Reply to Letter to the Editor

Re: ‘Ventricular arrhythmias induced by endothelin-1 or by acute ischemia: a comparative analysis using three-dimensional mapping’ (Cardiovasc Res 2000;45:310–320)

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Although the technique of three-dimensional mapping obviously does not provide direct evidence as to whether ET-1-induced ventricular arrhythmias are purely due to ischemia or to a combination of direct electrophysiologic effects and ischemia, we still believe that a number of aspects argue against the hypothesis that ET-1 related arrhythmogenesis is exclusively based on ischemia:

1. The fact that conduction and refractory properties remained entirely unaffected by ET-1.
2. The difference in the mechanism responsible for the maintenance of observed arrhythmias (purely focal vs. focal and reentrant).
3. The occurrence of severe arrhythmias in the presence of a minor degree of coronary blood flow reduction (24–32%), as indicated by previous studies using exactly the same dose of ET-1 [1,2].
4. The observation that bradycardia enhances the arrhythmogenic effect of ET-1 [3], whereas induction rates with programmed ventricular stimulation are low [2].
5. The fact that previous experimental studies failed to demonstrate a correlation between the severity of ischemia and the severity of ET-1-induced ventricular arrhythmias [4]. The predominance of focal arrhythmias originating from the subendocardium in both the ET-1 and the ligation group does not allow the conclusion that ischemia is the mechanism underlying both interventions, because this type of arrhythmia has been shown to be very common in both ischemic [5–7] and nonischemic arrhythmias [8,9].

As far as the potential mechanism underlying the growing prevalence of right ventricular foci with increasing duration of ET-1 infusion is concerned, we believe that recent experimental work supports the hypothesis of a systemic recirculation of ET-1. Although the elimination kinetics of ET-1 are still poorly understood, Parker et al. [10] could demonstrate in healthy individuals that intravenously applied ET-1 has a much longer terminal half life than previously reported. Furthermore, as shown experimentally in rats, plasma endothelin concentration after bolus administration of endothelin is significantly prolonged by bilateral nephrectomy [11]. These data clearly indicate that the pulmonary elimination of endothelin is incomplete and, thus, the endothelin plasma level might well increase with continuous i.v. infusion as applied in our study, although this has not been systematically studied yet.

We are convinced that our study indirectly supports the hypothesis derived from earlier experimental work that, apart from its vasoconstrictive properties, ET-1 exerts primary arrhythmogenic effects. However, further experimental data are required to directly prove this hypothesis.

References


