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UNVEILING CARDIO-ANKLE VASCULAR INDEX: AN INDEPENDENT PREDICTOR OF HYPERTENSIVE RESPONSE TO EXERCISE

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ABSTRACT

Introduction: There exists a correlation between hypertensive response to exercise (HRE) and the subsequent onset of hypertension and cardiovascular complications, regardless of an individual's resting blood pressure. It was hypothesized that the measurement of arterial stiffness using the cardio-ankle vascular index (CAVI) could serve as an autonomous prognostic indicator for HRE.

Method: A retrospective analysis was carried out between March and December 2020. Participants who underwent both CAVI and treadmill stress test (TST) assessments on the same day constituted the initial pool of participants. Retrospective chart reviews were conducted through the track care system. The HRE predictors were analyzed using univariate and multivariate logistic regression analysis. ROC analyses were employed to determine the area under the curve (AUC) for Cardio-Ankle Vascular Index (CAVI) > 8 in predicting hypertensive response to exercise.

Results: Out of the total 209 individuals recruited, 37 patients (17.7%) met the criteria for HRE. The observed CAVI result in the non-HRE group was 7.12 ±1.10, while in the HRE group, it was 7.62 ±0.93. A statistically significant difference was observed ($p = 0.005$). Whereas the multivariate analysis showed that CAVI and resting systolic blood pressure were significantly associated with HRE. The ROC analysis showed that CAVI was significantly associated with (predicting) the HRE.

Conclusion: This study has provided compelling evidence supporting the role of the Cardio-Ankle Vascular Index (CAVI) as an independent predictor of hypertensive responses during exercise.

Keywords: Cardio-Ankle Vascular Index, HRE, Hypertension

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INTRODUCTION

The phenomenon of abnormally elevated systolic blood pressure during exercise is commonly termed the hypertensive response to exercise (HRE). It lacks a universally agreed-upon definition, but contemporary research has typically characterized it as systolic blood pressure surpassing the 90th percentile, with thresholds approximately above 210 mmHg for men and 190 mmHg for women, or as a discrepancy between peak and baseline systolic blood pressure of at least 60 mmHg in men and 50 mmHg in women during exercise testing [1-3]. Studies indicate that exaggerated blood pressure elevations during physical exertion may escalate the risk of developing hypertension and left ventricular hypertrophy in normotensive individuals [3, 4]. Moreover, the HRE has emerged as a potential prognostic marker in various studies [2, 5, 6].

The mechanisms underpinning the heightened blood pressure response to exercise primarily involve increased peripheral vascular resistance and impaired endothelial function, resulting in inadequate vasodilation during physical activity [7, 8]. This could stem from heightened sympathetic nervous system activity or structural alterations in arteriolar walls compromising their vasoconstrictive response. Additionally, elevated arterial stiffness, as assessed by pulse wave velocity (PWV), has been tentatively associated with HRE, although further investigation is warranted to substantiate this correlation.

The cardio-ankle vascular index (CAVI), a novel metric reflecting arterial stiffness across arterial segments, has garnered attention as it offers a rapid assessment derived from ankle brachial index (ABI) measurements. Unlike PWV, CAVI is purportedly less influenced by blood pressure due to its correction within the calculation formula [9, 10]. CAVI holds predictive value across various cardiovascular conditions, including cerebrovascular disease [11], coronary artery disease [12], hypertension [13], diabetes mellitus [14], metabolic syndrome [15], and obstructive sleep apnea [16]. Moreover, it is regarded as a sensitive tool for the early detection of arterial alterations preceding functional impairment [17].

This study seeks to explore the potential utility of CAVI in forecasting hypertensive responses to

exercise. Such investigation could yield critical insights into the interplay between arterial stiffness and exercise-induced blood pressure fluctuations, thereby informing risk stratification and management strategies for individuals exhibiting HRE.

