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Inherited and modifiable factors need to be identified in young patients with atrioventricular block

Eva Roseboom, Alexander H Maass

Atrioventricular block (AVB) is among the leading diagnoses requiring pacemaker implantation. The incidence of this cardiac conduction disorder increases with age: from the UK Biobank, a community-dwelling cohort of approximately half a million participants, conduction disorders were far more present in those ≥65 years of age versus under the age of 55 (55/10,000 vs 11/10,000, respectively).1 AVB is defined as delayed or interrupted impulse conduction and can be caused by anatomical or functional disorders of the conduction system. An extrinsic or physiological AVB can be secondary to increased parasympathetic tone, and is often self-limiting and does not require therapy. Intrinsic or pathological AVB is subdivided into supraventricular and infraventricular, the former being predominantly benign and the latter requiring treatment. Intrinsic AVB can be acquired by a wide variety of underlying diseases which cause infiltration or fibrosis in myocardial tissue, or imbalance to the otherwise healthy conduction system. When there is no overt underlying cause for AVB, it is referred to as idiopathic. The presumed main theory is fibrosis of the conduction system, which is probably correct for the elder population. In the young, however, caution should be exercised, for this appears to be a group at risk. A previous study in otherwise apparent idiopathic AVB under the age of 50 showed an hazard ration (HR) of 6.8 within the first 5 years of pacemaker implantation on a composite endpoint of death from any cause and hospitalisation due to heart failure, ventricular tachyarrhythmias or cardiac arrest when compared with healthy controls.2 The reason for this substantially elevated risk is not completely clear, but is likely associated with a concealed underlying disease. A different theory suspects younger patients to be more prone to pacing-induced left ventricular dysfunction.3

Dysskilde and colleagues present extensive data on familial risk of AVB.4 With access to a nationwide cohort of all pacemaker and implantable cardioverter-defibrillator (ICD) implantations, they sought out consecutive Danish patients receiving a first-time pacemaker for AVB, only including mothers, fathers and sibships through data on parental links via civil registration. During a period of 37 years, they identified 26,544 index patients who received a first-time pacemaker due to AVB. The median age of parental index cases was 76.2 and 75.1 years (maternal and paternal, respectively) and was substantially higher than the median age of index sibling (51.4 years). They observed an relative risk (RR) of 2.3 (95% CI 1.9 to 2.7) of developing AVB for offspring to index parents compared with the general population, regardless of prespecified cardiovascular risk factors. For sibships, the RR was 3.5 (95% CI 2.3 to 5.4). However, we feel the most striking discovery lies in the age-related risk: for parental index cases who received their first pacemaker before the age of 50 years there was a 10-fold higher risk for offspring to develop AVB (RR 15.8 and 10.0 for maternal and paternal, respectively). As the index patient aged, the RR declined.

As the authors speculated, higher RR for offspring or sibships of young index patients can partly be due to (previously unknown) genetic factors. A recent study analysed a small cohort of 32 patients under the age of 55 years receiving pacemaker implantation for otherwise unexplained bradyarrhythmias. Over 50% had ≥2 ‘red flags’ (clinical or instrumental abnormalities suggestive for genetic cardiomyopathies) and were offered genetic testing. Interestingly, 10 out of 15 patients tested had pathogenic mutations, of which four cases for known genes associated with channelopathies or cardiomyopathies (SCN5A and LMNA). Six had variants of uncertain significance but were genes related to other cardiac diseases (ie, hypertrophic or dilated cardiomyopathy, long QT syndrome).5 Genetic screening should thus be performed in most young patients with acquired AVB, especially in patients with a family history of cardiac conduction disorders, sudden cardiac death (SCD) or cardiomyopathies. Before suspecting a genetic predisposition for AVB, however, other acquired underlying disorders should be ruled out.

