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The diagnostic role of pharmacological provocation testing in cardiac electrophysiology: a clinical consensus statement of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy, the Association of European Paediatric and Congenital Cardiology (AEPC), the Paediatric & Congenital Electrophysiology Society (PACES), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS)

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The pharmacological provocation test is a pivotal tool in cardiac electrophysiology for the diagnosis of potential causes of sudden cardiac death, sudden cardiac arrest (SCA), arrhythmias, symptoms, or ECG abnormalities. The 2022 European Society of Cardiology Guidelines for the Treatment of Ventricular Arrhythmias and Prevention of Sudden Cardiac Death offered guidance on provocation testing but did not describe the indications and requirements in depth. This clinical consensus statement, led by the European Heart Rhythm Association and approved by major international stakeholders, aims to advise the general cardiologist and the arrhythmia expert who to test and when, where, and how to do it. The statement focuses on current practice for the diagnosis of subclinical arrhythmia syndromes and the causes of SCA, building upon the recommendations of the Guidelines. We address the sodium channel blocker provocation test for patients suspected of Brugada syndrome as well as the use of epinephrine, isoproterenol, adenosine, ergonovine, and acetylcholine.

Keywords drug challenge • provocation testing • sodium channel blocker test • ajmaline • flecainide • procainamide • pilsicainide • epinephrine • isoproterenol • adenosine • ergonovine • acetylcholine • sudden cardiac death • cardiac arrest • Brugada syndrome • catecholaminergic polymorphic ventricular tachycardia • Wolff-Parkinson-White syndrome • coronary vasospasm • sudden arrhythmic death syndrome

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Introduction

The diagnostic pharmacological provocation test is a pivotal tool in cardiac electrophysiology. It offers a controlled environment to diagnose the potential causes of sudden cardiac death (SCD), sudden cardiac arrest (SCA), arrhythmias, symptoms, or ECG abnormalities. Testing may unmask latent arrhythmia syndromes and ECG patterns, contributing to the understanding of aetiology, triggers, and potential exacerbating factors.[1,2] They may therefore improve diagnostic accuracy for effective clinical management and targeted therapeutic interventions.[3] The 2022 European Society of Cardiology Guidelines for the Treatment of Ventricular Arrhythmias and Prevention of Sudden Cardiac Death (2022 ESC VA SCD) offered guidance on provocation testing but did not describe the indications and requirements in depth.[3] This clinical consensus statement aims to advise the general cardiologist and the arrhythmia expert who to test and when, where, and how to do it, with a focus on current practice for the diagnosis of subclinical arrhythmia syndromes and the causes of SCA, building upon the recommendations of the aforementioned Guidelines.

The sodium channel blocker (SCB) provocation test for patients suspected of Brugada syndrome (BrS) is an archetypal example of such a specialised provocation test. It is conducted under meticulously regulated conditions and is designed to induce and systematically observe ECG changes leading to a potential diagnosis.[3,4] Other diagnostic tests addressed in this document include epinephrine, isoproterenol, adenosine, ergonivine and acetylcholine. These are instrumental in delivering personalized treatment strategies for the patient and often their family.

The expert group was constituted from the ECGen Committee of the European Heart Rhythm Association (EHRA) of the ESC with representation requested from and then nominated by the European Association of Percutaneous Cardiovascular Interventions of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy, the Association of European Paediatric and Congenital Cardiology, the Paediatric & Congenital Electrophysiology Society, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society, and the Latin American Heart Rhythm Society. All co-authors contributed to the document text, approved it, and voted on clinical advice statements over two rounds. Only statements achieving at least 70% agreement were retained and *Table 1* indicates the type and strength of supporting evidence and icons as applied in the advice statements. These categories are not equivalent to the ESC Class of Recommendations or Levels of Evidence.

Generic advice statements

What to do	Strength of evidence
Evaluation of the appropriateness of provocative testing is advised prior to the test, including an evaluation of (relative) contraindications.	>90% agree
Contacting an experienced centre for advice is strongly advised when the appropriateness of testing is uncertain or disputable.	>90% agree
Acquisition of informed consent from the patient (or representative) is advised, covering the clinical indication with associated risks and the benefits of a positive or negative result, as well as potential side effects and potential complications of the test itself.	>90% agree

Table 1 Type and strength of supporting evidence

Type of supporting evidence	Strength of evidence	Icons
Published data[a]	>1 high-quality RCT Meta-analysis or high-quality RCT	
	High-quality RCT > 1 moderate-quality RCT Meta-analysis or moderate-quality RCT High-quality, large observational studies	
Expert opinion[b,c]	Strong consensus >90% of WG supports advice	>90% agree
	Consensus >70% of WG supports advice	>70% agree

[a]The reference for the published data that fulfil the criteria is indicated in the table of advice, if applicable.
[b]Expert opinion also takes into account: randomized, nonrandomized, observational or registry studies with limitations of design or execution, case series, meta-analyses of such studies, physiological or mechanistic studies in human subjects.
[c]For areas of uncertainty strong consensus/consensus that the topic is relevant and important to be addressed by future trials

Sodium channel blocker testing

Literature review

In patients with suspected BrS but without the spontaneous type 1 Brugada pattern, provocation with an SCB drug has been used historically to unmask the ECG pattern (*Figure 1*).[3] However, the proportion exhibiting the drug-induced type 1 Brugada pattern differs widely depending on cohort, indication, and SCB used (*Table 2*). Furthermore, there are concerns regarding the potential for false positives, especially with ajmaline. For instance, a drug-induced type 1 Brugada pattern has been reported in 16% of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), 18% with myotonic dystrophy, 27% with atrioventricular (AV) node re-entrant tachycardia, 16% with accessory pathways as well as 4% of controls.[11,23–25] In a French general population study of subjects with a baseline ECG suspicious for BrS, provocation with ajmaline revealed a type 1 Brugada pattern in 9%,[7] whereas a British study of 100 unrelated healthy Caucasian volunteers, 3% developed the type 1 Brugada pattern with ajmaline.[22] Indeed, the Shanghai consensus statement had downgraded the presence of an isolated SCB-provoked type 1 Brugada pattern from diagnostic of BrS to non-diagnostic, with additional relevant symptoms, genetic results, and/or family history being required to achieve a diagnosis of definite BrS.[26] The 2022 ESC VA SCD Guidelines state that BrS may be considered as a diagnosis when a drug-induced type 1 Brugada pattern is detected in the absence of other heart disease. The strength of recommendation only increases when relevant symptoms (syncope, nocturnal agonal respiration, and/or cardiac arrest) and/or family history (BrS and/or premature autopsy-negative SCD) are present.[3]

The proportion of patients undergoing SCB provocation for the first time and demonstrating the type 1 Brugada pattern ranges from 4% in a mixed cohort receiving procainamide to 54% in families with BrS receiving ajmaline and 60% in a mixed cohort receiving pilsicainide.[9,13,20] Two different approaches to provocation testing have been reported in the assessment of relatives of decedents with sudden death and a negative autopsy and toxicology [sudden arrhythmic death syndrome (SADS)]. One strategy is to offer testing to relatives in whom all other tests have been negative. Papadakis *et al.*[5] and Tadros *et al.*[6] observed that the type 1 Brugada pattern was induced by ajmaline in 20 and 13% of SADS relatives respectively. The other approach from van der Werf *et al.*[16] and Caldwell *et al.*,[15] employed ajmaline testing at the discretion of the clinician when the circumstances of the death of the decedent were suspicious for BrS or if the surviving relative had a type 2 or 3 Brugada ECG pattern (*Figure 2*) at baseline.[3] Lower yields of 5 and 10% respectively were observed. Similarly, in survivors of unexplained cardiac arrest (UCA), Ensam *et al.*[4] and Tadros *et al.*[6] detected the type 1 Brugada pattern after ajmaline testing in 22 and 14%, respectively. In contrast, van der Werf *et al.*,[16] reported a yield of 4% using the same discretionary method. Procainamide testing provoked a Brugada pattern in 6.9%.[21] Studies in clinical cohorts after pilsicainide diagnostic testing have also shown variable results (34–60%), with a greater proportion of the type 1 Brugada pattern evident in those with a suspicious baseline ECG.[8–10]

The evidence also suggests that the proportion of patients exhibiting the type 1 Brugada pattern with ajmaline is consistently higher than all other SCB agents. However, there are limited studies comparing SCB agents and the lack of a gold standard makes the assessment of specificity and sensitivity challenging. Cheung *et al.*[20] observed a

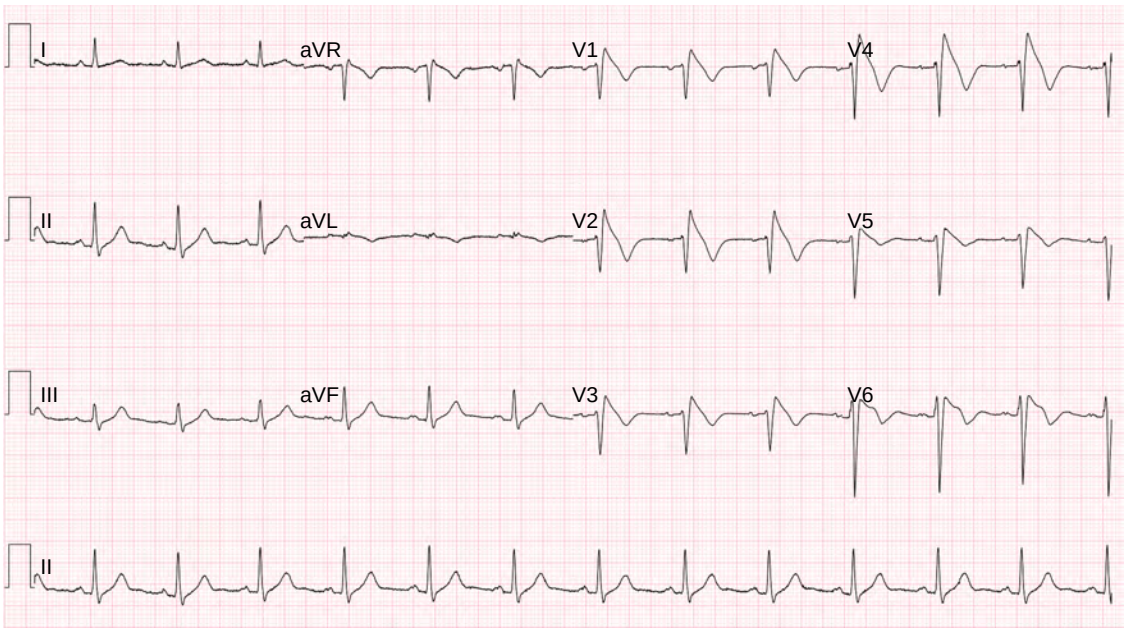


Figure 1 High precordial lead ECG showing the type 1 Brugada pattern in V1 to V5 with coved ST elevation >2 mm at the J point and associated T wave inversion. The type 2 pattern is evident in V6 with more concave ST elevation. V1 and V2 are in the fourth intercostal space, V3 and V4 represent V1 and V2 in the third intercostal space, and V5 and V6 represent V and V2 in the second intercostal space.

