Usefulness of temporary pacemaker during acetylcholine provocation testing

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1. Introduction

Acetylcholine (ACh) provocation testing as part of coronary function testing (CFT) has become an integral diagnostic tool when evaluating patients with angina and nonobstructive coronary arteries (ANOCA). ACh administration protocols vary in dose and speed of administration among different institutions. Fast ACh administration to specifically test for coronary spasm, such as with 20 s injections, have been recommended by several large groups, including the Japanese Circulation Society (JCS)[1] and the landmark CorMICA study that showed the benefit of CFT for evaluating patients with ANOCA.[2] Intracoronary ACh can result in transient sinus bradycardia and/or atrioventricular block particularly with higher and faster ACh administration. There is significant variability among international institutions in the routine use of a temporary transvenous pacemaker (TTP) to manage bradyarrhythmias during such procedures[3]. Current practice does not recommend routine use of a prophylactic TTP unless the right coronary artery (RCA) is selected for testing[3]. This recommendation is based on expert consensus due to a paucity of definitive evidence. Our objective was to evaluate the incidence of backup pacing during ACh provocation testing using fast administration and identify potential predictive factors.

2. Methods

In this multicentre prospective observational study, multi-vessel testing was systematically performed in consecutive ANOCA patients with suspected coronary artery spasm. Patients were requested to hold vasoactive medications for 24–72 h, depending on the drug's half-life. Administration of intra-arterial vasodilator drugs (e.g., nitroglycerin, calcium channel blockers) was avoided prior to ACh provocation testing in all patients. Diagnostic invasive coronary angiography (ICA) was performed to confirm the absence of obstructive coronary artery disease, defined as a visual stenosis of more than 50 % in combination with a measured Resting Full-Cycle Ratio (RFR) ≤ 0.89 and/or Fractional Flow Reserve (FFR) ≤ 0.80.

Prior to ACh provocation testing, a TTP was inserted into the right ventricle via the femoral vein. Activation was contingent upon a prolonged sinus pause (>5 s) or profound bradycardia (<30 bpm for > 30 s). Testing involved incremental doses of ACh in the left (20–200 µg) and right (20–80 µg) coronary arteries manually injected through a 6-French guiding catheter without side holes over 20 s. After each injection, cine-images were obtained to assess the change in coronary diameter through quantitative coronary angiography, as previously described [4]. If coronary artery spasm was induced with reproducible symptoms and ST-segment changes (see definitions below), the provocation test was terminated and concluded to be positive. When spasm was induced and

Table 1
Patient and procedural characteristics.

	ACh Provocation – LCA (n = 102)			ACh Provocation – RCA (n = 94)		
	Backup Pacing (n = 26)	No Backup Pacing (n = 76)	p-value	Backup Pacing (n = 58)	No Backup Pacing (n = 36)	p-value
Age, years	57.5+/-10.9	59.4+/-11.8	0.446	59.9+/-11.2	57.2+/-12.1	0.276
Women	17 (65.4 %)	40 (52.7 %)	0.402	27 (46.5 %)	21 (58.3 %)	0.266
Body mass index, kg/m^2	26.5+/-3.1	27.4+/-3.9	0.272	26.6+/-3.5	28.2+/-4.0	0.057
Coronary Risk Factors						
Hypertension	10 (38.5 %)	40 (52.6 %)	0.254	28 (48.2 %)	17 (47.2 %)	0.921
Hypercholesterolemia	17 (65.3 %)	48 (63.2 %)	1.000	39 (67.2 %)	19 (52.8 %)	0.161
Diabetes	3 (11.5 %)	14 (18.4 %)	0.541	10 (17.2 %)	5 (13.9 %)	0.666
Family History of CAD	10 (38.5 %)	20 (26.3 %)	0.398	17 (29.3 %)	10 (27.8 %)	0.873
Current Smoking	7 (26.9 %)	15 (19.7 %)	0.784	12 (20.1 %)	9 (25 %)	0.626
Previous coronary intervention	4 (15.4 %)	9 (11.8 %)	0.640	8 (13.8 %)	5 (13.9 %)	0.989
Cerebrovascular Accident	1 (3.9 %)	4 (5.3 %)	0.812	4 (6.9 %)	1 (2.8 %)	0.743
Obstructive Sleep Apnoea	2 (7.7 %)	9 (11.8 %)	0.725	5 (8.6 %)	4 (11.1 %)	0.689
Angiographic features						
Minor CAD	14 (53.8 %)	38 (50.0 %)	0.739	28 (48.3 %)	18 (50.0 %)	0.871
Coronary Dominance						
Right dominant	13 (50.0 %)	60 (78.9 %)	0.005	44 (75.8 %)	26 (72.2 %)	0.694
Left dominant	11 (42.3 %)	9 (11.8 %)	0.001	9 (15.5 %)	6 (16.7 %)	0.882
Co-dominant	2 (7.7 %)	8 (10.5 %)	0.970	5 (8.6 %)	2 (11.1 %)	0.884
Conduction Abnormalities						
Sinus bradycardia	7 (26.9 %)	13 (17.1 %)	0.276	15 (25.9 %)	3 (5.2 %)	0.036
Left anterior fascicular block	5 (19.2 %)	10 (13.2 %)	0.450	8 (13.8 %)	4 (11.1 %)	0.705
Left posterior fascicular block	3 (11.5 %)	14 (18.4 %)	0.541	12 (20.7 %)	3 (8.3 %)	0.193
First degree AV block	1 (3.8 %)	5 (6.6 %)	0.609	3 (5.2 %)	2 (5.6 %)	0.695
Second degree AV block	1 (3.8 %)	1 (1.3 %)	0.987	1 (1.7 %)	1 (2.8 %)	0.696
Third degree AV block	0 (0.00 %)	0 (0.00 %)	NA	0 (0.00 %)	0 (0.00 %)	NA
Right bundle branch block	1 (3.8 %)	1 (1.3 %)	0.987	1 (1.7 %)	1 (2.8 %)	0.696
Left bundle branch block	1 (3.8 %)	2 (2.6 %)	0.722	2 (3.4 %)	1 (2.8 %)	0.672

