ORIGINAL ARTICLE

Five-minute heart rate variability can predict obstructive angiographic coronary disease

D Kotecha,[1,2] G New,[3] M D Flather,[2] D Eccleston,[1] J Pepper,[4] H Krum[1]

► An additional appendix is published online only. To view this file please visit the journal online (http://heart.bmj.com/content/98/5.toc).

[1]Monash Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Australia
[2]Clinical Trials and Evaluation Unit, Royal Brompton Hospital and Imperial College, London, UK
[3]Box Hill Hospital, Monash University, Melbourne, Australia
[4]Department of Cardiothoracic Surgery, Royal Brompton Hospital and Imperial College, London, UK

Correspondence to
Dr Dipak Kotecha, Clinical Trials and Evaluation Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; dipak.kotecha@monash.edu

Accepted 1 November 2011
Published Online First 25 November 2011

ABSTRACT

Objective Obstructive coronary artery disease (CAD) is evident in only half of patients referred for diagnostic angiography. Five-minute heart rate variability (HRV) is a non-invasive marker for autonomic control of the vasculature, which this study hypothesised could risk-stratify cardiac patients and reduce unnecessary angiograms.

Design A prospective observational study (the Alternative Risk Markers in Coronary Artery Disease (ARM–CAD) study).

Setting Three cardiac centres in Melbourne, Australia.

Patients 470 consecutive patients undergoing elective angiography (with predominantly normal cardiac rhythm), regardless of co-morbidity.

Main outcome measures The presence of obstructive CAD (≥50% stenosis) on angiography.

Results Patients with obstructive CAD had significantly reduced HRV, particularly in the low frequency (LF) range (median 180 vs 267 ms^2 without CAD; $p<0.001$). There was a linear trend with the severity of CAD; median LF power (IQR) in patients with normal coronaries was 275 (612), with minor coronary irregularities 255 (400), single-vessel CAD 212 (396) and more severe disease 170 (327) ms^2; p value for trend 0.003. There was a similar reduction in LF power regardless of the anatomical location of coronary stenoses. Comparing patients with LF less than 250 and 250 ms^2 or greater, the adjusted OR for obstructive CAD using multivariate regression was 2.42, 95% CI 1.33 to 4.38 ($p=0.004$). No interactions were noted in subgroup analysis and HRV added to risk prediction irrespective of the baseline Framingham risk ($p<0.0001$).

Conclusion Low HRV is strongly predictive of angiographic coronary disease regardless of other co-morbidities and is clinically useful as a risk predictor in patients with sinus rhythm.

Clinical trial registration information http://clinicaltrials.gov/ct2/show/NCT00403351 www.armcad.com

Coronary angiography remains the gold standard method for defining the presence and severity of coronary artery disease (CAD) in symptomatic patients. We have previously reported the association of conventional risk factors with angiographically confirmed obstructive coronary disease.[1] Risk algorithms such as Framingham and SCORE were linearly associated with the extent of angiographic disease, but a number of common variables were poor indicators of CAD, including cholesterol, smoking, blood pressure and high-sensitivity C-reactive protein, possibly due to high rates of risk factor modification with statins and antihypertensive therapy. There is a clear need for additional methods to improve diagnostic precision, particularly as the prevalence of non-obstructive CAD on angiography may be greater than 50% in some populations.[2 3]

Heart rate variability (HRV) is a non-invasive marker for the autonomic nervous system, which controls cardiac function via efferent fibres to the vasculature, sino-atrial node and myocardium.[4] Afferent fibres contribute to feedback systems such as the baroreceptor reflex (stretch-sensitive mechanoreceptors in the carotid sinus and aortic arch), the direct stretch reflex (sensitive to increased atrial volume) and the Bainbridge reflex (responding to higher central venous pressure). Power spectral density analysis deconstructs HRV into its component frequencies, graphing variance (power) as a function of frequency (see supplementary appendix, available online only). High frequency power (0.15–0.40 Hz) is thought to be mediated solely by the parasympathetic system,[5–7] primarily attributable to respiration.[8 9] The physiological correlate of low frequency (LF) power (0.04–0.15 Hz) is more contentious and is probably mediated by both branches of the autonomic nervous system.[6]

Pathological autonomic responses have been noted in patients with CAD and previous literature has shown that HRV can identify those at risk of death, and differentiate patients with a complicated course following myocardial infarction.[10–13] Reduced HRV is a better predictor of arrhythmic complications, death after myocardial infarction and death due to progressive heart failure than traditional prognostic factors such as ventricular function.[14–16] Low variability is also a predictor of all-cause mortality in those free of apparent CAD as well as in chronic heart failure.[15 17 18] Despite these robust observations, HRV has not yet become a mainstream screening tool in the work-up of cardiac patients. Although unable to assess very low frequency oscillations, short duration HRV has distinct practical advantages to 24-h evaluation and a number of automated devices are now commercially available. We hypothesised that 5-min HRV would correlate with the burden of coronary atherosclerosis and be a useful clinical test, physiologically distinct from standard risk factors, to stratify the presence of angiographic coronary disease.

