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Original Article

Rate pressure product, age predicted maximum heart rate or heart rate reserve. Which one better predicts cardiovascular events following exercise stress echocardiography?

Mark Whitman[1,2], Carly Jenkins[1]

[1]*Cardiac Investigations Unit, Logan Hospital, Meadowbrook, Yatala, Australia;* [2]*School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia*

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Abstract: Background: Age-predicted maximum heart rate (APMHR) has been demonstrated to be a poor predictor of future cardiovascular (CV) events and is yet to be validated as a termination point during exercise testing. In contrast, maximum rate pressure product (MRPP) is recognized as a strong predictor of CV outcome with superior CV event prediction over APMHR. Heart rate reserve (HRR) has been shown to be a powerful predictor of CV mortality during exercise testing, however thus far, this is not confirmed for non-fatal CV events. The aim of this study was to compare APMHR, MRPP and HRR as predictors of CV events following otherwise negative exercise treadmill testing. Methods: After exclusions, 1080 patients being investigated for coronary artery disease performed an exercise stress echocardiogram (ESE) to volitional fatigue on a motorised treadmill. Blood pressure was measured manually, and ultrasound images performed as per current American Society of Echocardiography guidelines. Rate pressure product and HRR were calculated throughout the test and maximum values were identified. Patients were followed for 5.3±2.6 mean years. Results: From receiver operating characteristic analysis, cut points were established for APMHR (94.6%) (AUC 0.687), MRPP (25085) (AUC 0.729) and HRR% (95.9) (AUC 0.688). MRPP outperformed both APMHR and HRR% for the prediction of future CV events. Furthermore, on Cox proportional hazard analysis MRPP was the strongest uni- and multivariate predictor ($p<0.0001$) with APMHR and HRR% failing to reach any statistical significance. Conclusions: The current study demonstrates the substantial prognostic power of MRPP over both APMHR and HRR% to predict CV events following an otherwise negative ESE for myocardial ischemia.

Keywords: Rate pressure product, myocardial ischemia, exercise treadmill testing, age-predicted maximum heart rate, heart rate reserve, exercise stress echocardiogram

Introduction

Age-predicted maximum heart rate (APMHR) in patients performing exercise treadmill testing has been demonstrated to be a poor predictor of future cardiovascular (CV) events such as, fatal or non-fatal myocardial infarction, percutaneous coronary intervention (PCI)/balloon angioplasty, coronary artery bypass grafting, stroke or the development of significant heart failure [1, 2]. Likewise, the widespread use of an APMHR of 85% as a termination point during exercise testing has not been validated [1, 3, 4]. In contrast, the product of heart rate and systolic blood pressure, termed the rate pressure product (RPP), has been documented to be a strong predictor of CV outcome and superior to APMHR to predict CV events in those with normal exercise test results [1, 2]. During maximal exercise testing, the difference in heart rate from rest to peak, labelled the heart rate reserve (HRR) has been shown to be a robust predictor of CV mortality during both exercise and pharmacological stress testing [5-8]. The use of HRR to predict non-fatal CV events has not been described. There is considerable debate over which parameter (APMHR, RPP, HRR or metabolic equivalents) should be used to measure adequate myocardial workload during exercise stress testing in

otherwise normal tests [1, 9-11]. Establishing an appropriate cut-point of myocardial work considered enough to separate those patients that require further follow-up from those that don't, would be beneficial. Therefore, the aim of this study was to compare APMHR, RPP and HRR as predictors of future CV events in patients performing otherwise negative exercise treadmill testing.

Materials and methods

The study cohort originated from the Logan Hospital, a public hospital in southeast Queensland, Australia. Approval to perform the study was granted by the Metro South Health Service District Human Research Ethics Committee (QMS/61502) and conformed to the declaration of Helsinki. Retrospective data were gathered from consecutive exercise stress echocardiograms (ESE) performed between 01/01/2010 and 31/12/2016 (n= 1338). All patients provided informed consent prior to commencement. Tests performed for valve assessment (n=39), myocardial viability (n=20) and chronotropic competence (n=13) were not included. Only tests performed for the investigation of ischemic heart disease were included (n=1266) in the study. Tests considered positive, inconclusive or with resting left ventricular dysfunction (n=186) were excluded due to different management strategies in these groups. Therefore, the total number of tests remaining for analysis was 1080.

