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Clinical and coronary haemodynamic determinants of recurrent chest pain in patients without obstructive coronary artery disease — A pilot study☆,☆☆

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ABSTRACT

Background: Coronary haemodynamic testing frequently identifies abnormal pathophysiological parameters in patients with angina and non-obstructed coronaries on angiography (NoCAD) but the clinical utility of these measures has received limited attention.
Objective: This study aims to identify the clinical and coronary haemodynamic determinants of recurrent chest pain at one month in patients with NoCAD.
Methods: Patients with angina, NoCAD (<50% stenosis) and normal LV systolic function underwent invasive coronary haemodynamic testing involving: (1) angiographic TIMI frame and opacification rate, (2) microvascular functional measures including coronary flow reserve (CFR) and hyperaemic microvascular resistance (HMR), (3) coronary endothelial function assessment with low dose intracoronary acetylcholine (IC-ACh) infusions (0.18 μg/min & 1.8 μg/min over 2 min), and (4) *Provocative spasm testing* with high dose IC-ACh boluses (25, 50 and 100 μg). Clinical and health status were assessed at baseline and one month.
Results: In the 49 NoCAD patients (78% female, mean age of 54 ± 11) undergoing comprehensive coronary haemodynamic testing, 33 (67%) continued to experience chest pain at one month. Determinants of recurrent chest pain on univariate analysis included baseline chest pain status or a HMR > 1.9. Multivariate logistic regression analysis identified frequent angina at baseline (OR: 68.9 [4.1, 1165.0], p = 0.003), previous unstable angina admission (OR: 43.9 [3.5, 547.9], p = 0.003) and a HMR > 1.9 (OR: 15.6 [2.1, 114.0], p = 0.007) as independent predictors of recurrent chest pain.
Conclusion: In this small pilot study, an abnormal HMR was the only coronary haemodynamic parameter that was a determinant of ongoing angina at short-term follow-up.

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1. Introduction

Patients with angina with non-obstructive coronary artery disease (NoCAD) may constitute as many as 20–60% of elective diagnostic angiograms [1–3] and have a disconcerting prognosis with many experiencing on-going chest pain, diminished quality of life, frequent re-hospitalization, relatively high rates of progression to obstructive CAD and major adverse cardiac events [4–7]. Recent studies have shown a high prevalence of coronary vasomotor disorders in these patients [8], however the clinical relevance of these abnormal coronary vasomotor parameters has received limited attention. These coronary indices may include measures of coronary microvascular dysfunction (e.g. coronary flow reserve, index of microvascular resistance, hyperaemic microvascular resistance, microvascular spasm and TIMI frame count) and/or epicardial coronary artery spasm. The clinical utility of coronary spasm testing has been well evaluated including clinical validation with variant angina patients [9] and the impact of calcium channel blockade in reducing major cardiac events [10]. In relation to the coronary microvascular dysfunction parameters, coronary flow reserve predicts major adverse cardiac events in patients with NoCAD [11], and coronary microvascular resistance indices provide incremental information to account for myocardial ischaemia observed on myocardial scintigraphy in patients with stable obstructive CAD [12], as well as the presence of microvascular obstruction on cardiac magnetic resonance imaging in acute myocardial infarction patients [13]. However, the clinical utility of these indices in

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predicting patient-reported outcomes such as ongoing angina, has not been substantially evaluated. Accordingly, the aim of this study was to identify the clinical and coronary haemodynamic determinants of ongoing angina at one month following invasive coronary haemodynamic studies in patients with NoCAD.

2. Methods

2.1. Study population

2.1.1. Patient recruitment

Patients referred by their treating physician for elective coronary angiography, who had a clinical diagnosis of angina and known or anticipated to have NoCAD, were approached to participate in the study (Supplement Figure 1: Patient Recruitment Summary).

2.1.2. Inclusion criteria

Patients with (1) clinical diagnosis of angina, (2) persistent angina and (3) coronary angiography demonstrating normal or no obstructive coronary disease (<50% diameter stenosis); were included in the study. Persistent angina was defined as one or more episodes of pain per week despite at least one anti-anginal medication. This criterion had been previously validated for poor quality of life in patients with stable angina [14].