METHODS

Five hundred and fifty patients attending elective diagnostic coronary angiography were recruited in

three angiographic centres in Melbourne, Australia, from 2006 to 2008. Participants were enrolled consecutively following written informed consent. The only exclusion criteria were a precipitating acute coronary syndrome and previous heart transplantation. All patients were assessed prospectively, before angiography, with the angiography operators blinded to the results. The study was approved by the local ethics committees and conducted according to the Declaration of Helsinki.

Risk markers

Detailed methods have previously been published.[1] In summary, previous medical history, risk factors, medication history and measurements were obtained from the patient and their medical records and collated using a customised database (IM Medical Ltd, Melbourne, Australia). To estimate the overall baseline risk using conventional risk factors, Framingham scores were derived for each participant, which give an estimate of the 10-year absolute risk of total coronary disease events, including angina, recognised and unrecognised myocardial infarction and coronary deaths.[19] Left ventricular function was determined by ventriculography during cardiac catheterisation or on recent echocardiography when this was contraindicated and categorised into impaired/non-impaired by the clinical operator.

Electrocardiograms (ECG)

Twelve-lead ECGs were recorded using standard techniques with the participant supine using a commercially available portable ECG device (PC-ECG 1200; Norav Medical Ltd, Kiryat Bialik, Israel). ECG were assessed by an independent, blinded cardiologist for the presence of ischaemic features and rhythm abnormalities, and were classified as normal or abnormal.

Heart rate variability

HRV was measured in all participants when a good quality ECG signal was obtainable and when QRS width and PR interval were stable for correct acquisition of the RR interval. Three leads were used to obtain the ECG signal with participants lying supine, asked to breathe normally, and left undisturbed during the capture time (mean 5.38±0.52 min). To simulate actual clinical use, no attempt was made to control patient or environmental factors (eg, coffee and alcohol consumption) or to rest the participant before HRV capture. SphygmoCor software (version 8; Atcor Medical, Sydney, Australia) was used to quantify normal-to-normal RR intervals and deconstruct HRV into component frequencies, graphing variance as a function of frequency (power spectral density analysis; see supplementary appendix, available online only, for example).[4]

Coronary angiography

Coronary angiography was performed by experienced operators using standardised procedures and guidelines and classified as angiographically normal, minor coronary irregularities or the presence of obstructive CAD (≥50% stenosis in one or more native epicardial arteries or main tributary). For quality assurance, a random sample of 10% of angiograms at each centre were reviewed by two independent, experienced and blinded operators. In any situation in which there was uncertainty about classification, angiograms were reassessed and a consensus achieved by discussion.

Statistics

Values are presented as mean±SD, median±IQR or percentage. Categorical variables were compared with the χ^2 test and continuous variables with a two-tailed t test or non-parametric Kruskal–Wallis rank test. Trends in disease severity were established with the Cuzick and Altman test. OR for the presence of obstructive CAD were determined by logistic regression and are presented with 95% CI. The stepwise regression model included all variables presented in tables 1 and 2 plus dyspnoea

Table 1 Patient characteristics and angiographic CAD

Characteristic	Normal coronaries	Minor irregularities	Obstructive CAD (≥50% stenosis)	Trend p value
Number, n (%)	98 (20.9%)	90 (19.1%)	282 (60.0%)	
Age (years±SD)	58.0±11.8	64.2±10.0	66.9±10.2	<0.0001
Male gender	37.8%	61.1%	78.7%	<0.0001
Current smoker	13.3%	18.9%	15.6%	NS
Chest pain*	77.6%	63.3%	82.6%	0.060
Previous myocardial infarction	6.1%	6.7%	32.3%	<0.0001
Previous coronary intervention†	1.0%	8.9%	18.8%	<0.0001
Diabetes	10.2%	17.8%	25.9%	0.001
SBP (mm Hg±SD)	142.9±18.9	141.9±22.0	144.8±21.2	NS
DBP (mm Hg±SD)	81.3±8.3	78.6±10.2	78.7±10.5	0.024
Pulse pressure (mm Hg±SD)	61.5±16.8	63.2±19.8	66.0±18.2	0.023
Body mass index (±SD)	30.1±6.0	27.9±4.7	28.6±5.1	0.052
Total cholesterol (mmol/l±SD)‡	5.09±1.16	4.63±1.05	4.48±1.10	<0.0001
HDL-cholesterol (mmol/l±SD)	1.37±0.40	1.28±0.36	1.16±0.29	<0.0001
eGFR (ml/min/1.73 m^2±SD)	88.8±22.7	84.3±23.5	82.4±23.3	0.030
Significant valvular heart disease§	12.2%	12.2%	8.9%	NS
Impaired left ventricular function	10.2%	11.1%	20.4%	0.009
β-Blockers	24.5%	46.7%	51.4%	<0.0001
Renin–angiotensin–aldosterone agents¶	44.9%	55.6%	58.5%	NS
Statins	41.8%	60.0%	69.2%	<0.0001

*Rest or exertional central chest discomfort, unrelated to food or breathing.
†Percutaneous coronary angioplasty and/or stent.
‡Does not account for the effect of statin medication.
§Moderate or severe aortic or mitral stenosis/incompetence.
¶Includes ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists.
CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NS, not significant; SBP, systolic blood pressure.

