REC: CardioClinics

www.reccardioclinics.org

Editorial

Clinical use of acetylcholine in the cath lab, ready for prime time?

Uso clínico de acetilcolina en la sala de hemodinámica, ¿preparados para el gran momento?

*Andreas Seitz, Peter Ong**

Department of Cardiology, Robert-Bosch-Krankenhaus, Stuttgart, Germany

Acetylcholine (ACh) was first identified in 1915 by Henry Hallett Dale for its actions on heart tissue. It was later confirmed as a neurotransmitter by Otto Loewi and both received the Nobel Prize in Physiology or Medicine for their work in 1936. Furchgott and Zawatzki found that ACh led to vasoconstriction of endothelium-denuded rabbit aorta whereas it led to vasodilatation in vessels with intact endothelium.[1] This led to the discovery that ACh has a direct effect on vascular tone by binding to muscarinic receptors present on vascular endothelium as well as on vascular smooth muscle cells. Physiologically, binding on vascular endothelium releases nitric oxide and leads to vasodilatation and increased flow (Fig. 1). In contrast, binding on vascular smooth muscle cells leads to vasoconstriction and eventually to coronary spasm. Depending on the integrity of the endothelium as well as the reactivity of the vascular smooth muscle cells the net effect can be either vasodilatation or vasoconstriction. Based on these observations and the advent of research in interventional cardiology in the 1980s ACh was found to be a suitable substance for provocation of coronary artery spasm.[2] In addition, it was used for the assessment of endothelial function (mostly in lower doses compared to those used for provocation of coronary spasm). However, due to the emerging field of percutaneous coronary interventions the interest in coronary spasm (and ACh provocation testing), especially in the Western world, declined. In recent years, ACh testing has seen a revival also because several high-ranking studies have shown its utility and safety.[3,4] Moreover, international guidelines for the diagnosis of vasospastic angina are now available[5,6] and the current European Society of Cardiology guideline on management of stable angina has given a class IIa recommendation for the test.[7]

ACh provocation testing is most often applied in patients with angina and unobstructed coronary arteries in whom the cause of the chest pain is unknown. Contraindications represent obstructive pulmonary disease (i.e. severe asthma) as ACh may lead to bronchial spasms as well as chronic kidney disease because the ACh-test requires approximately 20–70 mL additional contrast depending on the result. Due to its short half-life ACh provocation testing can only be performed using an intracoronary injection approach. Thus, the ideal situation to perform ACh testing is immediately after a diagnostic coronary angiogram showing no relevant epicardial stenosis. The procedure can be performed via the diagnostic catheter and usually needs approximately 10–15 min for completion. Many centers start with the left coronary artery (LCA) as 2 vessels (left anterior descending and circumflex arteries) can be assessed at the same time with a single injection of ACh through the catheter in the left main coronary artery. However, other centers start with the right coronary artery (RCA) and only assess the LCA in case of an uneventful test in the RCA.

Interpretation of the ACh test is based on 3 parameters: (a) close monitoring of the patient's symptoms during the test (this requires absence of any sedation); (b) angiographic assessment of epicardial vasoconstriction and spasm (spasm is usually defined as a vasoconstriction >90% compared to the relaxed status after nitroglycerine); and (c) ischemic ECG

* *Corresponding author.*
E-mail address: Peter.Ong@rbk.de (P. Ong).

