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RESEARCH LETTER
Coronary artery disease

Circadian variation in acute myocardial infarction and modification by coronary artery disease: a prospective observational study

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Introduction

A circadian variation in the onset of acute myocardial infarction (AMI) has been consistently described, characterized by a morning peak between 6 a.m. and noon.[1] However, the mechanism and modifiers of the morning peak in AMI have not been fully elucidated. Since the coronary arteries vary in their susceptibility to sympathetic activity and to changes in systolic blood pressure which also display circadian variation, there may be a relationship between the culprit coronary artery and morning AMI. Since infarct location affects the incidence of acute heart failure and cardiovascular mortality post-MI,[2] it is important to clarify whether coronary anatomy also modifies the circadian variation of AMI.

Methodology

The Triggers and Modifiers of Acute Myocardial Infarction (TAMAMI) Study was a prospective, observational cohort study conducted at a tertiary hospital in Sydney, Australia between December 2005 and January 2017 with Human Research Ethics Committee approval. All patients who had coronary angiography following an acute coronary syndrome were screened for inclusion with the following criteria: (i) identifiable onset of chest pain or other typical symptoms, (ii) elevated biomarkers of myocardial injury (troponin and/or creatinine kinase myocardial band), (iii) obstructive coronary artery disease on angiography, and (iv) ability to complete a structured interview. The independent variable was the primary culprit artery as reviewed by an Interventional Cardiologist. The dependent variable was the time of symptom onset, categorized as morning (6 a.m.–noon) or non-morning, which was obtained by interview within 48 h of admission. Information was collected on confounders including those which have previously been shown to alter the circadian variation in AMI (diabetes, aspirin, beta-blockers, and weekday onset). Data were then analysed using IBM SPSS Statistics, version 26 (IBM Corp, Armonk, NY, USA). The normality of continuous variables was tested using the Shapiro–Wilk test. Chi-square analysis was used to analyse categorical data, and where data had more than two potential values (e.g. culprit artery), adjusted residuals were calculated to determine which cells were major contributors to the statistically significant result. Multivariate logistic regression analysis using backward elimination was used to determine independent predictors of morning AMI.

Results

In this study of 865 patients, we observed a circadian variation in AMI with a primary morning (6 a.m.–noon) peak: 17.6% between midnight and 6 a.m., 31.6% between 6 a.m. and noon, 28.3% between noon and 6 p.m., and 22.5% between 6 p.m. and midnight ($P < 0.001$). Morning AMI had a different distribution of culprit artery to non-morning AMI, which was associated with a significantly greater frequency of right coronary artery (RCA) occlusion and less frequent left anterior descending artery (LAD) occlusion (*Table 1*). On multivariate logistic regression, the culprit artery was an independent predictor of morning AMI, with RCA occlusion occurring more frequently than LAD occlusion (odds ratio 1.65, 95% confidence interval 1.19–2.28; $P = 0.003$). Whilst there was a higher incidence of AMI with triple vessel disease in the morning ($P = 0.031$), this was not statistically significant on multivariate analysis.

Discussion

There is a paucity of prior literature describing the circadian variation in the culprit artery or severity of coronary artery disease. In one study, Seneviratna *et al.*[2] also found that the proportion of ST-elevation myocardial infarction secondary to LAD occlusion was lowest during the morning. Patients with morning AMI in this study were also less likely to develop acute heart failure.

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Table 1 Demographics and invasive coronary angiogram findings by morning (6 a.m.–noon) vs. non-morning onset

