In this study we have investigated the expression and regulation of NOX in TCM patients with reversible impairment of LV-function compared to patients with dilated cardiomyopathy (DCM).
Methods: EMB of patients with new-onset non-valvular, non-ischemic cardiomyopathy with a severely reduced LVEF were evaluated. Patients with TCM (n=13) retrospectively fulfilled published clinical diagnostic criteria. DCM (n=10) was diagnosed according to current guideline recommendations. RNA was isolated from paraffin-fixed tissue of the right interventricular septum and analysed using an automated miRNA fluorescence reporter assay.
Results: NOX1, with its predominant regulator Rac1, are pivotal for the generation of O2·– in the myocardium. Patients with TCM showed a significantly lower expression of NOX1 compared to patients with DCM (0.005±0.0007, n=13, vs. 0.009±0.001, n=10, $p<0.05$). Interestingly, Rac1 was similarly abundant in both groups (0.03±0.002, n=13, vs. 0.03±0.003, n=10, $p>0.05$).
Analysis of NOX4, as the predominant myocardial source of H2O2, similarly revealed a decreased expression in patients with TCM compared to patients with DCM (0.003±0.0008, n=13, vs. 0.009±0.003, n=10, p=0.06).
NFkB and AKT/mTOR as effector proteins with a known redox-sensitivity showed no significant regulation between the two groups.
Conclusion: Patients with an arrhythmia-induced, reversible form of heart failure show distinct differences in the expression of ROS generating enzymes. With both NOX1 and NOX4 as O2·– and H2O2 producing NOX isoforms significantly less expressed in patients with TCM, we demonstrate differences in the pathophysiological processes of reversible and progressive heart failure.

5926
Electrically stimulating wide-areas of the epicardial surfaces of large mammalian ventricles is achievable with line electrodes

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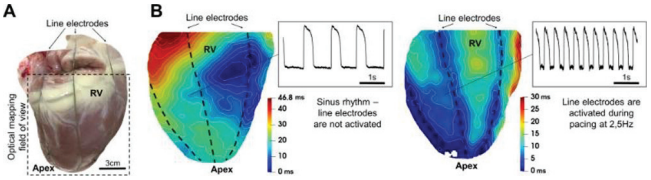
Background: The epicardial surface of the heart is an attractive target to administer antiarrhythmic electrotherapies. Electrically stimulating wide-areas of the epicardial surfaces of small mammalian ventricles (guinea pig, rat) is straightforward given their small myocardial volumes. However, it has yet to be proven for larger mammalian hearts with tissue properties and ventricular dimensions closer to humans.
Purpose: To address the feasibility of wide-area electrical stimulation on the ventricular surfaces of large mammalian hearts.
Methods: Porcine hearts (n=6) were excised and Langendoff perfused. Six 12 cm long stranded tinned copper lines were placed 3–4 cm apart on the epicardium; three on the RV and three on the LV (Fig. A). Lines were stimulated (2.5Hz, 2ms pulse width) both independently and simultaneously at different energies ranging from 0.6 to 39 mJ per pulse corresponding to threshold (thr), 2x thr and max (equipment limit) energies. Responses to line stimulation were monitored using a bath ECG and electrical activity was recorded by optical mapping using the voltage-sensitive dye Di-4-ANEPPS. Activation time (AT) maps were computed from both the RV and LV to compare each line electrode stimulation (independently or simultaneously) at thr, 2x thr and max energies.
Results: Regardless of the line stimulated, epicardial line stimulation was accomplished at energies ≥0.6mJ per pulse (Fig. B). AT was dependent on stimulation energies and whether the electrodes were activated independently or simultaneously. Fastest activation of 50% of the total map was achieved during max energy and with all electrodes activated simultaneously (15.5±4.4ms from the onset of stimulation) compared to thr and 2x thr (26.2±7.4 and 44.9±8.2ms), and also to single electrode activation (46.6±10.3, 39.9±8.3 and 20.9±3.9ms at thr, 2x and max energies, respectively). Less energy to reach the stimulation threshold was required when the electrodes were placed with strong electrical contact on the epicardium and in areas with little fat. Risk of partial ischemia was noticed due to possible vasculature occlusion.