significantly greater proportion of the type 1 Brugada pattern in a mixed cohort of patients undergoing provocation with ajmaline compared to a similar population undergoing provocation with procainamide (26 vs. 4% respectively, $P < 0.001$). However, in an analysis of systematically assessed UCA survivors (some of whom were included in the study by Cheung *et al.*[20]), Ensam *et al.*[4] did not find any significant difference in the prevalence of the type 1 Brugada pattern between those investigated with ajmaline and procainamide: 22 vs. 14% respectively ($P = 0.211$). Therasse *et al.*[30] also demonstrated a higher sensitivity of ajmaline (100%) over flecainide (77%) in obligate carriers in BrS families. The only study in which subjects received more than one SCB agent was undertaken by Wolpert *et al.*,[17] where 22 patients with a prior type 1 Brugada pattern following ajmaline provocation, underwent repeat testing with flecainide. Only 68% (15/22) reproduced the type 1 Brugada pattern.

The 2022 ESC VA SCD Guidelines recommend genetic testing for a pathogenic or likely pathogenic (P/LP) variant in the *SCN5A* gene in the proband (index case).[3] Historically, P/LP *SCN5A* variants were used as a gold standard in families to assess the sensitivity and specificity of SCB testing. Brugada *et al.*,[31] observed a 100% yield of the drug-induced type 1 Brugada pattern in 34 patients with a prior history of an intermittently spontaneous type 1 Brugada pattern and 11/11 patients across 3 families with a known *SCN5A* P/LP variant. Within the families investigated, *SCN5A*-negative patients did not display the type 1 Brugada pattern with ajmaline. In contrast, larger cohorts of *SCN5A* patients have identified a drug-induced type 1 Brugada pattern in 75–80%[12,19,32] with ajmaline, and 77% with flecainide.[19] However, a P/LP variant in the *SCN5A* gene is only identified in 20% of patients with BrS.[33,34] Furthermore, incomplete and age-dependent penetrance, variable expression, and genotype-phenotype mismatch are observed in BrS families. Genome-wide association studies have identified common genetic variation associated with BrS, whether diagnosed with provocation testing or not, independent of *SCN5A* status.[35–37] Indeed, genotype-negative relatives with a drug-induced type 1 Brugada pattern have been described in *SCN5A* families and shown to have a higher burden of common genetic variants—a higher polygenic risk score.[33,38] The same polygenic risk score was also associated with a positive response in a mixed population undergoing ajmaline testing.[39] There is, therefore, strong evidence in favour of a complex, polygenic pattern of heritability and the presence of an *SCN5A* P/LP variant in isolation is not an indication to perform an SCB test routinely. Indeed, *SCN5A* patients can exhibit an increased risk of ventricular arrhythmias (VA) during the SCB test.[40] Testing has, however, been undertaken in selected patients with P/LP *SCN5A* variants by the consensus statement co-authors to assess variant pathogenicity, segregation of phenotype, prognosis, and response to antiarrhythmic medications.

Another key determinant of the response to provocation is the baseline ECG. Baseline QRS duration, PR interval, ST elevation, and the presence of a type 2 or 3 Brugada ECG pattern are consistent predictors of response to SCB provocation. However, while the prevalence of BrS is estimated to be 1/2000, a type 2 or 3 Brugada ECG pattern can be observed in the general population at a relatively high prevalence (up to 2% in some studies).[41] Nonetheless, care should be taken to accurately distinguish a type 2 or 3 Brugada ECG pattern from a benign incomplete right bundle branch block (RBBB) ECG pattern that is unlikely to implicate BrS. Several methods focussing on the ß angle of the R′ and ST segment have been proposed (*Figure 2*).[27,29,42–46]

Administration of flecainide has been associated with a type 1 Brugada pattern in 3% of an Italian cohort of patients presenting with atrial fibrillation although less than 1% actually developed a spontaneous type 1 Brugada pattern.[47] In under-45-year olds presenting with atrial fibrillation, 17% had a type 1 Brugada pattern with ajmaline, a minority of whom had other features supportive of BrS.[48] The specificity of this finding for BrS is uncertain.

Sodium channel blocker provocation, particularly with Ajmaline, serves as an essential tool for guiding catheter ablation in symptomatic BrS patients thereby improving long-term outcomes.[49] It

Table 2 Studies reporting series of patients and heathy subjects/controls undergoing SCB testing and the proportion with the type 1 Brugada pattern

Authors	SCB agent	Clinical setting	Proportion with a type 1 Brugada pattern
Papadakis *et al.*[5]	Ajmaline	SADS relatives	136/670 (20%)
Tadros *et al.*[6]	Ajmaline	UCA survivors	11/54 (20%)
		SADS relatives	78/583 (13.4%)
Hermida *et al.*[7]	Ajmaline	Healthy subjects with suspicious ECGs	5/55 (9%)
Nakazawa *et al.*[8]	Pilsicainide	Mixed cohort with suspicious ECG	29/55 (53%)
Shimeno *et al.*[9]	Pilsicainide	Mixed cohort with suspicious ECG	35/58 (60%)
Ueyama *et al.*[10]	Pilsicainide	Mixed cohort	55/161 (34%)
Hasdemir *et al.*[11]	Ajmaline	Subjects with AVNRT	26/96 (27%)
		Asymptomatic controls	3/66 (4.5%)
Veltmann *et al.*[12]	Ajmaline	Mixed cohort	264/677 (39%)
Therasse *et al.*[13]	Ajmaline	Mixed cohort	81/272 (54%)
Quenin *et al.*[14]	Ajmaline	Relatives of unexplained sudden deaths without autopsy	17/94 (18%)
Caldwell *et al.*[15]	Ajmaline	SADS relatives	2/20 (10%)
van der Werff *et al.*[16]	Ajmaline	UCA survivors	3/69 (4%)
		SADS relatives	7/140 (5%)
Wolpert *et al.*[17]	Flecainide	Subjects with prior drug-induced type 1 Brugada pattern with Ajmaline	15/22 (68%)
Shen *et al.*[18]	Flecainide	Suspicious ECG in Singaporean Males	53/214 (25%)
Meregalli *et al.*[19]	Flecainide	Mixed cohort	64/160 (40%)
Cheung *et al.*[a20]	Procainamide	Mixed cohort	4/94 (4%)
	Ajmaline		86/331 (26%)
Somani *et al.*[a21]	Procainamide	UCA survivors and SADS relatives	12/174 (7%)
Ensam *et al.*[a4]	Ajmaline	UCA survivors	11/51 (22%)
	Procainamide		10/70 (14%)
Ensam *et al.*[22]	Ajmaline	Healthy subjects	3/100 (3%)
Peters *et al.*[23]	Ajmaline	Patients with ARVC	9/55 (16%)
Maury *et al.*[24]	Ajmaline	Patients with myotonic dystrophy and baseline ECG abnormalities	8/44 (18%)
	Flecainide		

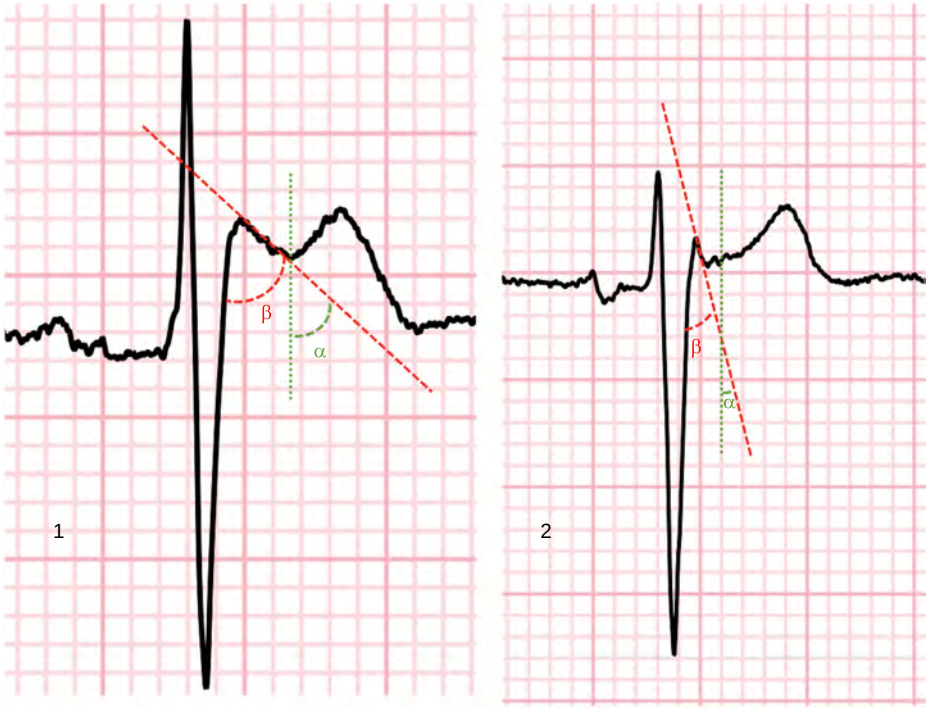
AVNRT, atrioventricular nodal re-entrant tachycardia; SADS, sudden arrhythmic death syndrome; SCB, sodium channel blocker; UCA, unexplained cardiac arrest.
[a]Overlapping cohorts.

increases by twofold the substrate size to be targeted for epicardial ablation.[50–52]

