Author's response to reviews

Title: Cardiac events in patients with idiopathic ventricular fibrillation excluding patients with the Brugada syndrome

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Version: 3 Date: 13 October 2004

Author’s response to reviews: see over
Thank you for consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to your reviewer’s comments.

**Reviewer # 1 (Dr Belhassen)**

**MINOR COMMENTS:**


   - Done

2. Could you include the circumstances of occurrence of the first VF episode before and after ICD regarding the possible role of exercise or stress?. Do you have any data about the occurrence of spontaneous VPC's with ultrashort coupling interval in your series of patients with IVF

   - The occurrence of VF episode is now described on page 4: “In 15 patients, the documented VF was seen during daily activity (one episode during sustained effort) and in 3 patients, during night time. Out of the 18 patients, 10 had a previous history of unexplained syncope.”

   - For the VPC with short coupling interval, we added a comment on page 8: “From the intracardiac electrograms, the arrhythmia initiation was always associated with PVCs with a mean coupling interval of 300 ± 35 ms. A long-short initiating sequence of VF was never observed. In five patients, multiple VF episodes were recorded by the ICD. All episodes for a single patient were associated with the same PVC coupling interval.”
3. Electrophysiologic study. Page 5. The protocol used in the study included extrastimuli with coupling intervals not shorter than 200msec. Many studies have shown that the coupling intervals of the extrastimuli play an important role in the ability to induce VF in patients with IVF (as well as those with Brugada syndrome) (1). Thus, the low inducibility rate of sustained ventricular tachyarrhythmias observed in your study should be discussed more in detail in regard to this important limitation.

- We revised our EP protocol definition as depicted on page 6:
  “Programmed electrical stimulation was performed in all patients using up to 3 extrastimuli at three different drive cycle lengths (600, 500, and 430 ms) delivered to the right ventricular apex. The coupling interval of the first two extrastimuli was not shorter than 180 ms and not shorter than 200 ms for the third extrastimuli.”

- The comment on our low inducibility rate is now detailed and some limitations were added in the manuscript on page 12: “Our findings differ from the observed 79% average inducibility rate reported by Belhassen et al. This may be due to different patient characteristics and different stimulation protocol. Our study excluded patients with Brugada syndrome known to have a high inducibility rate. Compared to our stimulation protocol, Belhassen et al. used up to three extrastimuli, two basic cycle lengths, two RV sites (first RVA then RVOT), and repetition of extrastimulation (n = 10 for double and n = 5 for triple) at the shortest coupling intervals that resulted in ventricular capture.”

4. Results. Page 7. The fact that 3 of 7 patients with inducible sustained tachyarrhythmias had a monomorphic VT induced is surprising. In the studies of IVF reported to date, the induced tachyarrhythmia was almost always polymorphic VT or VF. This point should be addressed by the authors. The cycle length and the QRS morphology (LBBB or RBBB pattern) of the monomorphic VTs should be indicated for each of these 3 patients. Since 2 of these 3 patients had several arrhythmic episodes recorded by the ICD, it would be interesting to know the cycle length and the QRS pattern of these arrhythmic episodes, and to compare them to those induced at EPS.

- Of these 3 patients, the mean cycle length was 230 ms and one was described as a ventricular flutter. We have addressed this comment on page 13 as followed: “Three patients had a fast monomorphic VT inducible even if the clinical presentation was aborted sudden cardiac death. This may suggest an underlying structural heart disease undetected with the current investigation. Although the cardiac function may be grossly normal, patients might have discrete abnormalities, which are currently unidentifiable.”

- The data concerning the LBBB and RBBB are no longer available for comments.
5. Long-term follow-up. Page 7. The authors should indicate if their patients were taken any antiarrhythmic drug after ICD implantation.

- We do not have the complete list of medication for all patients at discharge from ICD implantation. In table 1, you can appreciate that during follow-up, 11 out of 18 patients required additional AA drugs to avoid repetitive shocks. Also, we discussed AA management on page 10 and 13.

6. Long-term follow-up. Did the authors note any arrhythmic storm in their patients? Please also indicate that no significant cardiac abnormality developed during follow-up in those patients with the longest follow-up duration.

- There was no arrhythmic storm in this population. Text revised and comment added on page 8.
- “No significant cardiac abnormality developed during follow-up” was already written on page 9.