Conclusions: Electrically stimulating wide-areas of the epicardial surfaces of large mammalian ventricles is achievable with line electrodes. The energies produced per pulse (<39 mJ) were well below the human pain threshold (100mJ), which make it feasible for medical devices to painlessly stimulate wide-areas of the epicardium. Future electrode designs should maximize electrical contact in the presence of vasculature and fat.
Funding Acknowledgements: ANR-16-CE19-0009, ANR-10-IAHU-04

ARRHYTHMOGENIC CARDIOMYOPATHY: FROM PATHOLOGY TO PROGNOSIS

5954
Arrhythmogenic cardiomyopathy: a paradigm shift of the morphologic spectrum

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Background: Arrhythmogenic cardiomyopathy (AC) is a genetically determined heart muscle disease characterized by progressive myocardial atrophy with fibro-fatty substitution. Originally reported as a disease of the right ventricle (RV), in the recent years a biventricular (BiV) involvement with even dominant or isolated left ventricular (LV) variants (so called "left dominant" AC, LDAC have been reported.
Purpose: To assess the whole pathologic spectrum either macroscopic or histologic of AC and the mode of death/failure by reviewing our heart specimens archive.
Methods: We reviewed the AC heart specimens and histologic slides of three series: a) juvenile SD (<40 years, total N. 723); b) cardiac transplantation – CT, (total N. 912); and c) general autopsy archives – extra cases (total N. 1996). For each case, we looked for the mode of death or failure (congestive heart failure or arrhythmias); type of involvement (RV, BiV or LDAC) and other gross and histological features, including aneurysms or thrombosis, the transmural extent of fibro-fatty replacement and the presence of inflammatory cells, necrosis and "cardiomyopathic" changes.
Results: A total N of 129 AC heart specimens have been enrolled, including 73 juvenile SD cases, 33 CT cases and 23 extra cases.
In the SD group (49 M, mean age 26 years), the AC phenotype is RV in 8 (11%), BiV in 42 (58%) and LDAC in 18 (25%). RV aneurysms were detected in 19 (26%), in the absence of endocavitary thrombosis or LV aneuryms.
In the CT group (18 M, mean age 45 years), the AC phenotype is RV in 2 (6%), BiV in 29 (88%) and LDAC in 2 (6%). RV aneurysms were detected in 26 (79%), endocavitary thrombosis in 10 (30%) and LV aneurysms in 6 (18%). A "spongy-like" appearance was present in 5 cases (15%).
In the AC extra group (20 M, mean age 42), the phenotype is BiV in 16 (70%) and LDAC in 6 (26%). The AC phenotype was absent in two mutation carriers who died in adolescence ("pre-phenotypic stage"); the cause of death was extracardiac in one and ventricular fibrillation with a myocarditis picture in the other.
At histology, the fibro-fatty replacement of the RV was transmural in 68% of SD, 91% of CT (p SD vs CT <0,01) and 52% of AC extra (p CT vs extra <0,01). The fibro-fatty or fibrous replacement of the LV free wall was transmural in 9% of SD, 27% of CT and 9% of AC extra (p SD vs CT <0,01). Inflammation and cardiac myocyte necrosis were detected in 95% of SD, 67% of CT and 91% of AC extra cases.
Conclusions: The phenotypic spectrum of the disease is wider than it was thought in the past. BiV variants prevail with the highest frequency in the CT series, whereas the LDAC variant reaches the highest prevalence in the juvenile SD group. RV aneurysms are a common finding in CT at difference from the SD hearts. Fibro-fatty replacement is not necessarily transmural, being frequently confined to the sub-epicardial or midmural layers not only in the LV free wall, but even in the RV free wall.

5955
Anti-heart autoantibodies and arrhythmogenic cardiomyopathy: the role of inflammation in disease evolution

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Background: Several lines of evidence support the involvement of autoimmunity in Myocarditis and Dilated Cardiomyopathy (DC). Serum anti-heart autoantibodies (AHA) are organ and disease-specific autoimmune markers in Myocarditis and Dilated Cardiomyopathy. Biopsy-proven myocarditis is frequently reported in Arrhythmogenic Cardiomyopathy (AC) but its etiopathogenetic significance remains poorly understood.
Purpose: The aim of the study was to assess the frequency of AHA in AC patients and their relationship with a worst clinical phenotype.
Methods: We assessed serum AHA in 57 AC patients (52,6%male, mean age 32±12years) met the 2010 revised ESC Task force diagnostic criteria. AHA was detected by indirect immunofluorescence on cryostat sections of normal O blood group human myocardium and skeletal muscle, blindly from clinical and genetic diagnosis. All patients underwent clinical and non-invasive assessment including a 12 lead electrocardiogram, echocardiography, 24-hour Holter Ecg, exercise testing, late potentials ECG and cardiac MRI. At follow up all patients performed 12 lead electrocardiogram, echocardiography, 24-hour Holter Ecg and exercise testing.
Results: In 31 AC patients (54%) was detected the presence of AHA. At diagnosis AHA positive patients presented more often a familiar history of autoimmune disease (38,5% vs 11,4% p-value:0,05); they had more supraventricular extra beats (281,69±702,6 vs 24,45±45, p-value=0,05) and premature ventricular contraction polymorphism at Holter ecg (48,4% vs 15,4%, p-value=0,001). Furthermore, at initial echocardiography evaluation, the presence of AHA antibodies