Alternative scenarios and approaches that provoke the type 1 Brugada pattern have been described. The fever-induced type 1 Brugada pattern has been observed in 2% of consecutive patients presenting to an emergency department with a febrile illness, compared to just 0.1% in those without fever.[53] A spontaneous type 1 Brugada pattern has been identified during ambulatory high precordial 12-lead ECG monitoring in 13–34% of patients with a prior drug-induced type 1 Brugada pattern but no previous resting ECG evidence of a spontaneous type 1 Brugada pattern.[28,54,55] The development of the type 1 Brugada pattern during the recovery phase of an exercise stress test (EST) has been reported[56–58] but its utility in the systematic assessment of patients suspected of BrS is uncertain. Furthermore, in the setting of catheter ablation, enhancement of the epicardial substrate with the instillation of warm water has been described as an alternative to SCB provocation and may reduce the risk of refractory ventricular fibrillation and haemodynamic instability.[59]

Methods

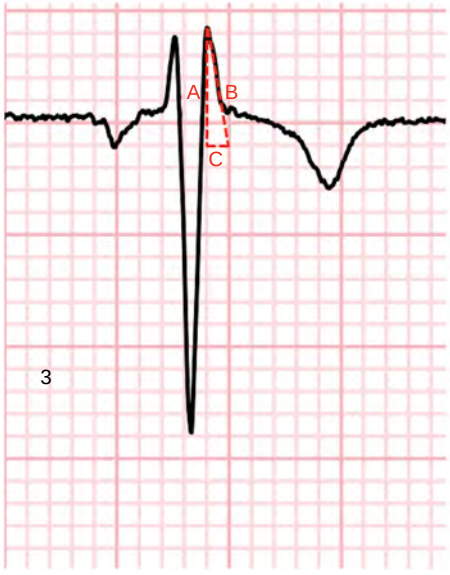
Protocols for SCB provocation testing differ between centres.[5,13,20,31,60–64] Protocols will depend on the availability of an SCB agent: either ajmaline, flecainide, pilsicainide, or procainamide (*Table 3*). Oral flecainide has even been used when other options are unavailable.[72] Ajmaline, when available, is preferred due to its short half-life and thus better safety profile, and partly its more potent effect.[17] Ventricular arrhythmia may occur during the test regardless of the SCB and includes premature ventricular contractions, non-sustained or sustained monomorphic or polymorphic ventricular tachycardia (VT), and ventricular fibrillation.[40,64,73–75] Ventricular arrhythmia is more often seen in patients with pre-existing prolonged conduction intervals and patients with *SCN5A* pathogenic variants. Transient complete AV block with ventricular asystole can also be seen, especially in older patients with pre-existing prolonged conduction intervals.[40] Therefore patients with pre-existing first-degree AV block and/or conduction abnormalities may benefit from performing testing in the cardiac catheter laboratory with temporary pacing and haemodynamic support available.



Base of triangle method at 5mm

A = 5mm from peak of R wave
B = downslope from R wave
C = base of triangle

Base of triangle >3.5mm (140ms) suggestive of underlying BRS



Triangle base:height ratio

E = height - from peak or R wave to isoelectric line
F = downslope from R wave
G = base of triangle at isoelectric line

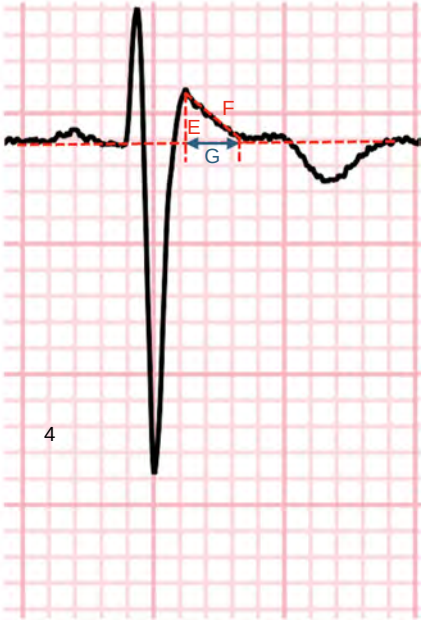


Figure 2 Type 2 and type 3 ECG patterns (panels 1 and 4, respectively) and different methods for measurement. The alpha and beta angles[27] are illustrated in panels 1 and 2, distinguishing between a non-diagnostic type 2 Brugada pattern (panel 1) and benign incomplete RBBB (panel 2). Both angles are greater in patients with likely BrS than in incomplete RBBB and are therefore more likely to be associated with the type 1 Brugada pattern following SCB testing (cut-offs for a positive result: $\alpha > 50°$, sensitivity 71% and specificity 79%; $\beta > 58°$, sensitivity 79% and specificity 83%). The base of the triangle method provides an alternative assessment of the β angle. In panel 3, the base of triangle (C) at 5 mm (0.5 mV—A) from the peak of the R wave is associated with induction of the type 1 Brugada pattern [cut-off C >140 ms (>3.5 mm) sensitivity 81% and specificity 82%].[28] Similarly, the duration of the base at the isoelectric line (G) illustrated in panel 4 associates with the type 1 Brugada pattern [cut-off G >60 ms (>1.5 mm) 95% sensitivity and 78% specificity] as does the triangle base (G):height (E) ratio.[29] BrS, Brugada syndrome; RBBB, right bundle branch block; SCB, sodium channel blocker.

Table 3 Different sodium channel blocker agents utilised in sodium channel blocker testing

Generic name	Drug class	Half-life	Comments	References
Ajmaline	1A	~5 min	Maximal dose 1 mg/kg up to 100 mg, infused continuously over 5–10 min or in boluses 10 mg/min	5,17,61,65,66
Flecainide	1C	~13–16 h	Maximal dose 2 mg/kg up to 150 mg, either continuously over 10 min or in boluses of 10 mg/min	17,19,31,67
Pilsicainide	1C	~3–6 h	Maximal dose 1 mg/kg, infused continuously over 5–10 min or in boluses 10 mg/min	62,68–70
Procainamide	1A	~3–5 h	Maximal dose 15–18 mg/kg or 1000 mg, either continuously over 5–20 min or in boluses achieving a rate of 100 mg/min	20,63,65,71

Advice statements for sodium channel blocker testing: methods and safety

What to do	Strength of evidence
An institutional SCB test protocol is advised to ensure appropriate organisational aspects and standardisation. This includes minimum safety requirements, location, lead placement, and criteria for when to stop test.	>90% agree
It is advised that the testing location is always in-hospital and is adjusted in case of presumed higher risk for adverse events (e.g. testing in the cardiac catheterisation laboratory in the case of pre-existent AV conduction disturbances, presence of an *SCN5A* variant, etc.).	>90% agree
Minimum safety requirements for an SCB test include as follows: • Suitably trained personnel. • 12-Lead ECG recording system. • Equipment to observe vital signs. • Basic and advanced life support and defibrillator on standby. • Availability of isoproterenol in case of arrhythmia.	>90% agree
It is advised that during the SCB test, ECG leads are recorded in higher right precordial positions (V1 and V2 in the second and/or third intercostal spaces).	
Ajmaline is preferred over flecainide when available for SCB testing.	>90% agree
During the SCB test, acquisition of ECGs is advised to be continuous, or at least every 30–60 s, and the test terminated when stopping criteria are met.	>90% agree

Continued

Continued

What to do	Strength of evidence
The criteria for stopping drug infusion during an SCB test are as follows: • Administration of the maximum dose according to body weight, • Type 1 Brugada ECG pattern, • QRS widening greater than 30% from baseline, • Ventricular arrhythmia more than isolated premature ventricular complexes, • Profound bradycardia or sinus arrest, • Type II second-degree or third-degree heart block, and/or • Allergic reaction.	>90% agree

What not to do	Strength of evidence
An SCB test is not advised in a patient with type 2 second-degree or third-degree heart block, severe sinus node dysfunction, or significant structural heart disease.	>90% agree
An SCB test is not advised in a patient with fever.	>90% agree

Preparation

It is preferred that SCB provocation testing is performed in experienced centres by experienced staff. The indications and (relative) contraindications and the rare risk of an adverse reaction will have been discussed and the patient and the team adequately informed. The patient will be informed about the procedure, its duration, and potential side effects. Most centres use their local general anaesthesia fasting protocol. Other potentially interacting drugs should have been stopped or evaluated for relevance.[76–78] The body weight of the patient determines the maximal dose

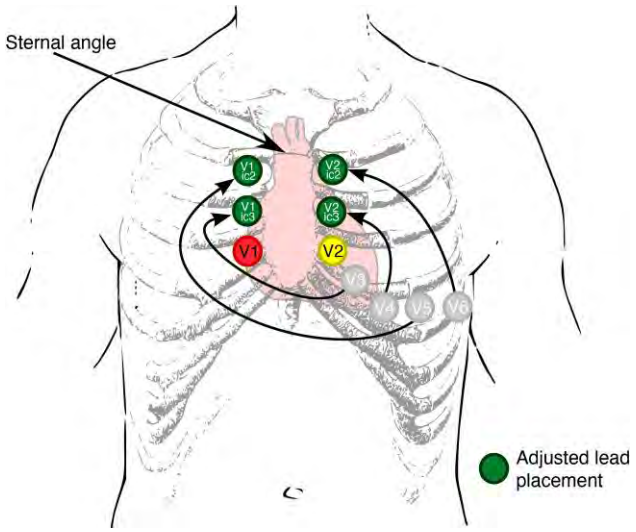


Figure 3 An example of adjusted high precordial lead placement of V1 and V2 during sodium channel provocation testing. All precordial leads are positioned over the right precordial fourth, third, and second intercostal (ic) spaces. This allows continuous assessment of all leads while the QRS duration can be monitored in the limb leads.

and baseline laboratory blood test results are usually required, such as liver & kidney function in the rare event of a cholestatic hepatitis.[79] Drug preparation may also differ as well as the location where the provocation tests are performed. Minimum requirements are a 12-lead ECG recording system, blood pressure monitor, and personnel and equipment for basic and advanced life support, a defibrillator, as well as isoproterenol in case of VA. Particularly important is the lead placement, with additional coverage of the right ventricular outflow tract (RVOT) in the sternal and/or parasternal second and third intercostal spaces (also known as high precordial leads), to enhance sensitivity,[61,80–84] without altering specificity. Different configurations have been used by different centres with *Figure 3* showing a commonly used 12-lead ECG lead rearrangement. ECG machines with 15 or 16 leads offer greater flexibility for lead placement and the recording of all high precordial and standard leads simultaneously.

