Aims An antiarrhythmic effect of spinal cord stimulation (SCS) has been recognized in an animal model. The actual mechanism is still mainly unknown. An adrenergic output reduction has been advocated as the main mechanism, although a modulation effect on the arrhythmic substrate has not yet been investigated. We studied T-wave alternans (TWA) modifications to test the hypothesis that SCS affects the arrhythmic substrate.

Methods and results We performed TWA assessment in three high-risk patients who previously had undergone implantation of both implantable cardioverter defibrillator and SCS to treat refractory angina. The test was performed after switching off the SCS and after 2 and 24 h stimulation at the default amplitude. The protocol was executed 2 months apart in order to assess the reproducibility of the results, collecting a total of 18 TWA reports. In all the three patients, we observed a significant reduction of TWA amplitude after 2 h stimulation. All the tests were classified as negative after 24 h stimulation with the nominal parameters.

Conclusion Spinal cord stimulation results in a decrease in the TWA magnitude, and thus it seems to positively affect the arrhythmic substrate in a time-dependent manner.

Keywords Cardiomyopathy; Spinal cord stimulation; Arrhythmia; T wave alternans

Introduction Spinal cord stimulation (SCD) is currently recognized as one of the major tools for the management of intractable angina. The actual mechanism of action has not yet been fully elucidated, but as a matter of fact, stimulation of the cervico-thoracic spinal segment provides an anti-ischaemic effect going well beyond the one of painkillers, as it was first believed. A great interest has recently risen about a possible antiarrhythmic effect, as sudden death and morbidity related to implantable cardioverter defibrillator (ICD)-repeated interventions are still a clinical problem in patients suffering from ischaemic cardiomyopathy and diffuse intractable coronary artery disease. In a canine experimental model, SCD was able to decrease the ventricular fibrillation threshold of the ischaemic myocardium. A comprehensive assessment of the antiarrhythmic effect of SCS has not yet been provided, particularly as far as the re-entry mechanism is concerned.

T-wave alternans (TWA) has demonstrated to be a reliable non-invasive test for the stratification of the arrhythmic risk in both ischaemic and non-ischaemic cardiomyopathy. Basically, TWA is believed to be the expression of alternating generation of short-long action potential sequences. One of the supposed mechanisms linking the generation of alternans to arrhythmogenesis is the dispersion of refractoriness across the myocardium, eventually leading to re-entry. We aimed at investigating the effect of SCD on the arrhythmogenetic substrate in patients with ischaemic cardiomyopathy by assessing TWA pattern modifications.

Methods Patients with a high arrhythmic risk profile, previously implanted with a spinal cord stimulator owing to intractable angina, were enrolled in the study. At the time of enrolment, patients were free of angina symptoms both at rest and during mild efforts, with the ongoing therapy. All three patients had undergone dual-chamber ICD implantation. The compatibility of the two devices was tested at the moment of the implantation according to the recommended protocols. Patients underwent a TWA assessment (Cambridge heart). The procedural details of the test and the criteria of interpretation have
been already described. Basically, a steady increase in the heart rate was obtained increasing the stimulation rate by steps of 5 bpm up to the target rate of 110 bpm.

All the patients were on full anti-ischaemic therapy including β-blockers titrated to the maximal tolerated dose.

The tests were classified as positive, negative, or indeterminate according to the currently accepted criteria. The maximal amplitude of the alternans (Valt max) has been recorded as well. In each patient, the test was performed after switching off the spinal cord stimulator for 24 h, after 2 h of SCS, and after 24 h. The same assessment was repeated after 2 months in order to ascertain the reproducibility of our findings.

The protocol has been approved by our local Ethics Committee.

Statistical analysis
Continuous variables are expressed as average ± standard deviation and are compared with the Friedman test.

Results
Eighteen tests were performed on three patients. The average age was 74 ± 4 years. All the patients had undergone SCS implantation because of advanced coronary artery disease, previous myocardial infarction, and repeated revascularization attempts; they were on full medical therapy and without any further interventional chances. The average ejection fraction was 32 ± 4.

All three patients displayed positive TWA reports, whereas the SCS was switched off. After 2 h of stimulation, the tests were still classified as positive, according to the classical criteria, but the quantitative analysis disclosed a significant decrease in the alternans magnitude (6.33 ± 2 vs. 2.9 ± 0.8 mcV, P = 0.02). After 24 h, all tests were negative (Figure 1). We did not observe any change in the basal heart rate and atrio-ventricular conduction among the different SCS conditions.

Table 1 summarizes the change in the TWA recordings.

Discussion
Since the first anecdotal reports of anti-ischaemic effect of SCD, a growing interest has been focused on possible clinical applications other than the analgesic one.

Some evidences show a protective effect of SCD on a canine model of ischaemia-triggered arrhythmias. Furthermore, it was previously demonstrated that regional heart denervation, possibly secondary to a scarring process or to an ischaemic insult, can lead to adrenergic supersensitivity. Thus, one of the mechanisms underlying the SCS effects could be a reduction in the adrenergic output through the sympathetic nervous network projecting to the heart. Microvolt TWA provides insight into the substrate vulnerability and gives a unique chance to investigate in vivo the effect of neuromodulation achieved by means of SCD on arrhythmic substrate remodelling and stabilization.

We observed the negativization of the alternans in all three patients after 24 h stimulation. We can reliably
exclude an aspecific effect of the SCS because TWA, although reduced, was still present after switching on the stimulator for 2 h. Thus, this finding suggests an actual time dependent remodelling effect on the arrhythmic substrate.

This effect cannot be explained only with a sympathetic withdrawal effect, because we did not observe any change in the basal heart rate and atrio-ventricular conduction; furthermore, all the patients were already on full therapy with beta adrenoreceptor blockers. Thus, a different mechanism, independent of a simple receptor-mediated neurohumoral modulation, is strongly suggested.

**Limitations**

Our findings, although quite striking, derive from a limited population. The small sample size is due to the limited number of patients with the desirable characteristics, i.e. carrier of a SCS, and displays a high arrhythmic profile. We undertake a prospective trial in order to confirm our results on strong clinical outcomes.

**Conflict of interest:** none declared.

**References**


**Table 1 Summary of the TWA test results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCS off</th>
<th>SCS on 2 h</th>
<th>SCS on 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>TWA rep: positive, Valt max: 6</td>
<td>TWA rep: positive, Valt max: 4</td>
<td>TWA rep: negative</td>
</tr>
<tr>
<td>Patient 2</td>
<td>TWA rep: positive, Valt max: 4</td>
<td>TWA rep: positive, Valt max: 2.5</td>
<td>TWA rep: negative</td>
</tr>
<tr>
<td>Patient 3</td>
<td>TWA rep: positive, Valt max: 8</td>
<td>TWA rep: positive, Valt max: 2.5</td>
<td>TWA rep: negative</td>
</tr>
<tr>
<td>Patient 1: after 2 months</td>
<td>TWA rep: positive, Valt max: 6.5</td>
<td>TWA rep: positive, Valt max: 2.5</td>
<td>TWA rep: negative</td>
</tr>
<tr>
<td>Patient 2: after 2 months</td>
<td>TWA rep: positive, Valt max: 6.5</td>
<td>TWA rep: positive, Valt max: 2.5</td>
<td>TWA rep: negative</td>
</tr>
<tr>
<td>Patient 3: after 2 months</td>
<td>TWA rep: positive, Valt max: 6</td>
<td>TWA rep: positive, Valt max: 3.8</td>
<td>TWA rep: negative</td>
</tr>
</tbody>
</table>

Valt max: maximal alternans amplitude (mcV).