was associated with a greater dimension of right ventricular outflow tract (RVOT) RVOTP:mm/m^2 17,39±2,72 vs 15,29±2,68 p-value=0,005; RVOT1: 23,775±3,4 vs 16,19±2,25 p-value=0,001; RVOT2:14,72±2,36 vs 13,15±1,71 p-value=0,006). At follow up visit (mean 6 years±2,7) AHA patients showed more syncopal episodes (10pt vs 2pt, p-value=0,04) more non sustained ventricular tachycardia at Holter ecg (14pt vs 1pt, p-value=0,0006) and more patients were in atrial fibrillation (5pt vs 1pt, p-value 0,06).
Conclusion: For the first time we demonstrated that the presence of AHA in patients with AC is associated with a more severe disease phenotype, indeed it were significantly correlated with the size of the RVOT, with the complexity of arrhythmias and with the presence of syncope and ventricular tachycardia at follow-up.

5956
Multimodality prediction of life-threatening ventricular arrhythmia in patients with arrhythmogenic cardiomyopathy; a prospective cohort study

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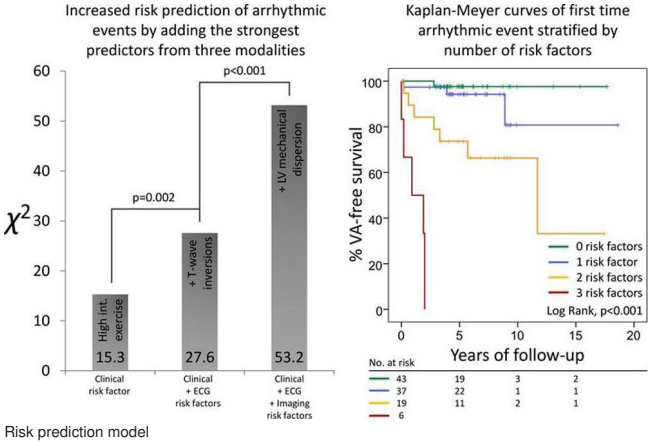
Background: Electrocardiogram (ECG) and cardiac imaging play key roles in the diagnostic criteria for arrhythmogenic cardiomyopathy (AC), but their roles in risk stratification of patients presenting without life-threatening ventricular arrhythmia are unclear.
Purpose: To identify predictors of first-time life-threatening ventricular arrhythmia by assessing clinical characteristics, ECG and cardiac imaging in a prospective cohort study of patients with AC.
Methods: We included consecutive AC probands and mutation positive family members with no previous life-threatening arrhythmic events, and followed them prospectively from time of diagnosis. The endpoint was the first life-threatening ventricular arrhythmia, defined as aborted cardiac arrest, appropriate ICD-shock or sustained ventricular tachycardia. At baseline, we assessed possible risk predictors from three categories; (1) clinical parameters, (2) ECG and (3) cardiac imaging (echocardiography and cardiac magnetic resonance imaging) according to the Task Force Criteria of 2010. In addition to traditional imaging criteria, we assessed left ventricular (LV) and echocardiographic strain parameters. LV mechanical dispersion was defined as the standard deviation of time from onset Q/R on ECG to peak negative strain in 16 LV segments. We recorded exercise habits, and defined high intensity exercise as >6 metabolic equivalents.
Results: We included 117 patients (29% probands, 50% female, age 40±17 years). During 4.2 (IQR 2.4 to 7.4) years of follow-up, 18 (15%) patients experienced life-threatening ventricular arrhythmia. The 1, 2 and 5 year incidence was 6%, 9% and 22%, respectively. History of high intensity exercise was the strongest clinical predictor, T-wave inversions ≥V3 was the strongest ECG predictor and greater LV mechanical dispersion by echocardiography was the strongest predictor from cardiac imaging (adjusted HR; 4.9 [95% CI 1.3–18.3], p=0.02, 5.8 [95% CI 2.1–16.1], p=0.001, and 1.4 [95% CI 1.2–1.6] by 10 ms increments, p<0.001, respectively). These parameters had incremental risk predicting value (Figure, left panel). Arrhythmia free survival in patients with all three risk factors was only 1.2 (95% CI 0.4–1.9) years, compared to 17.4 (95% CI 16.6–18.2) years in patients without any risk factors (Figure, right panel).



