# News on cardiac arrhythmias - Part I

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## Prevalence and clinical significance of sino-atrial Wenckebach block

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*Background.* **The clinical characteristics of patients with sino-atrial Wenckebach block (W-block) have not been specifically studied previously. The purpose of this study was to analyze the relation between varied clinical variables and occurrence of W-block.**

*Methods.* **In the group of 392 patients with symptoms that might be related to cardiac arrhythmias the standard electrocardiograms were reviewed to identify subjects with W-block.**

*Results.* **Of 392 patients, 28 (7%) had one or more sequences of W-block. Univariate analysis indicated that female gender and advanced age of patients, underlying heart disease, prolonged sino-atrial conduction time and prolonged sinus nodal recovery time were associated with the incidence of W-block. Stepwise discriminant analysis revealed that abnormal sino-atrial conduction time was the best predictor of W-block occurrence.**

*Conclusions.* **The W-block is often associated with prolonged sino-atrial conduction time, prolonged sinus nodal recovery time, and presence of underlying heart disease. Thus, in patients with unexplained syncope, dizziness or palpitation the occurrence of W-block suggests that structural sinus nodal dysfunction may be a cause for these symptoms.**

Second degree sino-atrial block occurs when the sinus impulses are unable to be conducted to the atria because of a block at the sino-atrial junction. Second degree sino-atrial block is of two types[1,2]. Mobitz type is easy to recognize and is marked by constant PP intervals, followed by a pause, which is a multiple of the preceding PP interval. Wenckebach type sino-atrial block (W-block) produces a more complex pattern, may resemble sinus arrhythmia or atrial premature contraction, and is one of the most difficult ECG findings to recognize by cardiologists.

The aim of this study was: 1) to evaluate the incidence of W-block among patients with symptoms that might be related to disturbances of heart rhythm, 2) to elucidate the relation of varied clinical factors, such as age, gender, structural heart disease, syncopal episodes, sino-atrial conduction time, and sinus nodal recovery time to occurrence of W-block.

### Methods

The study population consisted of 392 patients with symptoms that might be related to cardiac arrhythmias: syncope, dizziness or palpitation. All patients underwent a clinical evaluation including a history and physical examination, routine blood tests, 12-lead ECG, echocardiography, and 24-hour ECG monitoring. There were 252 males and 140 females aged 17 to 85 years (mean age 61 ± 18 years). Patients with documented sinus node dysfunction (sinus arrest > 3 s, complete or Mobitz type sino-atrial block, patients with atrial fibrillation or flutter and patients treated with antiarrhythmic drugs were not included in the study group. In 368 patients it was possible to determine sino-atrial conduction time estimated by subtracting the basic sinus cycle length from the atrial return cycle after spontaneous atrial premature beat recorded on 24-hour ambulatory ECG[3]. Additionally, electrophysiological studies were performed in 105 patients to identify an arrhythmic cause for unexplained syncope. In these patients a sinus node dysfunction was evaluated by the calculation of sinus node recovery time at basic cycle lengths of 600, 500, and 400 ms. To determine the prevalence and clinical significance of W-block, all standard ECGs were reviewed to identify patients

with this condition. The criteria for the diagnosis of W-block were the following: 1) sequence of gradually shorter PP intervals followed by a longer PP interval, which was less than twice the length of the preceding PP interval, or 2) the alternation of short and long PP intervals with a long PP interval shorter than two short PP intervals. The values calculated using Holter method sino-atrial conduction time > 150 ms and values of sinus nodal recovery time > 2 s were considered as abnormal[4,5].

**Statistical analysis.** All continuous variables are presented as mean ± SD. Comparisons of patients with and without W-block were made using the $\chi^2$ test or the Mann-Whitney's rank sum test. The discriminant analysis was used to find the best predictors that discriminate between patients with and without episodes of W-block. In this analysis, dichotomized descriptors (female, aged ≥ 60 years, presence of underlying heart disease, history of syncopal episodes, sino-atrial conduction time > 150 ms, and sinus nodal recovery time > 2 s were represented as a value of 1 if present. A p value of < 0.05 was considered as statistically significant.

## Results

Of 392 evaluated patients, 28 (7%) had one or more episodes of W-block on the 12-lead ECG. In 23 patients the sequences of W-block consisted of > 2 consecutively conducted sinus impulses before a pause. In the remaining 5 patients the W-block was type 3:2 and only 2 consecutive sinus impulses were conducted to the atrium before a blocked impulse. Patients with sino-atrial conduction abnormality were older, had a greater likelihood of a structural heart disease, and a longer sino-atrial conduction time and sinus nodal recovery time (Table I). Patients with W-block had significantly higher values of sino-atrial conduction time and sinus nodal recovery time compared with patients without W-block (Fig. 1). The mean values of sino-atrial conduction time and sinus nodal recovery time were 150 ± 59 and 2876 ± 416 ms, respectively, in the group of patients with W-block compared with 111 ± 45 and 1620 ± 689 ms, respectively, in the group of patients without W-block. Stepwise discriminant analysis of all variables with at least a trend toward predicting significance (p < 0.1) revealed that at final step the prolonged sino-atrial conduction time was the best predictor of W-block occurrence (Table II).

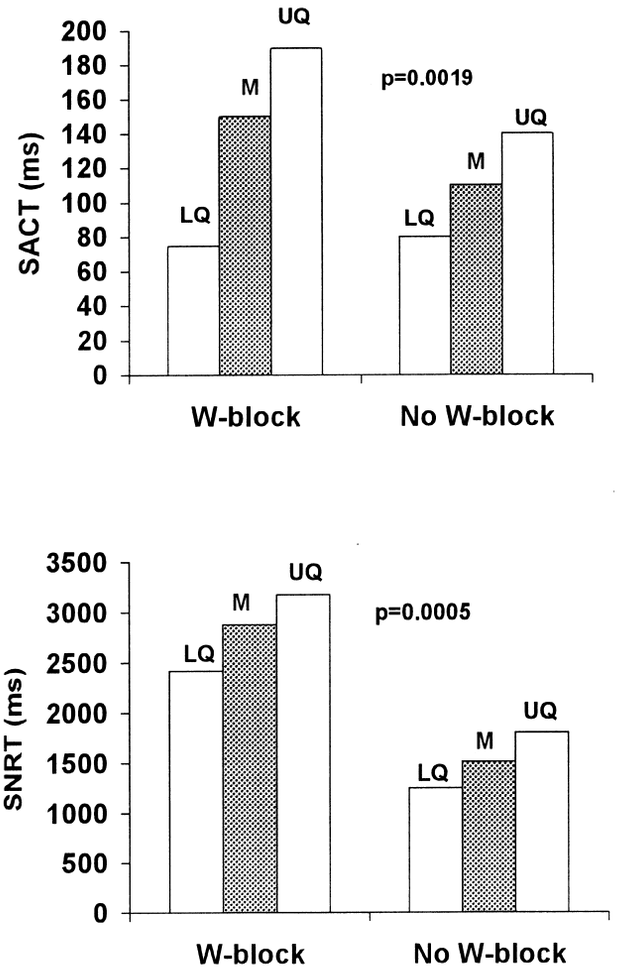


**Figure 1.** *Values of sino-atrial conduction time (SACT) and sinus nodal recovery time (SNRT) in the group of patients with sino-atrial Wenckebach block (W-block) and in the group of patients without W-block (No W-block). LQ = lower quartile; M = median; UQ = upper quartile.*