Performing the sodium channel blocker provocation test

The SCB test is performed by administration of the SCB of choice by either continuous infusion over 5–20 min or intermittent administration of boluses (*Table 2*). ECGs are recorded, often continuously, and evaluated regularly, at least every minute. Indicative signs of SCB infusion are a degree of PR interval prolongation and QRS widening. The test is terminated when the target dose is administered, or prematurely once a diagnostic type 1 Brugada pattern is observed in the standard or high precordial leads. The development of a VA (when more than isolated premature ventricular complexes are seen), significant QRS widening (generally regarded as ≥30% above baseline, although in many experienced centres up to a 50% increase is accepted),[13,61,85] significant AV conduction abnormalities (e.g. total AV block), extreme patient symptoms or other issues (e.g. allergic reaction) are also indications to prematurely terminate the test. However, for ajmaline, flushing or facial numbness is common, and patients should be warned of these symptoms. Furthermore, rapid infusion rates may increase the risk of adverse events, QRS prolongation may continue after termination of the infusion due to ongoing drug distribution, and additional attention given to on-time termination.[74,85] If VA causing haemodynamic compromise occur, intravenous isoproterenol can be administered alongside standard resuscitation techniques.

In the case of substrate ablation for symptomatic BrS patients, the test might be repeatedly performed and is the only circumstance where administration of SCB is appropriate in the setting of a spontaneous type 1 Brugada pattern.[49,51,52]

After the test

After termination of the test, ECGs are recorded until the QRS duration and PR interval return to baseline and the type 1 Brugada pattern, if seen, resolves. Observation time after the test depends on the half-life of the drug with ajmaline being the shortest. Some centres wait a minimum of one hour after an uncomplicated test, and longer if significant arrhythmias occurred during the test or ECG changes persist. The test result should be discussed with the patient and if positive appropriate measures taken such as instruction on avoidance of certain drugs and treatment of fever, blood sampling for DNA extraction and genetic testing, initiation of outpatient follow-up and cascade screening of relatives.

Interpretation

An unequivocal type 1 Brugada pattern is required for a positive result. This is characterized by J point elevation of at least 0.2 mV with coved ST elevation and T wave inversion. At least one ECG lead is required to demonstrate the type 1 Brugada pattern in standard or high positions (*Figure 3*): V1 and V2 in the second, third, and fourth intercostal spaces.[3]

To measure the J point elevation, use the isoelectric line (PQ and TP segments excluding U waves) as the baseline. The J point is defined as the end of the QRS complex, which can be identified most clearly in the limb lead, or if not feasible, in the lateral leads (i.e. lead II or V6) (*Figure 4*).[61] Measure vertically from the isoelectric line to the highest point of the J point in precordial leads V1 and V2, as well as those in high precordial position. Note that the J-point elevation is not always the same as the highest point of the ECG complex (*Figure 4*). J point elevation must be at least 0.2 mV (usually 2 mm on a standard ECG). The coved ST segment elevation should not include a horizontal line, rather the entire ST segment should have a continuous decline without concavity into a negative T wave below the isoelectric point. At least two beats on the ECG must fulfil the criteria. If the test is stopped prematurely and the type 1 Brugada pattern is not present, the test is considered 'negative' or non-informative.

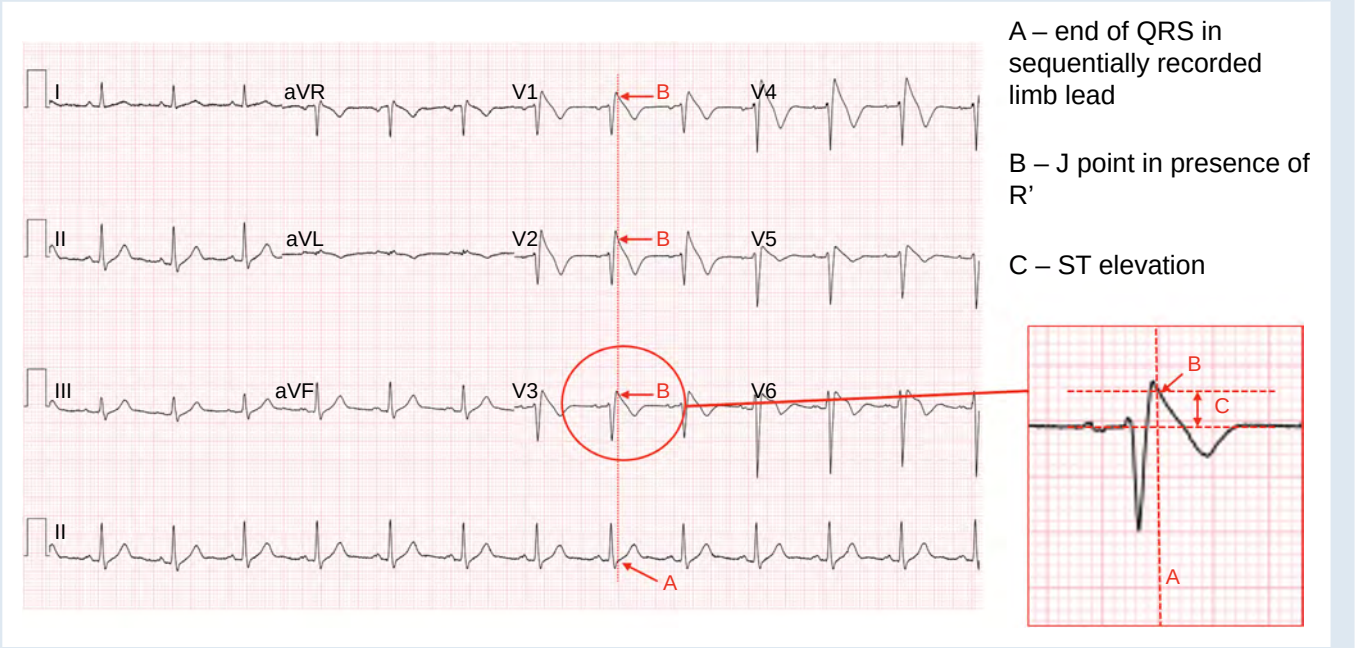


Figure 4 Identifying the J point (defined as the end of the QRS) can be challenging in the presence of R'. The end of the QRS can be identified in a sequentially recorded limb lead. The intersect (B) identifies the J point and C is the degree of ST elevation, from the isoelectric line (PQ and TP segments excluding any U wave) and J point. V1 and V2—fourth intercostal space, V3 and V4—third intercostal space, and V5 and V6—second intercostal space.[43]

Advice statements for sodium channel blocker testing: interpretation

Advice	Strength of evidence
A type 1 Brugada pattern requires J point elevation of at least 0.2 mV with coved ST elevation and T wave inversion, the timing of the J point (end of the QRS) being best measured in a limb lead, or if unavailable, a lateral chest lead.	>90% agree
A positive SCB test requires a type 1 Brugada pattern in at least one right precordial ECG lead consisting of V1 and V2 positioned in the standard (intercostal space 4) or high (intercostal space 2 or 3) precordial lead positions.	>90% agree

Clinical scenarios

Unexplained cardiac arrest survivors

In survivors of SCA due to ventricular fibrillation and patients with documented polymorphic VT, the 2022 ESC VA SCD Guidelines recommend that attempts should be made to exclude an alternative cause for the presentation prior to considering SCB testing.[3] A minimum range of staged tests is required including repeat post-arrest 12 lead and high precordial lead ECGs, transthoracic echocardiography, a coronary assessment, either with CT or invasively, an exercise stress ECG[4,21,86] and where available a contrast-enhanced cardiac MRI to exclude cardiomyopathy, myocarditis or cardiac sarcoid. If there is a suspicion of coronary artery spasm (CAS), then provocation with acetylcholine or ergonovine may be employed (see below). Thus, following a comprehensive assessment, SCB provocation will proceed if an alternative cause cannot be identified with certainty.

Family screening

Familial screening should be limited in the first instance to first-degree relatives of patients with BrS or decedents with possible BrS-related sudden death, diagnosed according to the Shanghai consensus statement and the 2022 ESC VA SCD Guidelines.[3,26] The different potential scenarios are laid out below.

Following a diagnosis of definite Brugada syndrome in a first-degree relative

In first-degree relatives of index cases with a definite diagnosis of BrS, SCB provocation testing is advised. The utility of ambulatory ECG for detecting a dynamic type 1 Brugada pattern has been described previously and may be employed prior to SCB provocation but is not routinely available in all expert centres.[54]

If genetic testing has been undertaken and no P/LP *SCN5A* variant is detected in the proband, then SCB provocation testing in a relative in the absence of symptoms or a suggestive but not diagnostic ECG (i.e. type 2 or 3 ECG pattern) should be offered.[3] This will take into consideration the low risk of arrhythmic events in asymptomatic relatives with a concealed type 1 Brugada pattern and that the 2022 ESC VA SCD Guidelines do not support ICD implantation.[3] It must also address the utility of advice including avoidance of Brugada-triggering drugs (www.brugadadrugs.org),[3,76] treatment of fever, avoidance of excessive alcohol, and emergency management of syncope including consideration for cardiac device therapy.[3,87] The benefit of exclusion of a diagnosis may also be important for the individual. Thus, shared decision-making is encouraged (*Figure 5*).

