Can progression to permanent atrial fibrillation be prevented by pacing?

Jens Cosedis Nielsen* and Mads Brix Kronborg

Department of Cardiology B, Aarhus University Hospital, Skejby Hospital, Brendstrupgaardvej 100, 8200 Aarhus N, Denmark.

Online publish-ahead-of-print 7 May 2014

This editorial refers to ‘Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial’, by G. Boriani et al., on page 2352.

The optimal pacing mode in patients with bradycardia has been searched for through a series of randomized controlled trials performed within the last two decades. It is well documented, and easy to understand, that single lead ventricular pacing disrupting the normal atrioventricular synchrony is associated with a higher incidence of atrial fibrillation (AF) than dual chamber pacing (DDD) preserving atrioventricular synchrony. Furthermore, in patients with sinus node dysfunction, prevention of AF seems to depend on a delicate balance between the avoidance of excess ventricular pacing and the avoidance of excessively long atrioventricular intervals, both factors promoting the occurrence of AF. Some previous studies have indicated an effect of atrial pacing algorithms in preventing AF. However, the majority of randomized trials investigating these algorithms showed no convincing effect on reducing AF, and the use of such algorithms is not recommended in the most recent guidelines on cardiac pacing.

The MINERVA randomized trial investigated the effect of a combination of preventive atrial pacing algorithms, different antitachycardia atrial pacing algorithms, and managed ventricular pacing (MVP) to minimize ventricular pacing in the subgroup of patients with bradycardia and indication for DDD pacing, who had paroxysmal or persistent atrial tachyarrhythmia without complete atrioventricular block. Using this combination of algorithms was associated with a lower risk of progression from paroxysmal or persistent atrial tachyarrhythmia to permanent AF during follow-up of almost 3 years. The effect on progression to permanent AF was statistically and clinically significant, with a hazard ratio of 0.39 when compared with normal DDD pacing.

The investigators should be credited for performing a large multicentre randomized controlled trial with a clinically relevant follow-up period investigating this topic, and for using a design with three treatment arms, two of which represented the pacing modes recommended in the current guidelines and used by most physicians—DDD pacing with a moderately prolonged atrioventricular interval or DDD pacing with MVP. In the light of previous findings, it is no surprise that incidences of death and stroke, and the hospitalization rate did not differ between treatment arms in the MINERVA trial. Few deaths and strokes were observed during the study, and the difference observed in the composite primary endpoint of permanent AF, death, or cardiovascular hospitalization was carried exclusively by a difference in progression to permanent AF. The finding that use of MVP alone had no effect on progression to permanent AF is in agreement with the results of the Danish Multicenter Randomized Trial on Single Lead Atrial Pacing versus Dual Chamber Pacing in Sick Sinus Syndrome as well as with the findings from the recent Prefer for Elective Replacement Managed Ventricular Pacing randomized (Prefer-MVP) trial.

One important limitation of the MINERVA trial needs to be considered. The study was performed as a single-blinded trial where the investigators, who were responsible for assessing the primary endpoint—including permanent AF, defined as ‘long AF duration coupled with decision not to convert the patient’—were aware of the assigned treatment of the patients. The lower incidence of cardiovascular events in the intervention group, with the pacing algorithms activated, supports that this treatment truly reduces progression to permanent AF. It cannot be excluded, however, that the single-blinded design may have introduced a bias in differentiated use of antiarrhythmic drug therapy and catheter ablation for atrial tachyarrhythmias in the three treatment arms during the conduct of the study.

The results of the MINERVA trial raise some important questions. Which pacing intervention is effective for different patient groups in preventing progression to permanent AF? Previous trials indicate that simple overdrive pacing or the combination of atrial preventive pacing algorithms used in the present study is not highly effective. Antitachycardia atrial pacing has been found to be moderately effective in terminating slow regular arrhythmias, but does not reduce AF burden. It is hard to believe that antitachycardia pacing delivered in the right atrial appendage is effective for terminating most episodes of AF, originating from the left atrium, and often with very high rate atrial activity (Figure 1). A subgroup of patients included in the MINERVA...
trial had atrial tachycardia or atrial flutter, but no documented AF. Analysis of the effect on progression to permanent AF in these subgroups may result in important information to increase our understanding of the effect of the different pacing algorithms.