7. IVF management. The authors, as most electrophysiologists worldwide, strongly believe that ICD therapy is the best mode of management for IVF patients. They should, however, recognize that other therapies, such as electrophysiologic-guided quinidine has been shown to be as effective than ICD [see Belhassen et al, JCE 1999 (2)] and that no randomized comparative studies (ICD vsquinidine) are presently available. A new confirmation of the extraordinary efficacy of quinidine in IVF has just been provided in a recent case report by Belhassen (3).

- This information was added in the discussion on page 12 as well as the references revised accordingly: “Antiarrhythmic drugs have also been used in this clinical condition. Belhassen et al. reported excellent results in his idiopathic VF population with EP-guided therapy with Class 1A drugs, primarily quinidine, with no death after a mean follow-up of more than 9 years. Also, recent evidence suggests that frequent premature ventricular contractions arising from the Purkinje system are responsible for initiation of ventricular fibrillation, and can be mapped and ablated in select patients. Until other proven therapy has been assessed prospectively, the possibility of VF recurrence mandates ICD implantation as currently proposed in ICD guidelines.”


- Done

9. References. The paper is well referenced. However, I would suggest the authors also to consider also referring to an article published by Wichter et al. in a book (4) as well as to references 1-3.
Some references were added

Reviewer # 2 (Dr Hermida)

Majors Compulsory revisions

1- The definition (page 5) of IVF should be completed. It seems important to specify that all known electrical diseases, as I suppose it was done, were excluded including WPW syndrome, short coupled torsades de pointes, catecholamine-induced ventricular tachycardia and congenital short QT syndrome

   • We have revised in our manuscript the IVF definition (see page 5): “Idiopathic VF was defined as VF in the absence of demonstrable cardiac abnormalities as previously reported. Thus, we excluded other known causes of VT/VF such as: WPW syndrome, congenital long QT syndrome, short-coupled torsade de pointes, catecholamine-induced polymorphic VT and Brugada syndrome.”

2- The recurrence of events in patients with not sustained polymorphic VTs is relatively expected and a shock from the ICD may only mean that one of the not sustained polymorphic VT has been shortened by the ICD (depending on the setting of the detection time) and that otherwise a spontaneous interruption would have occurred. As IVF is not a homogeneous syndrome, the initial presentation of the arrhythmia seems useful to report for each patient (in the table for example) to know who underwent recurrences. In other words, it seems interesting to distinguish recurrence in VF patients from recurrence in not sustained polymorphic VT patients. Thinking to this possibility, it could be overstated to affirm as at the end of the page 7 that “ICD effectively prevented sudden cardiac death in all patients with arrhythmia recurrence”.

   • We have addressed this comment on page 8 and 11 and put in perspective the impact of shock therapy. We have modified table 1 accordingly to specify the initial clinical event and to stress the issue that the initial event was not predictive of arrhythmia recurrence

   • Page 8: “There was no relationship between the initial clinical and arrhythmic presentation and subsequent arrhythmic events recorded from the ICD at follow-up (table 1)” and “The ICD effectively recognized and promptly treated all the polymorphic VT or VF recurrences and prevented the possible occurrence of sudden cardiac death. No death was reported during follow-up”

   • Page 11: “Our high ICD discharge rate could also be explained by the rapid ICD intervention for fast ventricular arrhythmia that could have been self-terminated.”
Discretionary Revisions

1-In my opinion, the title should reflect that only 12 on the 18 patients have had an IVF. The 6 remaining patients were not resuscitated from sudden death but experienced syncope and runs of polymorphic VT.

• No further comment since the manuscript described in details the entire population.

2-The recurrence rate, the low value of the EP study in predicting recurrences and the morbidity related to ICD use (mainly inappropriate shocks) are precisely reported. Perhaps some data concerning the electrical aspect of the recurrences may be also provided. Information about the arrhythmia leading to the sudden death when it was not caught before implantation of the ICD could be a posteriori interesting. For example the coupling interval of the first beat of VT/VT or the presence of short cycle/long cycle sequence...

• We added all the information that was available to address this comment on page 8: “From the intracardiac electrograms, the arrhythmia initiation was always associated with PVCs with a mean coupling interval of 300 ± 35 ms. A long-short initiating sequence of VF was never observed. In five patients, multiple VF episodes were recorded by the ICD. All episodes for a single patient were associated with the same PVC coupling interval. Since the stored electrograms in the present study were obtained from endocardial sites and were single-channel recordings, we cannot assess the origin of the PVCs.”