

Letter Regarding Article by Korte et al, "Female Mice Lacking Estrogen Receptor β Display Prolonged Ventricular Repolarization and Reduced Ventricular Automaticity After Myocardial Infarction"

To the Editor:

The article by Korte et al¹ was insightful in that it provided evidence that female mice with chronic left anterior myocardial infarction (MI) and lacking estrogen receptor β (ER β) have prolonged ventricular repolarization compared with noninfarcted ER β -deficient and wild-type mice. The prolongation of ventricular repolarization in the ER β -deficient mice with MI was demonstrated by the prolonged QT and QT_c interval with an associated reduction of the expression of Kv4.3 channel (coding for I_{to}). The authors surmised that the observed reduction in ventricular premature beats (VPB) and nonsustained runs of VPB in ER β -deficient mice with MI resulted from "reduced ventricular automaticity" and concluded that "ER β plays a significant role in ventricular repolarization and automaticity in the female mice heart after MI, which is mediated, at least in part by downregulation of Kv4.3 expression." The part of their conclusion dealing with reduced automaticity is neither demonstrated in the study nor justified. Absence of microelectrode studies prevents the conclusion that automaticity was involved in causing VPB. More importantly, reduction of outward currents (I_{to} , in this case) facilitates rather than reduces the emergence of all forms of "automaticity." In fact, in the failed heart model in which potassium channel downregulation develops, 2 simultaneous events emerge: prolonged repolarization and early afterdepolarization and early afterdepolarization-mediated triggered activity causing ventricular arrhythmias (for a review, see Tomaselli and Zipes²).

It would thus seem both counterintuitive and contrary to available evidence to propose that I_{to} downregulation reduces automaticity in the ER β -deficient mice with MI.

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1. Korte T, Fuchs M, Arkudas A, Geertz S, Meyer R, Gardiwal A, Klein G, Niehaus M, Krust A, Chambon P, Drexler H, Fink K, Grohe C. Female mice lacking estrogen receptor β display prolonged ventricular repolarization and reduced ventricular automaticity after myocardial infarction. *Circulation*. 2005;111:2282–2290.
2. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? *Circ Res*. 2004;95:754–763.

Response

We appreciate the interest of Dr Karagueuzian in our article.¹ The investigator raises the question whether downregulation of I_{to} could reduce automaticity in the ER β -deficient infarcted female mice.

In our work, we showed that in infarcted female β ERKO mice, ventricular repolarization is significantly prolonged and ventricular spontaneity is significantly decreased. This finding was accompanied by a significant and specific lower expression of Kv4.3 in β ERKO animals. We fully agree with Dr Karagueuzian that this article is not able to show that reduced automaticity is

strictly related to downregulation of Kv4.3 because microelectrode studies were not performed in this model. The potentially protective (not necessarily proarrhythmic) effect of prolonged repolarization with regard to ventricular arrhythmia has long been discussed,² and thus we do believe and discuss in the article that prolonged repolarization caused by reduced Kv4.3 (coding for I_{to}) could in this model be the cause of decreased automaticity. We argued that "from the data of this study, it can be hypothesized that prolongation of repolarization caused the reduction of ventricular spontaneity in the infarcted β ERKO animals." The experiments were not aimed to prove this hypothesis. It remains speculative whether an altered dispersion of repolarization has at least contributed to this effect (for a review, see Pham and Rosen³).

We absolutely agree with Dr Karagueuzian that more research is needed to clarify the mechanisms by which cardiac repolarization, potassium channel expression, and arrhythmogenesis are altered in the female mouse heart after myocardial infarction via ER β .

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1. Korte T, Fuchs M, Arkudas A, Geertz S, Meyer R, Gardiwal A, Klein G, Niehaus M, Krust A, Chambon P, Drexler H, Fink K, Grohé C. Female mice lacking the estrogen receptor β display prolonged ventricular repolarization and reduced ventricular automaticity post myocardial infarction. *Circulation*. 2005;111:2282–2290.
2. Antzelevitch C. Molecular genetics of arrhythmias and cardiovascular conditions associated with arrhythmias. *J Cardiovasc Electrophysiol*. 2003;14:1259–1272.
3. Pham TV, Rosen MR. Sex, hormones, and repolarization. *Cardiovasc Res*. 2002;53:740–751.

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