Exercise

Transthoracic echocardiography images were obtained with a Philips IE33 ultrasound machine (Philips Medical Systems, Andover, MA) in the left lateral decubitus position. Image analysis was performed as per American Society of Echocardiography guidelines [12]. The treadmill exercise was performed to volitional fatigue using the standard Bruce protocol on a computer-controlled treadmill system (Marquette Case, Milwaukee, WI) [13]. 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. RPP was calculated by multiplying heart rate by systolic blood pressure throughout the test and maximum RPP (MRPP) was identified. HRR was adjusted for age as a percentage using the formula: (maximum heart rate-resting heart rate/APMHR-resting heart rate) ×100 [7]. Mean follow up was 5.3±2.6 years by reference to medical records, mortality registry or contact with the patients' general practitioners.

Analysis

Quantitative data were summarised as mean ± standard deviation and the paired student t-test was used to compare rest and stress conditions. Categorical data were compared using Fisher's exact test. Sensitivity and specificity for MRPP, APMHR and HRR% were calculated with respect to CV events (CV mortality, non-fatal myocardial infarction, PCI/balloon angioplasty, coronary artery bypass grafting, stroke or minimum of stage 3 heart failure) [14] at mean follow-up using receiver operating characteristic (ROC) analyses. The longest vertical deviation from the diagonal line was chosen as the optimal cut-point. To assess the factors influencing future CV events, Cox proportional hazard models were created using variables selected from baseline and test data between those with and without CV events (**Tables 1** and **2**). The cut-points for MRPP, APMHR and HRR% were also included in the model with entry and multivariate retention set at 0.05 significance. Kaplan-Meier survival analysis was used to assess outcome with respect to CV events for those above and below the optimal cut point for MRPP. The log-rank test was used to assess statistical significance. Data analysis was performed using XLSTAT 2020.5 (Addinsoft, New York) with a 2-tailed *P* value <0.05 considered statistically significant.

Results

Demographics

The physical attributes and ESE measures of patients with and without CV events during follow-up are displayed in **Table 1**. **Table 2** lists the CV disease risk factors and medications of the patients at time of testing. There were significant increases in heart rate, systolic blood pressure and MRPP from resting values for both groups (p<0.01). Those with CV events were older; had lower heart rates at rest; performed less exercise at a lower myocardial work; exhibited more diastolic dysfunction and had more regional wall motion abnormalities on their resting echocardiograms (**Table 1**).

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

Variable	CV Events (n=96)	No CV Events (n=984)	*P*-Value
Age (years)	60.4±11.3*	53.7±11.6	<0.01
Men	62 (64.6%)	483 (49.1%)	0.11
Body mass index (kg/m^2)	28.9±5.3	29.2±5.6	0.60
Resting heart rate (bpm)	73±14	78±13*	<0.01
Resting systolic blood pressure (mmHg)	130±20	127±17	0.11
Resting rate pressure product	9521±2347	9934±2281	0.09
Maximum heart rate (bpm)	143±18#	161±19*,#	<0.01
Maximum systolic blood pressure (mmHg)	167±25#	172±21*,#	0.04
Maximum rate pressure product	23830±4610#	27595±4572*,#	<0.01
Test duration (min:sec)	7:24±2:30	8:25±2:34*	<0.01
Metabolic equivalents	8.9±2.6	10.1±2.7*	<0.01
Resting regional wall motion abnormalities	12 (12.5%)*	43 (4.4%)	<0.01
Diastolic dysfunction	27 (28.1%)*	106 (10.8%)	<0.01

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.

