L'angiotensine II et le TNFα ont été impliqués dans la progression de l'insuffisance cardiaque. Nous avons observé dans le myocarde défaillant post-infarctus une surexpression de l'angiotensinogène et du TNFα selon un gradient régional correspondant à celui de l'expression de Kir6.1. Ainsi l'expression de l'angiotensinogène et du TNFα corrélait positivement avec celle de Kir6.1 et négativement avec celle de Kir6.2 dans les différentes zones du myocarde post-infarctus. Nous avons observé dans des cardiomyocytes isolés normauxexposé à de l'angiotensine II ou du TNFα un profil d'expression des sous-unités KATP similaire à celui observé dans le myocarde défaillant post-infarctus, caractérisé par une surexpression de Kir6.1 et des sous-unités SUR et une répression de Kir6.2. Les cardiomyocytes exposé à de l'angiotensine II ou du TNFalpha montraient en réponse au diazoxide un courant KATP prononcé et un raccourcissement du potentiel d'action.

Nous avons confirmé que l'angiotensine II induisait in vitro l'expression du TNFα dans les cardiomyocytes. Qui plus est, l'expression régionale de l'angiotensinogène dans le myocarde défaillant post-infarctus corrélait positivement avec celle du TNFα. Enfin, la plupart des effets de l'angiotensine II sur l'expression des sous-unités KATP étaient réduits en présence d'un anticorps neutralisant le TNFα.

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 TORSADOGENIC PROPERTIES

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Currently, industrials and regulatory authorities are worried by Torsades 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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