2.1.3. Exclusion criteria

These included (1) admission for an acute coronary syndrome within the preceding month (2) prior coronary artery bypass grafting, (3) contra-indications to coronary haemodynamic assessment – patients with permanent pacemaker or defibrillator, severe renal or hepatic insufficiency, severe asthma, left ventricular systolic dysfunction (ejection fraction < 50%), or (4) alternative coronary explanations for the chest pain – obstructive CAD (flow limiting coronary stenosis i.e. derived fractional flow reserve (FFR) <0.80), spontaneous coronary spasm (but not catheter related spasm), spontaneous coronary artery dissection, or (5) other cardiovascular disorders - pulmonary hypertension, pulmonary embolism, hypertrophic cardiomyopathy, or valvular heart disease.

2.2. Study protocol

The Central Adelaide Local Health Network Ethics Committee approved the study, and written informed consent was obtained from all patients. Following informed consent, all coronary vasodilating drugs were discontinued 48 h before angiography, except for sublingual nitroglycerin as required. A baseline diagnostic coronary angiogram was performed via the femoral or radial artery to exclude obstructive CAD (≥50% diameter stenosis) in the right and left coronary arteries. In patients with NoCAD, a comprehensive invasive haemodynamic evaluation was conducted.

2.2.1. Clinical and health status data

Pre-defined clinical data elements (see Supplement Table 1) were collected including risk factors, chest pain characteristics, and medications. Health status (symptoms, physical limitations and quality of life) was assessed at baseline using Seattle Angina Questionnaire (SAQ) and repeated at one-month follow up by phone interview. SAQ is a well-established and validated disease-specific quality-of-life instrument for patients with angina that fulfills current performance measures for quantifying patients' symptoms and function [15,16]. Similarly, the self-administered Patient Health Questionnaire (PHQ-9) was undertaken at baseline and follow up to assess depression status. This PRIME-MD diagnostic scale has been validated for use in clinical care [17].

2.2.2. Invasive coronary haemodynamic testing

A 6F-guiding catheter was used to engage the left main coronary artery. A temporary pacing electrode was advanced into right ventricle via femoral venous approach and set to a threshold of 50 bpm. Combowire (dual sensor guide wire) was calibrated and advanced in the proximal to mid left anterior descending artery (LAD), ensuring a good Doppler signal waveform. ECG, pressure and flow velocity waveforms were recorded using the ComboMap system (Volcano Corporation San Diego, CA, USA). Systemic, coronary haemodynamics, 12 lead ECG were monitored throughout the protocol and the procedure was undertaken following anticoagulation with intravenous heparin (50–70 U/kg). Patients underwent a comprehensive invasive coronary haemodynamic evaluation that included the assessment of resting angiographic contrast flow, coronary microvascular hyperaemic function, coronary endothelial function and provocative coronary spasm testing. The details of these components are outlined below.

(1) Resting angiographic contrast flow assessment was undertaken for the diagnosis of the coronary slow flow phenomenon (CSFP), based upon the contrast opacification rate; i.e. requiring ≥3 beats to opacify the vessel (equivalent of TIMI-2 flow). The TIMI frame count was also calculated to provide a more quantitative measure of angiographic flow.

(2) Coronary microvascular hyperaemic function was assessed using coronary flow reserve (CFR) and hyperaemic microvascular resistance index (HMR) measured by a combined pressure/Doppler wire (Combowire, Volcano Corporation, San Diego, CA, USA). This procedure has been previously described in literature [18,19]. Following pressure equalization in aorta and then placement of Combowire in the LAD, baseline resting coronary physiology measurements including mean aortic and distal pressure (Pa & Pd) and average peak velocity (APV) were recorded over a 5-minute period and then reassessed following hyperaemic stimulus with intravenous adenosine (140 μg/kg/min) via femoral venous line was infused over 2 min. HMR was calculated as the distal coronary pressure divided by APV at maximal hyperemia and the HMR >1.9 was used to define coronary microvascular dysfunction [12]. CFR was calculated as a ratio of peak and baseline APV and the value of <2.5 was considered as an impaired flow reserve [20].