Table 2 ECG, heart rate variability and CAD

Parameter	Normal coronaries	Minor irregularities	Single-vessel CAD	Two or more-vessel CAD	Trend p value
Number, n (%)	98 (20.9%)	90 (19.1%)	94 (20.0%)	188 (40.0%)	
Abnormal ECG*	24.5%	42.2%	34.0%	45.7%	0.003
Ischaemic ECG†	23.5%	40.0%	30.9%	42.6%	0.007
Abnormal ECG rhythm‡	20.4%	25.6%	21.3%	25.5%	0.452
5-Min heart rate (mean bpm±SD)§	65.2±12.2	63.3±11.5	60.3±10.4	60.8±10.6	0.001
pNN50 (median %±IQR)¶ **	6.1±18.3	5.5±23.9	3.1±13.4	2.3±14.4	0.013
HRV index (median±IQR)**	7.6±4.4	7.2±4.8	6.6±4.3	6.4±3.3	0.001
Total HRV power (median±IQR)	1011±1727	1129±1960	756±1618	688±1227	0.042
High frequency power (median±IQR)	213±341	242±515	165±418	147±537	0.221
Low frequency power (median±IQR)	275±612	255±400	212±396	170±327	0.003

*Any abnormality on 12-lead ECG.
†Pathological Q-waves, ST or T-wave changes on ECG.
‡Heart block, atrial fibrillation, atrial flutter or frequent ectopics on ECG.
§Does not account for the use of β-blockers.
¶Proportion of adjacent sinus RR intervals differing by more than 50 ms (pNN50).
**Both pNN50 and HRV index moderately correlated with heart rate ($r=-0.3$; $p<0.001$ for both).
bpm, beats per minute; CAD, coronary artery disease; HRV, heart rate variability.

and the use of aspirin, clopidogrel, calcium channel blockers or vasodilators. A threshold of $p<0.1$ on likelihood ratio testing was used for variable inclusion. Variables significant in univariate analysis were used in the fixed multivariate model. Interactions were investigated for cross-tabulation of all variables and models were assessed for specification, classification and goodness of fit using the Hosmer–Lemeshow statistic. The cut-off value for LF power was determined using receiver operator curves with the Bayesian information criterion and the likelihood ratio test was used to confirm the additive value of LF power to conventional risk factors. A two-tailed p value of less than 0.05 was considered statistically significant. Analyses were performed on Stata Intercooled (version 9.2).

RESULTS

The study recruited 550 patients, of which 11 were excluded (five due to a preceding acute coronary syndrome, three due to unsuccessful coronary cannulation and three due to missing risk factor data). HRV measurement was successfully captured in 480 participants (89%). The most important factor limiting the acquisition of HRV was atrial fibrillation or flutter, which occurred in 2.3% of those with successful capture and 17.5% of participants in whom HRV was unobtainable ($p<0.0001$). Excluding patients with atrial fibrillation/flutter had no effect on further analyses and therefore the data presented include all participants with successful HRV capture. Rhythm abnormalities on the ECG were the only independent factor associated with the absence of HRV measurements in multivariate analysis (OR 2.62, 95% CI 1.44 to 4.74; $p=0.002$). The final sample size was 470, as 10 patients had uninterpretable ECG and were excluded. The majority of these patients (89.4%) were referred for angiography on the basis of cardiac symptoms. The remainder were referred to exclude CAD in patients with valve disease, heart failure, arrhythmias or for preoperative assessment.

Risk factor interactions

There were no major interactions of 5-min LF power with conventional risk factors and only a weak correlation with heart rate (see figure 1). HRV was reduced in patients with diabetes compared with those without diabetes with median LF power (IQR) of 157 (387) ms^2 versus 223 (400) ms^2, respectively ($p=0.048$). There was no effect of gender or smoking on HRV. One hundred and forty-three participants (30%) were assessed in the afternoon, but no time-related effect was noted on any HRV parameter.

Association with angiographic CAD

Table 1 displays baseline risk factors and selected medications according to the degree of angiographic disease for 470 participants with data available on all risk markers. Sixty per cent of patients assessed had obstructive CAD. Table 2 displays HRV and ECG parameters, demonstrating that a number of variables were crudely associated with the extent of angiographic CAD. LF power was statistically the most discriminating factor. There was a linear decrease in LF power as the extent of CAD worsened ($p=0.003$), and the optimal cut-off value for obstructive disease was determined as 250 ms^2. Figure 2 depicts the reduction in HRV frequency parameters according to the coronary artery territory affected. There was a uniform reduction in LF power by 25–30% irrespective of the anatomical location of CAD.

