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EDITORIAL COMMENT

The need for a pacemaker after alcoholic septal ablation in hypertrophic obstructive cardiomyopathy – Harmful, neutral or beneficial?

A necessidade de *pacemaker* após ablação septal alcoólica na miocardiopatia hipertrófica obstrutiva - prejudicial, neutra ou benéfica?

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Hypertrophic cardiomyopathy (HCM) is a common genetic disease, with an autosomal dominant inherited pattern and an estimated phenotypic prevalence of 1 in 500.[1] It is characterized by the presence of left ventricular (LV) hypertrophy unexplained by other cardiac, systemic, or metabolic diseases.[1] Diagnosis is established when two dimensional (2D) echocardiography or cardiovascular magnetic resonance shows a maximal end-diastolic wall thickness of ≥15 mm anywhere in the LV or a more limited hypertrophy (of 13–14 mm) in family members of a patient with HCM or in the presence of a positive genetic test.[1,2] Management and prognosis in HCM patients are mainly dependent on the prevention of sudden death; presence of obstructive or non-obstructive related heart failure and atrial fibrillation.[1,2]

Obstructive HCM is defined as a dynamic left ventricular outflow tract (LVOT) pressure gradient ≥30 mmHg and is present in 70% of all patients referred to specialized centers. Current European and American guidelines recommend septal reduction therapies (surgical myectomy or percutaneous alcohol septal ablation (ASA)) for obstructive HCM patients with a resting or provoked LVOT gradient ≥50 mmHg and medically-refractory, moderate to severe symptoms (NYHA class III–IV).[1,2] For decades the debate centered around whether adults eligible for both procedures should be referred to a newer, minimally invasive percutaneous procedure or to a more consolidated open heart surgery. The United States clearly advocating for surgical myectomy; the rest of the world adopting a more favorable position toward ASA. Randomized controlled trials comparing both strategies are unfortunately still lacking. But as experience with ASA increased, collected data and several meta-analyses revealed similar clinical efficacy in terms of symptom improvement/resolution (despite a more rapid and significant gradient reduction with surgery) and similar procedure-related mortality and long-term survival when procedures were performed in experienced centers.[1,2] Promisingly, both successful surgical myectomy and ASA confer a longevity that equals that observed in the general population.[3,4] These facts have translated into the clinical guidelines, where non-surgical candidates are referred for ASA; patients with associated cardiac diseases requiring surgical correction to surgical myectomy and no clear preference is given to any one technique when both are acceptable.[1,2] The exception being children, adolescents and young adults where myectomy is still preferred.[2]

But there are differences between the two techniques. ASA is more frequently associated with pacemaker

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implantation due to heart block and reinterventions for residual obstruction.[1,2,5] Myectomy requires sternotomy, with patients experiencing more pain and longer recovery times, and is associated with higher rates of periprocedural stroke.[1,2,5]

Pacemaker implantation after ASA has been reported in up to 20% of patients,[6] with more recent meta-analyses referring to a two-fold increase in risk in relation to myectomy (10% vs. 5%, p<0.001).[6] This happens because of the contribution of the coronary septal artery branches to the cardiac conduction's system blood supply (in particular to the right bundle branch).

The issue addressed by Grazina et al. in the article ''*Permanent pacemaker implantation after alcoholic septal ablation induced complete heart block: long-term impact*''[7] is therefore a pertinent and clinically important one for the every 1 in 10, to 1 in 5 patients requiring a pacemaker after ASA (10–20%).[5,6] Is their long-term outcome similar to ASA patients uncomplicated by pacemaker implantation, and therefore similar to an age and sex-matched population? Is it better? Dual pacing has been suggested for LVOT obstruction reduction in the past and could increase ASA's effectivity by further reducing the LVOT gradient or by allowing an up titration of gradient reducing medication. This said, results with dual-chamber pacing have not been consistent in the past and are not favored in the most recent guidelines.[1]

Or could pacemakers adversely affect ASA outcomes? Pacemaker implantation is not risk free, with periprocedural vascular, infectious, and pulmonary complications.[8] And in the long-term, pacemakers are associated with pacing induced cardiomyopathy, atrial fibrillation, lead failure, device malfunction and infection (pocket infection and endocarditis).[8]

In this retrospective analysis, 97 of 109 patients who underwent ASA between 2009 and 2020 were evaluated (12 were excluded, presumably for previous pacemaker/ICD implantation). Mean age was 65.2 years, 68% were female. Sixteen patients (16.5%) implanted a pacemaker during hospitalization (three with a defibrillator lead).[7] At two year follow-up, despite low programmed heart rates and the use of pacing reduction algorithms, median pacing percentage was 83%, with no patients with ventricular pacing rates below 1% and only 12.5% with 1–5% of pacing, suggesting correct selection for pacemaker and continued need for pacing[7] (although post-pacemaker increase in betablocker or calcium channel blocker cannot be ruled out).