Method

Participants

The study received approval from the Institutional Review Board of Hayatabad Medical Complex, Peshawar, Pakistan. All methodologies adhered strictly to relevant guidelines and regulations, with ethical approval obtained and consent waived for participants. Individuals engaged in the health preventive program at Hayatabad Medical Complex between March and December 2020, who underwent both CAVI and treadmill stress test (TST) assessments on the same day, constituted the initial pool of participants. Retrospective chart reviews were conducted through the track care system.

Inclusion criteria encompassed individuals aged between 18 and 80 years, possessing available data from both the treadmill stress test and CAVI evaluations, exhibiting sinus rhythm confirmed by electrocardiogram (ECG), and having requisite data accessible from the track care system, inclusive of comprehensive baseline characteristics, past medical history and medication profiles potentially impacting ankle-brachial index (ABI) and CAVI outcomes. Participants presenting significant supraventricular or ventricular tachyarrhythmias, as evidenced by ECG during CAVI measurement or TST, were excluded from the study. Moreover, individuals demonstrating substantial peripheral artery disease, defined by an ABI measurement of less than 0.9, were also excluded. Initially, 304 participants were enrolled during the screening phase, ultimately yielding 209 eligible participants for the study (Fig. 1).

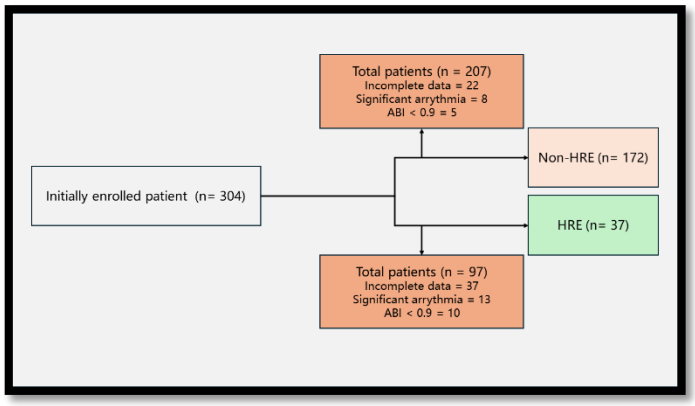

Fig 1. Flow diagram of patient selection

Treadmill stress test (TST)

Prior to engaging in an exercise stress test, patients are advised to adhere to several preparatory measures aimed at optimizing test accuracy and safety. These measures include abstaining from food intake for a period of 4 to 6 hours prior to the test and refraining from consuming caffeine-containing beverages, such as coffee, tea, and energy drinks, for at least 24 hours beforehand. Additionally, patients are discouraged from smoking or using any tobacco products on the day of the test. It is recommended that certain medications, particularly beta-blockers and other agents that block the atrioventricular (AV) node, be temporarily discontinued on the day of the test.

During the test, all patients undergo symptom-limited treadmill testing while undergoing continuous 12-lead electrocardiogram (ECG) monitoring. The standard Bruce protocol is employed, involving a gradual escalation of workload achieved by adjusting the treadmill speed and incline every three minutes. Blood pressure readings and a 12-lead ECG are obtained prior to the initiation of exercise, following each stage of the exercise (every three minutes), at the peak of exercise, and subsequently at 1-minute intervals during the recovery phase. Observations encompass the patient's reported symptoms, resting and peak heart rates, fluctuations in blood pressure, and any alterations noted in the ECG.

Exclusion criteria for the test include the onset of debilitating symptoms such as chest pain, dyspnea, or fatigue; the occurrence of significant cardiac

arrhythmias; notable ST-segment deviation exceeding 0.2 mV in conjunction with typical angina; achievement of the age-predicted maximum heart rate, calculated as 220 minus the patient's age; or the manifestation of any unusual blood pressure responses. An abnormal blood pressure response is defined by a decline in blood pressure exceeding 10 mmHg despite an escalation in workload, accompanied by other signs indicative of myocardial ischemia. Moreover, an exaggerated hypertensive response is characterized by a systolic blood pressure surpassing 250 mmHg or a diastolic blood pressure exceeding 115 mmHg [18].