Predictors of obstructive CAD

Reduced LF power was a strong and independent predictor of the presence of obstructive CAD in both stepwise and fixed multivariate analysis (see table 3). The adjusted OR comparing LF power less than 250 ms^2 and 250 ms^2 or greater in the fixed regression model was 2.42, 95% CI 1.33 to 4.38 ($p=0.004$). The median value cut point for LF power (211 ms^2) was also independently associated with obstructive CAD; adjusted OR of 1.86, 95% CI 1.04 to 3.34 ($p=0.037$). ECG variables were not independent of other risk factors.

The clinical value of reduced HRV as a predictor of CAD was assessed in a variety of subgroups including patients with and without diabetes or previous cardiovascular disease and according to gender, age group, hypercholesterolaemia and by high-sensitivity C-reactive protein. As demonstrated in figure 3, interaction p values were non-significant for all subgroups and similarly according to left ventricular impairment ($p=0.331$) and the presence of hypertension ($p=0.129$). LF power less than 250 ms^2 supplemented conventional risk factors and conversely removing this variable significantly reduced the fit of the model to the observed outcomes ($p=0.003$ on likelihood ratio comparison). LF power provided additional risk stratification with respect to the Framingham risk algorithm (figure 4A), and the overall model including HRV classified coronary

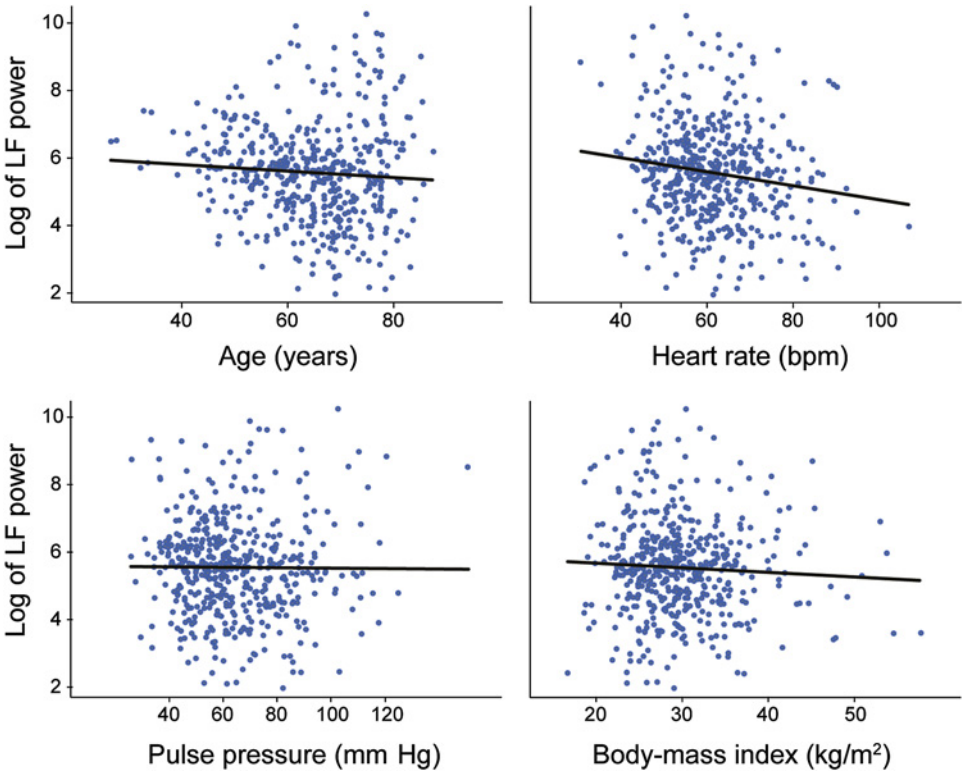

Figure 1 Low frequency (LF) heart rate variability power and cardiac risk factor. Scatter plots of natural logarithm of LF power against age, heart rate, pulse pressure and body mass index with associated regression line. Corresponding correlation values are −0.07 (p=NS), −0.16 (p<0.001), −0.01 (p=NS) and −0.06 (p=NS).

disease substantially better than Framingham variables alone (figure 4B).

DISCUSSION

This study sought to determine the ability of a 5-min bedside HRV test to predict the presence of CAD. Our data demonstrate a high correlation of HRV with angiographically defined disease in patients attending elective diagnostic coronary angiography. LF spectral power was inversely related to the extent of CAD and a cut-off value of 250 ms^2 was identified as a strong independent predictor of obstructive disease in this clinical cohort. HRV was applicable across patient subgroups, added to conventional risk factor assessment and was superior to standard 12-lead ECG recordings.