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=96)	No CV Events (n=984)	*P*-Value
CV disease risk factors	3.0±1.2	2.7±1.5	0.02
No risk factors for CV disease	5 (5.2%)	58 (5.9%)	>0.99
Family history of CV disease	24 (25.0%)	288 (29.3%)	0.57
Diabetes Mellitus	26 (27.1%)	171 (17.4%)	0.07
Smoker	19 (19.8%)	220 (22.4%)	0.71
Hypertension	68 (70.8%)	456 (46.3%)	0.01
Dyslipidemia	74 (77.1%)	473 (48.1%)	<0.01
Obesity	33 (34.4%)	379 (38.5%)	0.68
Prior coronary artery disease	48 (50.0%)	150 (15.2%)	<0.01
Medications per patient	3.2±1.7	1.7±1.7	<0.01
No medications	9 (9.4%)	353 (35.9%)	<0.01
β blockers	54 (56.3%)	211 (21.4%)	<0.01
Ca^{2+} blockers	22 (22.9%)	124 (12.6%)	0.02
ACE inhibitors	33 (34.4%)	202 (20.5%)	0.02
Angiotensin receptor blockers	22 (22.9%)	183 (18.6%)	0.43
Nitrates	13 (13.5%)	20 (2.0%)	<0.01
Statins	58 (60.4%)	413 (42.0%)	0.04
Diuretics	11 (11.5%)	67 (6.8%)	0.15
Aspirin	53 (55.2%)	331 (33.6%)	<0.01
P2y12 inhibitor	25 (26.0%)	85 (8.6%)	<0.01

Values show number of cases (n), ± SD or percentage (%) of the group. ACE; Angiotensin-converting enzyme.

They also had more prior coronary artery disease, used more CV medications, and overall presented with a greater CV disease risk (**Table 2**).

Statistical analysis

ROC analyses revealed an optimal cut point of 25085 for MRPP (sensitivity 75.2%, specificity 75.6%, area under curve (AUC) 0.729), 94.6% for APMHR (sensitivity 68.6%, specificity 60.7%, AUC 0.687) and 95.9% for HRR% (sensitivity 81%, specificity 48.2%, AUC 0.688). There was no statistical significance between the models (**Figure 1**). **Table 3** shows the outcome of Cox proportional hazard analysis, including uni- and multi-variate predictors of CV events. Only the presence of previous ischemic heart disease and a MRPP <25085 remained significant predictors. **Figure 2** illustrates the Kaplan-Meier curve for CV events with respect to the MRPP cut-point of 25085. The cumulation of CV events was significantly less in those above MRPP 25060 compared to those below at any juncture on the curve (p<0.01) (**Figure 2**). **Figure 3** displays the Kaplan-Meier analysis for cumulative CV events for both APMHR and HRR. Both heart rate parameters failed to achieve statistical signifi-

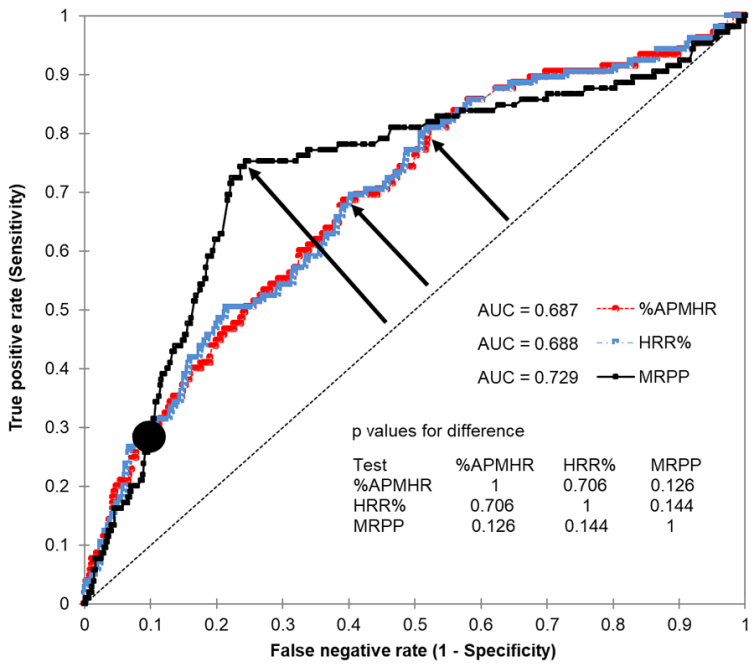

Figure 1. Receiver operating characteristic (ROC) curve for age-predicted maximal heart rate (APMHR), heart rate reserve (HRR%) and maximum rate pressure product (MRPP). The black arrows indicate the optimal cut-point. The black dot indicates the data point at 85% APMHR.

cance with respect to the cut-points until mean follow-up (**Figure 3**).