Cardio-Ankle Vascular Index (CAVI)

CAVI measurements were conducted utilizing a VaSera CAVI apparatus (manufactured by Fukuda Denshi Co. Ltd. based in Tokyo, Japan). During the procedure, subjects assumed a supine position with their head positioned centrally while bilateral cuffs were applied to their upper arms and ankles. Following a 10-minute resting period in this position, measurements of brachial and ankle artery pressures and waveforms, electrography, phonocardiography, and other relevant parameters were obtained.

The calculation of CAVI employed the following formula: CAVI = a[(2ρ/ΔP) × ln(Ps/Pd)PWV2] + b, where Ps represents systolic blood pressure, Pd signifies diastolic blood pressure, PWV denotes pulse wave velocity, ΔP corresponds to the difference between systolic and diastolic blood pressures, ρ denotes blood density, and a and b denote constants [19]. After the application of this formula, CAVI values were automatically derived. An abnormally increased arterial stiffness was defined by a CAVI value exceeding 8. However, it is imperative to note that in cases where the ABI ratio falls below 0.9, CAVI measurements become unreliable, necessitating the exclusion of such individuals from the study cohort.

Hypertensive response to exercise

The existing literature lacks a universally agreed-upon definition of hypertensive response to exercise (HRE). In the context of this investigation, HRE was delineated as systolic blood pressure (SBP) equal to or exceeding 210 mmHg in men, SBP equal to or exceeding 190 mmHg in women, or diastolic blood pressure (DBP) equal to or exceeding 110 mmHg in both genders [1-3]. This criterion was adopted based on prior research indicating a relationship between HRE and the subsequent development of hypertension, as well as an escalation in left ventricular hypertrophy. Moreover, HRE has been identified as a noteworthy prognosticator of significant cardiovascular events [2, 5, 6].

Statistical analysis

All statistical analyses were conducted using Stata 18 (Stata Corp. 2023. Stata Statistical Software: Release 18. College Station, TX: Stata Corp LLC). Categorical variables were expressed as frequencies and percentages, with comparisons between groups made using either Fisher's exact test or Pearson's chi-square test. Continuous variables were presented as mean ± standard deviation and assessed for normal distribution using the Kolmogorov–Smirnov test. Normally distributed quantitative variables were compared between groups using the independent samples T-test, while non-normally distributed variables were compared using the Mann–Whitney U test.

A univariable logistic regression analysis was performed to explore the relationships between different variables and hypertensive response to exercise. Significant variables identified in the univariate analysis were subsequently included in a multivariate logistic regression model. Furthermore, receiver operating characteristic (ROC) analyses were employed to determine the area under the curve (AUC) for Cardio-Ankle Vascular Index (CAVI) > 8 in predicting hypertensive response to exercise. The p-value was considered significant at ≤0.05 level.

RESULTS

Table 1 displays the baseline characteristics of the study participants. Out of the total 209 individuals recruited, 37 patients (17.7%) met the criteria for HRE. The gender distribution showed that 125 participants (59.8%) were females. A small proportion of the population had pre-existing medical conditions, including diabetes mellitus (8.1%), hypertension (20.1%), dyslipidemia (18.7%), coronary artery disease (3.3%), cerebrovascular disease (0.5%), and 14.8% were smokers. Regarding medication usage, only a small

proportion of patients were taking aspirin (4.3%), statins (8.1%), beta-blockers (5.3%), ACE inhibitors/ARBs (4.3%), and calcium channel blockers (1.9%). CAVI was 7.21 ± 1.08.

The CAVI comparison between the Non-HRE and HRE can be seen in Table 2 and Figure 2. The observed CAVI result in the non-HRE group was 7.12 ±1.10, while in the HRE group, it was 7.62 ±0.93. A statistically significant difference was observed (p = 0.005).