**Table I.** Univariate relation of evaluated variables to occurrence of sino-atrial Wenckebach block (W-block).

| | W-block | No W-block | $\chi^2$ | p |
|---|---|---|---|---|
| Male (%) | 46 | 66 | 4.19 | 0.0407 |
| Age > 60 years (%) | 68 | 45 | 5.70 | 0.0169 |
| Structural heart disease (%) | 71 | 46 | 6.51 | 0.0107 |
| Ischemic heart disease (%) | 57 | 36 | 4.95 | 0.0259 |
| Episodes of syncope (%) | 46 | 52 | 0.38 | 0.5373 |
| SACT > 150 ms (%) | 65 | 14 | 35.86 | < 0.0000 |
| SNRT > 2 s (%) | 50 | 9 | 7.86 | 0.0051 |

SACT = sino-atrial conduction time; SNRT = sinus nodal recovery time.

**Table II.** Discriminant analysis of evaluated predictors of sino-atrial Wenckebach block.

| | Wilks' λ | F-remove | p |
|---|---|---|---|
| SACT | 0.9767 | 84.52 | < 0.0000 |
| Structural heart disease | 0.8096 | 4.19 | 0.0414 |
| Age > 60 years | 0.8016 | 0.33 | 0.5651 |
| Female | 0.8009 | 0.03 | 0.8732 |

SACT = sino-atrial conduction time.

## Discussion

This study shows that the occurrence of W-block commonly indicates the presence of underlying structural cardiac disease and is often associated with coronary heart disease. Although W-block occasionally occurs in people who may be free from other cardiovascular abnormalities, it should not be dismissed as an innocuous phenomenon without a search for underlying heart disease and careful follow-up.

This is the first study to evaluate the relation between the occurrence of W-block and the duration of sino-atrial conduction time and sinus nodal recovery time. Thirteen patients with W-block had prolonged sino-atrial conduction time. Additionally, the values of sino-atrial conduction time were significantly greater in patients with than in patients without W-block. These observations indicate that in patients with W-block the conduction abnormality in the sino-atrial junction is persistent and more extensive. The prolonged sinus nodal recovery time also identified the patient groups with and without susceptibility to occurrence of W-block. This finding is not surprising because abnormal pauses occurring during sinus recovery in most instances reflect changes in sino-atrial conduction. Several investigators have considered sino-atrial block as the primary mechanism of prolonged pauses after rapid atrial pacing. This was clearly showed by persistence of sinus node electrograms during pauses[6,7].

**Study limitations.** Because all our patients had symptoms that might be related to cardiac arrhythmias, the applicability of the data to asymptomatic subjects with W-block is unknown. The results of this study do not provide information with regard to the prognostic value of W-block. To estimate the prediction value of W-block for higher forms of sino-atrial block, a longitudinal follow-up study is needed.

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# Provocative drug testing in Brugada syndrome family members: background, methodology and personal experience

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**The Brugada syndrome was first described by the Brugada brothers, Martini and Naccarella in Italy. It is a well-recognized clinical syndrome characterized by incomplete right bundle branch block, ST-segment elevation in the right precordial leads and sudden death.**

**A familial distribution of Brugada syndrome has been identified and the most important clinical issue is today to screen family members of affected subjects to identify those at the highest risk of dying suddenly. The genetic screening has been proposed, but unfortunately is positive just in ≤ 25% of the cases, even in cases with documented life-threatening ventricular arrhythmias. From the beginning, Brugada proposed various pharmacological tests to unmask the syndrome in genetically predisposed subjects otherwise phenotypically negative.**

**More recently, the role of drug testing, as the preliminary test for the selection of candidates for the electrophysiological test or programmed electrical stimulation has been proposed and practised even by our group. Some data of ours on the use of different pharmacological agents and also the original application of oral flecainide testing are presented and discussed in juxtaposition with the data in the available literature.**

## Introduction

The Brugada syndrome (BS)[1-72] was first described by the Brugada brothers[1-7,32], Martini et al.[1,11,35] and Naccarella et al.[10,19,29,38,39,44,48,60,62] in Italy. Two reviews of what we should now call the Brugada disease have recently been published, focusing on electrophysiolog-

ical characteristics, familial distribution, differential diagnosis, risk stratification, and prognostic implications of different diagnostic tools[1,71].

Furthermore, advances in the identification of the Brugada disease have been made, using both genetic screening[4,6,14,16,19,23,27,30-34] and definite criteria which have been proposed for the clinical and ECG diagnosis and risk stratification[25,28,29,35-43].

## From updates on Brugada pathophysiology to drug testing

In 1998, the acknowledgment of BS as an entity became unquestionable, when Chen et al. identified three mutations in the SNC5A gene of chromosome 3P21, -p24 which are responsible for BS and affect the $\alpha$ subunit of the $Na^+$ channel, causing a failure in the channel operation[4,6,14,30-34].

Specifically: 1) missense mutations or "wrong information" mutation affect exon 28 and in it, the amino acid glutamine is exchanged by leucine in codon 567 (L567Q) between domains I and II of the $Na^+$ channel. This mutation determines a temporary increase in cation entrance during phase zero, with acceleration of recovery from the inactivation state, 2) structural frameshift mutation which consists in the subtraction of a nucleotide in the SCN5A gene, 3) "splice donor" mutation or mutation that accompanies the donor that affects intron 7 and introduces two bases of amino acids; the last two cause a failure in the channel operation.

Makita et al. demonstrated the importance of the "overlooked" accessory $\beta_1$ subunit of the Na channel. Thus the authors explained that alterations related to the $\alpha/\beta$ subunits influence the functional state of the $Na^+$ channel, by causing a higher overlapping of activation and inactivation states, giving rise to a window current in T1620M and consequently, in ventricular fibrillation triggering (Figs. 1 and 2)[44,46,55,56,72].

