The physiology of cardiac muscle in thoracic veins is of interest as a source of ectopic activity which can lead to paroxysmal atrial fibrillation (Haissaguerre et al. 1998 N Engl J Med 339: 659-666; Chen et al. 1999 Circulation 100:1879-1886). We have shown that noradrenalin can induce automatic ectopic activity in the pulmonary vein of the rat (Maupoil et al. 2007 Br J Pharmacol 150:899-905). Here we describe the effects of adrenergic agonists upon the resting membrane potential recorded with intracellular microelectrodes from cardiac muscle in the left atrium (LA), pulmonary veins (PV) and superior vena cava (SVC) of the rat. Isolated tissues were continuously perfused with Krebs-Heinseleit solution aerated with 95% O2, 5% CO2 and maintained at 36-37°C.

The quiescent resting membrane potentials were: LA -84±1 mV (n=14), SVC -74±1 mV (n=14), PV -69±1 mV (n=17). In each tissue noradrenalin (10-5M) induced a biphasic response with an initial hyperpolarisation (LA -3±1 mV, SVC -9±1 mV, PV -8±1 mV) followed by a depolarisation (LA +1±2 mV, SVC +15±2 mV, PV +34±1 mV). Only in PV did noradrenalin induce automatic electrical activity when the membrane potential reached ~50 mV.

The α-adrenergic agonist cirazoline (10-6M) induced a monophasic depolarisation of the resting membrane potential in each tissue: to -80±2 mV in LA, to -49±1 mV in SVC and to -34±1 mV in PV. In no case did cirazoline induce automatic electrical activity.

The β-adrenergic agonist isoprenaline (10-7M) induced a monophasic hyperpolarisation of the resting membrane potential in each tissue: to -87±1 mV in LA, to -79±2 mV in SVC and to -80±2 mV in PV. Conclusions — 1. There are significant differences between the resting membrane potentials of the left atrium and both thoracic veins.

2. The responses of the resting membrane potential to adrenergic stimulation are qualitatively similar but quantitatively different with LA < SVC < PV.

3. Depolarisation is not sufficient to induce automatic electrical activity.

En conclusion nous avons identifié l’angiotensine II et le TNFα comme des médiateurs du remodelage des KATP dans la défaillance cardiaque. Ce modèle sera utile pour analyser les mécanismes moléculaires régissant l’expression des sous-unités KATP dans la défaillance cardiaque.

G017

FACTORS ASSOCIATED WITH THE INDUCTION OF ANTIDROMIC TACHYCARDIA IN THE Wolff-Parkinson-White SYNDROME

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Atrioventricular reentrant tachycardia (AVRT) is the most frequent inducible tachycardia in patients with a Wolff-Parkinson-White syndrome (WPW). The incidence and the causes of the induction of antidromic tachycardia (ATD) are unknown. The purpose of the study was to determine the data of patients with a WPW and with inducible ATD.

Methods — 605 patients had a WPW and tachycardias (n=312) or syncope (n=85); other patients were asymptomatic (n=208). Electrophysiological study (EPS) was systematic. In control state (CS), the higher rate conducted through accessory pathway (AP) was measured; programmed atrial stimulation with 1, 2 extrastimuli was performed to induce a tachycardia. Isoproterenol (0.02 to 1 μg/min-1) was infused and the protocol was repeated.

Results — ATD was induced in 44 patients (7%) (group I). Their data were compared to those of remaining patients (group II). Group I differed from group II by the following data: Female sex was less frequent in group I (29.5%) than in group II (47%); AP was more frequently left sided in group I (54.5%) than in group II (38%) (p<0.05). AVRT was induced less frequently in group I (34%) than in group II (57%) (p<0.01); maximal rate conducted through AP was higher in group I (215±52 b/min) than in group II (189±61) in control state, and after isoproterenol (281±57 in group I vs 236±61 in group II) (p <0.001). Some data were similar: Age was not different in group I (33.5±20 years) and II (34.5±17); the indications of EPS were similar (syncope, reentrant tachycardia, atrial fibrillation (AF) or asymptomatic WPW were the reasons for 16%, 43%, 11% and 25% of group I patients and 14%, 46%, 5.5% and 35% of group II patients); posteroseptal and right AP locations were similar in both groups ; AF was induced as frequently in group I (27%) as in group II (23%).

Conclusions — antidromic tachycardia was induced more frequently in men than in women, with a left lateral AP which conducted more rapidly than in other patients.

G018

EVALUATION OF IKR BLOCKING PROPERTIES OF DIFFERENT MOLECULES WITH OR WITHOUT TORSADOGIC PROPERTIES

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Currently, industrials and regulatory authorities are worried by Torresades de Pointes (TdP), a type of ventricular tachycardia, which can lead to sudden death. The most recent guidelines from the International Committee of Harmonization, recommend to assess properly the risk of TdP, by different approaches, among others an in vitro method. This method consists on studying the blockade of a voltage-dependant potassium channel, called hERG. Indeed, hERG channel, responsible for the IKr current, seems to be blocked by the majority of the torsadogenic molecules and, is thus considered as an important marker of pro arrhythmic risk.

CERB developed a bio-computerized database named TdPScreen® to predict the risk of TdP. Known molecules are classified according to their pro arrhythmic potential, from group A to C. The group A corresponds to drugs with numerous or several reports of TdP, the group B to compounds causing QT prolongation with TdP at very low frequency; and in group C to drugs with no report of TdP or QT prolongation. This database suggests that other factors than a single blockade of IKr could be involved in the genesis of drug-induced TdP.

We performed experiments in patch-clamp using HEK cells expressing stably the hERG channel. Different compounds from the different groups, above mentioned, were evaluated for their IKr blocking potency and compared to the TdPScreen® database.

Results show some torsadogenic drugs might exhibit very low IKr blocking properties (e.g. D-sotalol), whereas other non-torsadogenic drugs are potent IKr inhibitors (e.g. verapamil, diltiazem...).

These results, and others, indicate that drugs can block hERG current without any influence on TdP appearance.

We conclude that assessing pro arrhythmic potential of compounds, only on the blocking effects of IKr, in vitro, can lead to the eviction of interesting molecules.

G019

CHOLESTEROL DEPLETION ENHANCES KV1.5-ENCODED K+ CURRENT BY INCREASING RAB11-MEDIATED RECYCLING

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