Our data add to the body of evidence from previous studies linking HRV and CAD, although we focused on the prediction of obstructive CAD as defined by the gold standard coronary angiogram rather than clinical outcomes. Reduction in HRV as a surrogate for neurohormonal and sympathetic activation has been associated with CAD and impaired prognosis since the 1970s.[4] Despite numerous trials with robust evidence linking reduced HRV to adverse outcomes, no study has previously examined the use of HRV with a simple and quick device in the clinical environment with an unselected population. Traditional evaluation using 24-h ECG recordings have inherent problems such as movement artefact, changes relating to the circadian rhythm, issues of data filtering and the technical expertise required in translating results. Newer assessments of short duration HRV have considerable practical advantages and allow these technologies to be used with minimal training and a high degree of automation, while maintaining correlation with clinical events.[10]

A number of confounding variables have also limited the clinical use of HRV in the past, relating to both environmental

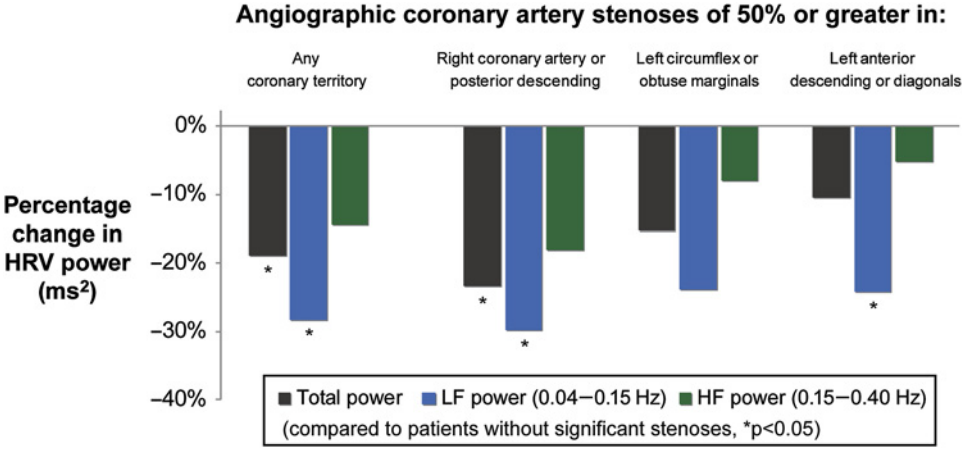

Figure 2 Heart rate variability (HRV) according to coronary artery territory. Reduction in HRV according to localisation of coronary artery stenoses in participants with sinus rhythm. Bars indicate difference in power spectral density in all patients with a significant stenosis (≥50%) for each coronary artery group compared with those without obstructive disease in that territory. *p<0.05 on two-tailed t test using log-transformed values. HF, high frequency; LF, low frequency.

Table 3 Multivariate regression for obstructive coronary disease

Stepwise multivariable regression			Fixed multivariable regression		
Variable	**OR (95% CI)**	**p Value**	**Variable**	**OR (95% CI)**	**p Value**
Previous MI	6.40 (3.08 to 13.3)	<0.001	Previous MI	5.67 (2.62 to 12.25)	<0.001
Male gender	3.39 (2.07 to 5.55)	<0.001	Male gender	3.18 (1.81 to 5.58)	<0.001
Regular nitrate	2.99 (1.41 to 6.35)	0.004	Regular nitrate	3.03 (1.37 to 6.71)	0.006
Clopidogrel	2.19 (1.06 to 4.55)	0.035	LF power <250 ms^2	2.42 (1.33 to 4.38)	0.004
LF power <250 ms^2	2.15 (1.33 to 3.46)	0.002	Diabetes	2.11 (1.11 to 4.01)	0.023
Diabetes	2.02 (1.12 to 3.63)	0.019	Age (per 10 years)	1.90 (1.45 to 2.50)	<0.001
Chest pain	1.80 (1.03 to 3.13)	0.038	Heart rate (per bpm)	0.97 (0.95 to 1.00)	0.026
Age (per 10 years)	1.72 (1.37 to 2.15)	<0.001	Abnormal ECG	1.46 (0.23 to 9.12)	0.686
Heart rate (per bpm)	0.98 (0.95 to 1.00)	0.020	Ischaemic ECG	0.96 (0.15 to 6.14)	0.965

Table 3 presents fully adjusted OR for obstructive coronary artery disease (CAD) (≥50% stenosis). Stepwise model (n=480) includes all variables in Table 1 plus dyspnoea and other medications (aspirin, clopidogrel, calcium channel blockers and nitrates) with stepwise removal at a threshold of p<0.1. The fixed model (n=470) includes all variables significantly associated with CAD in univariate analysis; all significant OR are displayed plus ECG variables for comparison. Interactions noted between gender/chest pain and gender/heart rate; however, inclusion of interaction terms had no impact on OR for other variables. Hosmer–Lemeshow χ^2=12.05 (p=0.149) for stepwise model and 4.51 (p=0.809) for fixed; non-significance implies adequate model fit.
LF, low frequency; MI, myocardial infarction.

and patient factors, including respiration, posture and the time of recording, as well as the impact of coffee and alcohol. These relationships are also affected by the presence of CAD and risk factors, with a blunted response to tilt compared with patients without coronary disease[20] and the usual circadian rhythm of autonomic tone notably diminished in patients with hypertension and CAD.[20 21] Despite these issues and recruiting a clinical population with a wide variety of co-morbidities, our analysis confirmed the value of HRV measurement. Unlike previous studies, no previous restrictions were placed on participants (such as a prolonged resting period) and no attempt was made to control breathing. The published literature suggests that the reproducibility of HRV is generally good for both healthy populations and those with CAD,[14 22 23] although day-to-day variations have been noted in some individuals.[24 25]