## Previous experiences with drug testing

In 1997, Nakamura et al. together with Brugada and our group, showed that some class I antiarrhythmic drugs, such as ajmaline, procainamide, propafenone, or flecainide may cause ST-segment elevation not present in the control ECG[47,48]. Furthermore, Chinusi showed that disopyramide had some variable effects in ventricular arrhythmia induction in patients who are Brugada carriers, by acting on the Ito channel, sometimes increasing ST-segment elevation and possibly normalizing it[45].

In 1999, Blazer and Antzelevitch for the first time included BS in the chapter on ion channel disease or channel disease or channelopathies[16,17,24,25,31,52].

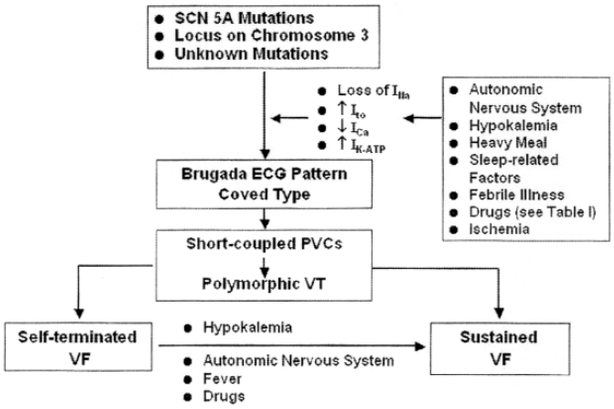


**Figure 1.** *Pathophysiologic mechanisms of Brugada syndrome: predisposing factors. PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia. From Antzelevitch et al.[72], modified.*

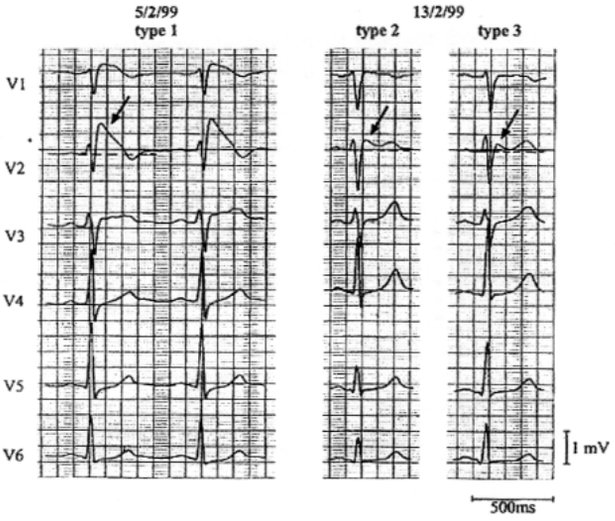


**Figure 2.** *New classification of Brugada ECG patterns. From Naccarelli et al.[44] and Naccarella et al.[60], with permission.*

The authors showed that the affected channels in BS are primarily the fast $Na^+$ channel and secondly, the initial $K^+$ outflow channel or Ito channel or transient outward current in phase 1 or 4 aminopyridine-sensitive channel and slow $Ca^{2+}$ inflow channel in phase 2 or L-type ("L-type slow or long lasting" Ca channel I Ca-L type I $Ca^{2+}$-L) (Fig. 1, Table I).

As described in the literature, different prognostic results have been reported in Brugada's[6,7,20,30,32], Priori's[25,28,33] and Naccarella's prospective databases[10,18,19,29], using different noninvasive and invasive diagnostic tests, probably also among different patient populations. This database prognostic information is mainly based on familial cases, taking into consideration the family history, previous episodes of cardiac arrest, of syncope and familial occurrence of sudden death. Also noninvasive and invasive tests such as drug challenges and programmed electrical stimulation (PES) alone or in combination have been used to risk stratify these patients[6,7,10,18,20,25,28-30,32].

Our data (156 subjects evaluated in 12 families of BS) suggest the importance of syncope in association with ST-T elevation, as a prognostic marker in family members of Brugada disease affected patients. Furthermore, some positive value and prognostic clinical utility of PES has been demonstrated in the patients previously recognized, on the basis of being family members of type 1 BS (coved type) vs type 2 BS (saddle back-like pattern)[29,34].

The percentage occurrence of sudden death and the percentage recurrence of sudden death per year, in patients with syncopal episodes, were more similar to those of patients with cardiac arrest or ventricular fibrillation, and not 0 as shown in Priori's database where subjects with syncope and typical ECG pattern had surprisingly the same outcome as asymptomatic patients[25,28,33].

Moreover, Priori in her prospective database of some Italian families showed some interesting data such as: 1) asymptomatic individuals with BS type ECG pattern present a very low risk of sudden cardiac death[25,33]; 2) symptomatic subjects with aborted sudden cardiac death present a 23% mortality rate in a mean follow-up of 33 months; 3) genetic mutations can be identified in only 15% of the cases; 4) the positive PES study had an accuracy of 50%; 5) pharmacological tests have only a 35% accuracy in asymptomatic carriers[28,33].

Similar results have been obtained using both pharmacological tests and PES in a large group of affected patients and family members collected by Corrado et al.[35] in northern Italy, including our own data.

All these data together reconfirm at least the benign prognosis of asymptomatic subjects with BS, even with a positive drug testing but they stress the importance of syncope as a very important symptom of prognostic significance, to be approached, from the diagnostic point of view, with PES and from the therapeutic point of view with the implant of a cardioverter-defibrillator[29,33,34].

Some important clinical features and diagnostic criteria have been stressed by Martini and Nava[1] in their paper. Furthermore, a recent paper on a consensus report defines more strict criteria to recognize the syndrome and a diagnostic methodology to be followed, including drug testing[41,44]. The consensus report differentiates three different subgroups of subjects (type 1, 2 and 3) with a different pattern of the ST-T segment. It is not known if all three have a genetic background, different clinical aspects and largely different prognostic evolutions[1,39,41] (Fig. 2).

We have to take into consideration in the differential diagnosis that the Brugada pattern can also be observed as a consequence of the different factors reported in table II.

