H027
COGNITIVE PROFILE IN HEART FAILURE AND HYPERTENSION

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Objective — To assess and compare cognitive levels and profiles of five cognitive functions according to hypertensive and heart failure status.

Methods — 111 hypertensive patients (24h-Ambulatory Blood Pressure Monitoring: day-systolic BP >135 mmHg, day-diastolic BP >85 mmHg, night-systolic BP >120 mmHg or night-diastolic BP >70 mmHg), 56 normotensive patients and 51 stable heart failure patients (Left Ventricular Ejection Fraction <45 %) all French speaking and without previously known dementia, depression (Beck Depression Inventory >21) or recent stroke, gender , years of education and hypertension.

A subgroup analysis on 60-75 years old patients, 41 hypertensive, 19 heart failure and 33 normotensive patients matched on age, years of education and gender, was performed. No significant difference on depression index, exposure to anxiolytics/hypnotics, sleep-apnea syndrome and other cardiovascular risk factors was observed. The cognitive profile (Fig 1) shows significant level differences between functions in heart failure compared to normotensive (normalized) with significant deficits in executive functions (p<0.01) and delayed memory (p<0.02), while cognitive functions are affected with the same level in hypertension except for recent memory.

Conclusion — We confirm that heart failure is an independent predictor of cognitive impairment, and affects more specifically language, executive functions, recent and delayed memory. Hypertension slightly impairs cognitive functions with the same level.

H028
INSIGHTS INTO THE GENETIC AND CELLULAR CONTROL OF PROXIMAL CORONARY ARTERY PATTERNING

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In humans, Tbx1 is the major candidate gene for DiGeorge (del22q11.2) syndrome, which includes heart malformations such as tetralogy of Fallot and Persistent Truncus Arteriosus (PTA). In Tbx1 null embryos, Second Heart Field (SHF) cardiac progenitor cell numbers are decreased leading to a hypoplastic outflow tract and PTA. Recently, we have shown that the Tbx1 phenotype is associated with reduction of a specific progenitor cell population that normally contributes to myocardium at the base of the pulmonary trunk. The Tbx1 mutant ventricular outlet thus has a predominantly subaortic identity supported by the presence of a single outflow valve with three leaflets. In addition, we demonstrated that coronary artery patterning is abnormal in Tbx1-nulls. Proximal coronary arteries course abnormally across the ventral region of mutant hearts and left and right arteries branch to the right/ventral sinus of the common outlet.

Coronary artery patterning defects are observed at early developmental stages at the level of the coronary plexus suggesting that SHF derived cells influence the cellular and molecular events responsible for the distribution and branching of proximal coronary arteries. We have identified Semaphorin3c as a Tbx1-dependent gene expressed in subpulmonary myocardium. However, Sema3c-null embryos do not show major coronary artery defects suggesting that Sema3c function overlaps with that of other genes affected in Tbx1 mutant embryos. We are now investigating the distribution and patterning of additional vascular guidance molecules as well as the distribution of neural crest cells and cardiac cushions which play critical roles in outflow tract development in wild type mice.

Our results provide new insights into the association between conotruncal defects and coronary artery anomalies and implicate SHF derived cells in coronary artery patterning. Ongoing research in collaboration with Necker Hospital (Paris) aims to investigate whether specific coronary artery anomalies are associated with PTA in DiGeorge syndrome.

H029
L'ALTÉRATION CONTRACTILE SOUS-ENDOCARDIQUE EST PRÉSENTE DANS UN MODÈLE CANIN DE DYSTROPHIE MUSCULAIRE DE DUCHENNE ET APPARAÎT COMME UN PHÉNOMÈNE CELLULAIRE INTRINSÈQUE

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Il existe un gradient de contractilité cardiaque à travers la paroi du ventricule gauche où les cellules du sous-endocarde (ENDO) se contractent davantage que celles du sous-épicarde (EPI). Ce gradient de contractilité est altéré au cours de l’insuffisance cardiaque ischémique et hypertrophique. L’objectif de cette étude a été de déterminer si chez le chien, le gradient de contractilité transmural peut s’expliquer par une hétérogénéité contractile cellulaire et d’évaluer l’impact d’une cardiopathie dilatée spontanée de dystrophie musculaire de Duchenne chez le chien GRMD (Golden Retriever Muscular Dystrophy) sur ce gradient transmural.

