Title: Ventricular Fibrillation Undersensing to Calculate a Safety Threshold for Baseline Rhythm R-wave Amplitudes

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To the Editor:

We have read with great interest the study of Mark L. Brown,(1) on ventricular fibrillation (VF) sensing using Medtronic implantable cardioverter defibrillators (ICDs). Dr. Brown describes the ventricular sensing process performed on Medtronic ICDs, but unfortunately his report does not show further data processed with proprietary filters. Dr Brown does criticize our recent report,(2) in which we documented that baseline rhythm (BR) R-wave amplitudes ≤2.5 mV (Interquartile range: 2.3, 2.8) show potential for high undersensing rates of VF electrograms dropping below the minimum nominal sensitivity during spontaneous VF. As we postulated, the latter might lead to a long delay or cessation of VF therapy with potentially fatal clinical consequences. While we consider Dr. Brown´s discussion of VF undersensing relevant, some of his assertions require comment and clarification.

First, the estimation of a safety threshold for BR R-wave amplitudes that prevents excessively high undersensing rates of VF episodes requires an initial analysis of VF amplitude distribution compared with BR R-waves. Importantly, VF criteria may substantially affect the results and potentially conceal any underlying relationship between BR R-wave amplitudes and the amplitude distribution of VF electrograms.(3) More specifically, a permissive cycle length (CL) criterion for VF episodes would include relatively slow rhythms with no or minimal amplitude variations in VF electrograms compared with BR R-waves. Thus, Ellenbogen *et al.* have reported both low variability and slightly decreased mean amplitude values (-5% to -15%) in patients with VT episodes ranging in CL between 240 and 360 ms.(4) However, Ruetz *et al*.(5) have reported that VF amplitude did not decrease significantly between 5 and 10 s after onset. The authors used very permissive VF criteria for spontaneous VF episodes with cutoff rates commonly established at CLs of 300-320 ms. Conversely, our series included much more rigorous criteria for spontaneous VF episodes (mean VF CL 189±29 ms; ~5.2 Hz) and wide consensus among experts during the rhythm classification process. Such data enabled us to demonstrate that the majority (77.6%) of VF electrograms showed lower amplitudes than the reference BR R-waves, with a negative median amplitude deviation of approximately -48.8% (IQR=-64.9,-5.3%).

From the foregoing, it is difficult to dispute our results regarding the relationship between BR R-wave amplitudes and the amplitude of electrograms in VF using as reference a series with substantially slower VF episodes or even including VT episodes.(5) Sample cases with evident changes in the amplitude of VF electrograms can be found in Lillo-Castellano *et al.*(2) The decrease in amplitude of the majority of VF electrograms compared with BR R-waves has important implications: the lower the BR R-wave amplitude, the higher the chances of VF electrograms dropping below the minimum sensing threshold (nominally 0.3 mV). In other words, regardless of the criteria used to detect activations during VF, all the VF electrograms with amplitudes below the sensing threshold will inevitably be undersensed. A representative VF tracing with an undersensed VF electrogram below the nominal sensitivity can be found in the supplemental material of Lillo-Castellano *et al.*(2) The scenario reported by Ruetz *et al.*,(5) without any significant decrease in the amplitude of VF electrograms compared with BR R-waves means that the safety threshold would be similar to the minimum sensing threshold. However, such a safety threshold value would be extremely dangerous for fast and spontaneous VF episodes.

Importantly, in Lillo-Castellano *et al.*(2) we further quantified VF amplitude distribution using four subgroups of BR R-wave amplitude at ≈5 mV intervals (≥2.2-to-<7 mV; ≥7-to-<12; ≥12-to-<17; ≥17). The decrease in amplitude of VF electrograms was progressively attenuated among subgroups of BR R-wave amplitude from the highest (≥17 mV) to the lowest (≥2.2-to-<7 mV) amplitude subgroup (median deviations -51.2% to +22.4%, respectively). Although the subgroup with the lowest BR R-wave amplitude range (≥2.2-to-<7 mV) included 23 out of 229 VF episodes,

the attenuation in amplitude decrease between BR R-waves and VF electrograms was highly consistent among subgroups and statistically significant.(2) The results provided sound data to support the use of the lowest amplitude subgroup to calculate the safety threshold using a progressive decrease in BR R-wave amplitude. It also enabled quantification of the percentage of VF electrograms dropping below 0.3 mV based on the histogram of VF amplitude distributions from the ≥2.2-to-<7 mV subgroup. The subgroup-derived undersensing risk function also provided the percentage of undersensed VF electrograms ≥0.3 mV. Finally, the safety threshold was established at the lowest baseline R-wave amplitude that could provoke undersensing of ≥25% of VF electrograms. The results showed that a BR-wave amplitude of 2.5 mV should yield 24.4% of undersensed VF electrograms dropping <0.3 mV, and only 0.6% of VF electrograms would be undersensed despite being ≥0.3 mV. Even though our methodology might not completely fulfill Medtronic sensing criteria of VF electrograms, this would only affect 0.6% of VF electrograms above the minimum nominal sensitivity.

Second, clipped electrograms/R-waves above the ICD dynamic range of ±8 mV may have limitations to accurately calculate BR R-wave amplitudes. However, this limitation does not affect electrograms in the group used to calculate the safety threshold (≥2.2-to-<7 mV). Moreover, in our series only 3454 out of 13953 VF electrograms (24.7%) required estimating the original amplitude by means of both the R-wave increasing and decreasing voltage slopes.(2) In current ongoing work we have validated this approach using artificial clipping at 5 mV of electrograms with knowing amplitude values to calculate the estimated peak. Interestingly, the mean error calculation was 1.7%±7.3%.

Third, it is important to note that we did not consider as undersensed VF electrograms any electrogram occurring during the 120 ms blanking period. Nevertheless, any manually detected electrogram within the blanking period must have been separated by at least 80 ms from the previous detected VF electrogram. The 80 ms time-window was important during VF intervals with fragmentation to properly select undersensed and blanked VF electrograms.

Fourth, in his Figure 3 Dr. Brown annotated our unfiltered electrograms in an attempt to discern whether undersensing after filtering (with our methodology) was relevant or not. However, this was pointless since VF sensing was based neither on the unfiltered signal nor on expert interpretation. Therefore, we stand by our report, and to avoid misinterpretation (Brown´s Figure 3), would have been glad to provide Dr. Brown with the raw signals so he could analyze them using the procedure that Medtronic ICDs use for sensing. This would have enabled meaningful discussion on the potential problems that may occur after rectification with fast and fractionated electrograms usually present during VF. In fact, we would have been be very interested in knowing whether the narrow spikes supposedly introduced into the electrogram with our methodology disappear or diminish with Medtronic proprietary software.

Finally, any interested reader will find more specific technical details about our methodology in Lillo-Castellano *et al.(2)*.

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Conflict of interest.

None

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