Table 1. Baseline characteristics of the study population (n = 209)

	N (%)/mean ± SD
Gender	
Male	84 (40.2)
Female	125 (59.8)
Age	49.71 ± 8.34
Diabetes mellitus	17 (8.1)
Hypertension	42 (20.1)
Dyslipidemia	39 (18.7)
Smoking	31 (14.8)
History of coronary artery disease	7 (3.3)
History of cerebrovascular disease	1 (0.5)
History of chronic kidney disease	0 (0.0)
History of peripheral arterial disease	0 (0.0)
Medicine	
Aspirin	9 (4.3)
Metformin	0 (0.0)
ACEI/ARB	9 (4.3)
Beta-Blocker	11 (5.3)
CCB	4 (1.9)
Statin	17 (8.1)
BMI	24.15 ± 3.40
Heart rate	71.92 ± 2.76
SBP (mmHg, rest)	123.62 ± 9.24
DBP (mmHg, rest)	74.50 ± 6.29
SBP (mmHg, Peak)	170.90 ± 6.33
DBP (mmHg, Peak)	76.99 ± 6.04
Pulse pressure (mmHg, rest)	47.75 ± 5.42
Pulse pressure (mmHg, Peak)	98.22 ± 19.89
Different SBP peak-rest (mmHg)	47.28 ± 11.33
Different DBP peak-rest (mmHg)	2.49 ± 8.78
Right ankle-brachial index	0.91 ± 0.11
Left ankle-brachial index	0.90 ± 0.11
CAVI	7.21 ± 1.08

ACEI/ARB – Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers CAVI – Cardio-ankle vascular

Table 2. Distribution of baseline characteristics across non-HRE and HRE groups (n = 209)

Baseline parameters	non-HRE (n = 172)	HRE (n = 37)	P-value
Gender			0.05
Male	64 (37.2)	20 (54.1)	
Female	108 (62.8)	17 (45.9)	
Age	49.14 ± 8.27	52.38 ±8.23	0.03
Diabetes	6 (3.5)	11 (29.7)	<0.001
HTN	28 (16.3)	14 (37.8)	0.003
Dyslipidemia	21 (12.2)	18 (48.6)	<0.001
Smoking	25 (14.5)	6 (16.2)	0.79
History of coronary artery disease	5 (2.9)	2 (5.4)	0.44
History of cerebrovascular disease	6 (3.5)	2 (5.4)	0.58
Medicine			<0.001
Aspirin	8 (4.7)	1 (2.7)	
Statin	10 (5.8)	7 (18.9)	
ACEI/ARBS	6 (3.5)	3 (8.1)	
Beta-Blocker	4 (2.3)	7 (18.9)	
CCB	3 (1.7)	1 (2.7)	
BMI	24.04 ±3.51	24.65 ±2.81	0.32
Heart rate (bpm, rest)	71.85 ±2.80	72.24 ±2.54	0.43
SBP (mmHg, rest)	119.88 ±4.03	141.03 ±6.17	<0.001
DBP (mmHg, rest)	72.51 ±4.49	83.76 ±5.05	<0.001
SBP (mmHg, Peak)	170.88 ±6.32	170.97 ±6.44	0.93
DBP (mmHg, Peak)	77.13 ±6.12	76.32 ±5.70	0.46
Pulse pressure (mmHg, rest)	47.49 ±5.27	48.97 ±6.00	0.17
Pulse pressure (mmHg, Peak)	92.59 ±17.27	124.35 ±3.97	<0.001
Different SBP peak-rest (mmHg)	51.01 ±7.68	29.95 ±9.28	<0.001
Different DBP peak-rest (mmHg)	4.62 ±7.59	-7.43 ±6.95	<0.001
Right ankle-brachial index	1.02 ±0.11	1.09 ±0.11	0.28
Left ankle-brachial index	0.90 ±0.11	1.05 ±0.11	0.16
CAVI	7.12 ±1.10	7.62 ±0.93	0.005

CAVI – Cardio-ankle vascular index, HRE – hypertensive response to exercise, BMI – Body mass index, ACEI/ARB – angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker

