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VIEWPOINT
Arrhythmias

Anti-Ro/SSA-antibody testing for isolated atrioventricular block in adults: a diagnostic and therapeutic work-up

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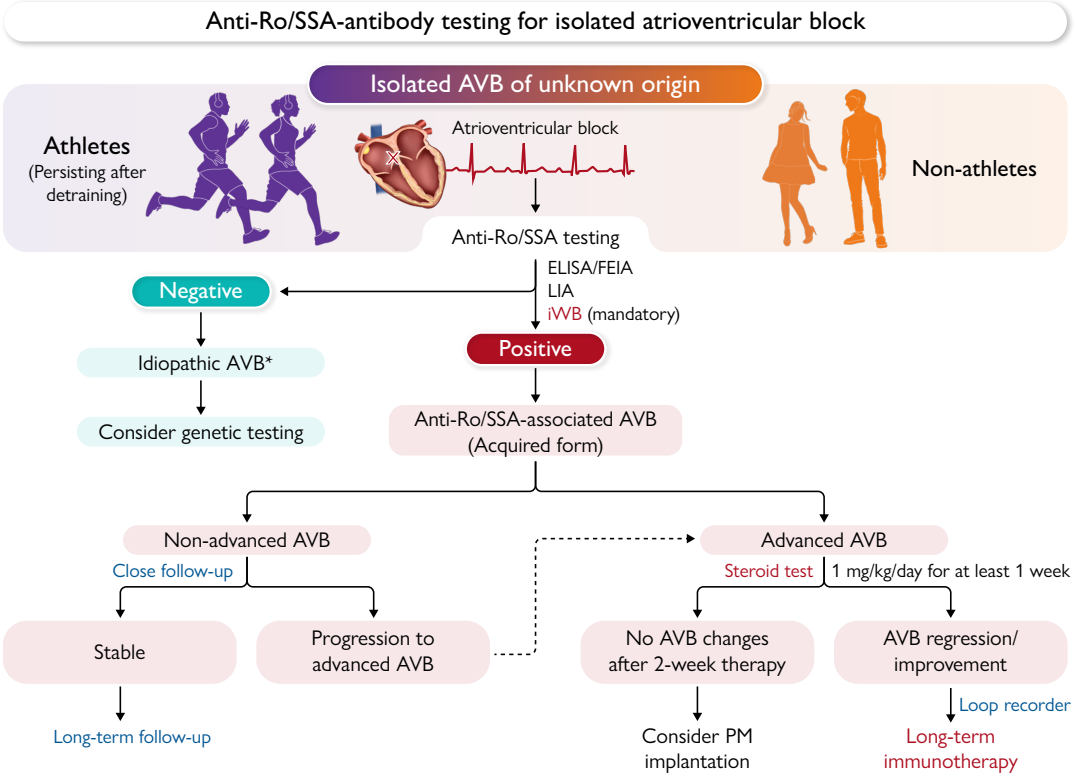
Graphical Abstract



Proposed diagnostic and therapeutic work-up for adults with AVB of unknown origin
*In the case anti-Ro/SSA testing is negative also in patient's mother, ruling out an anti-Ro/SSA-associated late progressive congenital form too[2,6,7]

Anti-Ro/SSA, anti-Ro/Sjogren syndrome-related antigen A-antibodies; **AVB**, atrioventricular block; **ELISA**, enzyme-linked immunosorbent assay; **FEIA**, fluoro-enzyme immunoassay; **iWB**, immune-western blotting; **LIA**, line-blot immunoassay; **PM**, pacemaker

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The recently released 'Abnormal electrocardiogram findings in athletes: a consensus statement of the European Association of Preventive Cardiology of the European Society of Cardiology' by Finocchiaro *et al*.,[1] references, for the first time, the potential relevance of autoimmunity in the pathogenesis of atrioventricular block (AVB) of unknown origin, i.e. without structural heart disease or other known causes, in athletes. Specifically, anti-Ro/SSA-antibody testing is now part of the diagnostic work-up of athletes with isolated AVB, also including non-advanced forms such as marked PR-interval prolongation >400 ms and diurnal second-degree Mobitz-1 AVB, as it could clarify the pathogenesis of the disorder and open new therapeutic avenues.[1]

