groups II (55%), III (65%). The changes could be related to primary angioplasty, systematic since 2000.

Conclusions — Induction of ventricular flutter or fibrillation is actually rarer than in years 1985/2000. The decrease corresponded with the development of primary angioplasty and revascularization. The induction of monomorphic VT < 270 b/min has not changed although a lower LVEF in patients studied since 2000.

G009 REGULATION OF THE CARDIAC SODIUM CHANNEL NAV1.5 BY A MEMBER OF MAGUK PROTEINS: SAP97
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Nav1.5 is the voltage-gated sodium channel that initiates the cardiac action potential. A precise regulation and localisation of Nav1.5 channels in cardiomyocytes is thus necessary for correct heart function. The three last amino-acids of Nav1.5 (SIV) constitute a PDZ-domain binding motif known to interact with the syntrophin-dystrophin complex and PDZ domains found in proteins of the MAGUK family. Among their multiple roles, MAGUK proteins can cluster proteins and localize them at the plasma membrane.

We investigated the interaction between SAP97, one cardiac MAGUK protein, and Nav1.5. We postulated that this interaction may be implicated in correct localisation, anchoring, turn-over and/or regulation of Nav1.5 biophysical properties.

Pull-down experiments performed with Nav1.5 C-terminus fusion proteins and human or mouse heart protein extracts revealed that the association between SAP97 and Nav1.5 depends on the PDZ-domain binding motif of Nav1.5. This interaction was specific for SAP97 and Nav1.5 as no pull-down could be detected with PSD95 or ZO-1, two MAGUK proteins also expressed in human heart. The functional consequences of this interaction were studied via patch-clamp experiments. Silencing of SAP97 reduced the whole-cell sodium current measured in HEK293 cells stably expressing Nav1.5 channels without decreasing the total protein amount. In control or silenced HEK293 cells, sodium current produced by Nav1.5 GSTV was reduced compared to WT. Immunostainings on frozen mouse heart slices demonstrated the colocalisation of Nav1.5 and dystrophin specifically at lateral membranes, but not at the intercalated discs. The possible colocalisation of Nav1.5 and SAP97 at the level of intercalated disks is currently investigated. This would support the hypothesis of the presence of two pools of Nav1.5 channels: one targeted at lateral membranes by the syntrophin-dystrophin complex, and another one targeted at intercalated discs by SAP97.

These findings strongly support the existence of an interaction between Nav1.5 and SAP97 in cardiac tissue. This interaction also depends on the presence of Nav1.5 PDZ-domain binding motif and may play a role in determining the channel density at the plasma membrane. Additional biochemistry, cytochemistry and biophysical experiments will allow us to further address this question.

G010 REGULATION OF VOLTAGE-DEPENDENT CALCIUM CHANNELS BY NEDD4-1
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Calcium entry into excitable cells can be regulated by controlling both the activity of calcium channels and the amount of channels available at the plasma membrane. Little is known about their internalisation and degradation. One post-translational modification shown to be involved in membrane protein internalisation and subsequent degradation is the attachment of ubiquitin moieties by ubiquitin-ligases. Previously, it has been shown that cardiac ion channels such as Nav1.5 and KCNQ1 are down-regulated by ubiquitin-ligases of the Nedd4 family. These regulations involve the interaction between the PY motif of the target channels and the WW motif of the ubiquitin-ligases. Despite the absence of such PY motif in the cardiac voltage-gated calcium channel Cav1.2, we investigated whether this channel could be regulated in the same manner as other cardiac channels as previously described.

We co-expressed, in HEK293 cells, L-type calcium channels and its two regulatory subunits Cavbeta and Cavalpha2delta1 together with ubiquitin-ligases, and examined by voltage-clamp whole-cell recordings the calcium current. We next determined by western blot and surface biotinylation assays the availability of the different subunits of calcium channels in total HEK293 lysates, and at the cell surface. Levels of ubiquitylation of the different subunits were assessed by pull-down GST-SSA and immunoprecipitation of Cav1.2 and its subunits.

We found that co-expressing the ubiquitin-ligase Nedd4-1 significantly reduced Cav currents, and decreased Cavalpha and its subunit protein levels. This effect was Nedd4-1 specific since none of the other members of the Nedd4 family we tested produced a similar effect. We also found that the effect of Nedd4-1 was dependent on the co-expression of the Cavbeta subunit. No Nedd4-1-dependent increase in ubiquitylation of the Cavalpha protein was found; and unexpectedly, the two regulating subunits Cavbeta and Cavalpha2delta1 were detected to be deubiquitylated upon Nedd4-1 co-expression.

Our data suggest that Nedd4-1 regulates the expression of Cav channels and its subunits by Nedd4-1 via an indirect mechanism constituting a new regulatory pathway to be determined. Further experiments will focus on the role of adrenergic receptors known to be ubiquitylated by Nedd4 and to bind to Cav1.2.

G011 INCIDENCE AND PROGNOSIS OF VENTRICULAR TACHYCARDIA IN APPARENTLY NORMAL SUBJECTS
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The prognosis of ventricular tachycardia (VT) is related to the presence of heart disease (HD). VT in patients without HD is considered as benign. However some sudden deaths were reported. The development of new methods as cardiac MRI has permitted to detect HD in some patients. The purpose of the study was to evaluate the incidence and prognosis of patients recruited since 30 years for VT and without apparent HD with conventional methods.
Population — 806 patients were admitted for sustained VT between 1978 and 2008.