As discussed by Lahiri *et al*,[26] the interplay of the autonomic nervous system with cardiovascular physiology is complex; however, our data would support the concept that the predominance of sympathetic activation and/or reduction in vagal tone may be a causative factor as well as a consequence of CAD. Sympathetic predominance can cause a reduction in low and high frequency HRV as well as total power (ie, reduced total variance in heart rate).[4 27] Our analysis identified LF power as the most sensitive predictor of coronary atheroma, even after adjustment for the use of β-blockers and heart rate. Experimental studies have identified dynamic changes in LF power in

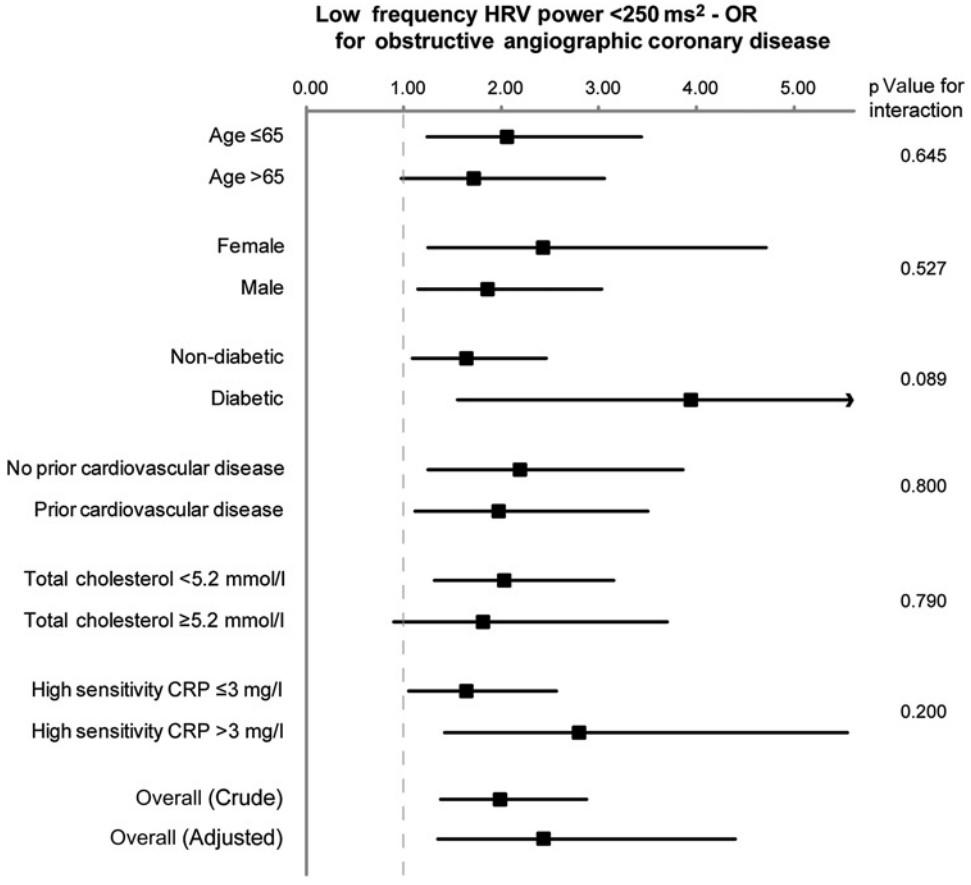

Figure 3 Subgroup analysis of low frequency heart rate variability (HRV) power. Total cholesterol of 5.2 mmol/l is equivalent to 200 mg/dl. CRP, C-reactive protein.