AV = atrioventricular, CAD = coronary artery disease, Values are mean ± or n (%).

did not resolve spontaneously within 3 min following the completion of ACh testing, or in instances of hemodynamic instability, nitroglycerin was administrated.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Sydney Local Health District Human Research Ethics Committee. Written informed consent was obtained from all participants. RR and ASCY had full access to all the study data and took responsibility for their integrity and the data analysis.

2.1. Definitions

Epicardial spasm was defined as a focal or diffuse epicardial coronary diameter reduction > 90 % in response to ACH compared with the relaxed state after intracoronary nitroglycerin, with a reproduction of recognizable symptoms and ischemic ECG changes. Microvascular spasm was diagnosed when there was a reproduction of recognizable symptoms with ischemic ECG changes in the absence of > 90 % epicardial diameter reduction in response to ACh. Ischemic ECG changes were defined as transient ST-segment elevation or depression of > 0.1 mV, or ischemic T-wave changes, in at least two contiguous leads.

2.2. Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, and analyzed using an independent samples *t*-test or Mann-Whitney *U* test, depending on data distribution. Categorical data were presented as count (%) and analysed using chi-squared or Fisher's exact test as appropriate. P-value < 0.05 was considered statistically significant. All analyses were performed using R version 4.2.2. (Vienna, Austria).[5].

3. Results

From December 16, 2021, to October 13th, 2023, this study was conducted across two tertiary referral institutions, including 196 vessels from 102 patients. The patient cohort had a mean age of 58.9+/-11.5 years, with 55.9 % of the participants being women. ACh provocation testing revealed coronary artery spasm in 60.8 % (62/102), with 50 % (51/102) exhibiting epicardial spasm and 10.8 % (11/102) having evidence of microvascular spasm. Among patients with epicardial spasm, a diffuse pattern was observed in 56.9 % (29/51), while 43.1 % (22/51) had focal spasm. Coronary artery spasm was mainly observed in the LCA (80.6 %), versus the RCA (33.9 %). In addition, multi-vessel spasm was evident in 30 patients (29.4 %).

During ACh provocation of the LCA (n = 102), 25.5 % (26/102) of patients required backup pacing. Dose-dependent analysis revealed no pacing requirement at 20 μg, 1 % by 50 μg, 10.8 % by 100 μg, and 25.5 % by 200 μg. When testing the RCA (n = 94), 61.7 % (58/94) required backup pacing, with rates of 20.2 % by 20 μg, 48.9 % by 50 μg, and 61.7 % by 80 μg. In assessing the LCA, patients with left coronary dominance were more likely to require backup pacing (42.3 % vs. 11.8 %, p = 0.001) [Table 1]. During RCA testing, backup pacing was increased in patients with baseline sinus bradycardia versus those without (25.9 % vs. 5.2 %, p = 0.036). Conduction abnormalities on baseline ECG showed no statistically significant difference between groups (p = ns). No patients required conversion to a permanent pacemaker. Atrial fibrillation occurred in 9.8 % (10/102) of patients, of which two required DC cardioversion prior to discharge. The remaining cases of atrial fibrillation spontaneously resolved within 30 min, with no need for treatment or consequent thromboembolic events. No episodes of ventricular tachycardia or fibrillation were observed.

