Dear Editor,

It was highly interesting to read the ‘Letter to the Editor’ by Duru et al. [1] regarding the arrhythmogenic action of endothelin-1 (ET-1). ET-1 is supposed to act as a paracrine hormone released due to stretch or myocardial ischaemia in vivo. ET-1 prolonged action potential duration with early afterdepolarization (EAD) formation in right bundle branch cells [2]. In in vivo experimental studies mono- and polymorphic nonsustained and sustained ventricular tachycardias (VT) often accelerating into ventricular fibrillation were observed during low dose (30–60 pmol/min) intracoronary (ic.) ET-1 administration [3]. At the time of the appearance of nonsustained VT-s 30% reduction of coronary blood flow without ischemic ECG alterations were observed. Furthermore, no ischemic lactate elevation in the coronary sinus could be observed [4]. Following 60 pmol/min ic. ET-1 infusion, a continuous prolongation of monophasic action potential (MAP) signs at 90% repolarisation (MAPD90) was detected before arrhythmia formation in all investigated regions (right and left ventricular apical/septal endocardial and right and left ventricular anterior epicardial sites). This was associated with EAD formation in approximately 50% of cases. However, the typical ischemic MAP changes, shortening of MAPD90, decreased MAP amplitude and upstroke velocity were not seen before the arrhythmias with low dose of ET-1 infusion [5].

Furthermore, treatment with the ET_A-receptor antagonist LU 135.252 (LU) (iv. 5 mg/kg) before ic. ET-1 infusion inhibited — presumably via myocardial receptors — the electrophysiological changes, MAP duration prolongation, EAD development and the formation of arrhythmias. On the other hand, LU failed to prevent in this dose the coronary vasoconstrictor responses elicited by ET-1 administration [6].

In contrast to the results of ET-1 infusion, administration of ET-1 in bolus (1 nmol and 2 nmol) caused severe ischemic ECG changes and yielded a prompt fall in coronary blood flow. Due to 1 nmol ET-1 bolus, MAP shortening and the decrease of the upstroke velocity in LVepi MAP signals were observed (ischemic effect) followed by an increase of MAPD90 in the reperfusion period (direct effect) [7].

When applying three dimensional mapping during 60 pmol/min ET-1 infusion and LAD ligation electrophysiological changes, local refractory period, left ventricular conduction time and total activation pattern were also different in the two groups. Besides focal mechanisms, macroreentry was also observed in the maintenance of the arrhythmias induced by subtotal LAD ligation, while no signs of reentry could be found during ET-1 infusion [8].

Certainly, we can not rule out the role of focal ischemia of ET-1 infusion, and the first reports on severe ventricular arrhythmias due to high-dose bolus administration of ET-1 presumably referred to the secondary arrhythmogenic effect of ET-1 via strong coronary vasoconstriction, coronary spasm or reperfusion. Presumably, ischemia can also play an important role in the maintenance of ET-1 induced arrhythmias. However, direct arrhythmogenic effect of ET-1 infusion was proven by both in vivo and in vitro experimental models.

The direct arrhythmogenic effect of ET-1 infusion — probably accomplished through myocardial ET_A-receptors — was demonstrated by both in vivo and in vitro studies [2–6].

References


