Comparison of Heart Rate Blood Pressure Product Versus Age-Predicted Maximum Heart Rate as Predictors of Cardiovascular Events During Exercise Stress Echocardiography

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Exercise stress echocardiograms (ESEs) are a functional cardiovascular (CV) test typically used for the investigation of coronary artery disease. ESEs are often terminated at a predetermined age-predicted maximum heart rate (APMHR) to facilitate timely acquisition of ultrasound images at peak exercise. Although an APMHR of 85% is often used, this has not been validated as a suitable termination end point. Heart rate blood pressure product (HRBPP) as an established measure of myocardial work may provide a more reliable assessment of cardiac workload. The aim of this study was to assess maximal HRBPP (MHRBPP) and APMHR as markers of cardiac workload during ESE, using CV events at mean follow-up as the outcome variable. After exclusions, 712 patients being investigated for ischemic heart disease, performed an ESE to volitional fatigue using the standard Bruce protocol. Patient demographics and test data were collected and patients followed for 4.4 ± 2.1 years. Cut-points for MHRBPP (25,060; area under curve 0.77) and APMHR (93.8% and 97.9%; area under curve 0.71; p = 0.12 for difference) were established from receiver operating characteristic analysis. Those achieving an APMHR >85% but MHRBPP <25,060 had significantly more CV events than achieving an MHRBPP >25,060 regardless of APMHR (p <0.05). In conclusion, the current study demonstrates the superior prognostic power of MHRBPP over APMHR alone for the prediction of future CV events in patients performing an otherwise negative ESE for the detection of myocardial ischemia. **(Am J Cardiol 2019;124:528−533)**

Generally, the diagnostic accuracy of the exercise stress echocardiogram (ESE) is superior to the exercise stress test (EST) however this often depends on the patient population being studied, the image quality and test interpreter skill level.[1−5] The added advantage of ESE is the acquisition of ultrasound images to detect regional wall motion abnormalities (RWMA) linked to myocardial ischemia, particularly when the resting electrocardiogram is uninterpretable.[5] ESEs are often terminated at an age-predicted maximum heart rate (APMHR) of 85% to allow the patient to move quickly into a supine position for peak image acquisition as RWMA may resolve quickly.[1,6,7] Heart rate blood pressure product (HRBPP), as an established estimate of myocardial oxygen consumption and, therefore, myocardial work,[8,9] is often recorded during an ESE but not commonly used as a marker of sufficient cardiac workload.[1] Maximum HRBPP (MHRBPP) has been shown to be a predictor of cardiovascular (CV) outcome during ESTs, displaying superiority over APMHR to predict CV events.[10] Therefore, MHRBPP may provide a more reliable assessment of cardiac workload than APMHR for the prediction of CV events during ESEs. The aim of this study was to compare MHRBPP and APMHR as predictors of future CV events in intermediate risk patients performing an otherwise negative ESE.

Methods

The study sample was retrieved from the Logan Hospital, a public hospital in southeast Queensland, Australia, and was approved by the Metro South Health Service District Human Research Ethics Committee, conforming to the Declaration of Helsinki. Retrospective data from consecutive ESEs performed from January 1, 2010 to December 31, 2014 for the investigation of inducible myocardial ischemia were included (n = 783). Any test considered positive by RWMA, electrocardiogram criteria, symptoms, or patients with >mild resting left ventricular dysfunction (n = 71) were excluded, as downstream management strategies would differ in this group. The total number of tests remaining for analysis was 712. Echocardiography images were obtained with a Philips IE33 ultrasound machine (Philips Medical Systems, Andover, Massachusetts) in the left lateral decubitus position. Image analysis was performed as per American Society of Echocardiography guidelines.[7] The treadmill exercise was

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Table 1
Physical characteristics and ESE measures for those with and without cardiovascular (CV) events during follow-up

