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ORIGINAL ARTICLE

Triggering of Acute Coronary Occlusion by Episodes of Vigorous Physical Exertion

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Background There is increasing recognition that heavy exertion can occasionally trigger an acute myocardial infarction (MI), although some uncertainties exist regarding the link. The primary aim of this study was to compare the relative risk (RR) of MI following vigorous exertion between those with confirmed coronary occlusion and those with a non-occluded culprit artery on acute angiography. Secondary aims were to determine if the risk of coronary occlusion is modified by the type of exercise (dynamic or isometric resistance), the frequency of regular exertion or whether the exertion was emotionally charged.

Methods Seven hundred sixty-two (762) participants with MI (410 with coronary occlusion TIMI 0,1), and 352 (46%) with a non-occluded culprit artery (TIMI 2,3) completed a questionnaire within 4 days of admission, detailing episodes of physical exertion in the 28 hours prior to symptom onset and the usual frequency of such exertion. Exertion exposures within 1 hour prior to symptom onset were compared to subjects' usual yearly exposure, with case-crossover methodology.

Results The RR of symptom onset following heavy physical exertion level $\geq$6 (exertion scale 1–8), was higher in those with TIMI 0,1 compared to those with TIMI 2,3 flow (RR 6.30, 95% CI 4.70–8.50 vs 3.93, 2.89–5.30). The increased risk of coronary occlusion following vigorous exertion was observed following both dynamic exertion and isometric resistance, and did not differ between exertion types. The highest risk of coronary occlusion following exertion was observed in those who were sedentary (regular vigorous exertion $<$1 day weekly) (RR = 77, 95% CI 46–132), whereas in those who frequently perform regular vigorous physical exertion ($>$4 days weekly), the RR of symptom onset during exertion was significantly lower, RR 2.3 (95% CI 1.5–3.6). There was no significant difference in relative risk based on whether the exertion was reported as emotionally charged.

Conclusions The relative risk that heavy exertion will trigger a non-fatal MI with an occluded artery is greater than for a non-occluded culprit artery. Both dynamic and isometric exertion increase the relative risk of event, while exposure to regular vigorous exertion reduces the relative risk.

Keywords Exertion • Trigger • Coronary occlusion • Myocardial infarction • Isometric • Emotional • Physical exertion

Introduction

Even though regular, moderate, physical activity has been associated with reduced population incidence of coronary artery disease, vigorous physical exertion has been identified as an occasional trigger of myocardial infarction (MI). Studies have reported exposure to heavy or vigorous physical exertion in up to 15% of MI patients, associated with an increased relative risk, especially in the first hour after exertion [1–3]. However, there are several uncertainties as to the

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relationship of exertion as a trigger of MI. These include whether there is a difference in triggering of MI with occluded versus non-occluded vessels, if dynamic and isometric exercise differs in their relative risk, and if the emotional state during exertion modifies the risk.

Evidence suggests that plaque rupture does not occur in a random fashion but may be triggered by external stressors that promote haemodynamic or prothrombotic responses [4]. These physiological changes in the presence of an unstable atherosclerotic plaque may cause plaque disruption and thrombosis [5]. Current understanding of the role of triggering activities has been helped by the development of case-crossover statistical methodology, where each subject is used for both case data (during the period immediately prior to the infarction) and control data (usual frequency of exposure to a potential trigger) [6]. Additionally, the emergence of primary coronary intervention allows the ability to diagnose acute coronary occlusion by angiography shortly after admission and assess findings in relation to prehospital triggering activities. While to date, studies of triggering have mostly included patients diagnosed with MI on admission by electrocardiography and cardiac blood markers, one study of patients who underwent primary angioplasty reported higher single vessel disease and intracoronary thrombus in exertion-related MI compared to non-exertion related MI [2].

The primary aim of this study was to evaluate and compare the risk of MI following episodes of vigorous physical exertion in patients with coronary occlusion (TIMI 0,1) and non-coronary occlusion (TIMI 2,3), admitted to an Australian tertiary referral hospital. Secondary aims were to determine if the risk of coronary occlusion following vigorous exertion was modified by the type of exercise (dynamic or isometric resistance), or whether the exercise was emotionally charged. Potential modifiers of risk including usual exertion frequency, gender, smoking status and prior use of beta blocker medications or aspirin were also evaluated.