Discussion

In the present study, MRPP outperformed APMHR and HRR% to predict future CV events. While MRPP failed to demonstrate statistical significance from APMHR or HRR% (**Figure 1**), additional Cox hazard model analysis revealed the cut-point for MRPP (25085) as the strongest uni- and multi-variate predictor of CV events during the mean follow-up of 5.3 years (P<0.0001) (**Table 3**). In contrast, the diagnostic model for APMHR could be considered modest at best (AUC 0.687) (**Figure 1**). The inability to achieve the cut-points of 85 or 95% APMHR during the treadmill testing failed to predict CV events (**Table 3**). Eighty-five percent of APMHR is often assumed a suitable level of myocardial work during treadmill exercise [15]. The current study found 85% APMHR demonstrated poor sensitivity (28.6%) for the detection of future CV events in otherwise negative ESEs (**Figure 1**). This would be an unacceptable miss rate in clinical practice and begs the question why this level of APMHR (85%) is still used as a marker of adequate myocardial work or as a termination point during exercise testing [1, 2, 4, 16]. Along with APMHR, HRR% was also ineffective at predicting CV events (AUC 0.688) (**Figure 1**). This differs to previous studies showing HRR as a predictor of CV mortality during bicycle and treadmill exercise testing [5, 6, 17]. These studies however looked at CV mortality only and not all CV events, focusing also on quartiles or tertiles of HRR rather than a fixed cut-point adjusted for age that our study employed. In a study by Engeseth et al., when HRR was adjusted for age, only those with low physical fitness remained at significant risk of CV death [6]. Another study by Cheng et al. showed HRR to be a better predictor of CV mortality than any parameter of heart rate, be that resting or APMHR, in men under the age of 40. They also demonstrated HRR as a better predictor than cardiorespiratory fitness in the same group of men [5]. The average age of our cohort with CV events was 60.4±11.3 years (**Table 1**), clearly outside the age range of Cheng et al. group. This could possibly explain the discrepancy with the current study. Only β-blocker use, prior ischemic heart disease or the inability to reach a MRPP of 25085 were univariate predictors of future CV events, with the latter two remaining as predictors on multivariate analysis. In the current study those with prior ischemic heart disease were more likely to be on a β-blocker and this may explain the use of β-blockers emerging as a univariate predictor of CV events. The long-term benefits of β-blocker used in coronary artery disease have seen mixed results in those without prior myocardial infarction [18-20]. Our cohort was not split into those with myocardial infarction and those without, however the number with resting regional wall motion abnormalities was low (**Table 1**). This suggests that β-blocker use in the current study was probably linked to prior coronary artery disease rather than being a true independent CV event predictor, a point supported by the drop out on multivariate an-

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	1.02 (0.99-1.05)	3.1	0.077	-	-	-
Hypertension	1.43 (0.79-2.59)	1.4	0.240	-	-	-
Dyslipidemia	1.28 (0.74-2.21)	0.8	0.384	-	-	-
Prior CAD	3.10 (1.76-5.48)	15.2	<0.0001	2.82 (1.86-4.27)	24.0	<0.0001
β-Blocker use	1.78 (1.10-2.90)	5.4	0.020	0.89 (0.54-1.47)	0.2	0.660
Ca^{2+} channel blocker use	1.03 (0.59-1.83)	0.1	0.909	-	-	-
ACE inhibitor use	1.44 (0.90-2.29)	2.3	0.127	-	-	-
Nitrate use	0.91 (0.44-1.87)	0.1	0.794	-	-	-
Statin use	0.69 (0.40-1.19)	1.8	0.179	-	-	-
Aspirin use	0.88 (0.55-1.43)	0.3	0.614	-	-	-
P2Y12 inhibitor use	0.67 (0.38-1.18)	1.9	0.166	-	-	-
<7:24 min:sec treadmill time	1.00 (1.00-1.01)	0.5	0.469	-	-	-
<8.9 METS	0.87 (0.62-1.24)	0.6	0.450	-	-	-
<85% APMHR	0.05 (0.00-0.33)	2.4	0.120	-	-	-
<95% APMHR	0.76 (0.37-1.56)	0.6	0.454	-	-	-
<96% HRR	1.69 (0.76-3.79)	1.6	0.202	-	-	-
MRPP <25085	7.36 (4.05-13.4)	42.8	<0.0001	9.30 (5.68-15.2)	78.3	<0.0001
Resting RWMA	0.77 (0.40-1.48)	0.6	0.437	-	-	-
Diastolic dysfunction	0.84 (0.51-1.39)	0.5	0.496	-	-	-