Variable	CV events (n = 58)	No CV events (n = 657)	p Value
Age (years)	60.0 ± 10.4†	52.8 ± 11.5	<0.01
Men	36 (62.1%)	316 (48.1%)	0.25
Resting heart rate (bpm)	75 ± 14	79 ± 14†	0.02
Resting systolic blood pressure (mm Hg)	132 ± 19	128 ± 18	0.18
Resting heart rate blood pressure product	9820 ± 2311	10212 ± 2435	0.24
Maximum heart rate (bpm)	143 ± 18*	164 ± 19*,†	<0.01
Maximum systolic blood pressure (mm Hg)	166 ± 27*	171 ± 21*	0.08
Maximum heart rate blood pressure product	23762 ± 4839*	28045 ± 4731*,†	<0.01
Test Duration (min:sec)	7:17 ± 2:48	8:42 ± 2:33†	<0.01
Metabolic equivalents	8.8 ± 3.0	10.4 ± 2.8†	<0.01
Resting regional wall motion abnormalities	9 (15.5%)†	25 (3.8%)	<0.01
Diastolic dysfunction	14 (24.1%)	89 (13.6%)	0.09
Mildly impaired resting ejection fraction	4 (6.9%)†	10 (1.5%)	0.02

Values show number of cases (n), mean ± SD or percentage (%) of the group.
* Significant from resting values p <0.05.
† Significant between CV event and no CV event group p <0.05.

administered on a computer-controlled treadmill system (Marquette Case, Milwaukee, Wisconsin), performed to volitional fatigue, using the standard Bruce protocol.[11] Manual blood pressure measurements were taken by an experienced operator at least once every stage, at peak exercise, and a minimum of twice during recovery. HRBPP was calculated by multiplying heart rate by systolic blood pressure (SBP) throughout the test and MHRBPP was identified. Mean follow-up was 4.4 ± 2.1 years by reference to medical records, inclusive of mortality registry or contact with the patients' general practitioners.

Quantitative data were summarized as mean ± standard deviation and the student *t* test or Fisher's exact test were used where appropriate. To establish a cut-point for MHRBPP and APMHR, receiver operating characteristic (ROC) analysis was used to calculate sensitivity and specificity with respect to CV events (CV mortality, nonfatal myocardial infarction, stroke or heart failure (minimum stage C),[12] percutaneous coronary intervention/balloon angioplasty or coronary artery bypass grafting) at mean follow-up as the outcome measure. The longest vertical deviation from the diagonal line was chosen as the optimal cut-point. Kaplan-Meier survival analysis was used to evaluate CV events, CV mortality and all-cause mortality for those above and below the optimal cut points. The log-rank test was used to assess statistical significance. Cox proportional hazard models were created to assess variables significant for CV events. Variables were selected from baseline differences between those with and without CV events (Table 1 and 2). Likewise, inability to achieve

Table 2
Cardiovascular (CV) disease risk factors and medications at time of stress test for those with and without CV events during follow-up

Variable	CV events (n = 58)	No CV events (n = 657)	p Value
CV disease risk factors	3.1 ± 1.3	2.1 ± 1.3	<0.01
No risk factors for CV disease	3 (5.2%)	78 (11.9%)	0.19
Family history of CV disease	17 (29.3%)	204 (31.1%)	>0.99
Diabetes Mellitus	19 (32.8%)	112 (17.0%)	0.03
Smoker	14 (24.1%)	156 (23.7%)	>0.99
Hypertension	39 (67.2%)	282 (42.9%)	0.04
Dyslipidemia	45 (77.6%)	322 (49.0%)	0.04
Obesity	17 (29.3%)	220 (33.5%)	0.78
Prior coronary artery disease	31 (53.4%)	91 (13.9%)	<0.01
Medications per patient	3.3 ± 1.9	1.7 ± 1.7	<0.01
No medications	6 (10.3%)	232 (35.3%)	<0.01
β blockers	31 (53.4%)	148 (22.5%)	<0.01
Ca2+ blockers	13 (22.4%)	71 (10.8%)	0.04
Angiotensin converting enzyme inhibitors	22 (37.9%)	139 (21.1%)	0.03
Angiotensin receptor blockers	13 (22.4%)	115 (17.5%)	0.49
Nitrates	9 (15.5%)	15 (2.3%)	<0.01
Statins	35 (60.3%)	269 (40.9%)	0.10
Diuretics	7 (12.1%)	44 (6.7%)	0.19
Aspirin	36 (62.1%)	244 (37.1%)	0.03
Nonvitamin K antagonist	2 (3.4%)	3 (0.5%)	0.06
P2y12 inhibitor	16 (27.6%)	53 (8.1%)	<0.01
Warfarin	4 (6.9%)	10 (1.5%)	0.02

Values show number of cases (n), ±SD or percentage (%) of the group.

the ROC cut-points was included in the model with entry and multivariate retention set at 0.05 significance. Multivariate analysis was performed to assess factors influencing the ability to achieve the ROC cut-points including age, smoking status, heart rate, and blood pressure medications. Categorical data were compared using the chi-square or Fisher's exact test, where appropriate. Data analysis was performed using XLSTAT 2018.7 (Addinsoft, New York) with a 2-tailed p value <0.05 considered statistically significant.

