Topic 02 – Heart failure and cardiomyopathy

January 16th, Thursday 2014

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First assessment of left ventricular systolic dysfunction by multimodality imaging in Tako-Tsubo cardiomyopathy

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Background: Tako-Tsubo cardiomyopathy is a stress-induced cardiomyopathy and is characterized by transient left ventricular (LV) systolic dysfunction. During the hospitalization, recovery may rapidly occur with a partial increase of LV ejection fraction. The aim of this prospective study was to assess LV systolic dysfunction in a large population of Tako-Tsubo cardiomyopathy.

Methods: The study population included 90 patients presenting with Tako-Tsubo cardiomyopathy (85 women, 71±12 y.o.). This is a substudy of the multicentric prospective TAKO-GENE study (ClinicalTrials.gov Identifier: NCT01520610). TTC was defined according to the Mayo-Clinic criteria and LV systolic function was assessed by multimodality imaging.

Results: Among Tako-Tsubo cardiomyopathy, a typical pattern was observed in 73 pts, an apical-sparing variant in 16 pts and an inverted Tako-Tsubo cardiomyopathy in 1 patient. Mean LV ejection fraction assessed by echocardiography was 39.3±11.4% and was significantly lower than LV ejection fraction calculated by LV angiography (43.1±12.7%, $p<0.05$) and by cardiac magnetic resonance (49.6±11.8%, $p<0.0001$). Assessment of LV ejection fraction was performed by echocardiography at admission, by LV angiography between day 0 and day 3 and by cardiac magnetic resonance between day 2 and day 7.

Conclusion: Echocardiography allows a fast and immediate assessment of LV ejection fraction whereas assessment of LV systolic dysfunction may be delayed by LV angiography and cardiac magnetic resonance.

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Prevalence and severity of sleep apnoea syndromes in cardiac amyloidosis patients.

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Background: Cardiac diseases are associated with a high prevalence of sleep apnoea syndrome (SAS) particularly in heart failure. Two types of SAS are known: central or obstructive. Heart failure can occur in patients with primary systemic amyloidosis (AL), senile systemic amyloidosis (SSA), and Transthyretin-Related Amyloidosis (TTR). There is no data about prevalence and severity of sleep disordered breathing in cardiac amyloidosis.

Aims: Assess the prevalence and severity of SAS in cardiac amyloidosis.

Methods: Patients prospectively referred in our cardiology department for cardiac amyloidosis underwent polygraphy to diagnose sleep apnoea syndrome (SAS) between 2010 and 2012. SAS was defined as an apnoea-hypopnoea index greater or equal to 5 events/h.

Results: Thirty five patients were included, of whom 15 had AL, 9 FAP and 11 SSA. Mean age, body mass index, NTproBNP, and left ventricular ejection fraction, of the overall cohort were respectively 72±12 years, 24±4kg/m², 5642±7812 and 48±13% and. The prevalence of SAS was 86%. 29% of syndromes were classified as central and 57% as obstructive. The mean apnoea hypopnoea index was 22±14 events/h and was superior to 30 events/h in 11 patients. SSA were significantly older but NTproBNP and LVEF were not different between the three type of amyloidosis. Apnoea hypopnoea index was more elevated in SSA and FAP than in AL ($p=0.01$).

Conclusion: The prevalence of sleep-disordered breathing is high in cardiac amyloidosis population, with most syndromes having an obstructive pattern. Effect of SAS treatment should be investigated in this population.

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Paradoxical Response to Exercise (PRE) in asymptomatic hypertrophic cardiomyopathy: a new description of dynamic outflow tract obstruction

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Background: Despite the association of symptoms with LV outflow tract obstruction in HCM, there exist paradoxical situations in which significant intraventricular gradients (>50 mmHg) at rest occur in conjunction with excellent exercise tolerance.

Objectives: To analyze left ventricular (LV) obstruction in hypertrophic cardiomyopathy (HCM) during exercise echocardiography.

Methods: To examine this phenomenon we performed exercise echocardiography and analyzed the clinical status in 107 HCM patients with and without resting obstruction.

Results: At rest, 69 patients had no obstruction while 38 exhibited an intraventricular gradient, 9 of whom exhibited a decrease in gradient of at least 30 mmHg (99±35 to 30±14 mmHg, $p<0.001$) during exercise (paradoxical response to exercise or PRE). PRE patients presented a significantly lower NYHA clinical class and higher left ventricular volumes and arterial pressure both at rest and during exercise than HCM patients for whom the gradient increased or did not change during stress echocardiography. Finally, PRE patients exhibited a trend toward a reduced rate of cardiac events.

