OUTCOME (EXERCISE TEST FOR ISCHEMIA) BY GENDER

Outcome	Female	Male	TOTAL
Hypertensive Response			
Exaggerated SBP	21 (32%)	4 (8%)	25 (21%)
Exaggerated DBP	29 (44%)	46 (90%)	75 (64%)
Exaggerated SBP & DBP	16 (24%)	1 (2%)	17 (15%)
Test for ischemia			
Negative	57 (86%)	44 (86%)	101 (86%)
Equivocal	4 (6%)	4 (8%)	8 (7%)
Positive	5 (8%)	3 (6%)	8 (7%)
TOTAL	66 (56%)	51 (44%)	117 (100%)

SBP = systolic blood pressure; DBP = diastolic blood pressure

Exaggerated BP. The most common BP was 200/100 mm Hg for those taking ARB and ARB+CCB, while it was 190/100 mm Hg for patients taking CCB. Meanwhile, there were no exaggerated blood pressures recorded among patients taking ARB+HCTZ.

Systolic BP. The lowest mean was observed among patients taking ARB+HCTZ and the highest was among taking CCB, with averages equal to 195.0±7.07 mm Hg and 206.0±13.42 mm Hg, respectively.

Diastolic BP. The lowest mean was recorded among patients taking CCB, and the highest was among those on ARB, with an average of 94.7±7.07 mm Hg and 101.2±6.12 mm Hg, respectively. Hypertensive response on different therapy regimen is presented in Table IV.

Recovery time. The most common was 6 minutes among all regimens except for those taking ARB+HCTZ, which has a much longer recovery time at 9 minutes. Hypertensive response on different therapy regimen is presented in Table IV.

Peak exercise. The most common BP measurement was

200/100 mm Hg for patients on ARB+CCB, 200/90 mm Hg on ARB only, and 190/100 mm Hg on CCB. On both systolic BP and diastolic BP, the lowest was mean recorded among patients on CCB. The highest means were among those taking ARB, shown in Table IV.

Monotherapy versus combination therapy. Results of the test revealed that monotherapy and combination agents were *not significantly different* from each other in terms of exaggerated BP (systolic and diastolic), exaggerated SBP, Peak BP, and recovery time. However, *significant differences* were seen among the four therapy agents (ARB, CCB, ARB+CCB, ARB+HCTZ) in terms of exaggerated DBP value, and recovery time for SBP and DBP. Those taking combination agents ARB+HCTZ have relatively longer recovery time than others. Also, exaggerated DBP was lower than others. The values are presented in Table IV.

The results of treadmill stress test among patients taking different therapy agents was compared and analyzed using Chi-Square Test of Independence and/or Kruskal Wallis Test at 5% level of significance. The exaggerated SBP and DBP response to exercise, longer recovery time, and positive outcome were seen in patients on combination therapy. There was a statistically significant relationship between recovery time and type of therapy; hence recovery time was significantly longer among patients on combination therapy than in monotherapy. Specifically, patients who were *taking ARB+HCTZ* have significantly longer recovery time compared to other patients taking other therapy agents. Hypertensive response on different therapy regimen is shown in Tables V and VI.

IV. DISCUSSION

In this study, the blood pressure responses were evaluated in patients currently on ARB, CCB, ARB + CCB and ARB +

HCTZ only. This is due to the low number of patients included on ACEi and none for the diuretic medications. The age-related exaggerated systolic and diastolic blood pressures observed in the middle age group were consistent with the study done by Uchechukwu and Ugwu, where they relate peak exercise SBP and DBP with advancing age due to increased sympathetic activity and attenuated parasympathetic activity [7]. However, in several studies, peak SBP and DBP were

higher in men [4], [7], in contrast to our study, where women have significantly higher peak blood pressures. Whether this is due to racial differences, gender and hormone related changes, it is uncertain and may need further studies to evaluate and confirm. One factor to consider is that more than half (56.4%, refer to Table I) of the population included in this study was female.

