

## **Regional and sexual inhomogeneity in the mammalian ventricular myocardium**

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The aim of our study was to examine the distribution of ionic currents and the concordant channel proteins in the apical (APEX) and basal (BASE) region and the epicardial (EPI) and midmyocardial (MID) layers of the human and canine ventricular myocardium. We compared the data obtained using human and canine cardiac tissue and opposed the electrophysiological and the immunohistological measurements as well. We also examined the effects of testosterone and estrogen on the ECG parameters and on the expression of cardiac ion channels in male and female dogs.

Conventional microelectrode whole-cell voltage clamp and Western blot technique were used on isolated cardiomyocytes. ECG records were taken from male and female anaesthetized dogs before and after castration, and following inverted hormone substitution.

We found that the duration of the action potential was shorter, the amplitude of the early repolarisation was larger on cells isolated from the APEX and EPI region of the ventricle compared to those of the BASE and MID region. There was no difference on the other parameters of the action potential or on the capacity of the cells.

During voltage-clamp measurements the amplitude of the transient outward potassium current ( $I_{to}$ ) and the slow component of the delayed rectifier potassium current ( $I_{Ks}$ ) were approximately twice as large on APEX and EPI cells than on BASE and MID ones. The amplitude and kinetic properties of the other examined ionic currents ( $I_{Kr}$ ,  $I_{K1}$ ,  $I_{Ca}$ ) were similar in cells from all examined origins. The results of the immunohistochemical experiments - consistent with the data of the current measurements - showed more intense apical expression only in the channel proteins of the  $I_{to}$  and  $I_{Ks}$ : the density of the Kv1.4, KChIP2, KvLQT1 and MinK were higher in apical than in basal samples of canine hearts. During the transmural comparison, only the Kv4.3, Kv1.4, KChIP2 and KvLQT1 proteins had higher expression level in the EPI region than in the MID one. We found similar ion channel protein expression pattern in the human samples than in the canine ones.

During the sexual difference investigation we found that heart rate was decreased and PQ interval increased by castration in both genders, while inverted hormonal substitution restored control values. Orchiectomy significantly increased the duration of QT and QTc intervals, QTc-dispersion, while testosterone treatment of castrated females had opposite effects. Expression of ion channel proteins responsible for mediation of  $I_{K1}$  and  $I_{to}$  currents (Kir2.1 and Kv4.3, respectively), was higher in normal males and in the testosterone-treated castrated females. Repolarization of canine ventricular myocardium is significantly modified by testosterone. This effect is likely due to augmentation of expression of  $K^+$ -channel proteins.

The regional and sexual differences found in the canine and human ventricular myocardium are remarkable regarding both dispersion and drug effects. Isolated canine ventricular myocytes are appropriate for the study of the electrical inhomogeneity of the human myocardium.

### **Keywords:**

cardiac electrophysiology, ionchannel, ionic current, action potential, regional inhomogeneity, electrocardiogram, sexual steroid