Increased stimulation threshold in a patient with autoimmune disease: successful management with oral prednisolone and azathioprine

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We report a patient with a systemic vasculitis and heart involvement with complete atrio-ventricular block. After pacemaker implantation, the stimulation threshold significantly increased resulting in exit block. Two adjunctive ventricular leads were implanted with temporary threshold improvement. Oral glucocorticoids decreased the stimulation threshold with a transient, dose-dependent efficacy but with remarkable side effects. Azathioprine, an immunosuppressive agent, obtained a sustained decrease of the stimulation threshold.

Introduction
After transvenous permanent pacing, the stimulation threshold usually stabilizes within ~2 months.1,2 However in some patients, a further rise in the stimulation threshold over a long period can result in exit block. A possible explanation is an excessive chronic inflammation around the electrode tip. Conduction disturbance and atrio-ventricular (AV) block have been reported in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and HLA-B27-associated disease.3–5 In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, a group of small-vessel vasculitis including Wegener’s granulomatosis, microscopic polyangiitis, and the Churg–Strauss syndrome, conduction disturbances are very rare. These vasculitis share common features such as involvement of arterioles, capillaries, and venules especially in kidneys and lungs. Moreover, the involvement of ANCA represents the common pathogenesis. Heart failure and pericarditis are the most frequent cardiac manifestations of ANCA-associated vasculitis. Few cases of AV block are reported.6–9

We report a patient with p-ANCA vasculitis, complete AV block, and a rise in the stimulation threshold, treated with prednisolone and azathioprine.

Case report
In September 2002, a 64-year-old woman was referred to our hospital due to dizziness. An electrocardiogram (ECG) showed a complete AV block. Two years earlier, an inflammatory cerebral mass involving intracranial nerves had been diagnosed and treated with prednisolone. A diagnosis of p-ANCA-positive vasculitis was made and a daily treatment of prednisolone 5 mg was started. Other autoimmune tests, including anti-Ro (ribonucleoprotein) SS/A and SS/B, were negative.

An echocardiogram showed normal ejection fraction, mild mitral, and aortic insufficiency. The patient underwent permanent dual-chamber pacemaker implantation (atrial endocardial electrode: St Jude Membrane 1474T; ventricular endocardial electrode: St Jude Membrane 1470T—lead 1). Atrial and ventricular threshold and impedance at the implantation were normal. Since March 2003, an increase in ventricular threshold was detected (3 V × 0.4 ms—Figure 1). In October 2003, the patient suffered from acute pancreatitis and prednisolone was discontinued. In November 2003, after a pre-syncopal episode, the ECG revealed regular delivery of pacing spikes with no ventricular capture. Battery depletion, lead fracture, or dislodgement was excluded. Lead impedance was unchanged. Serum electrolytes and pH were normal. No additional drugs had been started in the previous weeks. An echocardiogram showed moderate mitral and aortic incompetence with normal left ventricular ejection fraction. Prednisolone (5 mg po daily) was resumed and the stimulation threshold decreased. Two months later, an exit block was again detected (Figure 1). A new endocardial ventricular active fixation catheter was inserted in the right ventricular apex (lead 2). At the implantation time, threshold and impedance values were, respectively, 0.9 V × 0.5 ms and 884 ohm. In the following months, further progressive increase in the threshold was
observed (Figure 2). In June 2004, the patient underwent mitral and aortic valve replacement because of a severe aortic and mitral regurgitation; an epicardial catheter was implanted but not connected with the pacemaker (lead 3).

In June 2005, ventricular threshold was $5.5 V \times 1.5 ms$ and initial battery depletion was observed. A new battery was connected with the epicardial catheter (lead 3) resulting in the most favourable acute threshold ($3.2 V \times 1.5 ms$—Figure 3). Four months later, a new episode of exit block was detected. Uptitration of daily prednisolone to 50 mg uid improved the capture threshold. Corticosteroid was slowly reduced, but in October 2006, when the patient was on a 15 mg dose, a new exit block occurred. A combination of azathioprine (25 mg uid) with prednisolone (20 mg uid) was started. An improvement of the threshold (Figure 3) was obtained and maintained also with further reduction of prednisolone (10 mg uid) in combination with uptitration of azathioprine (50 mg uid). In January 2007, prednisolone was stopped due to vertebral collapse. A new battery was implanted for depletion and was connected with the first endocardial electrode implanted (lead 1) that showed the best acute threshold ($1 V \times 0.5 ms$). In the subsequent 20 months of follow-up, no threshold increase was detected (stable threshold $1 V \times 0.4 ms$) while the patient was on azathioprine 50 mg uid.

**Discussion**

In this patient, suffering a p-ANCA vasculitis with a systemic involvement, the stimulation threshold repeatedly increased resulting in exit block. The heart was diffusely involved with endocardial, valves, and conduction system localization. Excessive inflammation around the catheter tip, related to the autoimmune disease, accounts for the occurrence of exit block. As previously reported, oral steroids, acting as anti-inflammatory and antifibrotic agent, decrease the stimulation threshold but with only transient and dose-dependent efficacy and remarkable side effects. In our patient, immunosuppressive azathioprine succeeded in a better and sustained decrease in the threshold. This supports the hypothesis that exit blocks were strictly related to the autoimmune disease.

To our knowledge, medical literature does not report increases in pacing threshold in patients with autoimmune disease and restoration of cardiac pacing with azathioprine.

We conclude that in patients with autoimmune diseases and permanent pacing, an increase in the threshold could be conservatively managed with immunosuppressive therapy, aimed at reducing the inflammatory state of the disease along with the side effects of high dose of corticosteroids.

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**References**


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**Figure 2** The line shows ventricular threshold ($V \times ms$) of the endocardial RV electrode Medtronic Capsurefix (lead 2). The daily dosage of oral prednisolone is shown in grey.

**Figure 3** The line shows ventricular threshold ($V \times ms$) of the epicardial RV electrode (lead 3). The daily dosage of oral prednisolone is shown in grey. In October 2006, azathioprine was started, in association with prednisolone.


