Ventricular arrhythmia in coronary artery vasospasm – when should we consider a device?

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Introduction

Coronary artery vasospasm (CAS) is a disorder characterised by transient myocardial ischaemia due to epicardial coronary artery spasm. It is also known as vasospastic angina, variant angina or Prinzmetal's angina (after the original description in 1959). CAS typically presents as chest pain, usually occurring at rest, and a concurrent ECG recording showing ST elevation. Other ECG patterns are recognised including ST depression and T wave abnormalities (such as peaking and an increase in amplitude); the differences felt to reflect the burden of myocardial ischaemia. Silent presentations are also recognised from the use of continuous ECG recordings identifying transient ST segment deviation without ischaemic symptoms.

The European Society of Cardiology guidelines for the management of stable coronary artery disease (2013) recommends that in diagnosing suspected CAS, an ECG is performed during typical pain (class 1, LOE C) to look for transient ECG changes. It also recommends coronary angiography is performed to determine the presence and extent of any underlying coronary artery disease (class 1, LOE C). Continuous ambulatory ECG monitoring for ST segment deviation should be considered (class 2a, LOE C), particularly in cases where silent ischaemia is suspected. Provocation testing should also be considered to identify CAS in those with a clinical suspicion for CAS and angiographically normal or unobstructed coronary arteries (class 2a, LOE C).

What is the long term prognosis?

Single centre studies that have followed up consecutive CAS patients have shown survival to be 95-98% at one year and 89-97% at five years. Freedom from myocardial infarction similarly has been shown to be 83-86% at one year and 69-83% at five years. There is also some evidence that the most risk of a complication occurs within the first 3 months of the index event. Markers associated with a poor prognosis from these studies include:

- The presence and extent of concomitant coronary artery disease
- Degree of vasospasm disease activity (particularly concomitant anterior and inferior ST elevation implying multivessel spasm)
- The presence of an arrhythmia during an attack (which in one study, doubled the mortality rate).
- Smoking and alcohol consumption

Increased rates of survival were seen in those using calcium channel blockers and those with preserved baseline LV systolic function.
More recently, a novel clinical risk score has been developed from a large multicentre registry\(^9\) (the Japanese coronary spasm association risk score) to risk stratify those with CAS. They identified seven major predictors (each weighted based on their hazard ratio) which are summated to form a score which reflects either a low, intermediate and high chance of major adverse cardiac events (MACE). The seven predictors (from highest importance to lowest) are:

- A history of OOHVF arrest
- Active smoking
- Chest pain at rest
- Presence of significant coronary artery disease
- Multivessel spasm
- ST elevation on ECG
- Use of a beta blocker

The low, intermediate and high risk groups predict the incidence of MACE (2.5%, 7% and 13% respectively) and hence prognosis. Whether this score applies equally effectively to the UK population and can determine certain types of therapy is yet to be seen.

**Coronary artery spasm and arrhythmia**

Arrhythmia is increasingly being reported and recognised as a significant complication within the CAS population\(^10\)\(^-\)\(^12\). The incidence reported has been highly variable, which in part is a reflection of small groups with differing durations of follow up periods. A Canadian study\(^10\) of 114 consecutive patients with CAS found 17% had either sudden cardiac death (SCD) or were resuscitated from a ventricular arrhythmia (VA) over a mean follow up period of 26 months. 49% of all patients were identified to have had a serious arrhythmia recorded during episodes of spontaneous ST elevation during continuous ECG monitoring, which included ventricular fibrillation, ventricular tachycardia and high grade atrioventricular block. The only predictor for arrhythmia during vasospasm was maximal height of ST elevation (which is felt to reflect the burden of myocardial ischaemia during spasm). Significant arrhythmias were more commonly observed in the SCD group prior to lethal VA (84% versus 42%), and SCD was more prevalent in the group with documented arrhythmia (42% versus 6%).

A multicentre Japanese study\(^11\) found an incidence of arrhythmia of 14% in 349 patients within a mean follow up of 3.4 years. They found VA and high grade atrioventricular block to be equally prevalent (AV block was associated with right coronary artery spasm, but VA were independent of site of ST elevation).

The largest multicentre registry to date\(^12\) from Japan has shown an incidence of out of hospital cardiac arrest of 2.4% in 1429 patients with CAS. Variables associated with increased risk of SCD were left anterior descending artery spasm and a younger age. Further analysis showed that a higher risk of SCD occurred in those whose medical therapy was reduced or stopped in the preceding period, highlighting caution should be exercised prior to altering medications, even in apparently asymptomatic individuals.

Investigating for and diagnosing CAS is an important part of the work up following an apparent idiopathic out of hospital cardiac arrest (OHCA). Initial studies carried out in OHCA survivors with a structurally normal heart and absence of significant coronary artery disease
found CAS prevalence to be between 5% and 83%\textsuperscript{13-15}. These studies were limited by small numbers, lack of clarity on extent of coronary artery disease present, and differences in age and race. The largest study (and most recent) to date\textsuperscript{16}, looked at 1000 consecutive cases of OHCA and identified a prevalence of 7%.