Methods

Eight hundred and ninety (890) patients admitted with potential MI symptoms and confirmed raised blood troponin or creatine kinase-MB (CK-MB) underwent acute angiography ± coronary intervention for suspected acute MI, in Sydney, Australia, between 2006 and 2015. Consenting patients completed a detailed questionnaire within 4 days of hospital admission. During acute angiography, coronary blood flow was determined by the proceduralist using the Thrombolysis In Myocardial Infarction (TIMI) grading scale based on visual assessment of the infarct artery [7]. Of the 890 who underwent angiography, 762 had evidence of a culprit lesion and formed the sample for analysis. Ethics approval for this study was granted by the Local Health District Human Research Ethics Committee.

Data Collection

Following written informed consent, data were collected by an investigator (a research nurse) who interviewed consenting participants within 48 hours of hospital admission using a standardised questionnaire, previously developed for, and reported in, the Determinants of Myocardial Infarction Onset Study Investigators [8]. In addition to documenting demographic and clinical history, the questionnaire addressed the activities of the patients in detail within the 48 hours prior to symptom onset, and also the usual frequency of exposure to physical exertion in the prior year. Participants were not informed of the hypothesised duration of the hazard period when completing questionnaires.

Physical exertion was measured by use of a Physical Exertion Chart [i] that defines levels of exertion, as quantified on a scale of 1–8 metabolic equivalents (MET) [3] as follows:

1. **SLEEPING, RECLINING** – sunbathing, lying watching TV
2. **SITTING** – eating, reading, deskwork, sitting watching TV, highway driving
3. **VERY LIGHT** – office work, city driving, personal care, standing in line, strolling in the park
4. **LIGHT NORMAL BREATHING** – mopping, slow walking (e.g. shopping), bowling, sweeping, gardening with power tools
5. **MODERATE, DEEP BREATHING** – normal walking, golfing on foot, ballroom dancing, slow biking, fishing, slow dancing
6. **VIGOROUS, PANTING** – slow jogging, speed walking, tennis, swimming, fast biking, mowing with a push-power mower, heavy gardening, picking up garbage, shovelling
7. **HEAVY, GASPING/MUCH SWEAT** – running, fast jogging, moving boulders, competitive sport
8. **EXTREME, PEAK EXERTION** – sprinting, fast running, jogging up-hill, aggressive sports with frequent sprinting and no rest, pushing or pulling with all your might, unusually extreme work.

Participants identified their physical exertion levels in the 48 hours prior to symptom onset reporting both the intensity and the associated activity. Participants also reported their usual yearly frequency of exertion for each of these levels. All participants underwent emergency angiography immediately following hospital admission.

Statistical Analysis

The statistical analysis approach utilised the case-crossover design as previously described [3,8,9]. The design is considered appropriate for the identification of transient risk factors for sudden onset events as self-matching eliminates confounding by risk factors that are stable over time but often differ between study subjects (e.g. age, gender etc.) [9]. Firstly, physical exertion exposure within 1 hour prior to symptom onset (hazard period) was compared to the subjects own usual yearly exposure to such exertion (usual exposure). Self-matching eliminates confounding by risk factors that are stable over time but often differ between study subjects. Secondly, hazard ratios and associated 95% confidence intervals were calculated using the Mantel-Haenszel method [8]. The hazard ratio, the risk of MI symptoms occurring within 1 hour of exposure, is based on the observed exposure to levels of physical exertion in the hazard period to the expected usual yearly exposure to those levels of exertion. A hazard ratio algorithm was created in Excel and verified against prior published data [9,10]. Data were analysed using Excel 2010 (Microsoft Corporation, 2010) and IBM SPSS Statistics for Windows v24 (IBM Corp, Armonk, NY).

In the primary analysis, a comparison of relative risk (RR) between those with TIMI 0,1 and TIMI 2,3 was conducted. Differences between relative risks (RRs) were determined by calculating the ratio of RR (RRR = Risk 1/Risk 2), with the risks considered statistically significantly different if the Z score was $<$ or $>$1.96 and if the 95% CI did not pass through 1 [11].