Short-term mortality was excellent, with no in-hospital mortality for patients with or without pacemaker implantation after ASA. And pacemaker implantation did not add to short-term morbidity, with no pacemaker procedure-related complications (vascular, pocket-related, or pulmonary) being reported (and assumedly no endocarditis, although not specifically stated).[7]

Patients were followed for three years. All-cause-mortality at one-year was 1% in the no pacemaker group and 0% in the pacemaker group (p=0.66) and at three years 7% and 0% respectively (p=0.26).[8] Long-term pacemaker complications were not specifically reported (including pocket infection or endocarditis, lead failure, device malfunction, newly diagnosed atrial fibrillation or pacemaker induced cardiomyopathy), but, existing, they did not negatively impact on the primary (composite all-cause mortality and all-cause hospitalization) or secondary (composite all-cause mortality and cardiac cause hospitalization) outcomes, as these did not differ between pacemaker and no pacemaker patients (p=0.09 and p=0.22).[7]

These results mirror the very recently published study by Veselka et al.[8] based on a multinational European registry (the Euro-ASA Registry).[9] In this study, of the 1814 patients who underwent ASA, 170 (9.4%) received a pacemaker for AV block in the first 30 days post-procedure. A matched cohort of 278 was analyzed, 139 with pacemaker and 139 without. All-cause mortality at 30 days and over a mean follow-up of 4.9±4.1 years were not significantly different between both groups (p=1.00 and p=0.47).[8]

Together these two studies suggest that pacemaker for ASA induced AV block does not adversely impact outcomes post-procedurally or up to three to five years' follow-up.[7,8] This is reassuring news for the significant number of patients that require pacemakers after ASA.

Pacemaker complications, namely pacing cardiomyopathy, might have been attenuated in these studies due to:

(1) pacemaker induced reduction in LVOT obstruction (but in Grazina et al.'s study, in 1/3 of the cases, the leads were not apical[7])
(2) pharmacological reduction in LVOT obstruction due to increases in medication only possible in the presence of a pacemaker (although no data as to the percentage and dosage of betablocker and calcium antagonists after ASA is provided to evaluate this possibility), or
(3) perhaps more importantly, because of HCM's abnormally elevated LV function that may have accommodated an initial LV function decline.

However, with progressive reduction in LV function, during longer follow-ups, this may no longer hold true and heart failure related complications may become apparent only after longer periods of pacing.

Another aspect that underlines the importance of even longer follow-ups is that some pacemaker complications may take longer than three to five years to become apparent (infection, for example, is more common after a generator replacement than first implant, an impact that will only become noticeable after battery depletion, 10–15 years after ASA and pacemaker procedure).[8]

In conclusion, ASA has been accumulating data reassuring its efficacy and safety in comparison to surgical myectomy, but an increased need for pacemaker implantation is evident. Grazina et al.'s article revealed good short and medium to long-term outcomes.[7] Nevertheless, as ASA indications increase, and in particular if extended to younger populations, the evaluation of very long-term follow-ups in patients requiring pacemakers after ASA will be essential.

Last, but not least, new and potentially very useful therapeutic alternatives for obstructive HCM are the cardiac myosin inhibitors (CMi) (mavacamten and aficamten). These agents directly target the excess affinity between actin and myosin and consequent hypercontractility at the center of HCM's pathophysiology. In the VALOR-HCM study, mavacamten significantly reduced the number of patients meeting guideline criteria for septal reduction therapies (SRT) after 16 weeks of treatment.[10] Long-term freedom

from SRT is still to be determined, but results seem promising. Determination of CMI's role, as non-invasive, but long-term alternatives to SRT in obstructive HCM patients refractory to current pharmacological options will be fundamental.

Conflicts of interest

The authors have no conflicts of interest to declare.

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