TABLE IV
HYPERTENSIVE RESPONSE ON DIFFERENT THERAPY REGIMEN

CATEGORY	MONO		COMBINATION		P-value (ARB v. CCB v. ARB+CCCB v. ARB+HCTZ)	P-value (mono vs. combi)
	ARB	CCB	ARB+CCB	ARB+HCTZ		
Exaggerated						
SBP + DBP (mm Hg), mode (n)	200/100 (5)	190/100 (2)	200/100 (3)	-	0.175	0.706
Systolic (mm Hg), mean ± SD	201.2 ± 12.46	206.0 ± 13.42	196.0 ± 12.65	195.0 ± 7.07	0.484	0.148
Diastolic (mm Hg), mean ± SD	101.2 ± 6.12	94.7 ± 7.17	101.0 ± 5.48	97.5 ± 5.00	0.004**	0.179
Recovery Time, mode (n)	6 min. (7)	6 min. (3)	6 min. (3)	-	1.000	1.000
Recovery Time – SBP, mode (n)	6 min. (6)	6 min. (4)	6 min. (6)	9 min. (1)	0.036*	0.105
Recovery Time – DBP, mode (n)	6 min. (14)	6 min. (11)	6 min. (15)	9 min. (3)	0.021*	0.147
On Peak Exercise						
SBP + DBP (mm Hg), mode (n)	200/90 (7)	190/100 (5)	200/100 (8)	-	0.130	0.687
Systolic (mm Hg), mean ± SD	191.0 ± 18.86	183.7 ± 16.89	187.7 ± 15.53	186.7 ± 15.05	0.432	0.839
Diastolic (mm Hg), mean ± SD	99.2 ± 8.50	93.3 ± 7.61	97.0 ± 9.04	95.0 ± 5.48	0.064	0.910

** - Significant at 1% (<0.05)

BP = Blood pressure; SBP = Systolic blood pressure; DBP = Diastolic blood pressure;

TMST = Treadmill stress test; SD = Standard deviation

ACEi = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; HCTZ = Hydrochlorothiazide

TABLE V
TEST OUTCOME VERSUS THERAPY (GROUP)

Test Outcome	Therapy		P-Value
	Mono	Combination	
Hypertensive Response			
Exaggerated SBP	13 (20%)	12 (23%)	0.432
Exaggerated DBP	41 (62%)	34 (67%)	
Exaggerated SBP & DBP	12 (18%)	5 (10%)	
Recovery Time			
			0.002**
1 minute	5 (8%)	3 (6%)	
3 minutes	49 (74%)	23 (45%)	
6 minutes	11 (17%)	25 (49%)	
9 minutes	1 (1%)	0 (0%)	
Outcome			
			0.174
Negative	59 (89%)	42 (82%)	
Equivocal	5 (8%)	3 (6%)	
Positive	2 (3%)	6 (12%)	
TOTAL	66 (56%)	51 (44%)	

* - significant at 5% ** - significant at 1%

SBP = Systolic blood pressure; DBP = Diastolic blood pressure

The results showed no significant differences between monotherapy and combination therapy, except for the exaggerated DBP and recovery time. Exaggerated BP response to exercise was thought to be a cause of multifactorial factors that operate dependently with each other, specifically increased activation of the renin-angiotensin-aldosterone system (RAAS) and excessive stimulation of the sympathetic nervous system [13]. However, Chi Young Shim et al. only demonstrated a significantly increased Angiotensinogen II level at peak exercise [13]. A

monotherapy with ARB and combination therapy that also has the same drug as component (ARB+CCB and ARB+HCTZ), did not show any significant difference in terms of exaggerated SBP peak exercise BP. Since the dose, the duration, and the compliance to medications were not determined, the therapeutic level of the drugs may not be sufficient enough to prevent BP exaggerations on both groups during maximal exercise. On the other hand, exaggerated DBPs were significantly lower on patients taking CCB alone. This is comparable with the study done by Careira et al. that showed better BP control on patients taking CCB, and ACEi as least effective [17]. This response to exercise is attributable to the decrease peripheral vascular resistance through vasodilatation effect of CCB [17]. As mentioned in a study done by using cardiopulmonary exercise test (CPET), age is associated with HRE primarily due to changes in the cardiovascular system such as vascular stiffening and cardiac remodeling [5]. Since majority of the population included in this study belonged to the middle age group (89.7%, refer to Table I) and possibly have stiffer arteriolar system than the young patients, use of CCB has a trend of more BP-lowering effect during exercise. In patients who were taking ARB+CCB, the vasodilatory effect of CCB may not be on full potential due to dosing reasons. However as mentioned, the dosages were not determined thus limiting this conclusion.