The univariate analysis showed that being female, age greater than 55 years, having a history of diabetes, hypertension and dyslipidemia were significantly associated with HRE. The details can be seen in Table 3. Whereas the multivariate analysis showed that CAVI was an

Table 2. Univariate analysis to assess the predictors of HRE (n = 37)

Variable	OR (95% CI)	P-value
Gender (Female)	1.98 (0.96 – 4.06)	0.05
Age (>55 years)	1.86 (1.22 – 2.96)	0.04
Diabetes	0. 80 (0.25 –1.02)	<0.001
Hypertension	2.56 (1.87 – 3.73)	0.004
Dyslipidemia	1.14 (0.98 – 1.32)	<0.001
Systolic blood pressure (rest)	1.20 (0.96 – 2.12)	0.02
Diastolic blood pressure (rest)	1.02 (0.96 – 1.08)	0.03
Heart rate (rest)	1.04 (1.01 – 1.06)	<0.001
Pulse pressure (rest)	1.03 (1.02 – 1.03)	<0.001
Right ankle-brachial index	5.33 (3.60 – 7.90)	<0.001
Left ankle-brachial index	5.40 (3.64 – 8.01)	<0.001
CAVI	1.22 (1.16 – 1.28)	<0.001
Aspirin	7.99 (1.05 – 11.94)	0.04
Beta-blocker	1.42 (0.54 – 3.75)	0.02

CAVI – Cardio-ankle vascular index, OR – odds ratio, CI – confidence interval.

Table 4. Multivariate analysis to assess the predictors of HRE (n = 37)

Variable	OR (95% CI)	P-value
Model 1		
Gender (Female)	1.18 (0.97 – 3.06)	0.43
Age (>55 years)	0.99 (0.96–1.04)	0.36
Diabetes	2.12 (0.41–10.9)	0.32
Hypertension	0.48 (0.17–1.32)	0.18
Dyslipidemia	0.72 (0.25–2.04)	0.53
Aspirin	3.84 (1.15 – 6.53)	0.48
Beta-blocker	0.82 (0.15–4.5)	0.76
Cardio-ankle vascular index	2.32 (1.45 – 3.56)	0.001
Model 2		
Gender (Female)	1.16 (0.87 – 2.89)	0.54
Age (>55 years)	0.96 (0.0.93–1.03)	0.41
Diabetes	2.03 (0.37– 8.34)	0.45
Hypertension	0.43 (0.15–1.14)	0.62
Systolic blood pressure (rest)	1.06 (0.94 – 2.05)	0.04
Diastolic blood pressure (rest)	1.01 (0.96 – 1.09)	0.54
CAVI	2.34 (1.46 – 3.53)	<0.001

CAVI – Cardio-ankle vascular index, OR – odds ratio, CI – confidence interval. Model 1 and 2 were created to fit the number of events (37 HRE patients)