In families with a definitive BrS-causing P/LP *SCN5A* variant, screening of relatives should be performed using genetic testing as recommended in the 2022 ESC VA SCD Guidelines.[3,88] Relatives who do not carry the

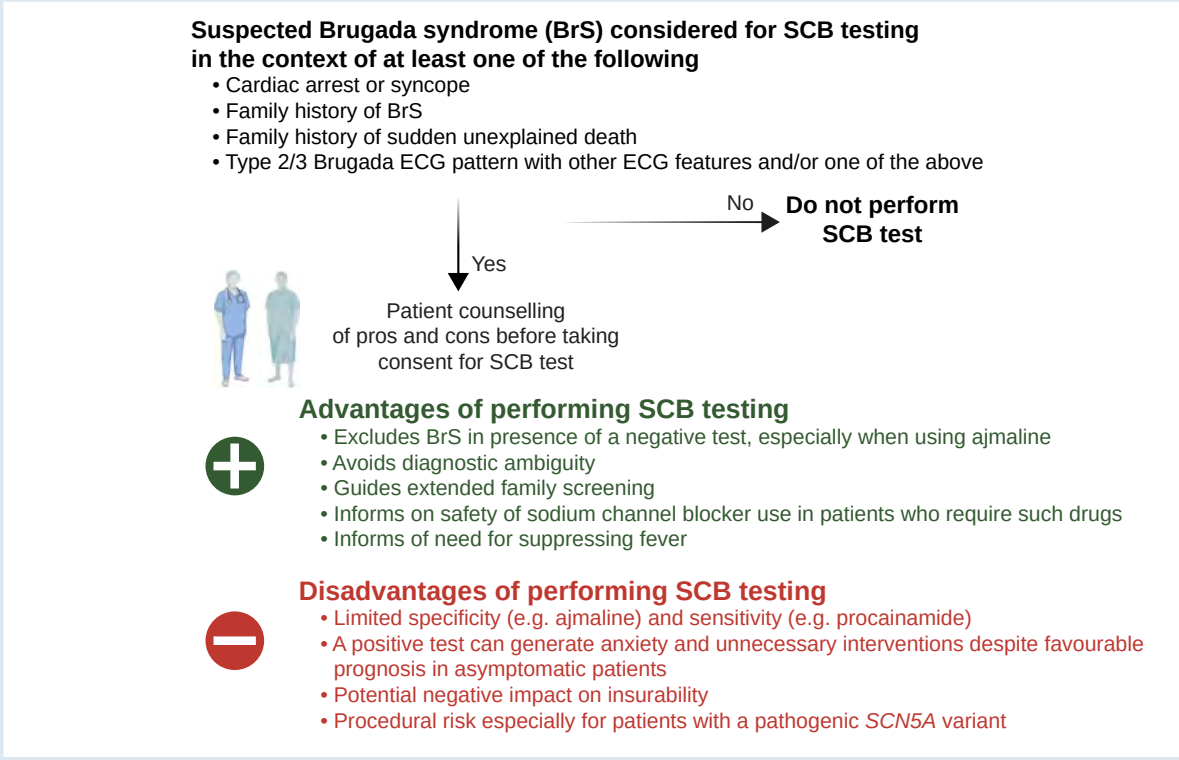


Figure 5 A schema for supporting shared decision-making for SCB testing for suspected Brugada syndrome. SCB, sodium channel blocker.

familial *SCN5A* variant can be reassured unless they are symptomatic or have an abnormal resting ECG. Genotype-negative relatives may still develop a type 1 Brugada pattern after SCB provocation testing, the implications of which are uncertain, although presumably avoidance of sodium channel-blocking drugs would be advisable. Patients with the familial *SCN5A* variant are generally managed similarly to patients with BrS including the aforementioned lifestyle advice. While the presence of a spontaneous type 1 Brugada pattern is an independent predictor of arrhythmic risk,[37] it remains unclear whether a drug-induced type 1 Brugada pattern confers increased risk in patients with P/LP *SCN5A* variants. Furthermore, provocation testing in patients with *SCN5A* variants can result in arrhythmic complications including life-threatening ventricular tachyarrhythmia.[13,74,89–91] Therefore, in general, SCB testing is best not performed in carriers of P/LP *SCN5A* variants, for diagnostic purposes. Nevertheless, provocative testing can still be undertaken in expert centres for selected cases where there is a clear clinical rationale including the assessment of *SCN5A* variants of uncertain significance or *SCN5A* variants with complex biophysical/clinical phenotypes (i.e. overlap syndromes) when the test result is expected to impact the management of the patient or their family.

Following an unexplained sudden death

The yield following SCB provocation in subjects with a family history of sudden unexplained death or autopsy-negative death (SADS) is well described[5] but shows variability across similar cohorts (*Table 2*). Potential factors associated with this variability have been described previously and errors can occur if alternate diagnoses are not excluded at autopsy or on evaluation.[6] To identify those with the highest likelihood of having a BrS following a SADS death in a relative, the age of the deceased, the mode of death, antemortem symptoms, and/or antemortem ECG recordings, should be scrutinised where possible. According to the 2022 ESC VA SCD Guidelines, relatives of the deceased should undergo comprehensive stepwise evaluation prior to SCB provocation, including baseline standard 12-lead and high right precordial lead ECGs, transthoracic echocardiography, and an exercise stress ECG.[3,5] In those with features suggestive of a possible underlying cardiomyopathy a cardiac MRI may be appropriate. Following the exclusion of other causes and appropriate counselling on the implications of a positive result (*Figure 5*), SCB provocation is advisable in a first-degree relative to a SADS victim who dies in circumstances that may be attributed to BrS (i.e. in sleep or at rest, during fever and/or with a documented type 1 Brugada pattern or suspicious ECG prior to death). However, some cases of symptomatic BrS and SCD likely to be due to BrS have symptoms during activity and will not have a spontaneous type 1 Brugada pattern prior to death.[92,93] Testing may therefore also be appropriate more generally in first-degree relatives in SADS families as well as in first-degree relatives of decedents with a premature unexplained sudden death in whom a postmortem was not available, was unreliable and the cause of death remains unknown. However, the potential that a false positive result may obscure the true cause is increased even following comprehensive assessment and exclusion of alternative causes and has to be judged carefully.

An isolated drug or fever-induced type 1 Brugada pattern in a relative

Patients with a drug or fever-induced type 1 Brugada pattern and without other relevant symptoms, clinical or familial history do not fulfil a definite diagnosis of BrS according to current consensus statement and guidelines.[3,26] It is therefore uncertain whether it is advisable that asymptomatic relatives of these patients undergo SCB provocation, as the implication of a positive result would be unclear and may represent polygenic heritability of the response to SCB drugs.[39]

Type 2 or 3 Brugada ECG pattern in asymptomatic individuals

Care must be taken to distinguish a type 2 or 3 Brugada ECG pattern from a benign partial RBBB pattern (*Figures 2* and *6*).[27,43,44,94] Many

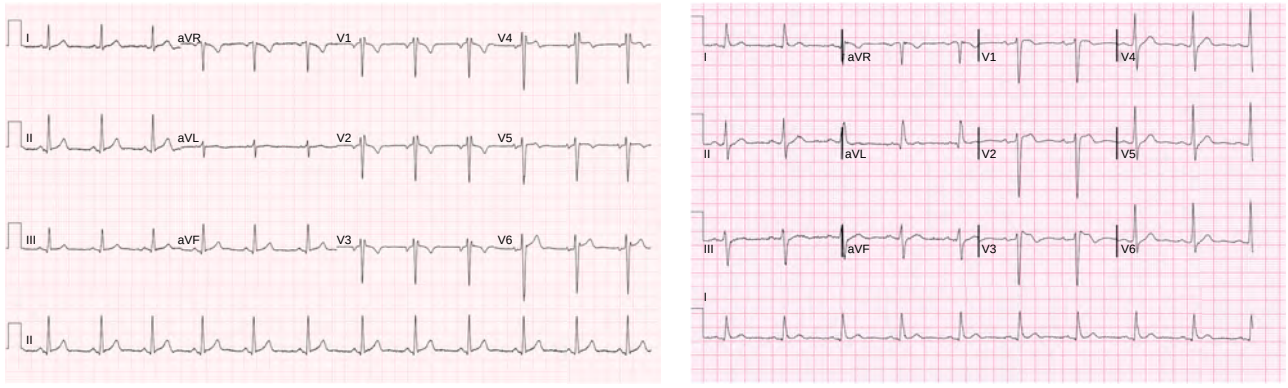


Figure 6 The left panel is a high precordial lead ECG displaying benign partial right bundle branch block with a sharp R′ without J point elevation in leads V1–V5 and a normal axis. BrS is unlikely and SCB testing difficult to justify in the absence of other supportive features. A standard 12-lead ECG is shown on the right panel displaying a type 2 pattern in lead V3. The R′ is broad and there is marked J point elevation >2 mm with a coved ST segment and leftward QRS axis deviation. BrS, Brugada syndrome; SCB, sodium channel blocker.

clinicians have systematically performed SCB testing in patients with a type 2 or 3 pattern to confirm or rule-out BrS. Such systematic SCB provocation testing is debatable in the context of significant concerns regarding the specificity of SCB testing as outlined above. In light of these data, the diagnosis of BrS in patients with a drug-induced type 1 Brugada pattern now requires additional evidence from the patient clinical history, family history, or genetic testing according to consensus statements and ESC guidelines.[3,26,88] In this context, performing provocative testing for asymptomatic patients with a type 2 or 3 Brugada ECG pattern and without a family history supportive of the condition is generally not of clinical utility and is not advised as a routine. However, if there are other ECG features supportive of the condition such as exaggerated saddleback ST elevation in the high precordial leads or leftward axis deviation (*Figure 6*), then SCB provocation may still be considered.

Documented type 1 Brugada syndrome pattern

There is insufficient evidence that an SCB challenge is useful for risk stratification in patients with an established diagnosis of BrS. As such, patients that already have documented type 1 Brugada pattern should generally not be tested according to the 2022 ESC VA SCD Guidelines.[3] There are exceptional circumstances however that could merit consideration for SCB provocation in these patients. First, patients who have a documented type 1 pattern in the context of a BrS phenocopy and in whom there is suspicion for BrS may undergo provocative testing in the absence of the phenocopy trigger. Such phenocopies include severe hyperkalaemia, myocardial infarction involving the conus arterial branch, sodium channel blocker intoxication.[95] Second, patients with BrS referred for catheter or surgical ablation of VA substrate may benefit from SCB provocation for substrate mapping. A recent multi-centre study of BrS patients who underwent arrhythmia ablation showed that, following ablation, patients without a type 1 pattern had a lower risk of recurrence compared to patients with persistent type 1 Brugada pattern (with and without sodium channel blockade).[49]

Early onset atrial fibrillation

Data on SCB testing in young adults with atrial fibrillation are limited.[47,48] In the absence of family history or other diagnostic features of BrS, the implications are uncertain. Nonetheless, if such patients are started on an SCB to treat atrial fibrillation it is reasonable to review subsequent ECGs for a type 1 Brugada ECG pattern.