**Table I.** Ion channels involved in the Brugada syndrome and potentially affected by drug testing.

There are four ion channels affected in the Brugada syndrome:

1) $I_{Na}$. This channel is primarily affected by the gene SCN5A mutation in chromosome 3. In its normal state the opening in the first fiber causes the fast inflow of $Na^+$ determining phase 0 the depolarization, which corresponds in the ventricles to QRS and in the atria to P wave;

2) $I_{to1}$, $I_{tof}$ or $I_{tofast}$, $I_{toA}$, $K^+$ "transient outward current", 4-aminopyridine sensitive outward current, $Ca^{2+}$-independent, voltage and time-dependent. The channel operates during short phase 1 that coincides with the J point in surface ECG;

3) $Ca^{2+}$ channel of slow or long-lasting phase 2 inflow of action potential or L-type $I_{Ca\text{-}L\ type}$, $I_{Ca^{2+}\text{-}L}$. It coincides with the ST segment in surface ECG;

4) $I_{k\text{-}ATP.}$ Time-independent $K^+$ current. Activated by intracellular adenosine triphosphate fall, pinacidil, nicorandil and cromalin. It causes shortening in action potential duration in the right ventricular outflow tract epicardium in Brugada syndrome and during ischemic states. It is inhibited by glybenclamide sulphonylurea.

From Antzelevitch et al.[72], modified.

**Table II.** Drugs and other factors responsible for acquired forms of the Brugada pattern.

| |
|---|
| Drug-induced |
| *Antiarrhythmic drugs* |
| $Na^+$ channel blockers |
| Class IC drugs (flecainide, pilsicainide, propafenone) |
| Class IA drugs (ajmaline, procainamide, disopyramide, cibenzoline) |
| $Ca^{2+}$ channel blockers (verapamil) |
| Beta-blockers (propranolol, etc.) |
| *Antianginal drugs* |
| $Ca^{2+}$ channel blockers (nefedipine, diltiazem, etc.) |
| Nitrates (isosorbide dinitrate, nitroglycerin, etc.) |
| $K^+$ channel openers (nicorandil, etc.) |
| *Psychotropic drugs* |
| Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine, etc.) |
| Tetracyclic antidepressants (maprotiline, etc.) |
| Phenothiazine (perphenazine, cyamemazine, etc.) |
| Selective serotonin reuptake inhibitors (fluoxetine, etc.) |
| *Other drugs* |
| Histamine $H_1$ receptor antagonists (dimenhydrinate, etc.) |
| Cocaine intoxication (electrolyte abnormalities) |
| I. Hyperkalemia |
| II. Hypercalcemia |
| Acute ischemia |
| I. Right ventricular infarction/ischemia |
| II. Vasospatic angina |
| Increaed insulin level |
| Hyperthermia (febrile state) |
| Hypothermia |
| Mechanical compression of the right ventricular outflow tract |
| Mediastinal tumor, hemopericardium, etc. |

## Personal observations on drug testing

**Patients and methods**. We screened 156 subjects belonging to 12 families with the typical BS. An informed consent was always obtained from all subjects and in the case of the patient being < 16 years, informed consent was obtained from both parents.

The drugs tested were mainly ajmaline at a dose of 1 mg/kg body weight (10 mg/min), flecainide at a dose

of 1.5-2.0 mg/kg body weight max (150 mg in 10 min), and procainamide at a dose of 10 mg/kg (100 mg/min) to exaggerate the ST-segment elevation or unmask the ST-T elevation in right precordial leads, if initially absent.

We also used oral flecainide at a dose of 50 mg twice a day which was increased to 100 mg twice a day and the final evaluation was performed on the fifth day while the patient reached the pharmacological steady state (Table III).

**Table III.** Results of the flecainide test.

| | |
|---|---|
| Family members of Brugada syndrome affected candidates | 10 |
| Positive test | |
| Flecainide | 9 |
| Procainamide | 3* |
| Reproducibility | |
| Flecainide | 7 |
| Procainamide | 1* |

* $p < 0.01$.

## Results

Our results are discouraging with procainamide, which showed a very low sensitivity in comparison to flecainide in the same group of patients (3/10 positive with procainamide and 7/10 positive with flecainide). Negative results were obtained with intravenous propafenone which showed, in some cases, a very important widening of the QRS and secondary ST-T elevation.

Also confusing was oral propafenone which showed contradictory results. Moreover, 25 patients who developed under chronic oral propafenone treatment for recurrent atrial fibrillation, an aspecific Brugada pattern, had a negative intravenous flecainide test, and in 4 cases a positive oral flecainide test.

Some encouraging results were obtained in 15 family members of Brugada patients using oral flecainide at the reported doses: 14 out of 15 developed, after a medium dose, a Brugada pattern of the coved type; 7/14 had also a positive PES; 3/7 had also a family history of sudden death or were symptomatic for syncope.

Both oral and intravenous flecainide showed a very high reproducibility over time in the same patients.

Out of 10 family members of Brugada cases in whom we used ajmaline (still available on the Swiss market) we found 9 positive cases and 0/10 in a control group of subjects of the same age referred for reciprocating supraventricular arrhythmias. This drug showed the best results and due to its short half-life no proarrhythmic or hemodynamic consequences were observed.

## Discussion and conclusions

As previously reported intravenous administration of certain drugs may modify the ECG pattern in BS patients or family members with a negative rest ECG. Thus, certain drugs are able to reveal a concealed form of BS. Specifically ajmaline (1 mg/kg body weight; 10 mg/min), flecainide (1.5-2.0 mg/kg body weight max; 150 mg in 10 min), and procainamide (10 mg/kg; 100 mg/min) have been proposed and used in the literature[33,39,41,47,48].

They all are able, to a different degree, to exaggerate the ST-segment elevation or unmask the ST-T elevation in right precordial leads if initially absent[41,47]. Sensitivity and specificity of these drug tests have been disputed, even in the presence of a positive genetic screening (genetic data used as the gold standard)[41].

There is a consensus that at least for procainamide, as observed also in our personal data, the test sensitivity is relatively low. Reproducibility of the test has not been clearly established, but is very poor in our experience. Furthermore we can affirm from our experience that the role of procainamide is limited, being able to induce a negative drug challenge, even in patients with a clear BS with some previous diagnostic ECGs for BS. Because of a low reproducibility, we advise to abandon procainamide test[33,48,60].

The same can be said, from our experience, also for intravenous propafenone and oral administration of the same drug both in regular doses and in loading doses. Therefore, the drug should be avoided, as a treatment in patients showing some degree of ST-segment changes, aspecific or acquired BS pattern, during a previous chronic treatment. Furthermore, these patients should not be considered BS carriers, in the absence of a family history, other ECG or clinical criteria or other evidence[33,48,60].

It has been suggested from the literature and our own experience that the drug challenge should be performed while the patient is continuously monitored (12 leads and blood pressure) and a defibrillator and all the necessary equipment for emergency treatment, including the insertion of a temporary pacing should be available[33,48,60].