https://doi.org/10.1016/j.rccl.2019.09.002

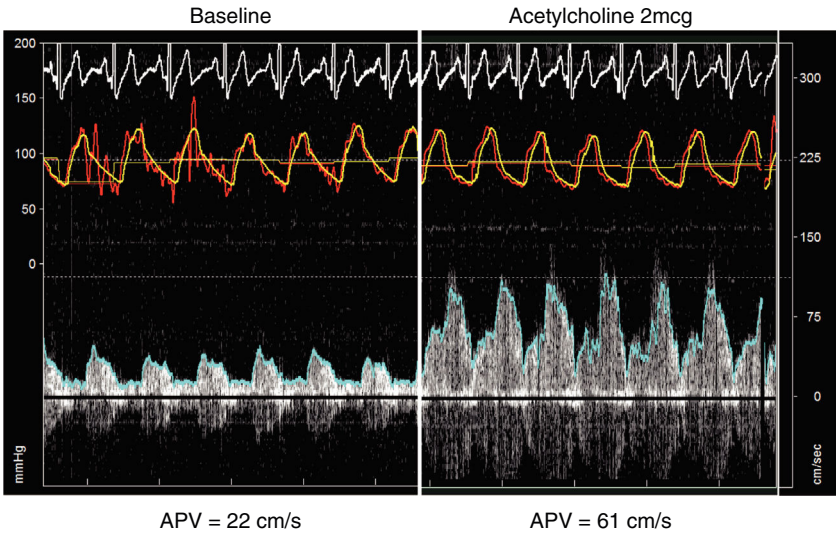

Fig. 1 – Physiological increase in coronary blood flow velocity in response to low-dose acetylcholine (2 μg i.c.) demonstrated by intracoronary pressure-/flow measurements. APV, average peak flow velocity.

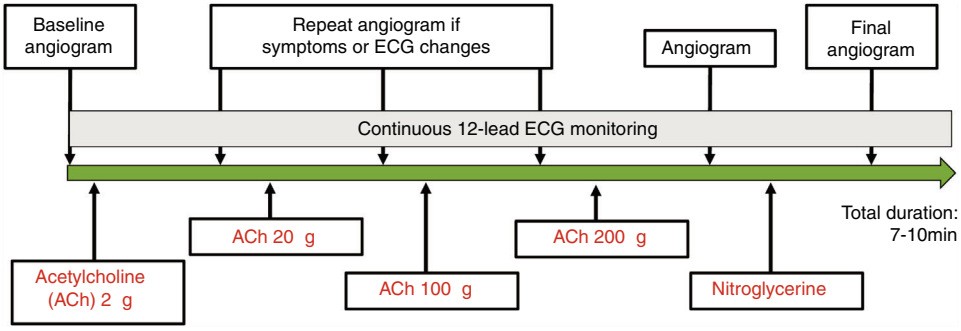

Fig. 2 – Flowchart on how to perform acetylcholine testing. ACh, acetylcholine.

changes during the test (this requires continuous 12-lead ECG monitoring during the test, ideally with radiolucent electrodes). It is important to follow a stepwise approach with increasing doses when performing ACh testing as some patients may develop coronary spasm at very low doses. Usually doses between 2 μg and 200 μg are used for provocation testing in the LCA (e.g. 2 μg, 20 μg, 100 μg and 200 μg).[8] If the RCA is only assessed when the LCA shows no abnormal result, a single dose of 50 μg or 80 μg is applied. After each ACh dose an assessment including a, b and c as mentioned above is made. If the patient develops coronary spasm, the test is stopped and nitroglycerine (usually 200 μg i.c.) is given. In the rare cases where a single dose nitroglycerine does not resolve the spasm, nitroglycerine injections can be repeated with close monitoring of the blood pressure. Another option is to give atropine (e.g. 1 mg i.v.) as this is the antagonist of ACh. Nitroglycerine should be given at the end of the test independent of the result and a final angiogram should be taken (Fig. 2). The outcome of the test can either be a normal test, an abnormal test or an equivocal test. An abnormal test can be either an epicardial or a microvascular spasm. Epicardial spasm is usually defined as reproduction of the patient's angina, ischemic ECG shifts during the test and ≥90% focal or diffuse coronary diameter reduction.[5] Microvascular spasm is defined as ischemic ECG shifts and reproduction of angina in the absence of epicardial spasm[6] (Fig. 3). An equivocal test is defined as the occurrence of only one or two of the abovementioned parameters (e.g. reproduction of angina only without ischemic ECG changes and without demonstrable epicardial spasm). A more detailed description of how to perform the ACh test and how ACh solutions are prepared has been published elsewhere in a video article.[9]

