REVIEW

Should an implanted defibrillator be considered in patients with vasospastic angina?

Un défibrillateur a-t-il sa place chez les patients présentant un angor spastique?

Romain Eschalier\textsuperscript{a,b,*}, Géraud Souteyrand\textsuperscript{a,b}, Frédéric Jean\textsuperscript{a}, Antoine Roux\textsuperscript{a}, Nicolas Combaret\textsuperscript{a}, Yannick Saludas\textsuperscript{a}, Guillaume Clerfond\textsuperscript{a,b}, Nicolas Barber-Chamoux\textsuperscript{a}, Bernard Citron\textsuperscript{a}, Jean-René Lusson\textsuperscript{a,b}, Pedro Brugada\textsuperscript{c}, Nicolas Barber-Chamoux\textsuperscript{a}, Bernard Citron\textsuperscript{a}, Jean-René Lusson\textsuperscript{a,b}, Pedro Brugada\textsuperscript{c}, Pascal Motreff\textsuperscript{a,b}

\textsuperscript{a} Cardiology Department, Clermont-Ferrand University Hospital, 58, rue Montalembert, 63000 Clermont-Ferrand, France
\textsuperscript{b} Clermont université, université d’Auvergne, CArdio-Vascular Interventional Therapy and Imaging (CaVITI), Image Science for Interventional Techniques (ISIT), UMR6284, Clermont-Ferrand, France
\textsuperscript{c} Cardiovascular Division, Free University of Brussels, UZ Brussel-VUB, Brussels, Belgium

Received 27 March 2013; received in revised form 16 October 2013; accepted 18 October 2013
Available online 25 December 2013

KEYWORDS
Coronary vasospasm; Implantable defibrillator; Sudden cardiac death; Ventricular arrhythmia

Summary Vasospastic angina is a frequent and well-recognized pathology with a high risk of life-threatening ventricular arrhythmias and sudden cardiac death. The diagnosis of vasospastic angina requires the combination of clinical and electrocardiographic variables and the results of provocation tests, such as ergonovine administration. Smoking cessation is the first step in the management of vasospastic angina. Optimal medical treatment using calcium-channel blockers and/or nitrate derivatives can provide protection, but life-threatening ventricular arrhythmias may occur despite optimal medical treatment and several years after the start of treatment. In this review, we evaluate the role of implantable defibrillators as a complement to

\textit{Abbreviations:} CAS, coronary artery spasm; ICD, implantable cardioverter defibrillator; LTVA, life-threatening ventricular arrhythmia; MACE, major adverse cardiac events; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Corresponding author. Cardiology Department, Clermont-Ferrand University Hospital, 58, rue Montalembert, 63000 Clermont-Ferrand, France.
\textit{E-mail address:} reschalier@chu-clermontferrand.fr (R. Eschalier).

1875-2136/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.acvd.2013.10.006
optimal medical management in patients with life-threatening ventricular arrhythmias due to vasospastic angina; this role is not well characterized in the literature or guidelines. We discuss the role of implantable defibrillators in secondary prevention in light of three recent cases managed in our departments and a review of the literature. An implantable defibrillator was implanted in two of the three cases of vasospastic angina with ventricular arrhythmias that we managed. We considered secondary prevention by implantable defibrillator to be justified even in the absence of any obvious risk factor. Ventricular arrhythmias recurred during implantable defibrillator follow-up in the two patients implanted.

Conclusion. — In patients with life-threatening ventricular arrhythmias due to vasospastic angina, an implantable defibrillator should be considered because of the risk of recurrence despite optimal medical management.

Résumé

Contexte. — L’angor spastique est une pathologie fréquente et connue de longue date ayant une morbimortalité non-négligeable. Il existe notamment un risque important de mort subite. Le diagnostic repose sur l’association de signes cliniques, électrocardiographiques et par la confirmation diagnostique par un test de provocation au méthergin. L’arrêt du tabagisme est le point essentiel du traitement. Il est associé à un traitement médicamenteux anti-spastique composé d’inhibiteurs calciques et/ou de dérivés nitrés. Malheureusement cette prise en charge est insuffisante et le risque de mort subite reste présent durant plusieurs années après que le diagnostic ait été porté. Dans cette revue, nous évaluons la place du défibrillateur automatique implantable en sus du traitement médicamenteux chez des patients ayant présenté une mort subite récupérée suite à un spasme coronaire dont la place reste floue.

Méthodes. — Nous discutons cette place à la lumière de trois cas que nous avons pris en charge et d’une revue complète de la littérature.

© 2013 Elsevier Masson SAS. Tous droits réservés.

Background

Vasospastic angina is one of the most important functional abnormalities of the coronary artery with a high risk of morbidity (myocardial infarction) and mortality [1,2] (sudden cardiac death [SCD] from severe life-threatening ventricular arrhythmias [LTVAs] [3,4]). Vasospastic angina accounts for 5% of cases of cardiac arrest from severe ventricular arrhythmias. Printzmetal et al. first described vasospastic angina in 1959 [5]. Diagnosis remains difficult and is based on combined evidence, especially as coronary artery spasm (CAS) can occur in the absence of any chest pain [6–8]. Per-critical electrocardiographical signs are highly suggestive, but diagnosis is usually confirmed by spasm-provocation tests during coronary angiography [9], with ergonovine or acetylcholine administration [10].