This indication stems from an accumulating body of evidence which demonstrates that anti-Ro/SSA antibodies, specifically the anti-Ro/SSA-52kD subtype, can cross-react with and inhibit the cardiac L-type calcium channel $Ca_v1.2$,[2,3] critically involved in promoting electrical conduction through the atrioventricular node and chronically downregulated in intensively trained athletes.[4] As a result, predisposed subjects with genetically determined and/or acquired low calcium channel reserve, such as athletes, can develop autoimmune AVB in the presence of circulating anti-Ro/SSA antibodies, even severe forms usually treated with pacemaker implantation. However, increasing evidence indicates that in these patients immunomodulating interventions, i.e. steroids as initial therapy gradually tapered and combined with steroid-sparing medications such as hydroxychloroquine (HCQ), azathioprine, and/or high-dose intravenous immunoglobulins, are safe and effective in rapidly and persistently reverse the conduction defect, avoiding or delaying pacemaker positioning (*Table 1*).[5–8]

Importantly, large studies demonstrated that these mechanisms have an unanticipated clinical and epidemiological impact in the general population and including among athletes. In 2015, Villuendas *et al*.[9] were the first to report that in a historical cohort of ∼3500 patients who underwent pacemaker implantation, ∼10% of those presenting with AVBs of unknown origin showed circulating anti-Ro/SSA antibodies. More recently, a nationwide retrospective study conducted in Israel on >100 000 subjects provided evidence that anti-Ro/SSA-positive individuals have a 2-times higher risk of AVB, either complete or incomplete, compared with controls, regardless of confounding factors, including history of structural heart disease or autoimmune disease (AD).[10] Moreover, our group found that in a prospective cohort of 2536 young athletes without structural heart disease, all cases presenting with advanced AVB had circulating anti-Ro/SSA-52kD antibodies, always in the absence of AD.[3] Collectively, such findings strongly support the view that anti-Ro/SSA antibodies represent an epidemiologically important cause of isolated AVB in adults of the general population, potentially reversible by immunomodulating therapies. Indeed, although such autoantibodies are frequently detected in patients with AD, such as Sjögren syndrome and systemic lupus erythematosus, they can be also found in a significant percentage of apparently healthy subjects (up to 2.5–8%, progressively increasing with age).[11,12]

To further substantiate and broaden this viewpoint, a recent cohort study involving ∼800 patients with heart failure, in most cases elderly, found that in these subjects anti-Ro/SSA positivity was independently associated with a 2.5-times higher risk of AVB, independent of a history of AD.[13] Such findings intriguingly suggest that the electrophysiological effects of these antibodies may be relevant also in elderly patients with concomitant structural heart disease, likely unmasking latent AV conduction disturbances due to ageing and/or tissue injury.

Based on this mounting body of evidence, the Consensus Statement included anti-Ro/SSA testing in the diagnostic flow chart to follow in athletes with AVB of unknown origin.[1] However, we believe that some important details regarding the specific laboratory anti-Ro/SSA testing methods to be used in clinical practice, likely omitted due to space limitations, must be presented to avoid incorrect labelling of a significant number of athletes (and non-athletes) as negative. Moreover, likely for the same reason, the authors did not provide any indication regarding the management and follow-up of these subjects, particularly in those with advanced AVB. In light of these considerations, this 'Viewpoint' seeks to address this knowledge gap by providing crucial additional information for clinical cardiologists and sports medicine physicians, along with a recommended diagnostic and therapeutic approach for routine practice.

First, it needs to be specified that while anti-Ro/SSA antibodies are frequently measured as a whole, they include two different subtypes, i.e. anti-Ro/SSA-52kD and anti-Ro/SSA-60kD,[14] the anti-52kD component being the only arrhythmogenic.[2,3,15] Indeed, although strictly associated at the molecular level to constitute the Ro-ribonucleoprotein, the 52 and 60 kD subunits are structurally very different,[14] the 52 kD component being the only one for which a significant sequence homology with the extracellular loop of the L-type calcium channel $Ca_v1.2$ has been demonstrated.[2] Thus, it is essential that the anti-Ro/SSA-52kD-antibody subtype is specifically demonstrated in a patient with isolated AVB to define it as anti-Ro/SSA-associated.