Methods — The following studies were performed: recording of ECG, signal averaged ECG, Holter monitoring, exercise testing (when possible), echocardiography, right angiography in patients with right VT, coronary angiography in patients older than 40 years and electrophysiological study.

Results — 74 patients (9%), aged from 11 to 75 years (mean 46 ± 18), 45 men, 29 women had normal echocardiogram and hemodynamic study. Right ventricular outflow tract (RVOT) VT was noted in 42 patients, verapamil-sensitive VT in 23; VT’s were right and left in 3 patients, related to a bundle branch reentry in 1, of undetermined origin in 4 patients. VT developed at exercise testing in 15 patients and was inducible or occurred with isoproterenol in 54 patients (73%). Erroneous diagnosis of supraventricular tachycardia with aberrancy was initially made in 5 patients. Beta blockers and/or antiarrhythmic drugs were initially prescribed. Defibrillator was implanted in one patient with syncopal RVOT-VT and 2 for a false diagnosis of right ventricle dysplasia made in 2002 at beginning of MRI. Catheter ablation for recurrent VT was performed in 3 patients with failure in one and in 1 patient for its job. Three patients were lost of view during follow—up (mean 11.5 ± 6.6 years); remaining patients, but one are alive without recurrent VT and without drugs in half of them; 1 patient died from non cardiac cause. One patient developed dilated cardiomyopathy; 2 had permanent atrial fibrillation.

Conclusions — VT in patients without apparent HD after conventional studies (echocardiography, hemodynamic study) represented 9% of VT and required rarely a non medical treatment.

G012
LONG-CHAIN ACYLCARNITINES REGULATE IHHERG WHILE MEDIUM-CHAIN ACYLCARNITINE DO NOT
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Free fatty acids are the primary substrate used by the heart to generate cellular ATP. Carnitine, acylcarnitine and carnitine-transferase are essential for normal metabolism of long-chain fatty acids in heart. Some of the arrhythmias observed following an ischemia are attributed to an accumulation of long-chain acylcarnitine into ad out the cells. It has also been observed that a deficiency in a carnitine transporter, OCTN2, normally found in heart, muscle and kidney, leads to a reduced plasma carnitine and acylcarnitine level. Such pathology was associated with the occurrence of ventricular fibrillation and eventually to sudden death. All these data suggest that acyl-carnitine (Acyl-CARs) can regulate ion channels. We studied the effects of different acyl-CARs at different concentrations on the hERG channel activity (iHHERG) which is known to participate to lethal arrhythmias.

HEK293 cells stably expressing hERG were studied in patch clamp. Acyl-CAR derivatives from medium — (C8 and C10) and long-chain (C16 and C18:1) fatty acids were applied intra- and extracellularly at different concentrations.

C8-CAR and C10-CAR had no effect at 3µm and 30µm whether they are applied intra- or extracellularly. C16-CAR and C18-CAR had no effect on the current when applied intracellularly. Extracellularly, 3µm C16-CAR or C18-CAR induced an increase of the current amplitude associated with different effects on the activation and availability properties. At this concentration, the long-chain acyl-CAR induced also a speeding of deactivation kinetic.

Long-chain acyl-CARs, but not medium-chain, regulate extracellularly iHHERG. When their level varies during diseases like primary systemic carnitine deficiency or ischemia, there must be an impact on the action potential which can explain some of the cardiac arrhythmias observed.

G013
PRÉVALENCE ÉLEVÉE DU SYNDROME DE BRUGADA CHEZ LES PATIENTS ATTEINTS DE MALADIE DE STEINERT
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Rationnel — La maladie de Steinert (DM1) est une maladie systémique associée à un risque élevé de mort subite en rapport avec des troubles conductifs et des arythmies ventriculaires. Le mécanisme de ces morts subites n’est pas connu. Notre objectif était de déterminer si le syndrome de Brugada est impliqué dans ces complications.

Méthode — Nous avons analysé les électrocardiogrammes de 500 patients atteints de maladie de Steinert. Les patients ayant un tracé ECG avec un Brugada de type 1 ont bénéficié d’un séquençage du gène SCN5A et d’un bilan cardiaque comprenant un holter ECG, une échocardiographie et une exploration électrophysiologique.

Résultats — Un ECG avec un aspect de Brugada de type 1 a été identifié chez 7 patients, soit une prévalence 80 fois plus élevée que dans la population générale. Le séquençage de SCN5A était normal chez tous les patients. Un patient a fait une mort subite en rapport avec une fibrillation ventriculaire et la stimulation ventriculaire programmée a déclenché des tachycardies ventriculaires polymorphes chez 5 patients.

Conclusion — La prévalence du syndrome de Brugada est plus élevée chez les patients DM1 que dans la population générale. Les patients présentant l’association de ces deux anomalies semblent exposés à un risque élevé d’arythmies ventriculaires sévères.

G014
IDENTIFICATION OF INTERSTITIAL CELLS OF CAJAL IN HUMAN PULMONARY VEINS
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Introduction — The major determinant of atrial fibrillation initiation is focal firing within the muscular portion of the pulmonary veins. We hypothesized that Interstitial Cajal cells, a known type of pace-