From our experience, we advise the use of lower doses of the considered drugs, mainly we strongly advise to use < 2 mg/kg of flecainide, because we documented a spontaneous occurrence of proarrhythmic events with higher doses of flecainide.

The drug administration should be stopped as soon as the test is positive or if ventricular arrhythmias are induced including premature ventricular contractions or when a widening of the QRS > 30%, as suggested by Priori et al.[33] and others[48,60], is observed.

The criteria to define a positive test are as follows:

- a J wave amplitude of > 2 mm absolute amplitude in lead $V_1$ and $V_3$ without right bundle branch block is considered positive, when the resting ECG is almost normal;

• in patients with type 1 ECG, drug testing is not considered necessary, because it is not of additional diagnostic value;
• in patients with type 2 and 3 ECGs, the test is recommended to clarify the diagnosis. In this respect, we found the intravenous flecainide test to be positive in more than 50% of the family members of BS[33];
• the oral test with flecainide is more specific in our experience showing more than 70% positive responses, probably because a more gradual accumulation of the drug and more effective block of ion channels is achieved with the oral administration of the drug. Conversely, in our experience, intravenous flecainide can show excessive alterations of the ECG pattern and serious proarrhythmic events. Furthermore, sometimes a completely negative response can be observed in comparison to an oral flecainide test in some subjects, because, the acutely administered drug is not adequately dosed to block ion channels (unpublished personal observations);
• conversion of a type 2 or 3 ECG to a type 1 is considered positive;
• an increase in J wave amplitude of > 2 mm without the development of a type 1 configuration must also be considered significant and should be re-evaluated over time;
• conversion of a type 3 to type 2 is not considered positive unless syncopal episodes are present in the history and a significant family incidence of sudden death has been documented[33,48,60].

We use drug testing to select patients to be proposed for PES to induce ventricular fibrillation or other sustained arrhythmias. In our experience, subjects with a positive test are easily inducible during PES with only one or two extrastimuli delivered in the infundibulum tract of the right ventricle[33,48,60].

After drug testing, ECG monitoring is recommended, until the ECG is normalized (flecainide plasma half-life is almost 20 hours for oral and sometimes shorter for intravenous administration). For oral flecainide test we recommend the repeat of the standard ECG 3 and 5 days, after discontinuation of the oral treatment. Procainamide has a very short half-life of 3-5 hours. We do not recommend any more the use of intravenous procainamide and we never used it after 1999. We are not aware that anybody used or suggested oral drug testing with procainamide[33,48,60].

Propafenone, flecainide and procainamide have been shown to determine a positive ECG pattern, during chronic therapy in patients suffering from atrial fibrillation, in which the drug has been used to prevent recurrences[48,60].

As previously reported in our experience, the significance of these ECG patterns mimicking the typical Brugada pattern is not completely understood. These are isolated asymptomatic cases in which a family history is rarely documented, and in which, at least in our experience, a clear BS has not been documented or proven before or after.

Serious ventricular arrhythmias can be induced and also ventricular fibrillation has been frequently documented at least with the use of flecainide at high doses[33,48,60] (true proarrhythmic event or arrhythmia due to an unmasked BS?).

In these cases, immediate discontinuation of drug infusion is required and some people support the idea of isoproterenol administration (1 to 3 μg/min) (Brugada personal observations) which we do not agree with, given the high risk of perpetuating ventricular arrhythmias, in this context.

We agree with the conclusion of Priori et al.[33,41] that the more Na channel blocking agents are needed to induce the BS pattern, the less likely it is that the patient is at risk under baseline conditions with a normal ECG.

Our cumulative experience with Corrado's database recently showed that at least asymptomatic subjects with a positive pharmacological test frequently show also a negative PES and have a benign prognosis[35]. Animal data confirm that a flecainide-induced Brugada phenotype does not necessarily indicate the presence of a BS, but simply show that Na channel blocking agents create the conditions under which the arrhythmic substrate may readily develop[41].

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## IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR LEAD FAILURE: DETECTION AND MANAGEMENT

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**The use of implantable cardioverter-defibrillators (ICDs) has evolved greatly over the last 10 years. The development of transvenous leads such as the results of randomized studies on ICD therapy in patients with life-threatening ventricular tachyarrhythmias published by the end of 1997, was responsible for their wide use. System failures are, however, still possible complications; particularly, lead failures are an important complication of ICD therapy and may cause dangerous inappropriate therapy or no therapy. Management of an implanted device complication has become a subspecialty of cardiology and special training is required to acquire those invasive skills needed to achieve a successful result. Management of complications ranges from abandonment of a failed lead and reimplantation of a new lead to removal of all implanted devices, and reimplantation of new devices. During the past decade, effective, low-morbidity techniques have evolved for transvenous extraction of leads making the management of chronically implanted lead complications easier.**

**This paper presents the experience developed at our institution in the treatment of ICD lead non-infective complications.**

## Background

The use of implantable cardioverter-defibrillators (ICDs) for the treatment of ventricular tachyarrhythmias has evolved greatly over the last 10 years. Technological advances in ICD therapy, in particular the development of transvenous leads, were to a large extent responsible for their wide use, such as the results of randomized studies on ICD therapy in patients with life-threatening ventricular tachyarrhythmias published by the end of 1997[1-12].

Modern leads are characterized by their multilumen design that incorporates straight wires and coiled conductors into a single electrode body. Conductors and insulation are sheathed with additional insulation layers. The most frequently used insulating materials are silicone, polyurethane, and fluoropolymers.

System failures are still possible complications. In contrast to the relative frequency of lead failure, either as a result of implantation error or deterioration of the lead materials, primary malfunction of the generator is rare. Lead failures are an important complication of ICD therapy and may cause dangerous inappropriate therapy or no therapy. Fractured conductors, compression, creeping, or insulation defects from abrasion can cause such lead dysfunctions. Chronically implanted leads will inevitably have an increased risk of failure due to defects despite all technological advances[13]. In the light of improving survival figures in patients with ventricular tachyarrhythmias and increasing number of ICD implantations, lead failures are becoming a clinical problem of ever increasing importance. Therefore, the question of which lead types necessitate extraction when a certain failure occurs and which leads can be left in place.

The key to understanding the unexpected device behavior is related to meticulous evaluation of the integrity of the leads and an understanding of the timing cycles of the specific device, which is facilitated by access to bidirectional telemetry.

Management of an implanted device complication has become a subspecialty of cardiology and special training is required to acquire those invasive skills needed to achieve a successful result. Management of complications ranges from abandonment of a failed lead and reimplantation of a new lead to removal of all implanted devices, and reimplantation of new devices.