Patients with epicardial spasm can have focal or diffuse spasm or a combination of both types. Studies have shown that prognosis in patients with focal spasm is worse compared to patients with diffuse spasm which is another argument to perform Ach-testing in order to assess the type of spasm.[10] Coronary microvascular spasm has long been neglected as it cannot be seen on conventional coronary angiography. The diagnosis is made indirectly in patients with reproduction of their usual symptoms, presence of ischemic ECG shifts on the 12-lead ECG and absence of epicardial spasm. It can also be fostered by concomitant assessment of myocardial lactate production from the coronary sinus.[11] However, this approach requires additional catheterization of the coronary sinus. In some patients epicardial and microvascular spasm may coexist[12] which has led to the hypothesis that patients with diffuse epicardial

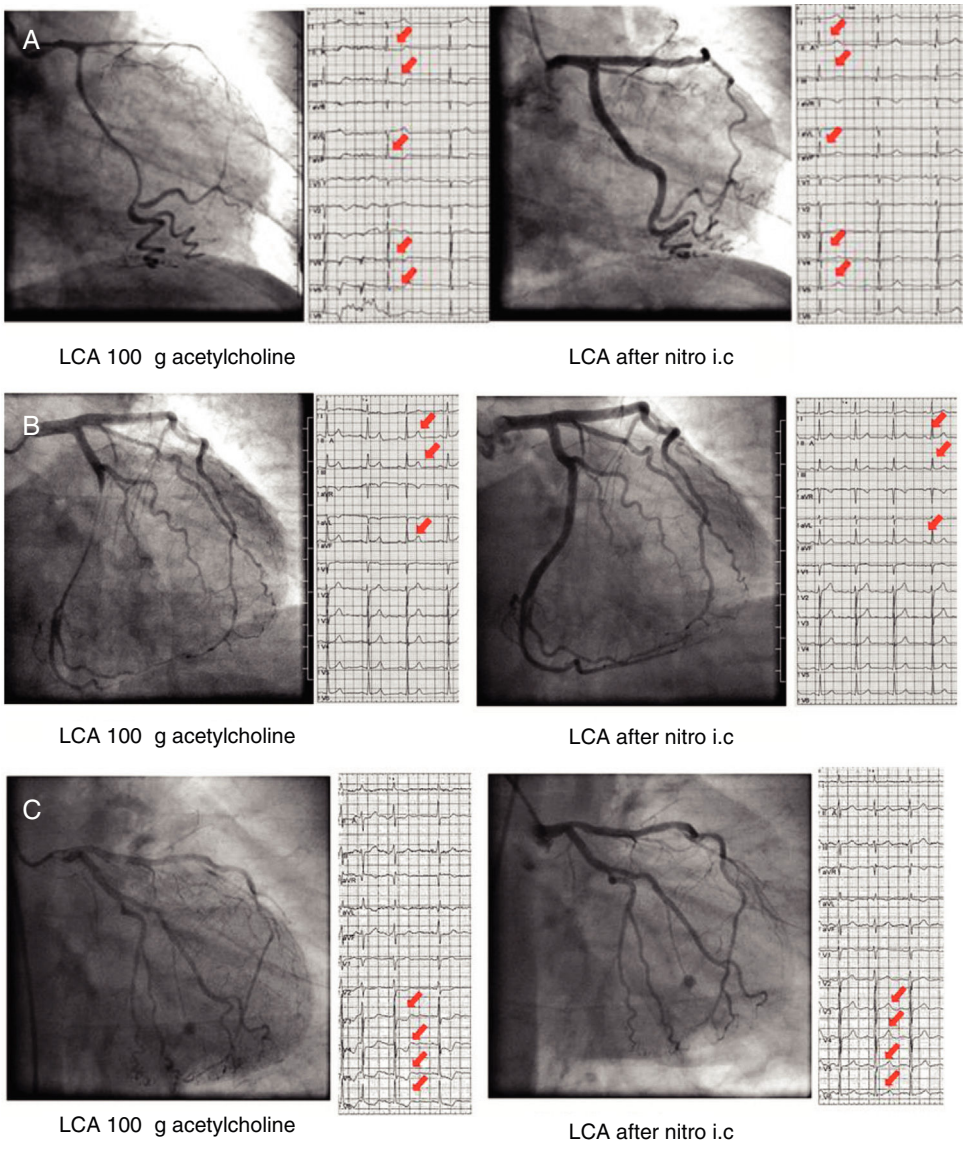

Fig. 3 – Representative cases reproduced with permission from Ong et al.[9] Left coronary artery angiograms and ECGs after 100 μg of acetylcholine (left panels). A, diffuse epicardial spasm, with concomitant ST-segment depression (red arrows). B, Prinzmetal-type epicardial spasm, with concomitant ST-segment elevation. C, coronary microvascular spasm, no epicardial spasm but ST-segment depression (red arrows) and reproduction of the patient's usual symptoms. The latter findings resolved after intracoronary nitroglycerine injection (right panels).

and microvascular spasm share a common pathophysiological background.

Despite convincing data regarding utility and safety, ACh testing is currently only performed in specialized centers worldwide apart from Japan where ACh testing is performed in more than 35 centers throughout the country. The fear of complications represents one major reason why ACh testing is not yet broadly applied in catheterization laboratories worldwide. However, several studies have shown that the rate of complications is comparable to the complication rate associated with a diagnostic coronary angiogram when a stepwise approach as described above is followed.[4,6] Recent data from the CorMicA trial[3] make the ACh provocation test even more attractive. In this study ACh testing was part of a so-called interventional diagnostic procedure (IDP) in patients with angina and unobstructed coronary arteries in whom not only a spasm test but also an assessment of coronary flow reserve using a dedicated wire was performed. Thus, the IDP allows for assessment of vasoconstrictor and vasodilator coronary abnormalities providing