Advice statements for sodium channel blocker testing: clinical scenarios

When to perform SCB provocation	Strength of evidence
It is advised that all patients undergoing an SCB test are counselled about the advantages and disadvantages of testing, including the generally low lifetime risk of life-threatening arrhythmia if asymptomatic, and the possibility of a false positive or false negative result.	>90% agree
An SCB test is advised for a patient with VF or polymorphic VT that remains unexplained following comprehensive clinical testing.	
An SCB provocation test is advised in an asymptomatic first-degree relative of an index patient with definite *SCN5A*-negative BrS.	>90% agree
An SCB provocation test may be appropriate to aid segregation analysis in relatives with a rare variant of uncertain significance in *SCN5A* and symptoms and/or a family history of BrS ± sudden death.	>90% agree

Continued

Continued

When to perform SCB provocation	Strength of evidence
An SCB test is advised for a patient with a type 2/3 Brugada ECG pattern and a history of cardiac or suspected cardiac syncope in the absence of significant structural heart disease.	 >90% agree
An SCB test is advised in a first-degree relative of a SADS[a] decedent whose circumstances of death are suggestive of BrS-related death (i.e. in sleep, during fever, and/or a suspicious ECG in the decedent). Comprehensive assessment and exclusion of alternative causes in the relative is required.	
An SCB test may be appropriate in a first-degree relative of a SADS[a] decedent where comprehensive assessment and exclusion of alternative causes in the relative and decedent have been performed.	 >90% agree
Following an unexplained sudden death where an autopsy has not been performed or has been performed inadequately, an SCB test may be appropriate in a first- or second-degree relative with a type 2/3 Brugada ECG pattern.	 >90% agree
An SCB test is only advised for subjects with a pathogenic *SCN5A* variant associated with BrS when there is a clear clinical rationale and only in an expert centre.	 >90% agree
Substrate ablation in BrS cases is advised to include SCB provocation (preferably ajmaline) to enable determination of the size of the substrate.	

[a]SADS = sudden death with a negative autopsy, including cardiac examination, with negative toxicology.

Areas of uncertainty	Strength of evidence
It is uncertain whether it is appropriate to offer an SCB test to genotype-negative subjects from *SCN5A* families.	 >70% agree

Continued

Continued

Areas of uncertainty	Strength of evidence
It is uncertain whether it is appropriate to perform an SCB test in an asymptomatic first-degree relative of an index patient who only has a drug-induced or fever-induced type 1 Brugada ECG pattern and no other ECG features, clinical or family history supportive of BrS.	 >90% agree
It is uncertain whether it is appropriate to perform an SCB test on a person aged under 30 presenting with atrial fibrillation for no other reason.	 >70% agree

When not to perform SCB provocation	Strength of evidence
Do not perform a diagnostic SCB test when a type 1 Brugada pattern has already been documented in the absence of suspected phenocopy.	 >90% agree
Do not routinely perform an SCB test in asymptomatic subjects with an incidental finding of type 2/3 pattern and no other ECG features, clinical or family history supportive of BrS.	 >70% agree

Special consideration in the paediatric population

The safety profile of ajmaline provocation in children varies across series.[74,96–98] Weight-based dosing, safety requirements, and procedural preparations are similar to adults. Experienced paediatric electrophysiologists should decide on the indication and undertake the test in a paediatric setting, with the availability of a paediatric intensive care bed as a precaution. Distraction techniques such as movies, cartoons, and music during the procedure are useful to avoid the need for sedation that might alter the result of the test. Moreover, the presence of one of the parents during the procedure may minimize the stress and the need for further medications.

It is appropriate to limit the test to children experiencing symptoms (arrhythmic syncope, especially febrile arrhythmic syncope, refractory febrile seizures with abnormal ECG) at whatever age this is required. When evaluating asymptomatic and apparently unaffected paediatric relatives with a family history of SADS and/or BrS, provocative testing can be delayed until after puberty unless symptoms or ECG changes evolve.[99] However, fever is the most significant trigger for the type 1 Brugada pattern in childhood and may present the best opportunity for diagnosing the risk for the condition.[100,101] Finally, a negative ajmaline test before puberty can become positive after puberty and in early adulthood (over 16 years of age) and may indicate risk.[96]

Advice statements for sodium channel blocker testing: special considerations in children

Paediatric specific advice	Strength of evidence
It is advised that a paediatric electrophysiologist will decide on the indication for an SCB test and undertake the test in a paediatric setting with a paediatric intensive care unit bed available.	 >70% agree
It is advised to attempt to record, if possible, an ECG with high precordial leads in children during a febrile episode before considering an SCB test.	 >70% agree
An SCB test is advised in children if symptoms and ECG findings indicate the need to make or exclude a diagnosis.	 >90% agree
An SCB test is not appropriate before puberty in the context of family screening when there are no symptoms or clinical or ECG abnormalities.	 >90% agree
It may be appropriate to repeat an SCB provocation test in patients with a previously negative test and an ongoing strong suspicion for BrS, once they are at least 16 years old.	 >90% agree

Epinephrine testing

Background

An epinephrine or isoproterenol infusion has been proposed to increase diagnostic yield in cases suspected to have catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQTS), and ARVC, all conditions susceptible to adrenergic stress.

Initially, epinephrine infusion was used for LQTS patients particularly when genetic testing was not readily accessible. The rationale for the test was that LQTS patients have a maladaptive repolarization response during rapid heart rate increases and the subsequent recovery phase. Two protocols were most frequently used,[102–107] both measuring the QT interval at regular time points during progressive epinephrine dose. The response of exaggerated QT prolongation to epinephrine was initially reported to have higher sensitivity and specificity for LQT1 patients,[102–106,108,109] while in contrast, this response was less evident in LQT2 and LQT3 patients[105] and more similar to controls.[106] There have, however, been reports of poor inter/intra-observer reproducibility in LQTS patients[110,111] because of significant changes in the T wave morphology or arrhythmias complicating QT interval assessment[106,110] and a high risk of false positive results, which can reach up to 20% of controls.[105] As a consequence, the 2022 ESC VA SCD Guidelines did not recommend epinephrine testing in LQTS. The expert group agreed with the recommendation and so no further advice was given.[3] Nonetheless, epinephrine testing is still being performed in cases suspected of having LQTS, especially in Japan.

Table 4 Protocols for epinephrine testing

Progressive protocol ('Mayo')
Baseline ECG—resting supine for 10 min in a quiet room Intravenous epinephrine infusion: • Commence at 0.025 μg/(kg/min) for 10 min • Increased to 0.05, then 0.10, and finally 0.20 μg/(kg/min) at 5-min intervals • Cease infusion after 5 min of 0.20 μg/(kg/min) or earlier if SBP >200 mmHg, or occurrence of VT, 10 PVCs/min, T wave alternans or patient intolerance
Bolus protocol ('Shimizu')
Intravenous epinephrine infusion: • Bolus of 0.10 μg/kg intravenous epinephrine • Followed by 0.10 μg/(kg/min) infusion for 5 min

VT, ventricular tachycardia.

In CPVT, VA typically occur during physical and/or emotional stress; therefore, investigators have subsequently used the epinephrine challenge to increase the diagnostic yield in cases of suspected CPVT but only when an EST was not feasible.[112,113] The CASPER registry of UCA survivors suggested that epinephrine infusion had better sensitivity in diagnosing 56% of cases ultimately confirmed as CPVT.[114] However, the number of CPVT patients in the study was small, with few *RYR2* P/LP variants (the CPVT1 subtype). In contrast, Marjamaa *et al.*[113] showed that in 81 CPVT patients (31% with a *RYR2* variant), epinephrine had low sensitivity when compared to a maximal EST, with up to 70% of *RYR2* patients having a false negative test because they did not achieve a heart rate as high as during exercise test. Data on the value of the epinephrine test in CPVT2–5 are not available. In the 2022 ESC VA SCD Guidelines, epinephrine testing may be considered for patients with suspected CPVT when EST is not feasible.[3]

A high-dose (45 μg/min) infusion of isoproterenol for three minutes has been used in patients with suspected ARVC.[115–117] The test was proposed to improve the early identification of cases with probable ARVC and arrhythmia susceptibility.[115] It was interpreted as being positive if polymorphic PVCs (>3 morphologies) and ≥1 couplet were observed or if sustained or non-sustained monomorphic or polymorphic VT with predominantly left bundle branch block morphology not typical for RVOT VT was observed. Patients ultimately diagnosed with ARVC had polymorphic VT with isoproterenol, while the majority of controls did not show arrhythmias.[116] Six patients who did not meet ARVC criteria but had a positive isoproterenol challenge fulfilled a definite ARVC diagnosis later at follow-up.[115] The potential of using this test as a predictor of spontaneous arrhythmic events is under investigation. It is still unclear if the test adds substantial new information compared to the 2010 Task Force criteria and there are no distinct recommendations on whether it should be performed in suspected or borderline cases with ARVC features.[118]

Methods

Standardized epinephrine protocols (*Table 4*) were initially performed in LQTS patients. ECG monitoring should be continuously performed

as well as repeated 12-lead ECGs with a speed of 50 mm/s being preferable for greater accuracy. An ECG is recorded before initiation, immediately after a bolus administration, and at 30-s intervals during the continuous infusion. Monitoring is required throughout the test and for at least 15 min after stopping the infusion, including blood pressure measurement at 2–3 min intervals.

Reactions during drug testing depend on individual sensitivity and include even at a low dosage, palpitations, supraventricular tachycardia (SVT) and VT, chest pain and hypotension, perspiration, nausea, vomiting, dyspnoea, skin pallor, dizziness, weakness, tremor, headache, trepidation, nervousness, feelings of anxiety, feeling cold in the extremities and reduced peripheral perfusion. Overall, the epinephrine test has not been associated with high arrhythmic risk. However, life-threatening arrhythmias may occur and the test is best performed in a protected environment where an external defibrillator is available and the staff involved in the test is certified as competent to perform resuscitation.[119]

Interpretation

In CPVT, the epinephrine test has been considered 'positive' and thereby indicative for CPVT diagnosis if any of the following occurs: >10 premature ventricular contractions (PVCs)/min, 3 consecutive PVCs, recurrent couplets, sustained bigeminal rhythm and/or bidirectional VT. The occurrence of a sustained polymorphic VT or VF is rare but is a potential risk of the procedure and should terminate the test.[113,114] However, this result is more likely to indicate an underlying RYR2 P/LP variant being present[86,114] compared to PVCs alone.

