Acetylcholine (re)challenge – from Diagnosis to Targeted Therapy

Authors:

Thomas J Ford[1,2,3] MBChB (Hons), PhD, FCSANZ, FRACP, FRCP Edin,

Philo Mikhail[1] MBBS

[1] *Department of Cardiology, Gosford Hospital, Central Coast, NSW 2250, Australia.*

[2] *Faculty of health and medicine, The University of Newcastle, Callaghan NSW 2308, Australia*

[3] *BHF Cardiovascular research Centre, ICAMS, University of Glasgow, UK*

Correspondence:

Address Dr Tom Ford
Department of Cardiology, Gosford Hospital, Central Coast LHD, NSW 2250, Australia.
Phone: +61 2 4320 2358
Email: tom.ford@health.nsw.gov.au

Provocation testing of the coronary circulation was first performed in 1949 almost 10 years before the advent of selective coronary angiography. Stein provoked chest pain with myocardial ischemia in five out of seven angina patients following peripheral administration of ergonovine but in none of the tested control subjects.(1) Variant angina was subsequently linked to coronary spasm demonstrated on coronary angiography in the early 1970s (2,3). An explosion of interest followed in the late 1970s and early 1980s however ergonovine fell out of favor due to its relatively long-half life, induction of hypertension and the potential for prolonged spasm refractory to intracoronary nitrate.(4,5) Acetylcholine (Ach) is now the preferred provocation agent with demonstrated safety in part related to its very short half-life.(6,7) Japanese investigators demonstrating high sensitivity (90%) and specificity (99%) for diagnosing coronary vasospasm.(8) Variant angina ("Prinzmetal's variant angina") is one relatively rare subtype of coronary vasospasm.(9) It is an endotype of vasospastic angina typically associated with focal occlusive proximal vessel spasm causing:

a) nitrate-responsive rest angina, associated with
b) transient ST segment elevation (≥0.1 mV in at least 2 contiguous leads).

The more common form of vasospastic angina is diffuse distal non-occlusive coronary spasm associated with ST depression. Furthermore, there is an additional endotype of abnormal ACh response termed 'microvascular spasm'(10). This is typically manifest following ACh challenge with reproduction of usual angina, transient ST segment deviation without significant epicardial vasoconstriction on angiography (< 90%). Microvascular and epicardial coronary vasospasm frequently co-exist but may respond differently to pharmacotherapy given the distinct coronary compartments involved. Endothelium-derived nitric oxide (NO) is

the main driver of large coronary vessel vasodilation, whereas the small resistance vessels that govern myocardial blood flow are much less responsive to NO donors like glyceryl trinitrate. In the standard ACh challenge, it is not always possible to determine whether microvascular spasm co-exists in patients with epicardial spasm.

Refining the Acetylcholine Challenge

In this study, Seitz et al aimed to determine efficacy of GTN in preventing coronary spasm and assess feasibility of rechallenge. The authors propose that the frequency of co- existing microvascular spasm in patients with epicardial spasm is an important unknown and that re-challenge after GTN may help determine its occurrence. INOCA patients with epicardial or microvascular spasm were enrolled. They performed ACh rechallenge 3 minutes after intracoronary nitroglycerine (GTN) with the aim of assessing the re-inducibility of microvascular and epicardial spasm after GTN. There were no adverse events. The main findings were:

(a) Isolated microvascular spasm is the most prevalent form of abnormal ACh response (58%).
(b) GTN prevented recurrent epicardial spasm in 85% (34/40) patients with epicardial spasm but only 20% of patients with microvascular spasm.
(c) 48% (19/40) patients with epicardial spasm have persistent microvascular spasm during ACh re-challenge despite pre-treatment with GTN.