4. Discussion

In this study of patients with ANOCA undergoing ACh provocation testing, the major findings included the following: 1) backup pacing in the LCA was observed in a quarter of patients, particularly at high doses; 2) almost two-thirds of patients required backup pacing during RCA testing; 3) patients with left coronary dominance were more likely to
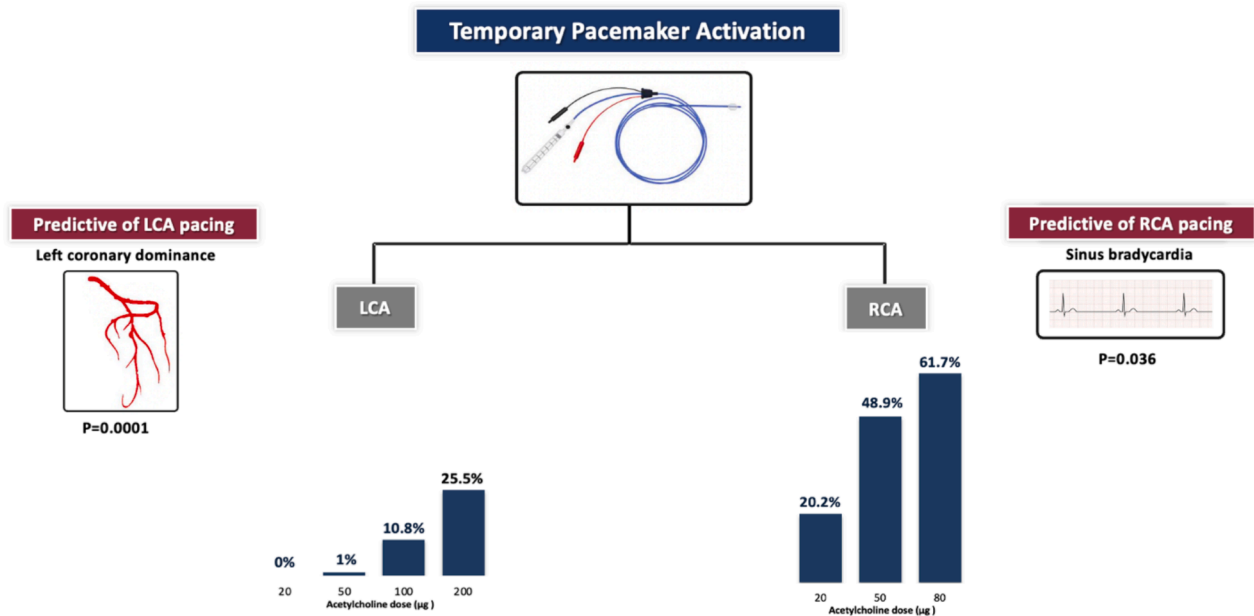
Fig. 1. Predictive factors and acetylcholine dose-dependent relationship for temporary pacemaker activation. LCA= left coronary artery, RCA = right coronary artery.

require backup pacing during LCA testing; 4) patients with baseline sinus bradycardia were more likely to require backup pacing during RCA testing [Fig. 1].

Contrary to conventional belief, which predominantly associates bradyarrhythmias with RCA testing, our data reveals a significant incidence during LCA testing. Coronary anatomical variations may characterise this increased occurrence. Despite most patients having sinoatrial and atrioventricular nodal arteries originating from the RCA, coronary arterial dominance may affect their origin, with some arising from the left circulation[6]. Such anatomical variance can expose these vessels to high doses of ACh and subsequent bradyarrhythmias. While some advocate for upfront TTP insertion, others lean towards its avoidance, contending that transient atrioventricular block typically self-resolves within seconds upon reducing the speed of ACh administration[7]. Although intentionally slowing ACh administration may alleviate transient bradyarrhythmias, it is essential to recognize that such adjustments could potentially compromise diagnostic yield and result in a false negative result when testing for coronary spasm[8].

Whilst acknowledging the importance of our findings, a notable limitation is the use of a fast ACh administration time of 20 s, which inherently predisposes to a higher likelihood of backup pacing. Nevertheless, this practice mirrors protocols employed by the Japanese Circulation Society (JCS)[1], the CorMICA study[2], and the Robert-Bosch-Krankenhaus institution[9].

5. Conclusion

Our study is the first to demonstrate the rates of significant bradycardia or pauses when using fast ACh injections for CFT and provides guidance as to the situations when TTP is required when performing these studies. Our experience supports the use of a prophylactic TTP during ACh provocation testing of the RCA, particularly in patients with baseline sinus bradycardia. For LCA testing, clinicians should consider a TTP in cases of left coronary dominance and with the administration of high ACh dose.

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CRediT authorship contribution statement

Rajan Rehan: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christopher C.Y. Wong:** Writing – review & editing. **James Weaver:** Writing – review & editing. **Pankaj Jain:** Writing – review & editing, Conceptualization. **Mark Adams:** Writing – review & editing, Supervision. **Jennifer A. Tremmel:** Writing – review & editing. **Martin K.C. Ng:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Andy S.C. Yong:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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