To determine the relative risk of coronary occlusion in those exposed to activity classified as either dynamic (e.g. running, swimming etc.) or isometric resistance (e.g. lifting), the 1-hour hazard period prior to symptoms was compared to a control period (i.e. 24–25 hours the previous day). This time period was chosen as it was considered participant recall would be most accurate regarding specifics of the activity in this timeframe. Data were analysed using Excel 2010.

Results

Exposure to Strenuous Exertion Prior to MI

Seven hundred-sixty-two (762) (86%) patients reported their physical activity both in the 48 hours prior to MI and their usual frequency of exercise of whom 91 (12%) reported exposure to vigorous exertion in the 1 hour prior to MI symptom onset. Participants reporting exercise triggered MI symptom onset were more likely to be classified TIMI 0,1 on admission angiography and be male Table 1.

Four hundred ten (410) (54%) participants had confirmation of occluded coronary blood flow of at least one coronary artery (TIMI 0,1) and 352 (46%) had coronary blood flow (TIMI 2,3) in the affected artery (non-occluded group) on admission to hospital. Participants admitted with coronary occlusion (TIMI 0,1) were less likely to have a history of hypertension, diabetes and less likely to be taking beta blocker medications and were more likely to have their primary culprit artery on the right (RCA 43% vs 32%) compared to participants with TIMI 2,3 (Table 2).

Association of Vigorous Activity and Risk of Coronary Occlusion

The RR of symptom onset following vigorous physical exertion (exertion level $\geq$6) within the 1 hour prior to MI compared to the usual frequency of such activity is reported in Table 3. In those with confirmed coronary occlusion (TIMI 0,1) the relative risk was higher than for those admitted with TIMI 2,3 (RRR = 1.65), Z score 2.22, (95% CI, 1.05–2.47), Table 2. More men reported experiencing physical exertion during the 1-hour hazard period prior to coronary occlusion (54 [15%] men vs 3 [5%] women, p = 0.03). There were no significant differences in past clinical history, demographic characteristics, smoking status, or site of an occluded artery or the number with single vessel disease between participants who reported vigorous exertion in the 1 hour prior to coronary occlusion, compared to those who did not.

Type of Physical Activity and Risk of Coronary Occlusion

Analysis of participants who engaged in vigorous physical activity during the 1 hour prior to symptom onset compared to the same time the previous day (24–25 hours earlier), revealed a RR of symptom onset following exertion of 4.08 (95% CI, 2.70–7.68). When this activity was reported to be dynamic in nature (n = 36), the RR was 8.25 (95% CI, 2.92–23.29) and when classified as isometric resistance (n = 14) the RR was 5.50 (95% CI, 1.22–24.81), which was not statistically different between groups. In cases where the nature of physical exertion was not clearly identified as mostly either dynamic or isometric resistance in nature (e.g. gardening or general housework), the RR of symptom onset within 1 hour was 1.50 (95% CI, 0.42–5.31).

"Emotionally Charged" During Exercise

Participants were asked if any episodes of physical exertion were "emotionally charged", defined as being unusually excited, angry, nervous, or competitive while vigorously exerting themselves. Fifty-one (51) participants reported being emotionally charged during vigorous exertion in the 24 hours prior to their MI, of whom 17 were exposed in the hour prior to symptom onset, associated with RR of 6.04 (3.42–10.09), not statistically different compared to those who reported not being emotionally charged during exertion, RR 6.49 (4.52–9.98), RRR = 0.93 (95% CI, 0.48–1.92), Z score −0.21.

Association of the Usual Frequency of Vigorous Exertion and Risk of Coronary Occlusion

Participants were classified according to their usual frequency of undertaking vigorous exercise as follows: $<$1 day weekly (58%), 1–2 days (8%), 2–3 days (7.7%), 3–4 days (4%) and $>$4 days weekly (23%). The associated RR of each group in relation to risk of MI onset are presented in Figure 1 with the highest risk observed in those who usually engaged in vigorous exertion $<$1 day weekly (RR = 77, 95% CI, 46–132), whereas in those who usually performed vigorous physical exertion $>$4 days weekly, the RR of symptom onset within 1 hour of exertion was 2.31 (95% CI, 1.49–3.60), significantly lower than those who physically exerted $<$1-day week (RRR = 33.3, 95% CI, 20.6–53.7) Z score 14.4.

Table 1 Sociodemographic characteristics and clinical history of study participants with and without vigorous exertion triggered myocardial infarction syndrome onset.