Analysis of the recovery period showed a statistically significant longer recovery time in patients taking ARB+HCTZ. Angiotensin receptor blocker exhibited the least effect on BP during maximal exercise and coupled with the relative hypovolemia provided by the thiazide, may cause a

more augmented sympathetic response, thus a delayed SBP decline. Laukkanen et al. showed that acute myocardial infarction (MI) was associated with incremental rise of 10 mm Hg per minute at 2 minutes after exercise and men with elevated SBP of >195 mm Hg after exercise compared with those with SBP <170 mm Hg [14]. Another study about delayed decline of SBP by Mcham et al. concluded that severe angiographic coronary artery disease (CAD) was associated with delayed blood pressure decline after graded exercise [15].

The positive test for ischemia in this study was not significant between patient in monotherapy and combination therapy, but there was a trend of positive results in the latter where there was also significantly longer recovery time. This was consistent with the previous studies that correlate delayed SBP decline to severe CAD and MI [14], [15]. To our knowledge, there is no existing evidence associating combination therapy to a longer recovery time and more so to having a significant CAD by angiography.

TABLE VI
TEST OUTCOME VERSUS THERAPY (SPECIFIC)

Test Outcome	Monotherapy		Combination Therapy		P-Value
	ARB	CCB	ARB+CCB	ARB+HCTZ	
Hypertensive Response					
Exaggerated SBP	8 (20%)	5 (20%)	10 (22%)	2 (33%)	0.819
Exaggerated DBP	24 (60%)	17 (68%)	30 (67%)	4 (67%)	
Exaggerated SBP & DBP	8 (20%)	3 (12%)	5 (11%)	0 (0%)	
Recovery Time					
1 minute	4 (10%)	1 (4%)	3 (7%)	0 (0%)	0.024*
3 minutes	29 (72%)	19 (76%)	21 (47%)	2 (33%)	
6 minutes	7 (18%)	4 (16%)	21 (47%)	4 (67%)	
9 minutes	0 (0%)	1 (4%)	0 (0%)	0 (0%)	
Outcome					
Negative	34 (85%)	24 (96%)	39 (87%)	3 (50%)	0.073
Equivocal	4 (10%)	1 (4%)	2 (4%)	1 (17%)	
Positive	2 (5%)	0 (0%)	4 (9%)	2 (33%)	
TOTAL	40 (34%)	25 (21%)	45 (38%)	6 (5%)	

* - significant at 5% ** - significant at 1%; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; ACEi = Angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; HCTZ = Hydrochlorothiazide

V. CONCLUSION

A monotherapy, specifically CCB, provided lower exaggerated diastolic BP compared to combination therapy during maximal exercise test in hypertensive middle age patients. Both mono and combination therapies provided better control on the recovery phase, except ARB + HCTZ which showed a longer recovery period. Moreover, our data were consistent with the previously done studies, which showed an association between delayed decline of SBP in the recovery period and development of CAD. The relationship between hypertensive patients on combination therapy with longer recovery time after maximal stress test and significant CAD by angiography needs further prospective study.

VI. LIMITATIONS OF THE STUDY

The beneficial effects of antihypertensive drugs in regard to exaggerated blood pressure response to maximal response were limited in this study due to several data insufficiency. First, the information about dosages, compliance, and duration of how long an antihypertensive drug(s) has been taken was not available in the worksheet provided for each patient. Second, the onset, duration, and current levels of blood sugar and cholesterol of patients with diabetes mellitus and dyslipidemia were not indicated. Information such as these was important for assessment of the effectiveness of antihypertensive drugs and if the above comorbidities have significant impact on the hypertensive response during

maximal exercise, and possibly in conjunction with the result of exercise test for ischemia.

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