Results

Table 1 displays the physical attributes of the patients together with their ESE measures for those with and without CV events during follow-up. Table 2 lists the CV disease risk factors and medications of the patients at time of testing. Those with CV events were older, performed less exercise with less myocardial work during their test and had more resting abnormalities on their echocardiograms (Table 1). They also exhibited more CAD, used more medications and overall displayed a greater CV disease risk (Table 2).

ROC analyses revealed an optimal cut-point of 25,060 for MHRBPP (sensitivity 76%, specificity 78.2%, [area under curve (AUC) 0.77]. For APMHR, the optimal cut-point was equal between 2 points; 93.8% (sensitivity 63.8%, specificity 69.4%) and 97.9% (sensitivity 79.3%, specificity 53.9%; AUC 0.71). At 85% APMHR, the sensitivity and specificity were 27.6% and 91.8%, respectively. The difference between the 2 models failed to reach statistical significance (p = 0.12; Figure 1).

There was no CV mortality throughout the follow-up period. Figure 2 illustrates the Kaplan-Meier curves for all-cause mortality and CV events with respect to the MHRBPP cut point of 25,060 and APMHR of 85%. There

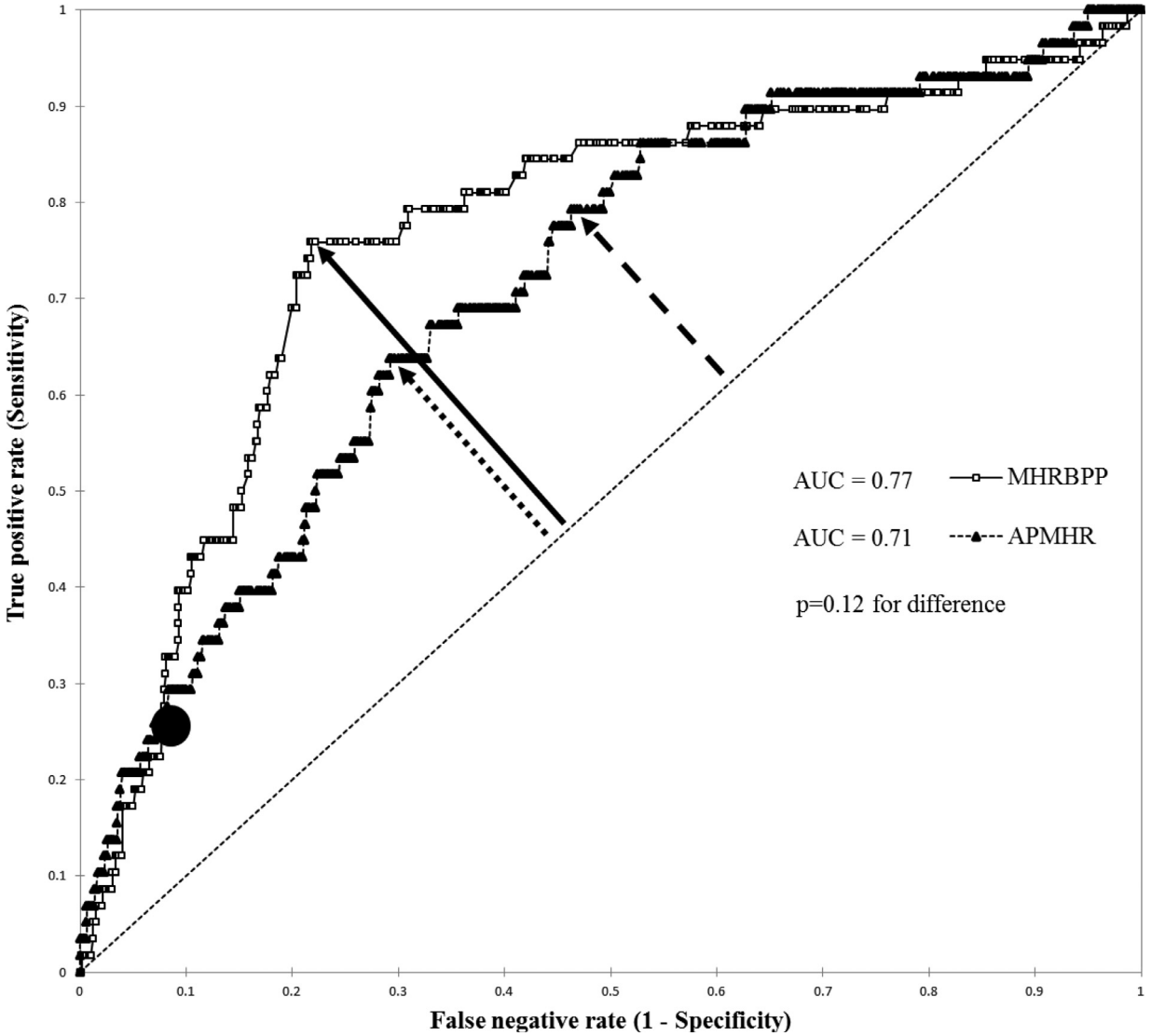
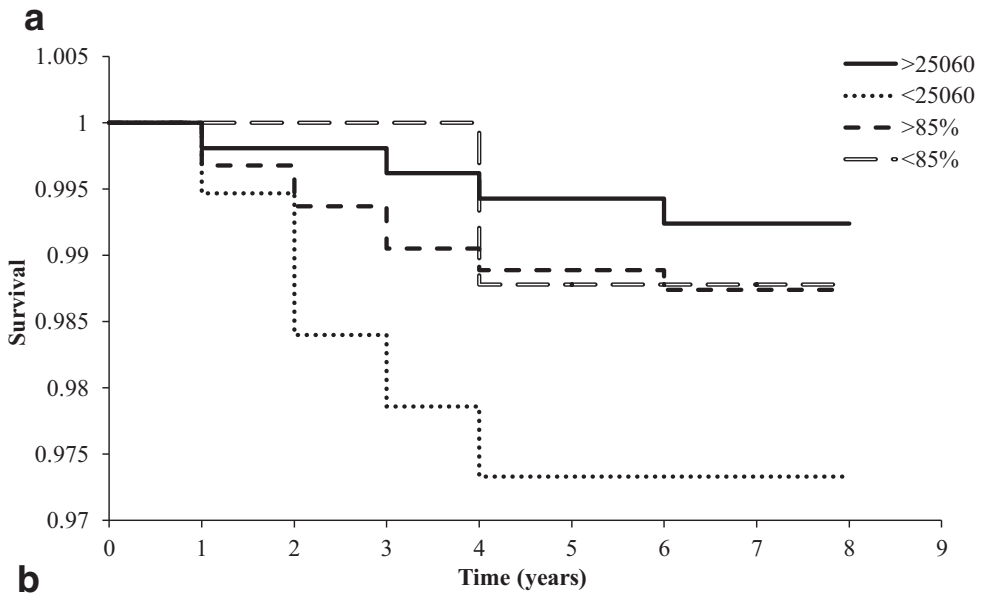
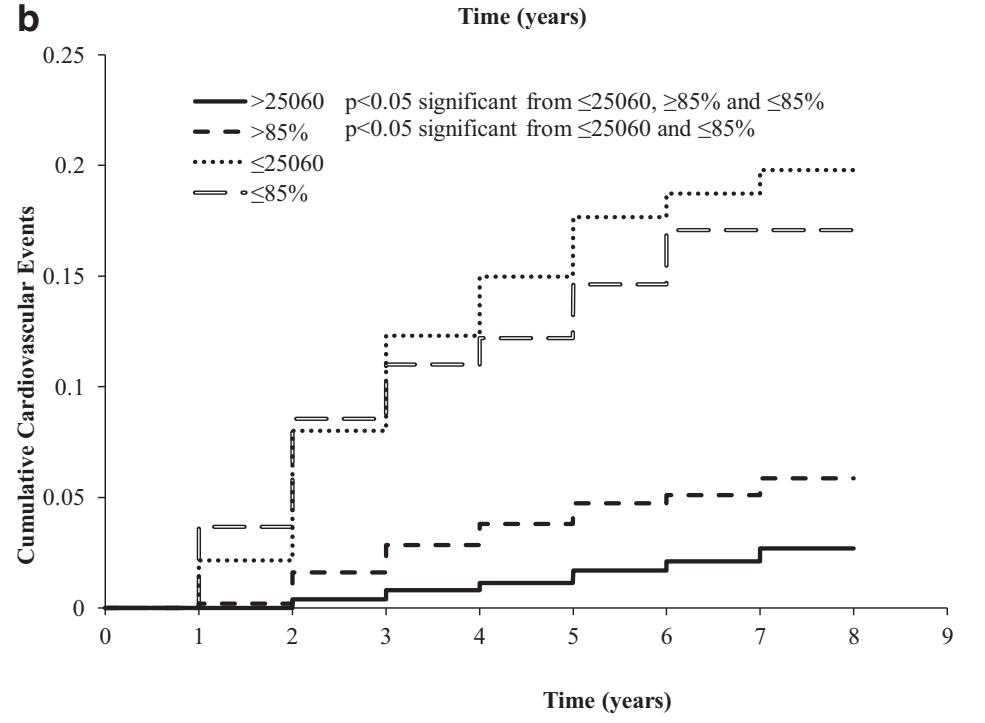