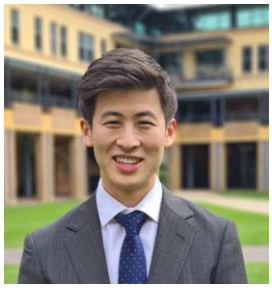
	All	Morning AMI (%)	Non-morning AMI (%)	*P*-value
All patients	865 (100)	273 (31.6)	592 (68.4)	<0.001*
Age (±standard deviation)	59.8 ± 12.7	61.2 ± 12.9	59.1 ± 12.6	0.028*
Male gender	734 (84.4)	230 (85.5)	494 (83.9)	0.542
Hypertension	400 (46.5)	125 (46.0)	275 (46.7)	0.841
Hypercholesterolaemia	412 (47.9)	137 (50.4)	275 (46.7)	0.315
Diabetes	136 (15.8)	37 (13.6)	99 (16.8)	0.231
History of smoking	519 (60.3)	164 (60.3)	355 (60.3)	0.995
Family history of IHD	350 (40.7)	113 (41.5)	237 (40.2)	0.717
Previous IHD	150 (17.4)	51 (18.8)	99 (16.8)	0.485
Previous CABG	51 (5.9)	19 (7.0)	32 (5.4)	0.370
Beta-blockers	89 (10.3)	30 (11.0)	59 (10.0)	0.644
Aspirin	128 (14.8)	43 (15.8)	85 (14.4)	0.591
ACEI/ARB	230 (26.7)	69 (25.4)	161 (27.3)	0.554
Prior diagnosed angina	116 (13.9)	37 (13.9)	79 (13.8)	0.977
Weekend AMI	240 (27.7)	76 (27.8)	164 (27.7)	0.967
Culprit artery				0.010* (excludes LM and BG)
Left anterior descending artery	375 (43.7)	98 (36.3)[a]	277 (47.0)[b]	0.032* (includes LM and BG)
Right coronary artery	318 (37.0)	117 (43.3)[b]	201 (34.1)[a]	
Left circumflex artery	127 (14.8)	41 (15.2)	86 (14.6)	
LM	9 (1.0)	2 (0.7)	7 (1.2)	
BG	30 (3.5)	12 (4.4)	18 (3.1)	
Vessels involved				0.031*
One	429 (49.6)	121 (44.3)[a]	308 (52.0)[b]	
Two	254 (29.4)	81 (29.7)	173 (29.2)	
Three	182 (21.0)	71 (26.0)[b]	111 (18.8)[a]	
Pre-PCI TIMI 0–1	470 (55.9)	151 (57.6)	319 (55.1)	0.492
Pre-PCI TIMI 2–3	371 (44.1)	111 (42.4)	260 (44.9)	
Post-PCI TIMI 0–1	9 (1.2)	0 (0.0)	9 (1.7)	0.064
Post-PCI TIMI 2–3	738 (98.8)	230 (100.0)	508 (98.3)	

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BG, bypass graft; CABG, coronary artery bypass graft surgery; IHD, ischaemic heart disease; LM, left main artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
*$P < 0.05$.
[a]Adjusted residual <2.
[b]Adjusted residual >2.

The higher proportion of RCA occlusion and lower proportion of LAD occlusion in morning AMI may be explained by flow variation over the cardiac cycle. Blood flow through the left coronary system predominantly occurs during diastole and is diminished during systole due to sub-endocardial compression from left ventricular contraction in contrast to flow through RCA which continues throughout the entire cardiac cycle as the systolic right ventricular intra-myocardial pressure does not increase to the same degree.[3] Atherosclerotic plaque within the RCA may therefore be more susceptible to the increased adrenergic activity and resultant excursions in systolic blood pressure which occur in the morning.

Further research is needed to confirm these findings in other studies and elucidate the exact mechanisms underlying the circadian variation of culprit arteries in AMI. This research might identify different strategies to prevent occlusion in patients with RCA vs. LAD disease which could have implications for outcome post-AMI.

Lead author biography



Dr Bernard Chan graduated from the University of New South Wales with first class honours and currently works as a basic physician trainee at Royal North Shore Hospital in Sydney, Australia. He has completed a Master of Public Health specializing in epidemiology and his research interests lie in the areas of preventive cardiology, electrophysiology, and structural heart disease. He is an associate investigator on the Triggers and Acute Modifiers of Acute Myocardial Infarction (TAMAMI) Study and the CONDUCT-TAVI trial which investigates the predictors of high-grade atrioventricular block after transcatheter aortic valve implantation.

Data availability

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