	Exertion triggered N = 91		Non-exertion triggered N = 671		P
Demographic					
Age in years mean ± (SD)	57.3	(13.2)	59.9	(13.1)	0.08
Male	84	(92%)	555	(83%)	0.02
Medical history					
Prior myocardial infarction	13	(14%)	88	(13%)	0.76
Diabetes mellitus	11	(12%)	108	(16%)	0.32
Hypertension	30	(33%)	288	(42%)	0.07
Hypercholesterolaemia	45	(49%)	315	(47%)	0.65
Current smoker	26	(29%)	230	(34%)	0.28
Medication history					
Beta blockers	4	(4%)	72	(11%)	0.06
Aspirin	16	(18%)	83	(12%)	0.16
Angiography					
Coronary occlusion (TIMI 0,1)	58	(64%)	352	(52%)	
Non-occluded coronary (TIMI 2,3)	33	(46%)	319	(48%)	0.04

Table 2 Sociodemographic characteristics and clinical history of study participants with and without coronary acute coronary occlusion on admission.

	Coronary occlusion group (TIMI 0,1) N = 410		Non coronary occlusion group (TIMI 2,3) N = 352		P
Demographic					
Age in years mean ± (SD)	58.7	(13.2)	60.6	(13.0)	0.06
Male	351	(86%)	288	(82%)	0.06
Medical history					
Prior myocardial infarction	50	(12%)	51	(14%)	0.32
Diabetes mellitus	51	(12%)	68	(19%)	0.009
Hypertension	149	(36%)	168	(48%)	0.001
Hypercholesterolaemia	184	(45%)	176	(50%)	0.16
Current smoker	126	(30%)	130	(36%)	0.07
Medication history					
Beta blockers	30	(7%)	46	(13%)	0.008
Aspirin	49	(12%)	50	(14%)	0.36
Occluded artery					
Left anterior descending	165	(40%)	171	(48%)	
Right coronary artery	173	(42%)	111	(32%)	
Circumflex artery	59	(14%)	58	(16%)	
Saphenous vein graft	12	(3%)	12	(3%)	
Left internal mammary artery	1	(<1%)	0	0	0.04
Artery disease severity					
Single vessel disease	205	(50%)	181	(49%)	
Double vessel disease	131	(32%)	92	(26%)	
Triple vessel disease	74	(18%)	79	(22%)	0.13

Table 3 Relative risk of coronary occlusion within 1 hour following vigorous physical exertion.

	RR	(95% CI)
Risk of symptom onset within 1 hour following vigorous physical exertion (level ≥6)		
All participants (TIMI 0-3)	5.04	(4.09 to 6.22)
Coronary occlusion group (TIMI 0,1)	6.30	(4.70 to 8.50)
Non coronary occlusion group (TIMI 2,3)	3.92	(2.89 to 5.30)

Modifiers of Coronary Occlusion Risk Following Physical Exertion

When analysed separately, the RR for men who performed vigorous physical exertion within 1 hour of symptom onset was 7.07 (95% CI, 5.16–9.68). Only three women were exposed to vigorous exertion within 1 hour (RR 2.28, 95% CI, 0.94–5.55), not allowing for a valid comparison of RRs with exposed male participants.

Thirty-three (33) (8%) participants with coronary occlusion were taking beta blocker medications of whom only two were exposed in the 1 hour prior to symptom onset (RR 3.94, 95% CI, 0.90–17.25). In those not taking beta blocker medications, RR was 6.48 (95% CI, 4.80–8.75). Due to low non-exposure in the beta blocker group, a valid statistical analysis comparing RRs was not possible between groups. Fifty-one (51) (12%) of participants were taking regular aspirin of which seven were exposed to vigorous exertion in the 1 hour prior to symptom onset associated with a RR 6.43 (95% CI, 2.78–14.91), not significantly different to a those not taking regular aspirin (RR 6.32, 95% CI, 4.62–8.64).

One-hundred twenty-six (126) participants reported being current smokers at the time of MI, of whom 21 were exposed to vigorous exertion prior to symptom onset associated with a RR 5.54 (95% CI, 3.29–9.34), not significantly different to non-smokers (RR = 6.76, 95% CI, 4.74–9.64).