Dans cette étude, la contractilité cardiaque a été explorée in vivo par échocardiographie et in vitro sur cellules permiéléesisé pour évaluer les propriétés contractiles des myofilaments (i.e tension active et passive, et sensibilité au Ca2+ des myofilaments (pCa50) à deux longueurs de sarcome).

Chez le chien sain, la vitesse de contraction des couches ENDO, mesurée in-vivo, était plus élevée par rapport aux couches EPI. Au niveau cellulaire, l’augmentation consécutive à un étirement de la sensibilité des myofilaments pour le calcium (Delta pCa50) était plus élevée dans les cellules ENDO. La dystrophie musculaire (DM) a induit une baisse de la fraction de raccourcissement de la paroi ventriculaire gauche des chiens GRMD ainsi qu’une réduction importante du gradient de vitesse de contraction transmural (ENDO-EPI) principalement due à une altération des couches sous-endocarde. Nous avons également observé que la DM induisait une baisse de la tension active maximale développée par les cellules ENDO. Par ailleurs, la DM a induit une augmentation de la pCa50 à faible longueur de sarcomère des cellules ENDO qui conduit à une diminution du Delta pCa50. Les cellules EPI n’étaient pas affectées par la DM.

Nos résultats montrent que le gradient transmural de contractilité observé in vivo chez le chien normal s’explique en partie par une hétérogénéité contractile cellulaire. Chez le chien porteur d’une dystrophie musculaire le gradient de contractilité transmural est altéré en raison d’une atteinte préférentielle des couches sous-endocarde. Cette anomalie déjà décrite dans les cardiopathies ischémiques et hypertrophiques apparaît donc ubiquitaire à l’insuffisance cardiaque.

Methods — Two months old-mice were analyzed. Heart tissue was fixed (formaldehyde 10%) and embedded in paraffin for immunohistochemistry or frozen for western-blot (WB) analysis. Immunofluorescence (IF) studies were performed on heart cryosections. ECG was recorded (PowerLab, DSI) under isoflurane anaesthesia and heart rate spectral variability (HRV) was performed (FFT) in low frequency (LF: 0.15-1.5 Hz) and high frequency (HF: 1.5-5 Hz) ranges; LH/HF ratio was also calculated.

Results — We first assessed expression of Ephrin-B1 by WB in heart from WT animals. A specific band around 47 kDa was detected in WT heart total protein extracts that was lost in KO mice. Further IF studies demonstrated broad expression of Ephrin-B1 protein throughout all heart compartments with different cellular localizations (cardiomocytes and micro/macrocirculation). Hematoxylin-eosin (HE) staining of paraffin-embedded heart sections from KO mice revealed loss of organized cardiac tissue characterized by the presence of wavy cardiomocytes in both septum and ventricles. Myocytes intersected at various angles with bundles wavy appearance. No inflammation, interstitial fibrosis or necrosis were noticed. These pathological observations correlated well with the lack of stiffness of hearts from KO mice compared with controls. When we examined ANS-dependent heart rate variability, LF-HRV was significantly reduced in KO mice (16.3±1.2 %) when compared to controls (48.5±6.2 %) without any change in HF, suggesting a specific loss of cardiac sympathetic innervation in these animals. LF/HF ratio was lower in KO mice (0.6±0.2 vs 1.3±0.2 in controls).

Conclusion — This study provides the first evidence for the presence of ephrin molecules in the adult heart tissue with a specific expression of Ephrin-B1 ligand. The use of ephrin-B1 genetic mouse model highly suggests a role for ephrin-B1 in heart tissue architecture and in sympathetic control of heart rate variability.