In ARVC and potentially related cardiomyopathies, isoproterenol infusion is considered 'positive', thereby indicating a potential arrhythmia predisposition if there are PVCs of >3 morphologies, frequent couplets, or sustained or non-sustained VT, either polymorphic or monomorphic. Denis *et al.*[116] observed polymorphic VT more frequently in 89% (33 out of 37) ARVC patients compared to 8% (3 out 37) of healthy controls. In another series with the infusion administered during an ablation procedure, most of the induced arrhythmias had an identical morphology to the clinical PVCs.[117] It is still unclear whether this test may help discern ARVC from RVOT VT or how useful it might be in other forms of arrhythmogenic cardiomyopathies since data are not in agreement or currently available.[116,117]

Clinical scenarios

As noted above epinephrine test has limited clinical use. As in the 2022 ESC VA SCD Guidelines, it should be restricted to the suspected CPVT cases where an exercise test is not possible.[3] It is unknown if the epinephrine test has a role in ARVC diagnosis and prognosis. The epinephrine test is not advised in suspected CPVT or LQTS cases instead of an exercise test.

Special considerations

Evidence in children is limited for LQTS and CPVT and non-existent for ARVC. In children, the technique mirrors adult protocols with adjustments for weight-based dosing according to Shimizu or Mayo protocols.[104,107] Paediatric cardiologists and electrophysiologists should assess the child's overall health, cardiac status, potential complications, and response to the test before proceeding. Staff should be trained in paediatric resuscitation protocols and the test conducted in a paediatric-friendly environment.[120]

Advice statements for epinephrine challenge

General considerations	Strength of evidence
An epinephrine challenge may be appropriate to diagnose CPVT only when an exercise ECG test is not feasible.	>90% agree
An epinephrine challenge may be appropriate to test for CPVT in cases of unexplained cardiac arrest, only when an exercise test is not possible, and especially where the circumstances are associated with an adrenergic trigger.	>70% agree
An epinephrine challenge is diagnostic of CPVT when bidirectional couplets or VT, and/or polymorphic VT are induced, in the absence of any structural, toxicological, or metabolic disorder.	>90% agree
It is uncertain if epinephrine challenge can be useful in individuals with suspected ARVC who do not meet diagnostic criteria for definite ARVC	>70% agree
It is uncertain if isolated ventricular ectopics during epinephrine challenge can be useful in diagnosing individuals with suspected CPVT who do not meet diagnostic criteria.	>70% agree

Adenosine testing

Background

Adenosine, a purine nucleoside, along with its related compound, adenosine 5′-triphosphate, interacts with the cardiac cell surface via the adenosine A_1 receptor, a G_i-protein-coupled receptor.[121] This binding of adenosine induces negative chronotropic and dromotropic (slower conduction) effects that are rapid onset, short duration, and dose dependent and are achieved by decreasing spontaneous sinus node depolarization and conduction velocity across the AV node.[122,123]

The negative dromotropic action on AV node conduction is the basis for its use in the acute management of paroxysmal SVT mediated by a reentrant mechanism involving the AV node.[124] Moreover, adenosine activates adenosine A_{2A} receptors, which leads to arterial smooth muscle relaxation and a decrease in vascular resistance. This underpins its systematic application in determining coronary fractional flow reserve during myocardial perfusion imaging and the evaluation of coronary artery disease.[125]

In addition to its therapeutic applications, adenosine testing in cardiac electrophysiology has been employed for identifying the presence of accessory pathway, dual AV node physiology, and dormant pulmonary vein conduction.[126–129] Moreover, it has been used to assess wide QRS tachycardia and to distinguish VT from SVT with aberrant QRS.[124]

Methods

The safety of adenosine administration during SVT or for the differential diagnosis of regular wide QRS tachycardia is well established[130,131] In this setting, adenosine is administered as an intravenous bolus with a maximal single dose of 24 mg until AV block or sinus pauses lasting 3 s occur. There is evidence that the success rate in terminating paroxysmal SVT is higher with a bolus of 12 mg (91%) compared to 6 mg (62%).[132] Adenosine administration is associated with a number of recognized transient drug-related side effects, including hypotension, bronchospasm, facial flushing, and headache[131–134] The most common pro-arrhythmic effect of adenosine is the appearance of transient episodes of atrial fibrillation. Adenosine-induced VA are rare and usually affect patients with a prolonged QT interval.[131]

Interpretation

Interruption by adenosine of a narrow or wide QRS tachycardia is indicative of a suspected re-entrant mechanism involving the AV node (AV nodal re-entrant and AV re-entrant tachycardias). In patients with narrow QRS tachycardia, this may indicate in some cases presence of a triggered focal atrial tachycardia.

In patients with sinus rhythm and previous SVT, a transient blockade of AV node by adenosine can unmask pre-excitation and this is indicative of Wolff-Parkinson-White (WPW) syndrome and re-entrant tachycardia mechanism involving an accessory pathway. In an SCA survivor, this could indicate potential causation by pre-excited and rapidly conducted atrial arrhythmias.[3]

When not to do it

Adenosine is contraindicated in patients with atrial fibrillation in the setting of WPW syndrome or presenting with irregular wide QRS tachycardia as it may lead to ventricular fibrillation resulting from AV blockade and anterograde fast conduction over the accessory pathway.[131,135] Other conditions where adenosine use is relatively contraindicated include hypersensitivity to the substance, pronounced hypotension, symptomatic aortic stenosis or left ventricular outflow tract obstruction, high-degree AV block, and severe bronchospasm. Moreover, because adenosine can trigger an increase in sympathetic discharge, it poses a risk of life-threatening arrhythmias in patients with LQTS and baseline QT prolongation[131,136] and must be considered carefully in the presence of underlying heart disease.

Special considerations

When administered in the new-born, initial doses are 200 μg/kg in rapid bolus and can increase up to 300 μg/kg in case of failure. Continuous monitoring of the ECG is mandatory as SVT tends to be incessant or rapidly recurrent.[137]

Advice statements for adenosine challenge

General considerations	Strength of evidence
Adenosine challenge may be appropriate in patients with a haemodynamically stable and regular wide QRS tachycardia for differential diagnoses purposes.	 >90% agree

Continued

Continued

General considerations	Strength of evidence
Adenosine challenge may be appropriate to perform in patients who are in sinus rhythm with documented SVT or a minimally pre-excited ECG to unmask the presence of an accessory pathway	 >90% agree
It is not advised to perform adenosine challenge in patients with haemodynamically unstable arrhythmias or with irregular wide QRS tachycardia	 >90% agree

Testing for coronary vasospasm in cardiac arrest survivors

Background

Coronary artery spasm resulting in arrhythmia is a rare but well-documented cause of syncope and SCD.[138–143] The diagnosis is often difficult given its unpredictable nature. A high degree of suspicion of CAS is therefore required. Provocative testing with acetylcholine or ergonovine (a smooth muscle stimulant) is useful when 'spontaneous' CAS remains undetectable by other means, particularly when CAS is identified as a potential cause of life-threatening arrhythmias.[141]

The long-term prognosis of SCA secondary to CAS is uncertain. Small studies have shown a recurrence of VA with a cumulative risk of SCD of 16.7% at 10 years of follow-up (16.% vs. 2.5% of healthy subjects, $P < 0.001$).[144] Possible explanations for the recurrence of cardiac arrest include multivessel spasm, failed medical treatment, medication nonadherence, and myocardial scar from injury at the time of the initial arrest.[145]

In one study, vasospasm was the cause of SCA in 2% of survivors, based on clinical presentation of incidental angiographic vasospasm in half of cases.[146] However, 30–75% of SCA survivors may have a positive coronary reactivity test indicative of spasm.[147] The indication for an invasive provocative test for CAS in cardiac arrest survivors should take into account individualized risks and potential benefits.[146–148] Tests for CAS are safe when carried out in specialist units following standardized protocols.[149–151] In this way, patient safety, diagnostic precision, and management can be optimized.[152,153]

Methods

The diagnostic work-up is advised to be managed in a centre with relevant, established experience. Medical therapy is withheld 48 h before the procedure, if possible. Coronary artery spasm is assessed by carrying out coronary angiography-directed infusion of acetylcholine or ergonovine in a stable patient. The most established approach for vasoreactivity testing is by intracoronary infusion of acetylcholine.[3,148,149,154,155] Informed consent should highlight off-label use of acetylcholine, indication, and risks.

While pharmacological protocols may vary somewhat between institutions, the underlying principles are the same (*Table 5*). The doses may be halved for infusion into a left dominant coronary artery and in the right coronary artery. Prompt recovery is typical, and intracoronary nitrates can be administered if necessary. Intracoronary ergonovine is an alternative to acetylcholine for the assessment of CAS and is implemented more commonly in centres in Asia than in elsewhere.[156] Transient bradycardia may occur immediately after intracoronary acetylcholine administration. This

Table 5 Indicative guide for intracoronary administration of acetylcholine in adults in the catheter laboratory for the diagnosis of coronary artery spasm

	Dose of acetylcholine	Duration of infusion
Automated pump		
Pre-prepared solution		
1. Step	0.182 µg/mL	2 min
2. Step	1.82 µg/mL	2 min
3. Step	18.2 µg/mL	2 min
Manual (in-lab)		
RCA/LCA (dominant)		
1. Step	2 µg	60 s/3 min pause
2. Step	20 µg	60 s/3 min pause
3. Step	50 µg (dominant)	20 s
LCA (non-dominant)		
1. Step	2 µg	60 s/3 min pause
2. Step	20 µg	60 s/3 min pause
3. Step	50 µg	20 s/3 min pause
4. Step	100 µg	20 s

LCA, left coronary artery; RCA, right coronary artery.

can be mitigated by asking the patient to cough or by giving intravenous atropine and/or nitrate. Temporary pacing is not routinely indicated. It is advisable that the cardiologist avoids or minimizes the use of intracoronary nitrate before acetylcholine administration. Glyceryl trinitrate has a shorter-acting effect than isosorbide dinitrate and hence is preferred. For intracoronary infusion of acetylcholine into a non-dominant, left coronary artery, the typical dose range is 0.2–100 µg (some centres, 200 µg), according to a locally agreed protocol. The maximum dose of acetylcholine for the right coronary artery and a dominant left coronary artery is 50 µg, although doses of 100 µg have been used. Dosing of acetylcholine should occur during continuous ECG and haemodynamic monitoring, recording the occurrence of symptoms. A cine angiogram is obtained initially and after each dosing. A dose of 200–400 µg of glyceryl trinitrate or isosorbide dinitrate can relieve coronary spasm.