Discussion

Our findings confirm the association between heavy physical exertion and risk of acute MI onset, in those who survived to hospital and that regular vigorous physical exertion reduces the relative risk of exertion as a trigger. Our findings extend prior understanding of the link by demonstrating that the risk is higher in those who have an occluded artery (TIMI 0,1) compared with those with a non-occluded vessel (TIMI 2,3); that there is no difference in relative risk between dynamic and isometric exercise as a trigger, and that the relative risk does not appear to be modified by the emotional state during exertion.

Our finding of a six-fold increase in RR of MI within 1 hour of vigorous exertion is consistent with previous studies of MI that reported RRs of 6.1 in the Stockholm Heart Epidemiology Program [12] and RR 5.9 in a US population [3], although higher than the RR (2.1) reported in a German population [1]. Our findings add to these studies by analysing the relative risk in patients with angiographically-confirmed MI on admission to an Australian centre and suggest that patients with exertion-triggered MI are at higher risk of presenting with an occluded artery on hospital admission than a non-occluded culprit artery. This novel finding supports the proposed role of vigorous exertion in promoting plaque rupture and thrombosis in susceptible individuals [2,4]. The finding that a higher proportion of patients presenting with coronary occlusion had engaged in vigorous exertion compared to those with non-occlusion, may be contributed to by a higher proportion of cardiovascular risk factors in the non-occluded group, that may have resulted in them being less likely to participate in vigorous exertion. This finding is consistent with a recent finding that patients on some cardiovascular medications, such as anti-hypertensives, are less likely to report triggering activities prior to MI onset [13].

The importance of considering triggering activities prior to MI symptom onset was recently highlighted by an observation that, when heavy physical exertion was a trigger of MI, the in-hospital mortality and 30-day rehospitalisation was reduced compared to when the trigger was not present [13]. In our study, we did not observe differences in relative risk of

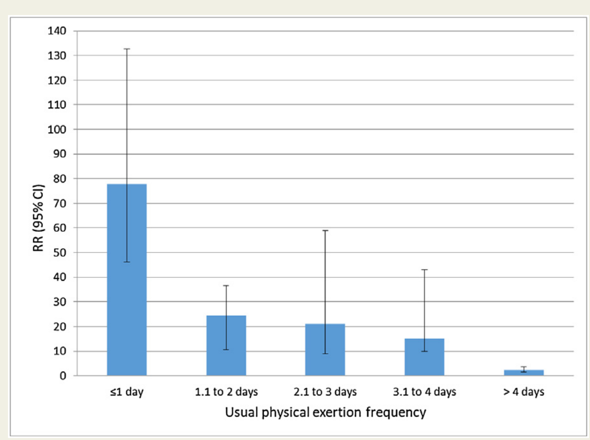

Figure 1 Association between frequency of usual exposure to vigorous physical exertion (level ≥6) and risk of coronary occlusion.

MI onset if participants reported being ''emotionally charged'' during exertion. This differs to the INTERHEART – study [14] where an additive effect of physical activity and emotional upset was reported. This difference between the two studies may be related to the assessment of emotional state in each study. In INTERHEART, participants reported if they were emotionally upset or angry during heavy physical exertion [14], whereas we defined being emotionally charged during exertion, as being ''excited, angry, nervous, or competitive'', which may not have been sensitive enough to discriminate normal competitive emotions from high emotional upset. Our findings would suggest being emotionally excited or competitive in participating in vigorous exertion, does not necessarily result in an additional risk, whereas being angry or emotionally upset during physical exertion, as assessed in INTERHEART, may result in an additional risk of MI.

Compared to those who exercised regularly, the risk was significantly higher in those who performed vigorous exertion infrequently (RR of 77 in those who exercised less than once weekly), although the RR of symptom onset still remained elevated (RR = 2.3) even in those who exerted frequently (> 4 times weekly) at this level. This finding highlights the paradoxical role of physical exertion in predominantly preventing CVD but occasionally triggering MI. A meta-analysis of epidemiological studies reports a dose-response relationship between activity and coronary heart disease (CHD) risk with regular mild exercise associated with a reduced risk of fatal or non-fatal MI by 14% and moderate exercise by 20% [15]. Additionally, interval training exercise has been shown to favourably modify CV risk factors in patients undertaking CV rehabilitation [16], although questions remain regarding optimal intensity in this setting [17]. While overall evidence supports the benefits of exercise in reducing long-term CVD, and although the absolute risk of MI during any one exposure remains very low, findings in the present study suggest that those with existing CVD risk factors who are at higher absolute risk, should be cautious in undertaking vigorous exertion without professional supervision or advice, especially if not conditioned to such activity.

