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Molecular and cellular determinants of cardiac tachyarrhythmias: from trigger to therapy

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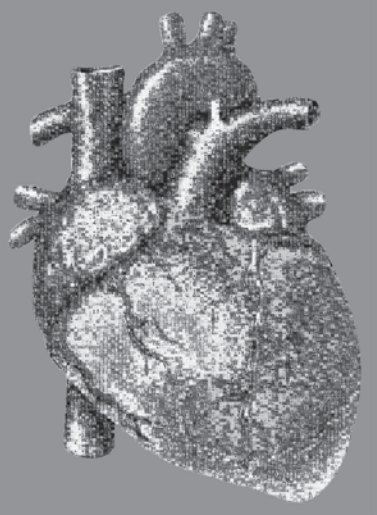
Chapter III

Appendix II

Prolongation of minimal action potential duration in sustained fibrillation decreases complexity by transient destabilization: reply

Wolkowicz PE, Umeda PK, Sharifov OF, Wang P, Mahtani H, Urthaler F.

Cardiovasc Res. 2013;98:155-6



TO THE EDITOR:

In their letter, Wolkowicz *et al*. raise a valid point questioning whether other effects of 2-aminoethoxydiphenyl borate (2-APB) might also have contributed to ventricular fibrillation (VF) initiation, especially its effects on voltage-independent calcium channels, as was also mentioned in the Discussion section of our manuscript recently published in *Cardiovascular Research*.[1]

In this study, we showed that prolonging the minimal action potential duration (APD) can decrease the complexity (e.g. number of rotors) during sustained VF. To induce fibrillation in neonatal rat ventricular cardiomyocyte monolayers and in adult rat hearts, we used 2-APB. We postulated that the re-entrant conduction patterns resembling VF after 2-APB treatment could be partly attributed to the effect of 2-APB on gap junctional coupling.[2]

The main purpose of our study was to study the maintenance properties of VF. Going into length on the mechanism by which 2-APB induces VF would defeat this purpose, as VF can show the same maintenance properties regardless of how it is initiated.[3] Hence, we fully agree with Wolkowicz *et al*. that 2-APB might contribute to VF initiation by other means than only gap junctional uncoupling. Considering that virtually all pharmacological agents are aspecific to some extent it can be expected that different, potentially interacting factors may be responsible for a certain effect.

In our study, we showed a significant decrease in conduction velocity after treatment with 2-APB. Wolkowicz *et al*. suggest that this decrease might have been caused by the use of electromechanical uncouplers[4] and voltage-sensitive dyes[5], and that the effect of 2-APB on gap junctional communication was too little to reach a threshold for arrhythmogenesis.[6] However, in the experiments using cardiomyocyte monolayers we did not use electromechanical uncoupling, while the same concentration of voltage-sensitive dye was used in control and 2-APB-treated cultures or in control and 2-APB-treated hearts. Hence, in our setup the aspecific effects of these pharmacological agents do not seem to provide a plausible explanation for the difference in conduction velocity. Nevertheless, the decrease in gap junctional uncoupling by BDM treatment[4] or the decrease in conduction velocity by di-4-ANEPPS[5] could effectively lower the degree of additional uncoupling needed to reach the arrhythmogenic threshold, which could help explain the tachyarrhythmias found after 2-APB treatment.

Furthermore, we show that in cultures with VF, prolongation of the minimal APD by BayK8644 and $BaCl_2$decreases the activation frequency and complexity of VF. Wolkowicz *et al*.,[7] however, found strongly increased activation frequencies when combining 2-APB with BayK8644 treatment. The differences in results could be attributable to the fact that different models and protocols were used. For example, in our study cells were first incubated with 2-APB for 20 min, after which they were subjected to optical

mapping and BayK8644 treatment.[1] In contrast, Wolkowicz *et al*.[7] used pre-treatment with BayK8644 and direct analysis of activation frequency after the addition of 2-APB. Possibly, the mechanisms causing high activation frequency after short- or long-term 2-APB treatment are different. Wolkowicz *et al*.[7] showed that the increased activation frequency is caused by abnormal automaticity, as a result an increase in APD by BayK8644 pre-treatment does not decrease the frequency. We show that after incubation for 20 min with 2-APB there is a predominant re-entrant activation pattern, in which BayK8644 decreases the frequency.[1] Nevertheless, this does not exclude the possibility that before re-entry initiation there is 2-APB-induced non-re-entrant automaticity in our setup as suggested by Wolkowicz *et al.*, which would strongly increase the chance of re-entry initiation in our cultures.

In conclusion, we acknowledge the issues Wolkowicz *et al*. raised in their letter and support the notion that indeed 2-APB-induced arrhythmias can be initiated by mechanisms other than gap junctional uncoupling. However, based on our data we feel that our model, in which stable re-entrant action patterns are observed after longer 2-APB incubation, allows for studies on sustained VF, despite the incomplete knowledge of its initiation. For more specific and mechanistic studies on the origin of arrhythmias genetic interventions based on viral vector technologies seem more appropriate,[8] especially when such interventions are designed to be cell type-specific and inducible. Nevertheless, additional research is needed to better understand the mechanisms behind 2-APB-induced arrhythmias, as this might contribute to the development of novel anti-arrhythmic strategies focusing on the pro-arrhythmic substrate and its underlying molecular mechanisms.[9]

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