Second, in clinical practice the most widely used laboratory methods for anti-Ro/SSA-antibody detection are immune-enzymatic tests (ELISA/FEIA) and line-blot immunoassay (LIA), all based on recombinant Ro antigens as substrate.[2,14] However, accumulating evidence indicates that immune-western blotting (iWB), using the extracted native proteins, is by far the most specific and sensitive test for detecting arrhythmogenic anti-Ro/SSA-52kD antibodies, probably due to the different molecular characteristics of the revealing antigen used.[2,14] Specifically, a recent study demonstrated that approximately only 1 in every 10 isolated AVB patients who tested anti-Ro/SSA-positive using iWB also tested positive by ELISA/FEIA or LIA.[2] Unfortunately, due to economic reasons, iWB is ever less commercially available worldwide, and, to our knowledge, the *ANA/AMA Immunoblot* by AID (https://www.aid-diagnostika.com/en/kits/immunoblots) is the only one still available on the market and perhaps not for long. As a result, if patients with isolated AVB are tested for anti-Ro/SSA antibodies by only employing ELISA/FEIA or LIA methods, as it usually occurs in clinical practice in most centres, there is a high probability that even if actually positive, these subjects will falsely test negative, depriving them of important therapeutic options, in the most serious cases potentially preventing or delaying pacemaker implantation.

Accordingly, the following diagnostic and therapeutic work-up is proposed and summarized in the *Graphical Abstract*. All subjects, both athletes and non-athletes, presenting with

Table 1 Clinical evidence supporting the effectiveness of immunomodulating therapies in improving or resolving isolated atrioventricular block in adults associated with anti-Ro/SSA antibodies

Study	Patients *n*	Age/sex	Autoimmune disease	AVB degree	Acute treatment	Short-term outcome	Time to response	Chronic treatment	Follow-up time	Long-term outcome
N Engl J Med., 2013[5]	1	26 years/♀	No	III°AVB	M-Pred 1 mg/kg/day	Normal AV conduction	Few days	AZA 100 mg/day + M-Pred 4 mg/day	12 months	Normal AV conduction
HeartRhythm Case Rep., 2015[6]	2	29 years/♀	No	III°AVB	M-Pred 1 mg/kg/day	Normal AV conduction	Few hours/days	NA	NA	NA
		21 years/♀		High-grade AVB		I°AVB		AZA 100 mg/day + Pred 6.25 mg/day	9 months	I°AVB
Circ Arrhythm Electrophysiol., 2022[8]	1	65 years/♂	No	High-grade AVB	M-Pred 1 mg/kg/day	I°AVB	Few hours	HCQ 400 mg/day	25 months	I°AVB
JACC Clin Electrophysiol., 2023[2]	9	55 years (median)/5♂-4♀	Autoimmune thyroiditis (*n* = 2) Guillain–Barrè syndrome (*n* = 1)	III°AVB (*n* = 4) High-grade AVB (*n* = 3) II°AVB (*n* = 1) I°AVB (*n* = 1)	*n* = 9 M-Pred 1 mg/kg/day	Normal AV conduction (*n* = 3) I°AVB (*n* = 4) II°AVB (*n* = 2)	Few hours/days	*n* = 5 HCQ 400 mg/day or AZA 100 mg/day or IVIG 2 g/kg/month ± Pred 6.25 mg/day	14.5 months (median)	Normal AV conduction (*n* = 3) I°AVB (*n* = 2)

I°/II°/III°AVB, first/second/third-degree atrioventricular block; AZA, azathioprine; HCQ, hydroxychloroquine; IVIG, high-dose intravenous immunoglobulins; M-Pred, methylprednisolone; Pred, prednisone; NA, data not available.

isolated AVB of unknown origin should undergo comprehensive anti-Ro/SSA-antibody testing with different methods, among which iWB is mandatory to be included. In the case that at least one test is positive for circulating anti-Ro/SSA antibodies, specifically the anti-Ro/SSA-52kD subtype, the diagnosis of anti-Ro/SSA-associated AVB shall be made.