Figure 1. Receiver operating characteristic curve for maximum heart rate blood pressure product (MHRBPP) and age-predicted maximal heart rate (APMHR). The bold arrow indicates the optimal cut-point for MHRBPP. The dotted arrow (93.8%) and dashed arrow (97.9%) indicate the optimal cut-points for APMHR. The black dot specifies the data point at 85% APMHR.





No at risk									
> 25060	528	446	415	364	286	224	151	59	0
≤ 25060	187	173	164	149	112	78	52	15	0
> 85%	633	542	505	448	355	274	185	68	0
≤ 85%	82	77	74	65	43	28	18	6	0

Figure 2. Kaplan-Meier curve for (A) all-cause mortality and (B) cardiovascular events for maximum heart rate blood pressure product > and ≤25,060 and age-predicted maximum heart rate > and ≤85%.

was no significant difference in all-cause mortality for all interactions of MHRBPP > or ≤25,060 and APMHR > or ≤85% (Figure 2). In contrast, the cumulation of CV events was significantly less in those achieving >25,060 MHRBPP or >85% APMHR compared with MHRBPP ≤25,060 and APMHR ≤85% (p <0.05; Figure 2). From 3 years follow-up, those attaining a MHRBPP >25,060 had significantly less events than those reaching >85% APMHR (p <0.05; Figure 2).

Table 3 shows the outcome of Cox proportional hazard analysis for predicting CV events. After adjustments, only age, the presence of diabetes, previous CAD, and an MHRBPP <25,000 remained as significant predictors.

No CV medication influenced the ability to achieve the cut-points for APMHR and MHRBPP. For all cut-point levels of APMHR (<85%, <94%, <98%) only a younger age was a significant factor for the inability to achieve above these levels (p <0.05). There was no significant factor

Table 3
Univariate and multivariate predictors of cardiovascular events from exercise stress echocardiogram results

Variable	Univariate hazard ratio (95% CI)	Chi square	p Value	Multivariate hazard ratio (95% CI)	Chi square	p Value
Age	1.06 (1.02-1.10)	9.1	0.003	1.06 (1.03-1.09)	16.8	<0.0001
Men	1.14 (0.54-2.40)	0.2	0.738	-	-	-
Diabetes Mellitus	2.57 (1.28-5.17)	7.0	0.008	2.77 (1.48-5.17)	10.2	0.001
Hypertension	2.58 (1.09-6.11)	4.7	0.031	2.02 (0.91-4.48)	2.9	0.086
Dyslipidemia	0.94 (0.44-2.00)	0.1	0.872	-	-	-
Prior coronary artery disease	3.20 (1.51-6.80)	9.2	0.002	2.56 (1.43-4.57)	10.0	0.002
β-Blocker use	1.22 (0.63-2.37)	0.4	0.551	-	-	-
Calcium channel blocker use	0.63 (0.28-1.42)	1.2	0.265	-	-	-
Angiotensin converting enzyme inhibitor use	1.36 (0.70-2.66)	0.8	0.365	-	-	-
Nitrate use	2.72 (1.05-7.05)	4.2	0.040	2.17 (0.99-4.75)	3.7	0.052
Aspirin use	0.66 (0.34-1.27)	1.6	0.213	-	-	-
P2Y12 inhibitor use	0.51 (0.23-1.13)	2.7	0.099	-	-	-
Warfarin	0.33 (0.08-1.41)	2.3	0.133	-	-	-
<7:17min:sec treadmill time	3.64 (0.45-29.8)	1.5	0.228	-	-	-
<8.8 metabolic equivalents	0.19 (0.02-1.56)	2.4	0.122	-	-	-
<85% Age-predicted maximum heart rate	1.53 (0.67-3.48)	1.1	0.311	-	-	-
<94% Age-predicted maximum heart rate	0.63 (0.25-1.55)	1.1	0.312	-	-	-
<98% Age-predicted maximum heart rate	1.83 (0.68-4.92)	1.4	0.232	-	-	-
Resting regional wall motion abnormalities	0.30 (0.00-0.91)	4.6	0.033	0.43 (0.15-1.20)	2.6	0.105
Maximum heart rate blood pressure product <25060	7.64 (3.40-17.2)	24.2	<0.0001	6.21 (3.26-11.8)	30.9	<0.0001
Mildly impaired resting left ventricular ejection fraction	6.03 (1.30-27.9)	5.3	0.022	3.59 (0.94-13.8)	3.5	0.063