**Medical therapy**

Calcium channel blockers are the cornerstone of medical therapy in CAS. They are effective in preventing ischaemic attacks >90% of the time\textsuperscript{17}. They also have some evidence of benefit in arrhythmia as a small follow up study showed freedom from further VA over a period of 58 months in 86% of patients\textsuperscript{18}. Long acting nitrates and nicorandil have additive symptomatic benefit as coronary vasodilators\textsuperscript{19}. A number of patients however have ongoing coronary vasospasm despite two agents (medically refractory cases) and this is as high as 20%\textsuperscript{20}. The absence of ongoing symptoms should also be regarded as insufficient evidence of response to medical therapy, as asymptomatic episodes of spasm are common, and arrhythmia can still occur during these episodes (albeit less frequently than during symptomatic ones)\textsuperscript{21}.

Coronary artery stenting has received interest from the interventional community as an option for CAS. Case reports and small case series have suggested benefit can be obtained in those with medically refractory spasm in terms of ischaemic symptoms and burden of arrhythmia\textsuperscript{22-24}. What these reports suggest is that stenting may be useful in the acute situation to bailout patients with drug refractory symptoms, but data on long term follow up or the results of a randomised control trial are lacking. In addition, they are not a replacement for medical therapy as spasm within the coronary arterial tree continues even after stenting\textsuperscript{25}. This is reflected upon by the guidelines which don’t recommend stenting as a therapeutic option\textsuperscript{5}.

**Use of internal cardiac defibrillators in CAS**

The latest guidelines from the European Society of Cardiology do not recommend the implantation of an internal cardiac defibrillator (ICD) where a reversible or treatable cause is identified\textsuperscript{26}. Although the majority of patients with CAS will respond to medical therapy, there remains a subset of the population who are refractory (both poor and non-responders). This group remain at risk of VA, and there are an increasing number of case reports of the use of secondary prevention ICDs to prevent SCD\textsuperscript{27-34}. Implantation can therefore be said to be justified as life-saving based on appropriate device therapy being administered in the varied follow up periods of these cases.

So should all patients with VA and CAS undergo an ICD implant? The answer is no as most cases will respond to medical therapy and the need for an ICD may be avoided, even after OHCA\textsuperscript{18}. The real question is where the dividing line should be when considering a device implantation.
The ability to determine who needs an ICD remains suboptimal because it is unclear who will and who won’t respond to medical therapy. In addition, it is unclear what an appropriate length of time to wait on optimal medical therapy is before deciding it isn’t sufficient to reduce the arrhythmogenic risk and an ICD is warranted. Although evidence suggests most events occur within three months of the index event 7-8, further episodes can occur late10-12 and occur without warning given possibility of asymptomatic episodes of spasm21. The risk of VA is therefore more likely to be dynamic with time rather than an enduring lifetime risk35, however long term follow up studies are lacking. This makes the later decision about whether to replace a generator at end of life even harder.

Algorithms have been proposed34 to determine who should get an ICD, but are weakened by the fact they are based on small numbers and do not necessarily apply to all comers. In addition, the literature is dominated by studies in the Japanese population (who have a higher incidence of CAS3) and whether this growing knowledge can be applied to patients in the UK is unclear (although there is no current evidence of different outcomes based on ethnicity).

Although a prognostic risk score has been developed, it cannot yet determine who should receive a secondary prevention ICD9. Prognosis matters when weighing up the benefit versus risk of an ICD implant for secondary prevention (3-6% implanting complication and 10% inappropriate shock rate)36. There is also currently no role for primary prevention devices due to inability to accurately predict risk.

Finally, an ICD is insufficient at protecting all those with medically refractory CAS from sudden death (as evidenced by reports of pulseless electrical activity during follow up33) reiterating that arrhythmia is not the sole cause of sudden death in this patient group. Although these are small numbers, they matter as implantation of an ICD needs to take into account whether the device is capable of terminating all VA and prognosis is not significantly affected by a competing mechanism that will not respond to device therapy.

**Conclusion**

CAS can cause significant VA in a minority of cases. For most of these, medical therapy is sufficient in treating symptoms and probably reduces the burden the VA. Most VA occur within 3 months of index presentation but this is debatable based on short follow up periods and inability to adequately detect asymptomatic episodes. There is limited evidence that coronary stenting can prevent further VA, therefore should not influence the decision regarding an ICD. At present, there is a single prognostic risk score available but it is unclear how it can be applied to clinical decision making. ICD have a role in the management of CAS but in selected patients with ongoing VA despite maximal medical therapy, and whether they bring enduring survival benefit is unclear. Given the case reports of appropriate therapy, CAS cannot be said to be a fully reversible and treatable condition that would preclude a OHCA survivor from receiving an ICD. A rather simple statement is to ask for a randomised control trial, but the likelihood of getting one suitably powered with a clear outcome is low. Until then, individualised assessment of risk should be made, ideally through a multi-disciplinary team approach, to this complex issue.
References


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