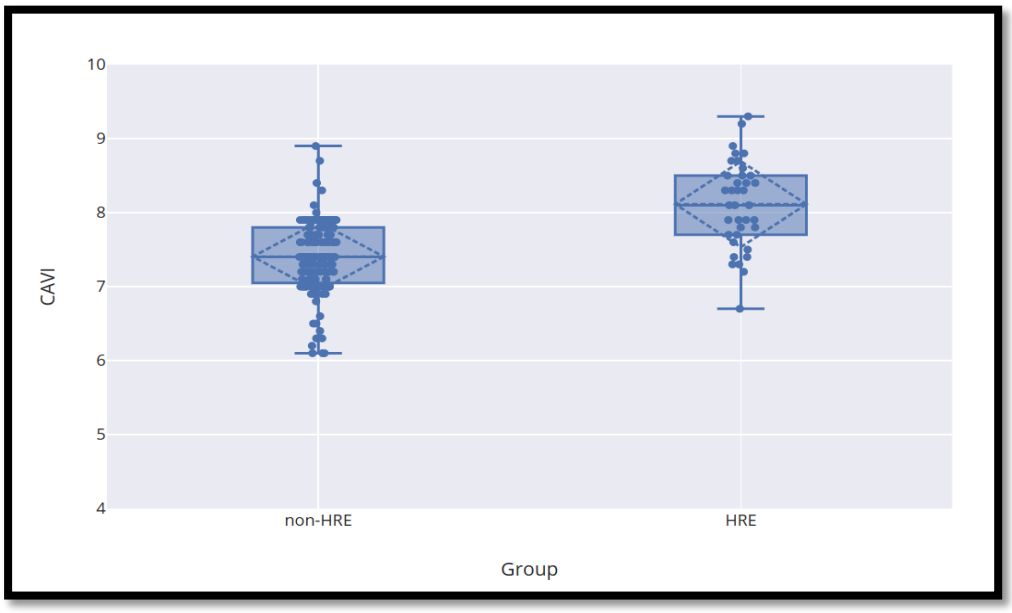

Figure 2. Comparison of the CAVI between non-HRE and HRE group, CAVI – Cardio-ankle vascular index, HRE – hypertensive response to exercise

Previously, abnormal results have been identified when CAVI was greater than 8 [20]. The ROC analysis showed that CAVI was significantly associated with (predicting) the HRE. The area under the curve (AUC) was 0.66 (95% CI = 0.55 – 0.77, p = 0.005). The details are given in Figure 3.

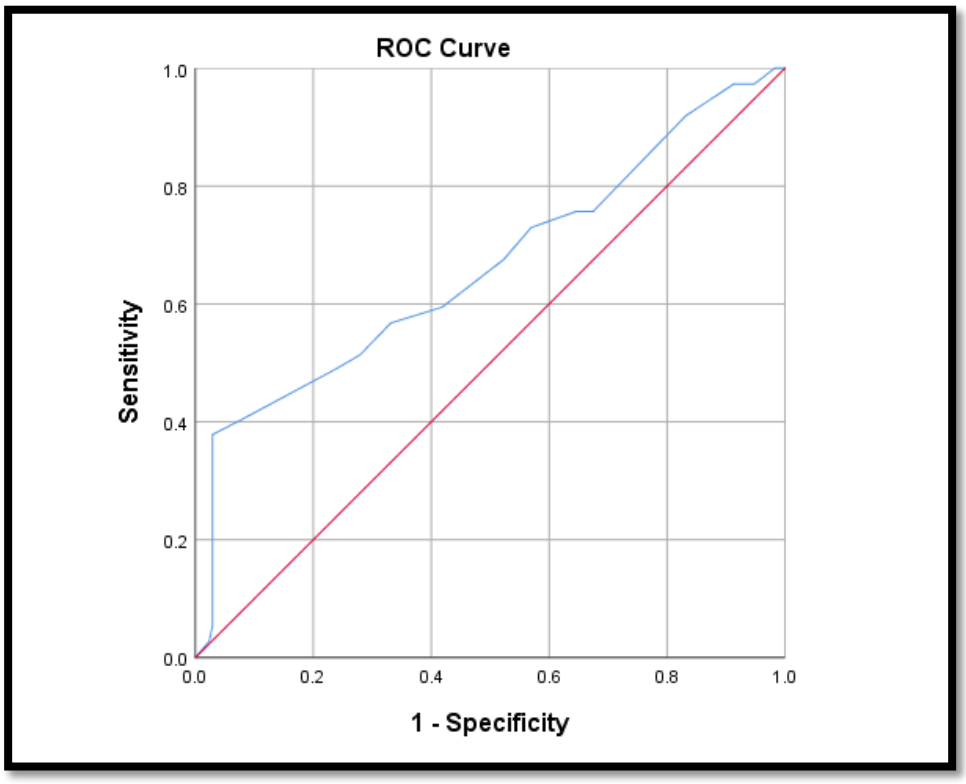

Figure 3. The ROC curve of CAVI to predict HRE, CAVI – Cardio-ankle vascular index, AUC – area under the curve, CI – confidence interval.