During the past decade, effective, low-morbidity techniques have evolved for transvenous extraction of leads[14-16] making the management of chronically implanted lead complications easier.

## Implantable cardioverter-defibrillator lead failure diagnosis

The evaluation of patients with a suspected ICD system problem must be intended to gather as much information as possible. These include the indications for the device implant, the operative record of the implantation, the model of all portions of the implanted system; moreover, the programmed parameters and measured data are absolutely crucial for a correct evaluation of the device. Knowledge of the present programmed settings, combined with the baseline data against which the current results can be compared, are extremely important. Many devices have special programming features that may appear to be malfunctions to clinicians not completely familiar with the particular system under scrutiny.

Even in the current high-technology environment of implanted devices, the history and physical examination continue to be important. The patient should be asked about symptoms relating to potential device malfunction. These include presyncope, syncope, palpitations, slow or fast pulse rates, and extracardiac stimulation. It is also important to obtain any history of trauma to the area where the device is located, exposure to intense electromagnetic signals or therapeutic radiation, use of electrocautery or defibrillation (internal or external) or programming changes by other medical personnel. In otherwise asymptomatic ICD patients, repeated shocks may suggest false signal detection.

Physical maneuvers may be useful to unmask an intermittent symptom or malfunction during an examination. Positional changes (sitting or standing up) or having the patient perform in-place exercise or isometric maneuvers may accelerate the heart rate to allow observation for sensing (proper tracking and inhibition). Manipulation of the device and lead may disclose an intermittent lead fracture, loose connection, or insulation failure that was not evident while the patient was lying quietly on the examination table. Other helpful maneuvers include movement of the patient's ipsilateral arm (reaching overhead or reaching behind the back), isometric exercise (pressing hands together in front of the chest or reaching around the chest to scratch the opposite side), and doing sit-ups in the case of an abdominal implant are helpful in identifying an intermittent problem.

By using telemetry, the programmed settings should be both retrieved and printed. The latter is important because it documents the initial settings and serves as a reference in case the clinician wishes to restore the device to the same settings when the evaluation is complete. If measured telemetry is available, these data should be requested and printed. The same recommendation holds for models that have extensive histograms, trend data, or other diagnostic counters. After the mode and rate have been verified, an evaluation of the remaining programmed parameters is appropriate. The identified output, pulse width, sensitivity, and refractory periods should be reviewed for each channel and correlated with the ECG. The presence and status of any special programmable features should be checked. The latter includes rate-modulation behavior, endless-loop

tachycardia prevention and termination algorithms, hysteresis, search hysteresis, time-of-day-dependent or circadian sensor-based rate changes, rate-adaptive atrioventricular delay, differential paced and sensed atrioventricular delay, rate smoothing, and others. Other diagnostic information is now routinely available in all ICDs, including charge times, capacitor reformation times, high-voltage lead impedance.

Lead impedance is one of the most important elements of the measured data. Proper interpretation of lead impedance, however, is dependent on the manufacturer and model of the lead used, the method of measurement, and the historical values of an individual lead impedance. The other parameters of the lead performance, including pulse voltage, pulse charge, pulse energy, and current, should also be correlated with the measured impedance. A marked discrepancy between observed and expected values may identify a telemetry error or measurement error within the generator rather than a primary problem with the lead. It is prudent to repeat the measurements several times if a conflict is noted.

ICD leads serve dual functions; the construction of the ICD leads is therefore more complex than that of the pacemaker leads. Two types of sensing leads have been developed: 1) a true bipolar sensing lead, with an independent defibrillation coil on the same electrode; and 2) an integrated bipolar lead, in which the distal electrode and the more proximal coil to the distal electrode are used as the sensing electrode pair. The additional wire conductors requiring independent insulation mandate electrodes of greater diameter and complexity and, by inference, provide a greater potential for complications. These electrodes are more prone to crush fracture or insulation material failures. To test the integrity of the right ventricular electrode, the operator needs to interrogate the sensing and pacing as well as the defibrillation conductors. Sensing and pacing function is tested by using the external programmer. Sensing in sinus rhythm and during ventricular tachycardia and fibrillation is analyzed to assess sensing integrity. Oversensing in sinus rhythm may occur as a result of a very small ventricular signal, large T waves, far-field sensing of P waves, interference due to a fractured conductor, or "noise" from a loose terminal pin set-screw. The integrity of the high-voltage electrodes can be verified on the basis of the analysis of impedance values and delivered energies during an ICD shock. It is also possible to administer a low-energy shock in sinus rhythm to obtain the high-voltage lead impedance. Such testing is discouraged in an outpatient setting because of the discomfort that even a low-energy shock is likely to cause to the patient. Less invasive means of testing the high-voltage lead integrity are now present in some ICDs.

If a system problem is suspected, postero-anterior and lateral chest radiographs should be obtained. It is usually better to request a slightly overpenetrated exposure to visualize the intracardiac segment of the leads for position and integrity. Requesting a thoracic spine exposure technique provides optimal penetration for visualization of the leads. It is recommended, whenever possible, that chest radiographs taken after the implantation be compared with the current. The film should be inspected for evidence of conductor disruption, insulation failure as inferred from a deformity in the conductor coil because the insulation is radiolucent, proper lead placement in the generator connector block, electrode perforation, dislodgment or malposition of a lead. Close attention should be paid to the infraclavicular area, where pressure from the clavicle and first rib may cause lead failure. In some cases, overlapping leads or leads overlying other structures may make it difficult to visualize a deformity of the conductor coil. If a problem is suspected, multiple views, including oblique and uncommon views may be required.

On occasion, a fluoroscopic evaluation of the patient may be useful. This shows many of the mechanical or positional problems and defects listed earlier. It also provides a dynamic view of the lead system, facilitating identification of excessive electrode movement consistent with an unstable lead, or there may be insufficient slack with respiratory movement placing traction on the lead and tension at the electrode-tissue interface. Either of these would provide an explanation for an intermittent capture or sensing problem.

## Implantable cardioverter-defibrillator lead failure management: indications to removal

In case of pseudomalfunction often it can be managed simply by reprogramming the ICD; however, when ICD lead failure is diagnosed removal and reimplantation is in most cases the treatment of choice because leaving the failed lead in place may expose the patient to successive complications (venous occupation, interferences, etc.). Therefore, attention will be focused to the indications and techniques of transvenous removal, which require particular facilities and training.

The indications for lead removal have generally been described according to the "Byrd classification"[15]. The categories of "mandatory", "necessary", and "discretionary" have served well during the developmental phase of lead extraction technology and physician skills.