influencing MHRBPP other than the components maximum heart rate and maximum SBP ($p < 0.05$).

Discussion

The current study demonstrates MHRBPP as a reasonable prognostic measure of future CV events (AUC = 0.77). Although the overall diagnostic model between MHRBPP and APMHR failed to reach significance ($p = 0.12$; Figure 1), no level of APMHR predicted future CV events (Table 3). In comparison, inability to achieve the ROC cut-point for MHRBPP >25,060 was a strong uni- and multivariate predictor of CV events (Table 3). An APMHR of 85% is often used as a marker of sufficient stress during treadmill exercise.[13] Our study found this value exhibited poor sensitivity (27.6%) for the detection of future CV events in otherwise negative studies (Figure 1). The use of 85% APMHR comes from studies demonstrating that failure to achieve this level is a marker of chronotropic incompetence.[14,15] No study has shown this level of APMHR as a sufficient marker of cardiac workload during exercise yet many still use this as a termination point during exercise testing despite guideline recommendations.[2,16,17] The current study shows even achieving an APMHR >85% did not predict a better outcome compared with an MHRBPP >25,060 (Figure 2).

There was a significant difference for CV event frequency during follow-up between those achieving an MHRBPP >25,060 and those below (Figure 2). Previous work by Whitman et al demonstrated similar results in those with poor functional capacity but MHRBPP >25,000 during an EST.[10] In the current study, resting left ventricular dysfunction was found to be an independent predictor of future CV events (Table 3). Elhendy et al demonstrated similar results with resting echocardiogram abnormalities and poorer CV outcomes in those unable to achieve 85% APMHR and, although not discussed, an inability to reach an HRBPP of 25,000 during an ESE.[15] Advancing age, diabetes, hypertension and the presence of CAD have all been shown to increase CV disease risk.[18,19] This is confirmed in the current study as these risk factors were all significantly different between the CV event group and the no CV event group ($p < 0.05$; Table 2). The greatest predictor for CV events in the current study was failure to reach an MHRBPP of >25,060 (Table 3). In a study by Sadrzadeh Rafie at el,[20] HRBPP reserve (the difference between rest and maximal exercise) was a stronger predictor of CV outcome than even exercise capacity, a known CV prognostic marker.[21] Similarly, we found the inability to achieve an MHRBPP >25,060 to be a strong CV event predictor with exercise capacity failing to predict CV events in the current study (Table 3). The ability to increase SBP alone during an ESE has been associated with a significantly lower risk of future CV events.[22] Therefore, it appears the blood pressure response during exercise is equally as important as the heart rate response and should be used in conjunction (i.e., MHRBPP) to maximize the prognostic power for the prediction of CV events.

There are some limitations to this study. Firstly, our study is a single center cohort and therefore the decision to perform an ESE may have been subject to selection bias. Secondly, whereas most of our patients were risk stratified as intermediate/moderate risk for CV disease, the total event rate during follow-up was only 8% suggesting a lower overall risk. Finally, like all predictive models, care should be taken not to replace clinical suspicion in patients deemed to be at sufficient future CV event risk.

In conclusion, the current study demonstrates the superior prognostic power of MHRBPP over APMHR alone for the prediction of future CV events in patients performing

an otherwise negative ESE to volitional fatigue. Although APMHR has been used as a marker of sufficient myocardial work in the past, the present study demonstrates the value of MHRBPP during exercise testing and warrants further investigation in this area.

Disclosures

The authors have no conflicts of interest to disclose.

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