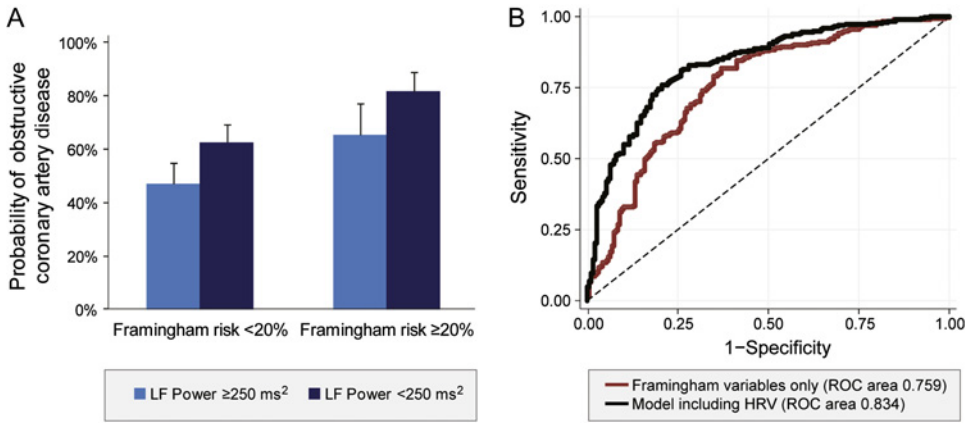

Figure 4 Classification of coronary disease using Framingham and heart rate variability (HRV). Panel A depicts the probability of obstructive native coronary artery disease according to Framingham 10-year absolute event risk of total coronary disease and low frequency (LF) HRV power. No interaction between Framingham risk and LF power was noted (p=0.630) and all probabilities were significantly different (likelihood ratio χ^2=27.24; p<0.0001). Panel B depicts receiver operator curves (ROC) comparing Framingham model variables (bottom line; age, gender, total and high-density lipoprotein cholesterol, systolic blood pressure, diabetes and smoking) with the stepwise multivariate model including HRV (black line; see table 3 for variables). The significant difference in ROC area (χ^2=15.30, p<0.0001) confirms the improved classification of coronary disease with the HRV model.

patients with myocardial ischaemia during balloon coronary occlusion[28] and direct correlations between LF power and the wall motion score index during dipyridamole on stress testing.[29]

Heart rate itself is a well documented marker of mortality.[30 31] A higher heart rate decreases the duration of diastole, diminishing left ventricular filling and coronary artery perfusion. It also causes disruption of atherosclerotic plaques, promoting thrombus formation and myocardial infarction.[32 33] Despite a progressive increase in overall mortality with heart rate in the Framingham cohort, the proportion of deaths specifically caused by cardiovascular disease was not different at any given heart rate.[34] An excess of non-cardiovascular deaths at higher heart rates illustrates the poor specificity of heart rate as a marker of CAD. In our analysis, this association was confounded by the high rate of β-blocker prescription (45% overall) and LF power remained a more sensitive predictor of coronary disease.

Although the Framingham risk score is defined for a population without preceding cardiovascular disease, the risk factors it contains are commonly used to stratify CAD risk in clinical practice. LF HRV discriminated obstructive angiographic CAD regardless of the baseline Framingham risk. The OR point estimate for LF power less than 250 ms^2 remained similar in the crude analysis and after adjusting for conventional risk factors, albeit with a slightly broader CI, as would be expected. There was also a reasonable increase in the c-statistic, confirming our previous hypothesis that conventional risk factors may be insufficient in this population, particularly when there is a high degree of risk-modifying interventions.[1] This is evidenced by the lack of modifiable risk factors such as blood pressure, smoking and lipid values in the final multivariate model.

The limitations of our analysis are also potential strengths by simulating actual clinical application. Only a single measurement of HRV was obtained and no attempt was made to control environmental factors before recording. Correct capture of sinus RR intervals was dependent on automatic algorithms and patients with irregular cardiac rhythms or broad bundle branch blocks may fail to capture sufficient RR intervals for an estimation of HRV. In our study HRV capture was unsuccessful in 11% of participants, which is an important clinical limitation of this technology. We did not assess the reproducibility of HRV measurement in our study due to the time constraints existing in the clinical setting, although earlier publications have addressed this issue, as noted above. Furthermore, we used Fourier transform algorithms, which are known to have less spectral definition than autoregressive or fractal analyses.[4] The population for this study was determined by referral for coronary angiography. We cannot exclude significant verification (or work-up) bias, but this was minimised by recruiting consecutive patients, not considering the reason for referral and subjecting all participants to the diagnostic and verification tests.[35]

CONCLUSIONS

Measuring HRV was simple, non-invasive and suitable for both primary care and hospital environments. Reduced LF power was a strong and independent predictor of obstructive angiographic coronary disease, regardless of baseline risk factors. Our results highlight that 5-min HRV is a potential clinical tool for risk stratification in patients with sinus rhythm and not solely for research studies. Furthermore, the short duration of measurement has specific advantages in addition to practical considerations, including the assessment of HRV following changes in management and drug therapies.

Acknowledgements This work was only possible with the support of patients and research staff involved in the ARM–CAD studies. The authors would like to thank Box Hill Hospital Cardiology Department, the Northern Hospital Catheter Laboratory and the Alfred Heart Centre. The authors would also like to acknowledge the late Philip Poole-Wilson (Imperial College, London), as well as Andris Ellims and Will Wilson from the ECG and angiographic core laboratory (Royal Melbourne Hospital, Melbourne, Australia).

Funding The ARM-CAD study was investigator initiated and supported by the Monash Centre of Cardiovascular Research and Education in Therapeutics, Melbourne, the Royal Brompton and Harefield NHS Trust Clinical Trials and Evaluation Unit, London, and an unrestricted research grant from IM Medical Ltd, Melbourne.

Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by Monash University, Alfred Hospital HREC, Eastern Health HREC, Northern Hospital HREC.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Kotecha D,** Flather M, McGrady M, *et al*. Contemporary predictors of coronary artery disease in patients referred for angiography. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:280–8.
2. **Patel MR,** Peterson ED, Dai D, *et al*. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;**362**:886–95.
3. **Wang XL,** Tam C, McCredie RM, *et al*. Determinants of severity of coronary artery disease in Australian men and women. *Circulation* 1994;**89**:1974–81.
4. **Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.** Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;**93**:1043–65.