*Mandatory indications mean that leads must be removed.* Mandatory conditions are those in which leaving the leads in place would be life-threatening or disabling like septicemia, endocarditis, lead migration (e.g., perforating, causing arrhythmia, causing emboli), device interference (e.g., abandoned implantable defibrillator lead), obliteration of all usable veins.

*Necessary indications* mean the leads should be removed. Necessary conditions are those in which the lead removal would correct a problem or prevent a life-threatening situation from developing, but the existing problem is not considered life-threatening like pocket

infection, chronic draining sinus, erosion, vein thrombosis, lead migration (not presently causing life-threatening problem), potential device interference, lead replacement (e.g., supernumerary, extract and implant thrombosed vein).

Discretionary indications mean the leads could be removed. Discretionary conditions are those in which it is preferable to remove the leads but in which it would rarely be considered a medical necessity like pain, malignancy, lead replacement (e.g., abandoned lead for < 3 to 4 years).

However, this classification (proposed for both pacemaker and ICD patients) should be revised in a more extensive way for ICD patients.

In 1997 a NASPE Policy Conference was held which established indications, facilities and training for chronically implanted lead transvenous removal[17]. The indications were formalized as follows:

• class 1 (conditions for which there is general agreement that leads should be removed):

a) sepsis (including endocarditis) as a result of documented infection of any intravascular part of the pacing system, or as a result of a pacemaker pocket infection when the intravascular portion of the lead system cannot be aseptically separated from the pocket;

b) life-threatening arrhythmias secondary to a retained lead fragment;

c) a retained lead, lead fragment, or extraction hardware that poses an immediate or imminent physical threat to the patient;

d) clinically significant thromboembolic events caused by a retained lead or lead fragment;

e) obliteration or occlusion of all useeable veins, with the need to implant a new transvenous pacing system;

f) a lead that interferes with the operation of another implanted device (e.g., pacemaker or defibrillator);

• class 2 (conditions for which leads are often removed, but there is some divergence of opinion with respect to the benefit vs risk of removal):

a) localized pocket infection, erosion, or chronic draining sinus that does not involve the transvenous portion of the lead system, when the lead can be cut through a clean incision that is totally separate from the infected area;

b) an occult infection for which no source can be found, and for which the pacing system is suspected;

c) chronic pain at the pocket or lead insertion site that causes significant discomfort to the patient, is not manageable by medical or surgical technique without lead removal, and for which there is no acceptable alternative;

d) a lead that, due to its design or its failure, may pose a threat to the patient, though not immediate or imminent if left in place;

e) a lead that interferes with the treatment of a malignancy;

f) a traumatic injury to the entry site of the lead for which the lead may interfere with reconstruction of the site;

g) leads preventing access to the venous circulation for newly required implantable devices;

h) non-functional leads in a young patient;

• class 3 (conditions for which there is general agreement that removal of leads is unnecessary):

a) any situation where the risk posed by removal of the lead is significantly higher than the benefit of removing the lead;

b) a single non-functional transvenous lead in an older patient;

c) any normally functioning lead that may be reused at the time of pulse generator replacement, provided the lead has a reliable performance history.

Whenever the pacing related component of the ICD lead fails but defibrillation function remains intact, the choice between extraction of the ICD lead and implantation of an additional pacing lead remains controversial. The risk of extraction needs to be weighted against the risk of a hidden or later defect of the defibrillation function. The risk of an unapparent defibrillation malfunction depends on the type of lead and lead failure (true bipolar vs integrated system, coaxial vs multilumen lead, silicone vs polyurethane insulated lead). There are no firm data to predict that the defibrillating capacity of the lead will not be affected. Extensive testing of the ICD system, including comparison of the high voltage impedance and electrogram far-field morphology, might reduce the probability of a high voltage defect but cannot rule it out completely. However, polyurethane leads should be extracted on detection of any lead failure. Such leads fail most commonly on the basis of metal ion oxidation and environmental stress cracking. These processes are progressive and probably involve the entire lead rather than only one component. Coaxial lead failures also require extraction because external forces are likely to affect all conductors according to the lead structure with the risk of failure of all inner structures. Leads with an integrated bipolar pacing and sensing functions should be removed in cases of pacing or sensing failure because the integrity of the distal defibrillation coil used for the pacing and sensing functions may also be defective. In summary, most ICD leads with failure of the pacemaker-related component should be removed. Only in some cases an additional lead should be considered. It is better to implant an additional pacing lead in cases of suboptimal pacing/sense threshold or an obvious defect of the proximal pacing electrode between the header of the device and the Y-connector of the lead.

Leads with a failure of the defibrillation function should be removed. An additional defibrillating lead may expose to oversensing and inadequate therapy delivery because of electrical spurious signals deriving from the friction between the defibrillation coils. In addition, there is the potential risk of a short circuit between the two defibrillation coils causing ineffective shock energy delivery.

**Transvenous techniques for lead removal**

Until to date the most extensive experiences have been performed by the use of mechanical sheaths and powered sheaths.

*Mechanical sheath dissection* was introduced in clinical practice by Byrd et al.[16] in the late '80s. The most widely used extraction system is provided by Cook Vascular Inc. This system is provided with locking stylets and dilator sheaths; they are used as a first choice when the proximal end of the lead is exposed (superior approach). The technique, in case of superior approach, consists of a combination of traction by the locking stylet, mechanical dilation of adherences by the dilating sheaths and countertraction at the tip of the lead by the outer telescopic sheaths. A transvenous workstation with a tip deflecting wire, Dormier basket and loop retriever is the choice tool in case of totally intravascular leads (inferior approach). The most recent results of US Extraction Database were reported for 6420 leads in 4090 patients[18]; 93% of leads were completely extracted, 5% were partially extracted, and 2% were not removed. Major complications occurred in 1.6% of patients, including a 0.2% mortality rate.

The VascoExtor system by VascoMed consists of a locking stylet provided with a remote control anchoring mechanism at the tip. A rotating motor can be applied to the stylet in order to facilitate the advancement or the withdrawal of the stylet; the system can be used on a wide range of coil lumen dimensions. A dilator sheath and a transfemoral workstation provided with a snare-loop catheter for intravascular lead extraction are also available. In a multicenter European study[19], removal attempts were made for 150 leads. Complete removal was possible in 122 cases (81%), partial removal was possible in 18 cases (12%), and failure to remove the lead in 10 cases (7%). There were no serious complications associated with the procedure. None of the patients died.