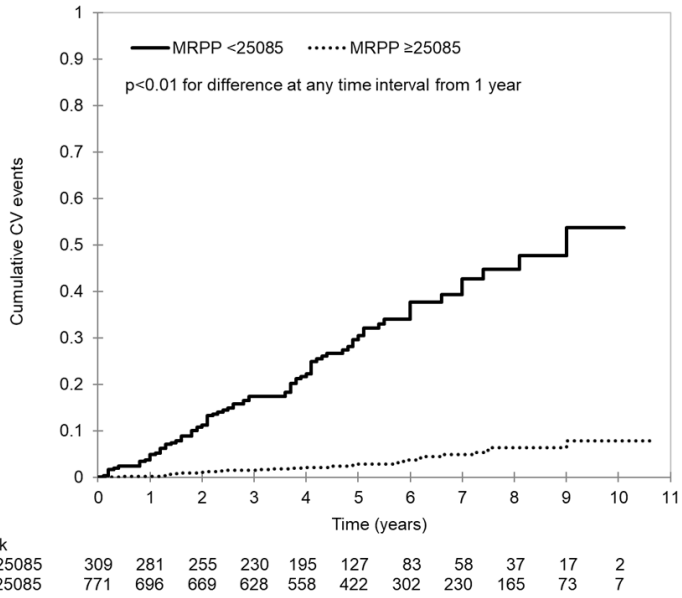

Figure 2. Cumulative cardiovascular events (CV) for those achieving <25085 or ≥25085 maximum rate pressure product (MRPP).

alysis. It has long been acknowledged that the presence of ischemic heart disease increases the risk of future CV events, first reported by Kannel et al. in the Framingham study [21]. We confirmed this in the current study with those having prior ischemic heart disease three times more likely to have a CV event (**Table 3**). The strongest predictor of future CV events however was the inability to reach an MRPP of 25085 with a nine times greater risk demonstrated on multivariate analysis in those unable to reach this level (**Table 3**). Whitman et al. previously showed comparable levels of MRPP to be as predictive of CV outcome. Much like the current study, MRPP outperformed APMHR for the prediction of CV events, even in the setting of mild LV dysfunction [2] or poor functional capacity [1]. There is mounting evidence demonstrating the benefits of RPP as a marker of adequate myocardial work beyond that of APMHR and HRR [1, 2]. As an established surrogate measure of myocardial oxygen consumption during exercise [22, 23] it is