comprehensive data on coronary vascular dysfunction in this setting. The CorMicA study demonstrated that a stratified medical therapy based on the result of the IDP compared to standard clinical follow-up leads to improvement of quality of life at follow-up. This underscores the importance of the IDP especially in patients with angina and unobstructed coronary arteries in whom quality of life is often significantly impaired.

Conclusion

Intracoronary ACh provocation testing is an established and safe diagnostic method to assess coronary spasm (epicardial as well as microvascular). It should be part of the diagnostic armamentarium in the state-of-the-art catheterization laboratory and should be especially considered in patients with angina despite unobstructed coronary arteries.

Funding

This work was funded by the Robert Bosch Foundation and the Berthold Leibinger Foundation.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

REFERENCES

1. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*. 1980;288:373–376.
2. Yasue H, Horio Y, Nakamura N, Fujii H, et al. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. *Circulation*. 1986;74:955–963.
3. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol*. 2018;72:2841–2855.
4. Ciliberti G, Seshasai SRK, Ambrosio G, Kaski JC. Safety of intracoronary provocative testing for the diagnosis of coronary artery spasm. *Int J Cardiol*. 2017;244:77–83.
5. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008). *Circ J*. 2010;74:1745–1762.
6. Beltrame JF, Crea F, Kaski JC, et al., Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J*. 2017;38:2565–2568.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal*. 2019, https://doi.org/10.1093/eurheartj/ehz425.
8. Ong P, Athanasiadis A, Borgulya G, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation*. 2014;129:1723–1730.
9. Ong P, Athanasiadis A, Sechtem U. Intracoronary acetylcholine provocation testing for assessment of coronary vasomotor disorders. *J Vis Exp*. 2016, http://dx.doi.org/10.3791/54295.
10. Sato K, Kaikita K, Nakayama N, et al. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. *J Am Heart Assoc*. 2013;2:e000227.
11. Sun H, Mohri M, Shimokawa H, Usui M, Urakami L, Takeshita A. Coronary microvascular spasm causes myocardial ischemia in patients with vasospastic angina. *J Am Coll Cardiol*. 2002;39:847–851.
12. Ong P, Athanasiadis A, Mahrholdt H, Borgulya G, Sechtem U, Kaski JC. Increased coronary vasoconstrictor response to acetylcholine in women with chest pain and normal coronary arteriograms (cardiac syndrome X). *Clin Res Cardiol*. 2012;101:673–681.