DISCUSSION

The present study has revealed that arterial stiffness, as assessed by CAVI, was a statistically significant predictor of HRE. These results offer new insights into the influence of arterial stiffness on elevated exercise systolic blood pressure. Notably, the study found that in individuals without HRE, the CAVI value was 7.12 ± 1.106, while in those with HRE, it was 7.62 ± 0.93 (p = 0.005), supporting the hypothesis of a mechanistic association between HRE and arterial stiffness, independent of established cardiovascular risk factors. Furthermore, the study highlighted that CAVI, acting as a surrogate marker for arterial stiffness, can discern against arterial compliance. The research identified a CAVI threshold greater than 8 as optimal for predicting HRE. Receiver operating characteristic (ROC) curve analysis indicated that CAVI is a statistically significant predictor of HRE, with an area under the curve (AUC) of 0.0.662 (95% CI = 0.55 – 0.77, p = 0.002).

These findings suggest that CAVI could be clinically valuable in identifying arterial stiffness in individuals at heightened risk of cardiovascular disease. However, it is essential to acknowledge that the study's outcomes may not be broadly applicable to patients with established cardiovascular disease, as the study cohort primarily comprised individuals at low to intermediate atherosclerotic cardiovascular disease (ASCVD) risk levels. Moreover, when considering HRE as the dependent variable, univariate analysis identified female gender, age >55 years, diabetes mellitus, hypertension, dyslipidemia, beta-blocker usage history, resting pulse pressure, and CAVI as significant predictors for HRE. Intriguingly, conventional ASCVD risk factors did not emerge as significant in the multivariate analysis.

This investigation employed a specific threshold criterion: a systolic blood pressure (SBP) of 210 mmHg or higher for men and 190 mmHg or higher for women or a diastolic blood pressure (DBP) of 110 mmHg or higher for both sexes. These thresholds were determined based on surpassing the 90th percentile of blood pressure responses during maximal or peak intensity exercise. Previous research has validated these cut-off points, demonstrating their correlation with future hypertension [5, 21], increased left ventricular hypertrophy [6], and a heightened risk of major adverse cardiac events [22]. Sharman et al. also illustrated the utility of HRE in identifying masked hypertension, using the same cut-off values as our study, through 24-hour ambulatory blood pressure monitoring (ABPM) [23]. Additionally, studies have identified the CAVI as an independent risk factor for masked uncontrolled hypertension [23]. The CAVI values observed in the masked hypertension group closely align with those seen in individuals exhibiting HRE in our study. Proposed mechanisms for HRE include endothelial dysfunction and increased arterial stiffness [24]. Chung et al. further substantiated the relationship between arterial stiffness, assessed via brachial-ankle pulse wave velocity (baPWV), and HRE, affirming the consistency with our study's cut-off point [25]. Notably, our findings also parallel previous observations of a higher prevalence of HRE in women, emphasizing the relevance of the chosen threshold. Thus, the selected cut-off value aptly signifies a threshold for HRE, correlating with the CAVI outcomes identified in our study.

Our study is subject to several limitations. Firstly, it was a retrospective analysis conducted at a single center, drawing data solely from medical records. This resulted in a participant pool predominantly comprising individuals with low to moderate risk profiles, with insufficient representation of those afflicted with heart disease or individuals at high risk thereof. Secondly, the CAVI, while a promising measurement, exhibits noteworthy inter-observer and intra-observer variability. As multiple technicians conducted our CAVI studies, variations in measurement techniques may have occurred, alongside potential discrepancies arising from variances in the emotional stress conditions experienced by patients during the assessments.

CONCLUSION

This study has provided compelling evidence supporting the role of the Cardio-Ankle Vascular Index (CAVI) as an independent predictor of hypertensive responses during exercise. The integration of CAVI measurements into routine exercise assessments holds promise in facilitating early detection and intervention for individuals predisposed to exercise-induced hypertension. However, a comprehensive evaluation may be

warranted to validate these findings further and ensure their clinical applicability.

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