H030

LOSS OF EPHRIN-B1 DISRUPTS MYOCARDIAL ARCHITECTURE AND LEADS TO ABNORMAL SYMPATHETIC HEART RATE VARIABILITY

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Background — Ephrin-B1 is a ligand from Eph/Ephrin family involved in cell-cell interactions. If the role of ephrine molecules is well known in embryonic tissue, their expressions/functions in adults remain unclear and to date, no study have paid attention to their potential implication in heart physiopathology.

Aim — To characterize the cardiac phenotype of ephrin-B1 knockout mice.

Methods — Two months old-mice were analyzed. Heart tissue was fixed (formaldehyde 10%) and embedded in paraffin for immunohistochemistry or frozen for western-blot (WB) analysis. Immunofluorescence (IF) studies were performed on heart cryosections. ECG was recorded (PowerLab, DSI) under isoflurane anaesthesia and heart rate spectral variability (HRV) was performed (FFT) in low frequency (LF: 0.15-1.5 Hz) and high frequency (HF: 1.5-5 Hz) ranges; LH/HF ratio was also calculated.

Results — We first assessed expression of Ephrin-B1 by WB in heart from WT animals. A specific band around 47 kDa was detected in WT heart total protein extracts that was lost in KO mice. Further IF studies demonstrated broad expression of Ephrin-B1 protein throughout all heart compartments with different cellular localizations (cardiomocytes and micro/macrocirculation). Hematoxylin-eosin (HE) staining of paraffin-embedded heart sections from KO mice revealed loss of organized cardiac tissue characterized by the presence of wavy cardiomocytes in both septum and ventricles. Myocytes intersected at various angles with bundles wavy appearance. No inflammation, interstitial fibrosis or necrosis were noticed. These pathological observations correlated well with the lack of stiffness of hearts from KO mice compared with controls. When we examined ANS-dependent heart rate variability, LF-HRV was significantly reduced in KO mice (16.3±1.2 %) when compared to controls (48.5±6.2 %) without any change in HF, suggesting a specific loss of cardiac sympathetic innervation in these animals. LF/HF ratio was lower in KO mice (0.6±0.2 vs 1.3±0.2 in controls).

Conclusion — This study provides the first evidence for the presence of ephrin molecules in the adult heart tissue with a specific expression of Ephrin-B1 ligand. The use of ephrin-B1 genetic mouse model highly suggests a role for ephrin-B1 in heart tissue architecture and in sympathetic control of heart rate variability.

H031

SHORT-TERM HEART RATE REDUCTION INDUCED BY IVABRADINE ADMINISTERED TO RATS WITH WELL-ESTABLISHED HEART FAILURE IMPROVES CARDIAC FUNCTION, AUGMENTS NEO-ANGIOGENESIS AND REDUCES MYOCARDIAL HYPOXIA

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Long-term heart rate reduction (HRR) initiated in a pathophysiological situation of moderate left ventricular (LV) dysfunction prevents the deterioration of cardiac function. This is probably related to short-term effects of HRR, i.e. improved myocardial perfusion and reduced O2 consumption, and long-term HRR effects on LV structure, i.e. improved capillary density. However, it is currently unknown 1) whether the short-term effects of HRR are sufficient to improve LV function when HRR is initiated in a setting of well-established chronic heart failure (CHF) and/or 2) whether short-term HRR triggers/activates early mechanism(s) involved in the structural long-term effects of HRR. Thus, we assessed, in a rat model of CHF (coronary ligation), the effects of short-term HRR induced by the If current inhibitor ivabradine (Iva; 10 mg/kg/day as food admix for 4 days starting 93 days after ligation). The table shows heart rate (HR; beats/min), cardiac output (CO; ml/min), LV end-systolic pressure (LVESP; mmHg), LVESP-volume relation (LVESPV; mmHg/Relative