AVB due to ischaemic heart disease, electrolyte imbalance or cardiomyopathy can easily be discovered with minimum additional tests which are often already available, or because patients present with symptoms. Yet, not all underlying pathology is manifest at time of presentation. Overt ST-elevation myocardial infarction can be accompanied by AVB; however, stable coronary artery disease (CAD) can also cause AVB. An earlier British study analysed 30 patients aged 45–65 with paroxysmal or permanent AVB. Of those, 13 (43%) had severe CAD corresponding with the site of the AVB (eg, left anterior descending coronary artery stenosis associated to infranodal conduction delay).6

Sarcoidosis, a multisystem granulomatous infiltrative disease, is known to affect myocardial tissue causing AVB, heart failure, ventricular tachycardia (VT) and SCD. Cardiac sarcoidosis (CS) is a notoriously difficult diagnosis, especially when isolated. A definite histological diagnosis is obtained by endomyocardial biopsy, a procedure subject to sampling error due to the heterogeneous distribution. A clinical diagnosis requires histological proof of extra-CS and otherwise claims of cardiac involvement, such as unexplained left ventricular ejection fraction<40%, sustained VT, advanced heart block, patchy uptake on positron emission tomography or late gadolinium enhancement on cardiac MRI. A Finnish study reported histological CS and giant cell myocarditis (GCM) in respectively 19% and 6% of 72 patients <55 years who underwent pacemaker implantation for initally idiopathic AVB.7 Alarming, 39% of patients with CS or GCM had a major adverse cardiac event during an average follow-up of 2 years. We feel this corroborates the importance of additional imaging, for in AVB due to CS pacing might not suffice and an ICD can be indicated.

Diagnosing the underlying disease can in some cases prevent unnecessary pacemaker implantations, especially in infectious aetiologies. Bacterial, viral or parasitic myocarditis can generate transient high-degree AVB. A previous study by van der Linde showed AVB in 77% of patients with Lyme carditis, a disseminated infection of Borrelia burgdorferi which is tickborne and endemic in Europe.8 Lyme carditis is a clinical diagnosis based on positive Lyme serology and signs of acute myocarditis. It is almost always self-limiting after antibiotic treatment and rarely requires permanent pacing. AVB following myocarditis as a result infection
with Trypanosoma cruzi in Chagas disease is more prevalent in specific regions of South America, and associated with high mortality due to heart failure and ventricular arrhythmias. Viral myocarditis can cause AVB, in most cases related to severe myocardial infiltration but can also occur without overt myocardial dysfunction. In addition to infectious disease, metabolic disorders should also be ruled out as they can cause reversible AVB. Our standard laboratory testing protocol is shown in table 1.

We feel a detailed and methodical preimplantation analysis should be performed in all young patients with new-onset AVB, the importance of which is also emphasised in the recently published European Society of Cardiology guidelines on cardiac pacing. Before pacemaker implantation, we have a regional agreement between community hospitals and our tertiary referral centre to discuss all patients under 60 years of age with AVB with at least two experienced cardiac electrophysiologists. Furthermore, we have a protocol in place that can aid physicians who are less accustomed to the work-up of these patients (figure 1).

In young patients with AVB, it is critical to identify underlying heart disease to determine who is at risk for SCD and might benefit from ICD therapy, and to define proper treatment in reversible AVB to prevent unnecessary device implantations and unnecessary right ventricular pacing with the risk of dyssynchronous heart failure.

**Table 1  Laboratory investigations to be performed in young patients with AVB**

<table>
<thead>
<tr>
<th>Primary laboratory testing</th>
<th>Additional laboratory testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood count</td>
<td>ACE</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Soluble interleukin-2 receptor levels</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>M-protein</td>
</tr>
<tr>
<td>High-sensitive troponin</td>
<td>Heavy and light chains</td>
</tr>
<tr>
<td>N-terminal pro-brain natriuretic peptide</td>
<td>Antinuclear antibodies</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>Transferrin saturation</td>
</tr>
<tr>
<td>Lyme serology</td>
<td>Serum ferritin levels</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>Viral serology</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Genetic testing</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; AVB, atrioventricular block.

The present study by Dysskilde et al emphasises the potential role inheritable risk factors in young patients with AVB. Genetic testing should be offered after other underlying disease has been ruled out. Even if genetic testing or routine ECGs screening is not desired by patients, family members could be instructed to be alert of symptoms related to bradycardia.

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