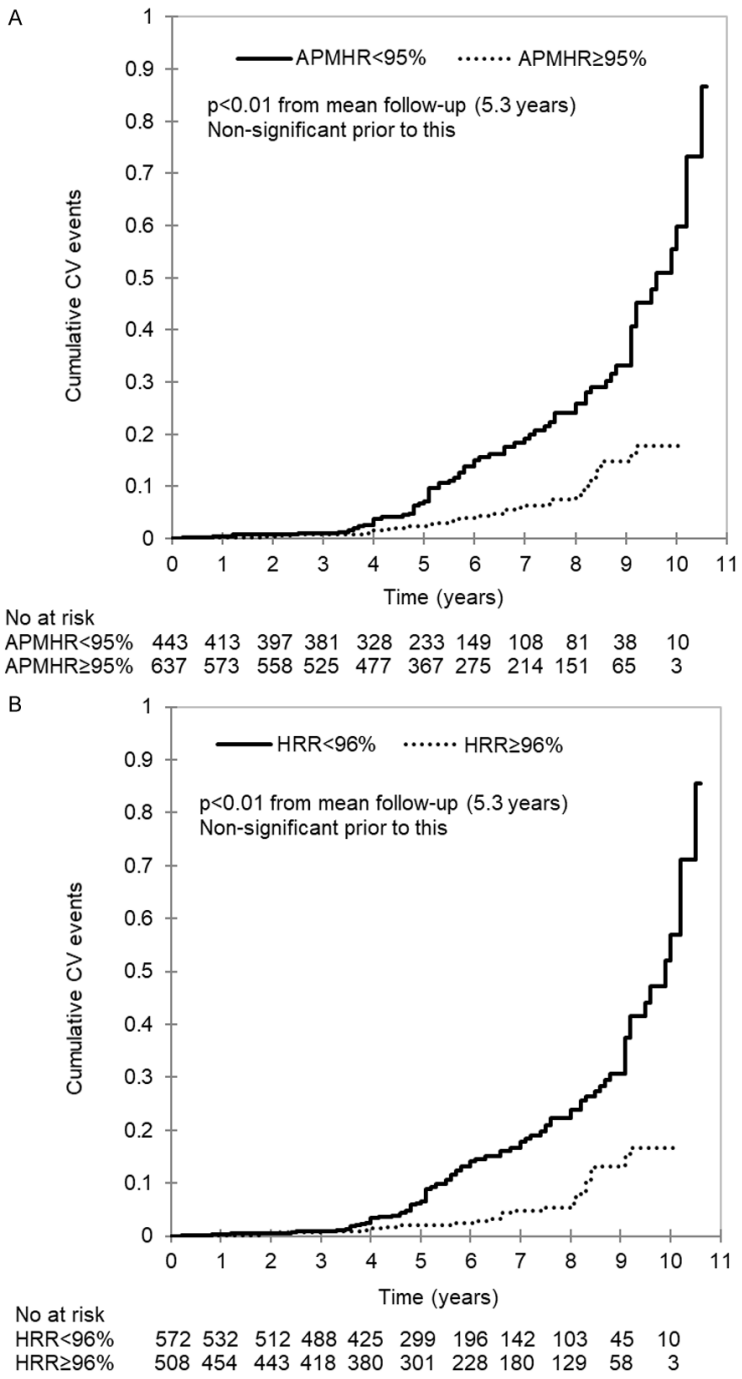

Figure 3. Cumulative cardiovascular events (CV) for those achieving (A) <95% or ≥95% age-predicted maximum heart rate (APMHR) and (B) <96% or ≥96% heart rate reserve (HRR).

not surprising to the authors that RPP outperforms both in this area. APMHR and HRR do not take the blood pressure response into account and even an exaggerated increase in SBP during ESE has been associated with reduced CV events on follow-up [24].

There are some limitations to this study that need to be considered. Firstly, the study was performed at a single centre and therefore the decision to perform the ESE may be subject to selection bias. Secondly, while each test was performed to volitional fatigue the threshold level may differ between patients creating an element of subjectivity. Thirdly, a larger multicentre study would assist in decreasing the present limitations; and finally, work investigating the possible mechanisms involved in MRPP would be beneficial.

Conclusion

This study demonstrates the superior prognostic ability of MRPP over both APMHR and HRR% to predict future CV events following an otherwise negative ESE for myocardial ischemia. The current study displays abundant evidence to suggest the practice of using APMHR or HRR% as markers of adequate myocardial work, to be inferior to MRPP. Therefore, we recommend the use of the latter as a more accurate measure of myocardial workload during exercise treadmill testing.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mark Whitman, Cardiac Investigations Unit, Logan Hospital, Yatala, Queensland 4207, Australia. Tel: +61-617-3299-8876; Fax: +61-617-3299-8117; E-mail: mark.whitman@health.qld.gov.au

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