Among such subjects, those presenting with advanced AVB, i.e. higher than second-degree Mobitz-1 (second-degree Mobitz 2, 2:1, high-grade, and third-degree AVB), should undergo a steroid test (1 mg/kg/day prednisone-equivalent for at least 1 week, better intravenously for the first 3 days). If, during this treatment period, the AVB resolves or improves to a non-advanced form, a long-term immunomodulatory treatment could be started followed by a loop-recorder placement to monitor therapy effectiveness over time. A proposed therapeutic regimen consists in the early introduction of a steroid-sparing medication, primarily hydroxychloroquine (azathioprine, high-dose intravenous immunoglobulins, or other immunomodulating drugs might represent alternatives), followed by a slow steroid tapering (e.g. 6.25 mg prednisone, i.e. a quarter of tablet of 25 mg, every 7–10 days until reaching a dose of ∼15 mg/day; then 1.25 mg, i.e. a quarter of tablet of 5 mg, every 7–10 days) until reaching the minimum effective dose, ideally <5 mg/day. Conversely, in subjects with no significant changes even after prolonged full steroid therapy for 2 weeks, pacemaker implantation should be considered.

In subjects with less advanced anti-Ro/SSA-associated AVB (including marked PR-interval prolongation >400 ms and diurnal second-degree Mobitz-1 AVB), a therapeutic intervention will not be indicated, but a close follow-up should be started. If the AVB degree is stable, the follow-up should be maintained in the long-term, progressively prolonging time intervals among controls (3 months, 6 months, 1 year). Conversely, if a progression to advanced AVB is observed, the work-up discussed above shall be followed (*Graphical Abstract*).

In conclusion, in all athletes and more broadly in all adults with isolated AVB, anti-Ro/SSA testing is strongly recommended, provided that the laboratory techniques employed also include native Ro52 antigen-based iWB, as this may open the way to innovative anti-arrhythmic strategies based on immunomodulatory interventions. Collectively, we strongly hope that companies will be motivated to restore broad access to iWB and to develop new high-throughput techniques capable of identifying the greatest number of subjects, frequently young, who could be candidates for alternatives to pacemaker therapy. Indeed, from a commercial perspective, it can be anticipated that the number of subjects across Europe eligible for anti-Ro/SSA testing would be substantial. Based on the data released by the Italian National Olympic Committee, in Italy only the overall sports community, competitive or non-competitive, consists of ∼12.8 million athletes (www.coni.it). Since the expected prevalence of anti-Ro/SSA-associated advanced AVB in this population is 0.12%,[3] it can be estimated that there are ∼15 000 cases in Italy alone and therefore >150 000 throughout Europe (which has a population more than 10 times than Italy). While these numbers are significant, the actual number of subjects eligible for testing is far greater. First, as indicated in the Consensus Statement, athletes with less advanced AVBs should also be tested, and these forms are, at least, as common as advanced AVB.[1] Moreover, there is an even larger population of non-athletes, further and massively expanding these numbers. In this regard, a recent study estimated that in the general population <50 years there may be an incidence of ∼4–5 cases of anti-Ro/SSA-positive advanced AVB per year per 1 million inhabitants,[2] i.e. >3000 new cases every year throughout Europe.

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Declarations

Disclosure of Interest

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Correction

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Correction to: Sudden cardiac death after myocardial infarction: individual participant data from pooled cohorts

This is a correction to: Niels Peek, Gerhard Hindricks, Artur Akbarov (et al), Sudden cardiac death after myocardial infarction: individual participant data from pooled cohorts, *European Heart Journal*, Volume 45, Issue 43, 14 November 2024, Pages 4616–4626, https://doi.org/10.1093/eurheartj/ehae326

The name of the 48th co-author should read: “Ivo Roca-Luque”. In section Disclosure of interest, initials “I.R.” should read “I.R.L”.

The errors are outlined only in this correction notice to preserve the version of record.