*Powered sheaths techniques* were developed in the '90s using a source of energy (excimer laser, radiofrequency) to make dissection of binding sites easier and faster.

Laser energy is delivered at the edge of a special sheath; the circumferential zone of optic fibers at the end of the sheath delivers a 308 nm laser beam that is effective for about 1 mm. In an ideal situation, the sheath is passed over the lead, vaporizing each binding site until the sheath reaches a point about a few millimeters from the heart wall. The lead is then removed from the heart wall using countertraction.

A recent paper reported the US experience with laser sheaths[20]; 2561 pacing and defibrillator leads were treated in 1684 patients at 89 sites in the United States. Of the leads, 90% were completely removed, 3% were partially removed, and the balance were failures. Major perioperative complications (tamponade, hemithorax, pulmonary embolism, lead migration, and death) were observed in 1.9% of patients, with in hospital death in 13 (0.8%). Minor complications were seen in an additional 1.4% of patients. In the European multicenter experience[21], 179 leads in 149 patients were extracted in 11 centers. Complete extraction was achieved in 89.5% of the leads, 6% were partially extracted, and 4.5% of the extractions failed. Complications were few but included one ventricular perforation that did not need surgery; two other perforations were related to the reimplantation of leads and required surgery.

Radiofrequency energy powers the electrosurgical sheaths which are used to ablate the encapsulating fibrous tissue in a manner similar to the laser sheath method. The electrosurgical sheath works as a bipolar electrosurgical cutting instrument, similar to the conventional devices used for hemostasis and cutting. The electrical arc placed at the tip of the sheath cuts the fibrous tissue. An outer sheath is used as a workstation and for counterpressure and countertraction. This technique is to date under clinical evaluation in the United States; early reports showed effectiveness and safety similar to mechanical and laser extraction.

Though the results of mechanical sheaths and powered sheath techniques are similar, the duration of procedures and, consequently, the radiation exposure are shorter using powered sheaths; on the other hand, the use of powered techniques is more expensive and is affected by higher rate of major complications. In the next future the cost/benefit ratio of both techniques will require a careful evaluation; probably most procedures could be performed by mechanical techniques while powered sheath techniques could be reserved for selected difficult cases.

Technological advances in transvenous lead removal can be achieved by modifying the techniques and the approaches as well as improving the materials.

In our personal experience[22,23] and in many reports[24] it was observed that success rate of removal was strongly affected by the presence of free-floating leads, calcified scar tissue or the impossibility of advancing a stylet into the lead. In presence of these factors, an approach through the right internal jugular vein presents some advantages. Most of free-floating leads can be exposed via the jugular approach and thus they can be submitted to a standard procedure for exposed leads. In addition the straight course of the lead from the jugular vein to the right atrium or ventricle allows the dilation along the longitudinal axis of the lead, allowing an easier dilation and countertraction. These conditions appeared to increase the effectiveness of mechanical dilation and to reduce the risk of complications. According to these observations we developed a jugular approach (removal of leads from the internal jugular vein) for free-floating and difficult exposed leads[25].

Finally, another recent technological improvement in the field of transvenous removal is the use of intracardiac echography, performed using catheters provided with an echo-transducer at the tip. The use of intra-

cardiac echography during transvenous removal procedures can allow to determine the relationships between leads and most anatomical structures better than fluoroscopy; it can be very useful either to detect the presence of vegetations and their outcome during dilation, or to monitor the possible occurrence of complications. However, because of the costs, the need of an additional venous puncture and a dedicated operator, we may suppose a great utility of intracardiac echography in selected cases, such as difficult leads, multiple leads, suspicion of vegetations, old leads, free-floating leads[26].

## Implantable cardioverter-defibrillator lead extraction: personal experience

Since 1996, we managed 93 patients (84 men, 9 women, mean age 59.2 years, range 8-80 years) with 116 ICD leads (mean pacing period 44.8 months, range 4-123 months). The indications to ICD leads removal were infection (local or systemic) in 85 leads and non-infective in 31 leads. Among these 31 non-infected ICD leads, 28 were ventricular and 3 were in the superior vena cava (mean pacing period 50.7 months, range 5-123 months). Patient and lead characteristics are listed in table I and indications to removal in table II.

After removal attempt by manual traction, avoiding excessive coil lengthening, we performed mechanical dilation using the Cook Vascular extraction kit and, if necessary, other intravascular tools (Catchers and Lassos, Osypka). When the removal through the implant vein was not possible we used the approach through the internal jugular vein. The major difficulties in removing ICD leads compared to pacemaker leads consists of encasement of the proximal defibrillation coil at the junction between the superior vena cava and the innominate vein, and the dense adhesion of the distal coil involving the tricuspid valve[27].

It also appears that ICD lead tips are encased by denser scarring than pacemaker leads perhaps because ICD leads are heavier and bigger than pacemaker leads.

Nonetheless, all the leads were successfully removed; manual traction allowed the removal of 3 leads (2 ventricular, 1 caval); in most cases extensive dilation of adherences was necessary. The jugular approach was necessary to remove 5/31 (16.2%) leads. No major complications were observed.

**Table I.** Patient and lead characteristics.

| | |
|---|---|
| No. patients | 26 |
| Sex (M/F) | 20/6 |
| Age (years) | 54 (range 8-71) |
| No. leads | 31 |
| Implantation site | |
| Superior vena cava | 3 |
| Ventricular | 28 |
| Pacing period (months) | 50.7 (range 5-123) |

**Table II.** Non-infective indications to implantable cardioverter-defibrillator lead removal; number of indications is higher than lead number, because more than one indication was present for some leads.

| Indications to lead removal | No. leads |
|---|---|
| Oversensing | 14 |
| Undersensing | 2 |
| Inappropriate therapy | 10 |
| Not reliable after ventricular lead removal | 2 |
| Subclavian crush | 3 |
| Interference | 2 |
| High pacing threshold | 2 |
| Conductor fracture | 5 |
| Aborted shocks | 1 |

## Conclusions

Managing ICD lead failures covers a spectrum of knowledge and techniques. Clues to the problem and its cause can be found in the patient's history, physical examination, and the various diagnostic tests integral to the devices and retrieved through bidirectional telemetry. When a "software problem" is detected, reprogramming may be enough to solve it; when a "hardware problem" is present, the solution in most cases is extraction of leads. Extraction of ICD leads, though often technically difficult, is an effective and safe procedure. Some of these procedures have the potential for tearing the heart and veins, precipitating a life-threatening complication. To minimize the incidence of these complications and to ensure a satisfactory resolution, training in these procedures and the availability of surgical support, should a problem arise, are essential.

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