This study is the first to evaluate the safety and feasibility of ACh re-challenge during the index provocation procedure The concept of ACh-rechallenge is novel and the manuscript is very well illustrated. The paper's central illustration is a wonderful Sankey plot of diagnostic

reclassification revealed by the ACh rechallenge. All centers are experienced with provocation testing particularly those in Stuttgart who have published the largest cohort of angina patients undergoing rapid bolus dose ACh testing in the Western world.(6). The problem of microvascular spasm is under-recognized and clinically relevant. Microvascular spasm is an overlap syndrome which can be a form of microvascular angina but also seen in patients with vasospastic angina. There are three main clinical translations of this important study:

1. Nitrates are much less effective in preventing microvascular spasm (20%) than in epicardial spasm (85%). Angina patients with microvascular spasm are more likely to require alternative antianginal medications.
2. Persistent chest pain in vasospastic angina patients treated with nitrates may be due to ongoing ischemia from microvascular spasm.
3. Lastly but perhaps most importantly, the ACh re-challenge could be repurposed to evaluate patient response to other vasoactive medications given in the cath lab. For example, the ACh rechallenge could be trialled following intracoronary calcium channel blockers or even beta-blockers to assess propensity to constriction.

Despite the study's novelty and strengths, there are some important considerations before wider adoption of ACh rechallenge in practice. The authors themselves point out that the response to pharmacotherapy in the real-world clinical setting may vary considerably from the controlled catheter laboratory environment. Randomized placebo-controlled therapeutic trials evaluating the efficacy of antianginal agents (and non-pharmacological interventions) for patients with epicardial and/or microvascular spasm are needed.

The trial design would have benefitted from a control arm evaluating ACh test and retest with placebo (e.g. normal saline). Indeed, the test – retest reliability of acetylcholine provocation testing has not been studied in a single lab session. Diagnosis of microvascular spasm is more subjective compared to subtotal occlusive epicardial spasm as it depends on self-reporting of angina with ECG changes.(11) In one large cohort, about 28% of patients undergoing ACh testing were inconclusive.(12) The devil is always in the details and the 'grey zone' that typifies coronary physiological assessment is relevant. Measuring coronary blood flow response to ACh or coronary sinus lactate sampling would increase accuracy for diagnosing microvascular spasm at the expense of time, cost, complexity and reduced wider uptake.

Finally, the ACh protocols were not standardized which may in part relate to the registry design with roughly one third of patients recruited retrospectively. ACh administration time and dose varied between the centers and is important determinant of propensity to constriction - 100mcg ACh bolus over 20 seconds delivers a far higher intracoronary ACh concentration than 28.8mcg infusion per minute over 3 minutes.(13)

Future considerations

The increased interest into invasive coronary physiological assessment is promising for patients but also highlights the evidence gap in angina treatment.(14) Over the past decade, over 350 angina review articles have been published however guideline recommendations for treatment are largely empirical and based on historical studies with small cohorts of patients who did not undergo detailed invasive assessment. Understanding of angina

pathophysiology is hampered by lack of mechanistic data and as a result, treatment remains too empiric. What are the contributors to myocardial ischemia for our individual patient, how does this associate with their symptoms and how can we optimize their treatment or better still modify their disease?

Acetylcholine rechallenge is a promising concept that could be a useful clinical and research tool to consider patients' response to vasoactive medications including nitrates, calcium channel blockers or even beta-blockers. This study highlights a simple but elegant way of considering how individual angina patients with coronary spasm may have treatment tailored based on provocation testing response during coronary angiography.

Conflict of Interest Disclosures

TF: Consultant/speaker/honorarium from Abbott Vascular, Boston Scientific, Boehringer Ingelheim, Biotronik, Bio-Excel and Novartis.

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Figure Title

Acetylcholine (re)challenge – Moving from Diagnosis to Targeted Therapy

Figure Legends

The traditional approach (left) to provocative acetylcholine testing allows for diagnosis of epicardial coronary spasm or microvascular spasm without differentiation of endotypes. The ACh rechallenge (right) after administration of GTN might help target therapy by differentiating between GTN responsive and GTN non-responsive epicardial spasm as well as diagnosing mixed epicardial and microvascular coronary spasm. The same patient with vasospastic angina in the Figure (adapted from Seitz et al) has epicardial spasm during challenge but also co-existent microvascular spasm during re-challenge to ACh despite GTN. Further rechallenges after administration of alternative vasodilatory medications may further help direct therapy.