Endothelial dysfunction associated with loss of nitric oxide secretion remains the main physiopathological factor implicated in vasospastic angina [11,12], but other pathways are being explored [13] without any effective alternative treatments. Currently, calcium-channel blockers usually bring the spastic angina under control and ensure a good long-term prognosis [14], without, however, providing optimal efficacy in all patients. Furthermore, patients with vasospastic angina who survive LTVAs are a particularly high-risk population [15]. As medical management is not completely effective, an implantable cardioverter defibrillator (ICD) may offer a complementary management strategy, particularly in the secondary prevention of LTVAs due to vasospastic angina.

We discuss the role of ICDs in the secondary prevention of SCD from severe LTVAs due to vasospastic angina in light of three recent cases managed in our centre and a review of the literature.

Case studies

First case

A 52-year-old female smoker was admitted for a first non-ST-segment elevation myocardial infarction with angiographically healthy coronary arteries. She was discharged on isosorbide mononitrate (40 mg/day), a calcium-channel blocker (verapamil, 120 mg twice daily), a statin (atorvastatin, 80 mg/day) and aspirin (160 mg/day).

Six months later, the patient was hospitalized for a cardiac arrest; she received early resuscitation manoeuvres and two shocks delivered by a semiautomatic defibrillator for ventricular fibrillation (VF). The post-resuscitation electrocardiogram showed alternation between normal repolarization and a pathognomonic pattern of Prinzmetal’s angina (Fig. 1A and B). Emergency coronary angiography showed a diffuse — nearly occlusive — spasm of the entire coronary tree (Fig. 2A: circumflex and left anterior descending arteries > 90% spastic occlusion), relieved only by intracoronary isosorbide dinitrate injection (which confirmed the diagnosis of vasospastic angina: the combination of the presence of a > 90% transient occlusion of at least one coronary artery with signs/symptoms of myocardial
ischaemia and a positive drug induction test by intracoronary isosorbide dinitrate). The coronary arteries were angiographically healthy after this injection (Fig. 2B).

Given the recurrence of symptoms and LTVAs due to vasospastic angina under optimal medical treatment, we decided to implant an ICD and the patient was discharged with amlodipine (10 mg/day), nicorandil (10 mg/day), nifedipine (30 mg/day), atorvastatin (80 mg/day) and double antiplatelet therapy because of acute coronary syndrome due to CAS (aspirin [100 mg/day] and clopidogrel [75 mg/day]).

At 18-month follow-up, ICD interrogation showed several episodes of ventricular tachycardia (VT), with a maximum duration of 14 seconds, which is too short for the ICD to treat.

Second case

A 54-year-old male smoker was admitted after a cardiac arrest resuscitated by two external shocks delivered by a semiautomatic defibrillator without signs of cardiogenic shock. The post-resuscitation electrocardiogram showed huge T waves in anterior leads. The emergency coronary angiography highlighted a spastic proximal left anterior descending artery associated with a mid left anterior descending artery occlusion with an aspect of thrombus in a milking portion (Fig. 3A). The occlusion was relieved by thromboaspiration and implantation of a bare-metal stent. Evolution was favourable, without neurological sequelae or myocardial damage (no echocardiographic scar). Despite combined amiodarone (200 mg/day) and bisoprolol (10 mg/day) treatment, the patient exhibited several episodes of sustained VT.

We decided to perform a second coronary angiography 1 month later because of sustained VT; this showed occlusive spasm (associated with chest pain) at the end of the left main coronary artery, relieved by intracoronary isosorbide mononitrate administration, without any significant stenosis, confirmed by optical coherence tomography imaging (no plaque rupture or coronary artery dissection) (Fig. 3B).

The initial cardiocirculatory arrest was retrospectively attributed to vasospastic angina of the proximal left anterior descending artery complicated by thrombosis and embolism in the mid left anterior descending artery. Despite adapted treatment (nifedipine [30 mg/day], verapamil [240 mg/day], atorvastatin [80 mg/day], ramipril [3.75 mg/day], aspirin [75 mg/day], prasugrel [10 mg/day] and nicotine in a patch [35 mg/day] with cessation of

Figure 1. Electrocardiogram changes due to vasospastic angina. A. Electrocardiogram with pathognomic pattern of Prinzmetal’s angina in inferior leads (arrows) and signs of ventricular excitability (asterisk) after resuscitated sudden cardiac death. B. Normalization of electrocardiogram a few minutes later after intravenous administration of isosorbide mononitrate, without signs of acute coronary syndrome.
ICD in vasospastic angina

We required spasticity again. A 56-year-old smoking), episodic polymorphic VT continued for 5 weeks. We finally decided to implant an ICD because of the ineffectiveness of optimal medical treatment in controlling spasticity and ventricular arrhythmias. An ICD check-up at 18 months found persistent non-sustained episodes of VT, not requiring ICD treatment, under optimal medical treatment.