(3) Coronary endothelial function was assessed with low dose intracoronary acetylcholine (IC-ACh) infusions 10^{-6} mol/L (0.18 μg/min) and 10^{-5} mol/L (1.8 μg/min) administered over 2 min respectively [21,22]. Combowire remained in-situ and Doppler measurement of peak velocity was obtained at the end of each acetylcholine infusion, before contrast injection. Post acetylcholine cine images were obtained for each concentration for quantitative coronary angiography (QCA) assessment (see below). We ensured that coronary flow returned to baseline before each infusion. Epicardial coronary artery endothelial dysfunction was defined on the basis of absence of a vasodilation (including vasoconstriction) to the ACh infusion i.e. no change or reduction in coronary diameter in response to the ACh infusion [23]. Microvascular endothelial dysfunction was defined as a coronary blood flow increase <50% from baseline [7]. Coronary blood flow response was calculated from the Doppler-derived time-velocity integral and vessel diameter by the following equation: *Coronary blood flow = π (average peak velocity/2)(vessel diameter/2)* [2]. Vessel diameter was calculated at the mid-LAD segment, just distal to the Doppler wire tip.

(4) Coronary spasm provocation testing was performed using incremental bolus doses of IC-ACh (25, 50 and 100 μg) administered over 20 s in left coronary system, with coronary angiography was performed within 1 min of each injection. Provocative testing was concluded following either the induction of occlusive/sub-occlusive coronary artery spasm, or by attaining the maximal ACh dose without inducing coronary spasm. Right coronary artery (RCA) was assessed for inducible spasm using 25 & 50 μg IC-ACh boluses, if no spasm was documented in left system. The provocation test was considered diagnostic for *vasospastic angina* if ACh administration induced (i) chest pain, (ii) ischaemic ECG changes, defined as transient ST-segment depression or elevation ≥0.1 mV in at least 2 contiguous leads on 12 lead continuous monitoring [24–27], and (iii) ≥90% vasoconstriction in epicardial artery [28]. A diagnosis of "*microvascular spasm*" was made if ACh administration induced (i) chest pain, and (ii) ischaemic ECG changes as above, in (iii) the absence of coronary artery constriction (<90%). *Basal epicardial coronary artery tone* was determined by the change in coronary artery diameter from baseline images in response to 150 μg of intracoronary nitroglycerine administered into the right and left coronary arteries, at the end of the procedure.

2.3. Angiographic data analysis

Two independent clinicians analyzed angiographic data in the angiography core lab using McKesson Cardiology Solution v. 13.0. TIMI flow grade was assessed as previously described in literature [29] and the TIMI frame count was measured with a frame counter on the cine viewer. The number of cine frames required for contrast to first reach standardized distal coronary landmark was used to calculate frame count in each coronary artery and it was corrected with fraction of two; as angiographic image acquisition was undertaken at 15 frames/s. LAD frame count was further adjusted for length by dividing the TIMI frame count by a factor of 1.7 [30].

Quantitative coronary angiography (QCA) was undertaken via a computer-based edge-detection method. Cine film images of lumen diameters were quantified by a projector-based cross-hair technique. Luminal diameters were determined at baseline and in response to vasoactive agents 5 mm distal to the Combo wire tip for endothelial function assessment and at maximal constricting segment for vasospasm.

Coronary physiology parameters including continuous pressure and Doppler velocity analysis in response to vasoactive drugs were undertaken on dedicated transducer (Volcano ComboMap v 1.9) directly connected to combowire and did automatic calculations of APV, CFR, HMR & FFR at peak hyperaemic response.

2.4. Statistical analysis

Sample size was calculated on the principle of a minimum of 10 events per each predictor variable [31,32]. We sought to examine three clinically-relevant potential predictors, and given previous studies show at least two thirds of patients would have recurrent chest pain on follow up [33], we therefore aimed to recruit minimum of 45 patients. Results are expressed as mean +/− SD for normally distributed data and median (25th–75th percentiles) for data that were not normally distributed. Fisher Exact test was used to assess for differences between categorical variables. Student *t*-tests or Mann Whitney rank-sum tests were used to assess for differences between groups for continuous variables. Logistic regression model was fitted to identify the determinants of recurrent chest pain. Variables that were significantly associated with one-month chest pain at $p < 0.20$ in univariate analysis were selected for inclusion in multivariate logistic regression. The final independent predictors were identified using backward elimination. p value of ≤0.05 was considered statistically significant. Statistical analysis was performed with STATA Version 11. 2 for MAC and Graph pad Version 7 for MAC.

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