Risk prediction model

Conclusions: History of high intensity exercise, T-wave inversions ≥V3 on ECG and greater echocardiographic LV mechanical dispersion were strong and independent predictors of life-threatening ventricular arrhythmias. AC patients without any of these risk factors had minimal arrhythmic risk, while having more than one risk factor increased the risk dramatically. This may guide decisions on primary preventive ICD implantation in these patients.

HYPERALDOSTERONISM AND HYPERTENSION: LOOK HARDER!

5970
Who to test for primary aldosteronism: development of a decision tool to select the right patients

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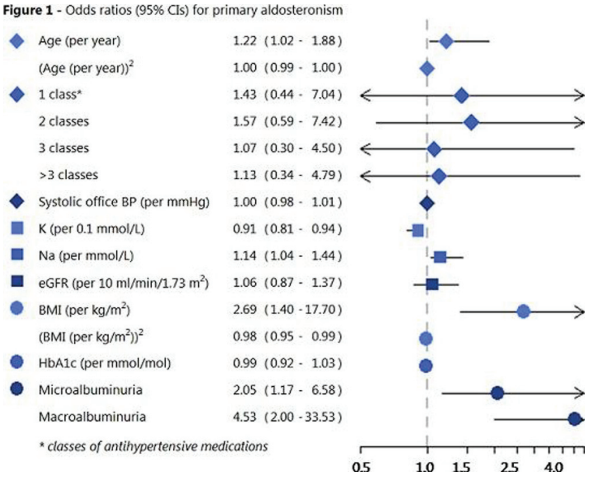
Background/Introduction: Primary aldosteronism (PA) is one of the most common causes of secondary hypertension, occurring in 4–10% of hypertensive patients. Targeted therapy can reduce blood pressure as well as cardiovascular and metabolic disease. Diagnostic testing for PA, however, is burdensome and costly. Therefore, under- and overdiagnosing in clinical practice should be avoided.
Purpose: The aim of this study was to develop a decision tool with high sensitivity and negative predictive value, in order to select those patients to further test for PA.
Methods: In this cross-sectional study, patients referred to our University Medical Centre with difficult-to-control hypertension who were analysed through a highly standardized diagnostic protocol between January 2010 and October 2017 (n=827) were included. PA was diagnosed by a combination of laboratory tests performed in supine position after washout of antihypertensive medications influencing renin or aldosterone levels: 1) elevated aldosterone-to-renin ratio (>5.0 pmol/fmol/s, which has been shown to reach a sensitivity of 100% in our hospital), confirmed with 2) non-suppressible aldosterone after saline infusion (>280 pmol/L). Two patients were excluded because of a missing confirmation test. We performed multivariable logistic regression analysis including pre-specified clinical characteristics (age, number of antihypertensive classes, systolic office blood pressure, serum potassium, serum sodium, BMI, eGFR, HbA1c and albuminuria) to build the model for our decision tool. Values missing at random were singly imputed by weighted probability matching. No variable selection was performed. After correction for optimism using a bootstrap-based shrinkage technique, test reliability, discriminative performance and test statistics were determined.
Results: PA occurred in 34 (4.1%) of 825 verified patients. The shrinkage factor for coefficients was 0.69. Odd ratios are depicted in Figure 1. Predicted probabilities of PA agreed well with observed frequencies and the area under the ROC curve was 0.79 (95% CI 0.70–0.87). A predicted probability of 1.5% was the most optimal cut-off value, preventing unnecessary testing in 23% of patients with difficult-to-control hypertension and carrying a sensitivity of 0.97 (95% CI 0.90–1.00) and a negative predictive value of 0.99 (95% CI 0.98–1.00).

Figure 1 - Odds ratios (95% CIs) for primary aldosteronism



Conclusion: This decision tool with nine easy to measure clinical variables provides a reliable method to select patients to be tested for PA in the hospital setting. It reduces the amount of patients to be tested from ~90% (as suggested by the current Endocrine Society Guideline) to 78%, therefore contributing to a reduction of diagnostic burden and costs. Before widespread use in clinical practice this decision tool should be externally validated.

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Predictors of the results of the confirmatory tests for the diagnosis of primary hyperaldosteronism in hypertensive patients with an aldosterone-to-renin ratio greater than 20

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