Third case

A 56-year-old male ex-smoker, who had started smoking again 1 week previously, complained of chest pain at rest over the previous 24 hours. The most recent pain attack was followed by a brief loss of consciousness.

The patient was admitted to our intensive care unit. Clinical examination was normal. A resting electrocardiogram showed negative T waves in anterior leads. A coronary angiography via a right femoral approach found thin non-significant atheroma throughout the coronary tree. An ergonovine administration test (intravenous injection of 0.4 mg of ergonovine) induced an explosive response, with mid left anterior descending artery occlusion and clinically symptomatic onset of sustained VT (Fig. 4A and B). Loss of consciousness, VT and angiographical abnormalities quickly resolved on intracoronary isosorbide dinitrate injection. The patient was discharged with verapamil (240 mg/day), aspirin (75 mg/day) and rosuvastatin (10 mg/day), without recurrence of angina symptoms. As symptoms were under control and treatment compliance and definitive cessation of smoking could be relied upon, no ICD was implanted. At 17-month follow-up, the patient remained symptom free, with a normal cardiological examination.

Discussion

These three cases, along with many previous reports [16], show the difficulties in the management of resuscitated SCD induced by a severe LTVA (VT or VF) following CAS. At present, there are no consistent guidelines to help clinicians to decide whether to implant an ICD in such patients. ICD implantation is recommended by some groups [17] but advised against by others [18]. In this discussion, we review the literature and seek to provide management advice.

Vasospastic angina is a severe and potentially lethal pathology, with a high risk of SCD from severe LTVAs (VT or VF). The prognosis of vasospastic angina under optimal medical treatment is quite good (98% death-free survival and 92% major adverse cardiac events (MACE)-free survival [cardiac death, non-fatal MI, hospitalization due to unstable angina pectoris and heart failure] at 5-year follow-up) [10]. By comparison, the prognosis for survivors of an out-of-hospital cardiac arrest due to vasospastic angina is still poor (72% MACE-free survival at 5 years [15]). Moreover, the potential risk of recurrence is underestimated and persists long after diagnosis [19], because of the loss of efficacy of medical treatment and the long-term discontinuation in many patients. The severity of the disease depends on the number of arteries affected by the spasm: a diffuse spasm has a poorer prognosis than single vessel involvement [20].

Figure 2. Diffuse coronary artery spasm (A) before and (B) after relief by administration of intracoronary isosorbide mononitrate.

Figure 3. Angiocoronarography and optical coherence tomography. A. Initial angiocoronarography with thrombus in circumflex artery (arrow). B. Optical coherence tomography of left main descending artery without significant stenosis.
Medical treatment is the pivotal part of the management strategy, using non-dihydropyridine calcium-channel blockers [14] and/or nitrate derivatives, both of which provide proven protection against recurrence. Unfortunately, this treatment is insufficient, even when given optimally, and it fails to eliminate all risk of recurrence of vasospastic angina and hence of severe LTVA. Cessation of smoking is mandatory. There is consensus for prescription of statins and low-dose aspirin, but beta-blockers, as vasoconstrictive treatments, are classically avoided [21].

An ICD may thus not be indicated in primary prevention in patients without spasm-related SCD. The role of ICDs in secondary prevention after resuscitated SCD due to vasospastic angina is unknown.

The current debate is whether or not secondary prevention by an ICD should concern all cases of recovery from SCD from severe LTVA due to vasospastic angina. Risk factors (hypothermia [22], ionic disorder, smoking, drug abuse [23], cold environment [22], hypomagnesemia [24], etc.) and comorbidities should be assessed before an ICD is proposed.

Another issue is the role of ergonovine and acetylcholine provocation tests [25] for prognostic rather than diagnostic purposes [9] in these patients: mixed-type multivessel spasm had a significant prognostic impact on vasospastic angina patients, whereas the arrhythmic complications during the provocation tests did not [10].

Therefore, despite the above-mentioned limitations, we considered ICD to be indicated for the secondary prevention of SCD from severe LTVA due to CAS in two of our three patients, in line with opinions defended elsewhere [26,27]. We subsequently designed an algorithm to help our departments to decide whether to implant an ICD, according to our recent cases and a review of the literature (Fig. 5).

**Figure 4.** Images of vasospastic angina before and after ergonovine administration. A. Initial angiocoronarography, left coronary view, with non-significant atheroma. B. Angiocoronarography, left coronary view, after ergonovine administration, highlighting a mid left anterior descending artery occlusion (arrow) and onset of ventricular tachycardia.

**Conclusions**

The question of ICD implantation in the secondary prevention of resuscitated SCD from severe LTVA due to vasospastic angina remains unanswered. In our opinion, arrhythmia management should not be excluded. The failure and complications of optimal medical control led us to
opt for secondary prevention by ICD implantation in LTVAs due to vasospastic angina.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

We thank Mr. McGill for editing this manuscript and Drs. Lamaison and Brahic for patient follow-up.

References