Regular aspirin did not appear to modify the RR of MI during exercise in this sample with no significant difference in RR observed between those taking or not taking prior aspirin. Few participants with exertion triggered coronary occlusion were regularly taking beta blocker medications, making a valid comparison not possible with those not on beta blockers. However, a prior prospective observational study has reported that prior use of beta blockers and aspirin may be associated with less exertion-related acute myocardial infarction [2].

More men had vigorous exertion triggered coronary occlusion than women in our sample (17% vs 5%). This is consistent with the suggestion that MI is more likely to be associated with physical exertion in men [2,18]. The absolute risk of sudden death within 30 minutes of heavy physical exertion in male physicians was reported to be one sudden death per 1.51 million episodes of exertion [19] versus 1 death in 36.5 million hours of exertion in females [20]. Lower incidence rates of events in women have been proposed to be related to delays in coronary artery disease development and lower heavy exercise participation [18].

We did not observe significant differences in risk of coronary occlusion dependent on the type of exertion reported, either dynamic or isometric resistance in nature with the risk associated with each activity type. To our knowledge, this is the first report of separately evaluating the RR of isometric exertion. Isometric exercise has been associated with acute changes in heart rate and blood pressure, especially in older individuals [21]. Unlike dynamic exercise, there may be less opportunity for warming up muscles prior to isometric exertion and it has been suggested that some of the associated MI risk may be controlled for by avoiding the Valsalva manoeuver (holding the breath) during the contraction phase of activity, which has been shown to elicit blood pressure responses similar to aerobic running when effort is within 80–100% of one maximum repetition [18,22].

Increased cardiovascular risk during dynamic activity is of public interest, especially considering the increased rate of participation in mass participation events such as marathons in the past 40 years [18], and reports of fatal events during marathons of between 1 per 80,000 and 1 per 200,000 participants [23]. Our findings that regular physical exertion is associated with reduced relative risk of MI during exertion support the benefit of being physically conditioned to undertake vigorous exertion, especially if exerting at high intensity. Additionally, it has been suggested that risk may be reduced immediately following exertion by adopting precautionary practices, when possible, such as slow walking or jogging as a warm down to facilitate decreased venous return via the leg muscles, decrease venous pooling and subsequent risk of poor perfusion and ischaemia after abrupt cessation of vigorous activity [24].

Study limitations relate to the use of patient self-report for physical exertion status, which may have led to participant bias in reporting. However, to combat this, we utilised a standardised questionnaire as previously reported [3] and participants were unaware of the hazard period of interest. Additionally, we performed an analysis comparing exposure in the hazard periods to both usual reported frequency as well as comparing to the same time the previous day, with both methods revealing similar risk levels. We acknowledge that our findings only relate to individuals who survived the MI event following an episode of physical activity, although physical exertion has been previously associated with triggering of sudden cardiac death [19,20]. While the use of case-crossover methodology eliminates confounding factors that are stable over time but may differ between subjects, we acknowledge that the method does not fully adjust for other temporal factors. We observed wide CIs related to the risk of those who performed vigorous physical exertion <1 day weekly. This high variability in risk may have been related to other factors associated with why a person may not exert themselves vigorously, frequently, such as physical injury, which we did not assess in the participant interviews. A strength of our study is that angiographic confirmation of a culprit artery enables differentiation of study participants from those presenting with symptoms, and may have been related to coronary artery disease, but without a culprit vessel.

In conclusion, this study adds to the small, but growing body of evidence linking vigorous physical exertion with triggering a non-fatal MI, with the relative risk that exertion may trigger an occluded artery greater than for a non-occluded culprit artery. Dynamic and isometric exertion both increase the relative risk while regular vigorous exertion reduces the relative risk. Future studies, with larger sample sizes, identifying the most vulnerable individuals during times of exposure may improve predictive models for when an MI will occur during exertion and inform future novel preventative therapies.

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