Serious adverse events including life-threatening arrhythmias or death are rare. The most recent studies have reported a 0% mortality rate with very few patients experiencing events. These included mostly arrhythmias reversible by treatment including atrial fibrillation (<4%), VT/fibrillation (<2%), and SCA (0.1%).[157] The most common adverse events included bradycardia and transient paroxysmal atrial fibrillation that usually resolve spontaneously under medical observation in the catheter laboratory and therefore do not require treatment. Events were more common with right coronary reactivity testing compared with left coronary artery testing.[149,157]

Interpretation

The vasoactive response reflects the functions of the endothelium and smooth muscle cells.[158] In a survivor of out-of-hospital cardiac arrest (OHCA), vasoconstriction may be causally implicated in myocardial ischaemia leading to VA. Epicardial coronary spasm is defined according to the COVADIS criteria requiring reproduction of chest pain and ischaemic ECG changes in association with ≥90% vasoconstriction leading to flow limitation[159] (*Figure 7*). On occasions, severe microvascular spasm may develop, with coronary flow transiently reducing or ceasing in the absence of epicardial CAS, i.e. the diameter of the coronary diameter is maintained in association with transient reduction of flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade ≤2) while the patient experiences chest pain that correlates with ischaemic changes on the ECG.

Indications

The 2022 ESC VA SCD Guidelines recommend testing for CAS in OHCA survivors if there is a clinical suspicion for CAS, such as a history

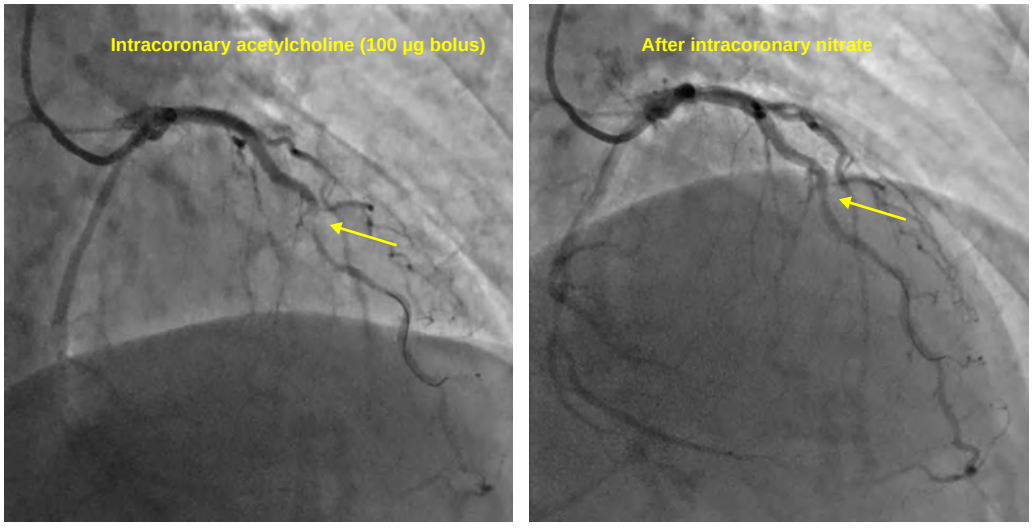


Figure 7 Example of coronary vasospasm. A practical, video-assisted guide for coronary function testing is available online.[160]

of chest pain or exertional circumstances of cardiac arrest, and all other tests are normal.[3] Guidelines, however, do not offer recommendations regarding the assessment of CAS in survivors of OHCA without a clinical picture compatible with CAS or when an ICD should be indicated for secondary prevention of lethal arrhythmias in CAS patients.[3] Identifying CAS is vital to define appropriate management strategies, as treatment with calcium channel blockers significantly reduces the risk of recurrent life-threatening arrhythmias in CAS patients.[143] The use of provocative tests for spasm has been reported to be safe in the setting of acute coronary syndrome and non-obstructive coronary artery disease.[161]

When not to do it

It is inappropriate to undertake provocative testing using acetylcholine in the setting of haemodynamic instability, early stages of acute myocardial infarction, heart block, NYHA III/IV heart failure (including cardiogenic shock), left main stenosis >50%, three-vessel obstructive coronary artery disease, two-vessel obstructive disease with total occlusion, and severe bronchial asthma. Contraindications to provocative testing with ergonovine include pregnancy, severe hypertension, severe left ventricular dysfunction, severe aortic stenosis, and high-grade left main coronary stenosis.

The following general warnings exist for acetylcholine administration: patients with severe asthma, acute heart failure, hyperthyroidism, Parkinson's disease, peptic ulcer disease, and or urinary tract obstruction.

Special considerations

In paediatric and adolescent cardiac arrest survivors, the use of ergonovine and acetylcholine as provocative agents remains largely unexplored. As in adults, there is insufficient evidence to support their routine use in this population. Limited data, primarily derived from case reports, has shown certain efficacy and safety profiles in adolescent presenting with angina due to reversible microvascular changes secondary to myocarditis.[162] The use of ergonovine or acetylcholine in children and adolescents is approached with caution and on a case-by-case basis, with careful consideration of potential risks and benefits. Ergonovine is contraindicated in pregnancy.

Advice statements for provocative testing for coronary artery spasm in the cardiac arrest survivor

General considerations	Strength of evidence
The diagnosis of CAS requires reproduction of chest pain and ischaemic ECG changes in association with ≥90% vasoconstriction leading to flow limitation.	>90% agree
Testing for CAS is advised to be performed by operators with relevant established experience.	>90% agree
Testing for CAS in cardiac arrest survivors is advised if CAS is suspected to have a causal role and if all other tests are normal.	>90% agree

Continued

Continued

General considerations	Strength of evidence
Testing for CAS is advised only in haemodynamically stable patients.	>90% agree
Testing for CAS is not advised in patients with severe left main stem or severe three-vessel coronary artery disease.	>90% agree
It is uncertain if CAS testing can be useful in assessing all individuals presenting with unexplained cardiac arrest after comprehensive testing.	>90% agree

Provocation testing during pregnancy and lactation

Physiological adjustments in pregnancy may lead to changes in pharmacokinetics and pharmacodynamics of drugs that can vary among individuals and depend on the stage of pregnancy.[163] It is also essential to carefully assess the risk of excretion of drugs into breast milk and their potential effect on the new-born. Unfortunately, there is a lack of solid scientific data to guide decisions around the administration of drugs for provocation testing, so it is crucial to weigh the usefulness of performing these against potential negative effects on the child (foetus or new-born) or mother. As such, adenosine, SCBs, and other drugs discussed in this document, may mainly be administered for therapeutic rather than diagnostic purposes during pregnancy. During lactation, most drugs, particularly those with very short half-life, can be administered safely. *Table 6* summarises the effects of drugs used in provocation testing and their potential risks during pregnancy and lactation.

Advice statements for pregnancy and lactation

General considerations	Strength of evidence
It is advised that provocation testing is postponed until after delivery unless it enables critical management decisions in the pregnant woman.	>90% agree
It is advised that provocation testing is postponed until after lactation unless it enables critical management decisions in the lactating woman.	>90% agree

Table 6 Provocation test in pregnancy and lactation

Drug	Placental transfer	Terato-genic	Safety in pregnancy	Potential risks in pregnancy	Transfer to breast milk
Acetylcholine	Unknown	No	Yes (limited human data—animal data lacking)	Maternal: Unknown Foetal/neonatal: Unknown	Unknown (very short half-life)
Adenosine	Unclear (short half-life)	No	Yes	Maternal: Flushing Transient chest pain Bradycardia Foetal/neonatal: No foetal adverse events reported (limited human data)	No (very short half-life)
Ajmaline	Unknown	Unknown[a]	Unknown	Maternal: Unknown Foetal/neonatal: Unknown	Unknown
Epinephrine	Yes	No	Yes	Maternal: Unknown Foetal/neonatal: Unknown	Unknown (very short half-life)
Ergonovine	Unknown	Unknown[a]	Unknown	Maternal: Unknown Foetal/neonatal: Unknown	Unknown
Flecainide	Yes	Animal data contradictory	Yes (limited human data—contradictory animal data)	Maternal: Visual/central nervous system effects PR/QRS widening first-degree AV block QTc prolongation Atrial flutter Foetal/neonatal: Neonatal QRS widening with long exposure (concentrates in amniotic fluid) QTc prolongation Proarrhythmia	Yes (low levels)[b]
Isoproterenol	Yes	No	Yes	Maternal: Unknown Foetal/neonatal: Unknown Foetal/neonatal: Central nervous system effects	Unknown (very short half-life)
Pilsicainide	Unknown	Unknown[a]	Unknown	Maternal: Unknown Foetal/neonatal: Unknown	Unknown
Procainamide	Yes	Unknown[a]	Yes (limited human data—animal data lacking)	Maternal: Nausea and vomiting QTc prolongation Proarrhythmia, Torsades de Pointes, Uterine irritability Premature birth	Yes

Continued

Table 6 *Continued*

Drug	Placental transfer	Terato-genic	Safety in pregnancy	Potential risks in pregnancy	Transfer to breast milk
				Foetal/neonatal: QTc prolongation Proarrhythmia, Torsades de Pointes	
				Foetal/neonatal: Central nervous system effects Embryotoxicity in animal studies	

AV, atrioventricular.
[a]Avoid during first trimester and only administer when strictly necessary.
[b]Breastfeeding is possible if the mother is treated with the drug.[163]

Future perspectives

The clinical role of provocative testing is to reveal an underlying concealed diagnosis, especially for genetic disorders such as BrS and CPVT and otherwise ill-defined diseases such as CAS. Their utility is limited by the lack of gold standards for diagnosis upon which these tests can be validated. Establishing gold standards is, however, becoming achievable for polygenic genetic disorders such as BrS where more granular and accurate genomic data may permit such diagnostic development.[164] Furthermore, it is possible that novel interpretation of the baseline ECG prior to provocation, using conventional approaches[45] and artificial intelligence algorithms,[165–167] may facilitate the selection of patients with a higher risk for a diagnosis, predict the outcome of testing, and render provocation testing unnecessary in some patients. The accuracy and utility of these algorithms may then be enhanced by a multimodal approach incorporating ECG, genomic, and clinical data.[39] This will require robust methods and large deeply phenotyped and genotyped cohorts for discovery and validation. In the interim provocation testing will still be employed, but in a context-specific approach as advocated by this consensus statement, to avoid misdiagnosis and its disruptive effect on patients and their families.

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