5. **Akselrod S,** Gordon D, Ubel FA, *et al*. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;**213**:220—2.
6. **Pomeranz B,** Macaulay RJ, Caudill MA, *et al*. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;**248**:H151—3.
7. **Toledo E,** Gurevitz O, Hod H, *et al*. Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. *Am J Physiol* 2003;**284**:R1079—91.
8. **De Jong MJ,** Randall DC. Heart rate variability analysis in the assessment of autonomic function in heart failure. *J Cardiovasc Nurs* 2005;**20**:186—95.
9. **Saul JP,** Berger RD, Chen MH, *et al*. Transfer function analysis of autonomic regulation. II. Respiratory sinus arrhythmia. *Am J Physiol* 1989;**256**:H153—61.
10. **Bigger JT,** Fleiss JL, Rolnitzky LM, *et al*. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation* 1993;**88**:927—34.
11. **Huikuri HV,** Koistinen MJ, Yli-Mayry S, *et al*. Impaired low-frequency oscillations of heart rate in patients with prior acute myocardial infarction and life-threatening arrhythmias. *Am J Cardiol* 1995;**76**:56—60.
12. **Rich MW,** Saini JS, Kleiger RE, *et al*. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. *Am J Cardiol* 1988;**62**:714—17.
13. **Tsuji H,** Venditti FJ, Manders ES, *et al*. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994;**90**:878—83.
14. **Bigger JT,** Fleiss JL, Rolnitzky LM, *et al*. Stability over time of heart period variability in patients with previous myocardial infarction and ventricular arrhythmias. The CAPS and ESVEM investigators. *Am J Cardiol* 1992;**69**:718—23.
15. **Nolan J,** Batin PD, Andrews R, *et al*. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK—heart). *Circulation* 1998;**98**:1510—16.
16. **Odemuyiwa O,** Malik M, Farrell T, *et al*. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991;**68**:434—9.
17. **Huikuri HV,** Mäkikallio T, Airaksinen KE, *et al*. Measurement of heart rate variability: a clinical tool or a research toy? *J Am Coll Cardiol* 1999;**34**:1878—83.
18. **Tsuji H,** Larson MG, Venditti FJ Jr, *et al*. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996;**94**:2850—5.
19. **Wilson PW,** D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837—47.
20. **Huikuri HV,** Niemelä MJ, Ojala S, *et al*. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. *Circulation* 1994;**90**:121—6.
21. **Guzzetti S,** Piccaluga E, Casati R, *et al*. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. *J Hypertens* 1988;**6**:711—17.
22. **Pitzalis MV,** Mastropasqua F, Massari F, *et al*. Short- and long-term reproducibility of time and frequency domain heart rate variability measurements in normal subjects. *Cardiovasc Res* 1996;**32**:226—33.
23. **Sandercock GR,** Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. *Int J Cardiol* 2005;**103**:238—47.
24. **Pinna GD,** Maestri RR, Torunski AA, *et al*. Heart rate variability measures: a fresh look at reliability. *Clin Sci* 2007;**113**:131—40.
25. **Sinnreich R,** Kark JD, Friedlander Y, *et al*. Five minute recordings of heart rate variability for population studies: repeatability and age-sex characteristics. *Heart* 1998;**80**:156—62.
26. **Lahiri MK,** Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008;**51**:1725—33.
27. **Ori Z,** Monir G, Weiss J, *et al*. Heart rate variability. Frequency domain analysis. *Cardiol Clin* 1992;**10**:499—537.
28. **Joho S,** Asanoi H, Remah HA, *et al*. Time-varying spectral analysis of heart rate and left ventricular pressure variability during balloon coronary occlusion in humans: a sympathoexicitatory response to myocardial ischemia. *J Am Coll Cardiol* 1999;**34**:1924—31.
29. **Petretta M,** Spinelli L, Marciano F, *et al*. Wavelet transform analysis of heart rate variability during dipyridamole-induced myocardial ischemia: relation to angiographic severity and echocardiographic dyssynergy. *Clin Cardiol* 1999;**22**:201—6.
30. **Diaz A,** Bourassa MG, Guertin MC, *et al*. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005;**26**:967—74.
31. **Palatini P.** Heart rate: a strong predictor of mortality in subjects with coronary artery disease. *Eur Heart J* 2005;**26**:943—5.
32. **Heidland UE,** Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation* 2001;**104**:1477—82.
33. **Sulfi S,** Timmis AD. Ivabradine—the first selective sinus node I(f) channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006;**60**:222—8.
34. **Kannel WB,** Kannel C, Paffenbarger RS, *et al*. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987;**113**:1489—94.
35. **Mower WR.** Evaluating bias and variability in diagnostic test reports. *Ann Emerg Med* 1999;**33**:85—91.