Another issue to be considered when employing an increased amount of atrial pacing is device battery longevity. Will the battery drain associated with use of pacing algorithms as in the intervention group lead to premature battery depletion and need for generator replacement? This is not obvious in a study with 3 years of follow-up. In post-marketing follow-up, the EnRhythm pacemaker used in the MINERVA trial seems to have a shorter longevity than earlier and later models without this combination of pacing algorithms.9 Furthermore, in the ASSERT trial, testing atrial overdrive pacing for prevention of AF, pacemaker generator replacement for battery depletion was significantly more common in the group with atrial overdrive pacing.10 Combining the increased amount of atrial pacing with MVP to minimize ventricular pacing as in the MINERVA trial may reduce the significance of this problem, but we still need to learn that. The increased battery drain need to be balanced against the fact that quality of life was not superior in the intervention group, and that anticoagulation in these patients should be indicated according to their CHA2DS2-VASC score, not according to whether they have paroxysmal or permanent AF. Generator replacement is associated with a three-fold higher risk of device infection than first implantations, and battery longevity therefore is very important to keep in mind.11

The findings from the MINERVA trial are valid for patients who need a DDD pacemaker, who have paroxysmal or persistent AF, or other atrial tachyarrhythmia, and who do not need constant ventricular pacing. These results cannot be extrapolated to other patient cohorts such as patients without previous AF or patients who need more complex implanted devices such as cardioverter-defibrillators or cardiac resynchronization therapy devices.

Before recommending widespread use of specific pacing modes, new pacing algorithms, or alternative ways to deliver cardiac pacing—as exemplified by the different types of leadless pacing—the medical community must require testing of such new treatment options in well-designed randomized controlled trials. Results of such trials are the basis for producing new guidelines. Therefore, we have to welcome the results of the MINERVA trial, expanding our knowledge within the field of preventing progression to permanent AF by cardiac pacing.

Conflicts of interest: J.C.N. has received speaker’s fees from Biotronik, Medtronic, St Jude Medical, Biosense Webster, and Actelion, and a research grant for the MANTRA-PAF trial from Biosense Webster. M.B.K. has received speakers fees from Biotronik.

References


CARDIOVASCULAR FLASHLIGHT

Unilateral pulmonary oedema in dextrocardia

Hesham R. Omar*

Internal Medicine Department, Mercy Medical Center, 1410 N 4th Street, Clinton, IA 52732, USA

*Corresponding author. Tel: +1 3127149272, Email: hesham.omar@apogeephysicians.com

A 65-year-old male was hospitalized for progressive shortness of breath, orthopnoea, and haemoptysis. He is known to have situs inversus totalis and was being treated for non-ischaemic dilated cardiomyopathy, HIV, and diabetes mellitus. On examination, he was tachypnic, tachycardic, afebrile with jugular venous distension, bilateral lower extremity oedema, left lung basal crackles, and a pansystolic murmur over the cardiac apex radiating to the right axilla and S3 gallop. B-natriuretic peptide (BNP) was 1800 pg/mL (normal ≤ 100) and white blood cell count was normal. Chest X-ray showed left lung opacity (Panel A) that occupied the upper and middle lobes of the trilobed left lung on CT scan (Panels B and C) which also ruled out pulmonary embolism. Echocardiogram showed reduced left ventricular systolic function and moderate mitral regurgitation. We challenged the emergency department diagnosis of pneumonia and intravenous diuresis was instated which rapidly resolved the patient’s symptoms with marked improvement in the left lung opacity 48 h after admission (Panel D), conforming to the diagnosis of unilateral pulmonary oedema (UPE). UPE is rarely encountered in congestive heart failure and is associated with higher mortality than bilateral pulmonary oedema due to the delay in diagnosis. It usually involves the right upper lobe (contralateral to the heart) with main explanation being a severe mitral regurgitation jet that predominantly affects the upper right pulmonary vein. Other explanations include the poorer lymphatic drainage of the right lung, decreased flow in the left pulmonary artery due to compression by the left-sided cardiac enlargement, prolonged rest on one side in patients with cardiac decompensation, or if there is pre-existing disease affecting the parenchyma or vasculature of a lung. In the presented case, UPE occurred in the left (contralateral to the heart) upper and middle lobes (notice the arrows at fissure sites in Panel C) as the patient had situs inversus with dextrocardia. Important clues that aid in achieving the diagnosis are the clinical evidence of congestive heart failure, absence of symptoms and signs of infection, elevated BNP, and normal procalcitonin. UPE can be confused with pneumonia leading to inappropriate initial therapy and hence the importance of maintaining a high index of suspicion for timely diagnosis and management.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com.