Conclusions: Our study identified a new subgroup of HCM patients, designated PRE, based on a decreased intraventricular gradient during exercise. The reduced exertional obstruction may account for the better functional class and trend to less clinical events in PRE patients.

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Genotype/phenotype analysis and pathophysiology of desmoglein-2 propeptide cleavage-site mutations in arrhythmogenic right ventricular cardiomyopathy

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Background: Desmoglein-2 (DSG2) mutations are common causes of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). A hot spot of missense mutations targets the consensus cleavage-site of DSG2 pro-peptide (Arg-X-Arg/Lys-Arg) by Kex2-like proprotein-convertases (PCs). We identified heterozygous missense DSG2 mutations of the cleavage site (p.R46W, p.R46Q, p.R49H and p.K48N) in ten probands out of 200 independant ARVC probands and seven additional relatives. This study analyses the phenotype associated to these specific mutations and experimentally explores their molecular consequences.

Methods and Results: The pro-DSG2 cleavage site mutations were associated with a severe phenotype with diffuse RV dilatation, severe RV dysfunction and frequent LV involvement leading to end-stage heart failure in 3 out of 17 mutation-carriers. Through ex vivo and in vitro analysis by expressing a WT or mutant DSG2-GFP fusion protein in cellular models, we demonstrated that all mutations prevented efficient propeptide cleavage. However mutants pro-DSG2 were correctly addressed to the intercellular junctions. We demonstrated that the presence of propeptide led to the abolition of interactions between the N-ter EC1 domains of the cadherins.This was accompanied with a mis-incorporation of pro-DSG2 into desmosomes as revealed by iF labelling at low Ca2+ concentrations compared to WT DSG2, due to an EGFR-dependant internalization of mutant pro-DSG2 and of its partners PKP2 and PG. Finally, we observed by WB an increase in the soluble pool of mutant pro-DSG2 compared to the WT DSG2 when cells were submitted to mechanical stress.

Conclusion: DSG2 propeptide cleavage-site mutations are associated with a severe phenotype and an increased risk of heart failure. Our experimental results indicated a loss of DSG2 adhesiveness properties and a decrease of the incorporation of mutant DSG2 into desmosomes due to propeptide cleavage abolition that could play an important role in ARVC pathophysiology.

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Left ventricular non-compaction: predictors of outcomes

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Introduction: According to the ESC Working Group on Myocardial and Pericardial Disease, left ventricular non compaction (LVNC) is still an unclassified cardiomyopathy. Although LVNC is associated with a high incidence of morbidity and mortality, reports about prognosis are contradictory. So we sought to assess the incidence and the predictors of major complications and myocardial contractile recovery.

Methods: This retrospective study enrolled 32 patients who fulfilled the diagnostic criteria of LVNC.Clinical data, cardiac echography and MRI database of our institution was searched for all these patients. Follow-up included an interval history, a focused physical examination and a transthoracic echocardiogram.

Results: The mean age at diagnosis was 48.3±16.4 years. The most frequent symptom at diagnosis was dyspnea NYHA class III/IV (43%). The mean LV end-diastolic diameter was 66.4 mm and the mean EF was 29.5%. Duration of follow-up was 480 days. Major complications were heart failure in 13 patients (40%), thromboembolic events in 3 patients (9%) and ventricular tachycardia in 1 patient (3%). There were no unregistered deaths. There was no predictive role for any variable to specific complications. A worse NYHA class, a lower baseline LVEF, LV dimensions, wall thickness and E/é ratio did not predict MACE. During the follow-up 4 patients (12%) showed myocardial contractile recovery and 9 patients (28%) showed an improvement, with a increase in the mean LVEF to 38.5% (p<0.001). LV systolic improvement was inversely associated with the presence of a left bundle branch block (p=0.071) and LV end-diastolic volume (p=0.052).

Conclusion: Our study demonstrates a high incidence of complications in LVNC disease. However, a relatively large number of patients may show a significant improvement in the LV systolic function shortly after the onset of symptoms. The improvement is unlikely to occur in patients with left bundle branch block and dilated LV.

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Usefulness of right ventricle 2D strain in arrythmogenic right ventricle dysplasia/cardiomyopathy

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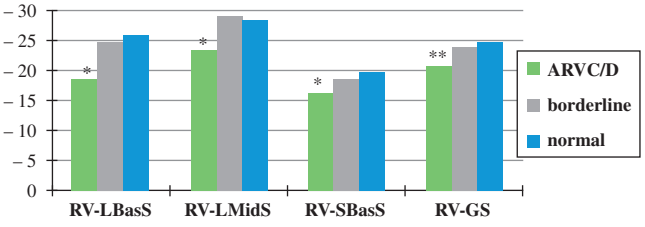
Background: Diagnosis of Arrhythmogenic Right Ventricular (RV) Dysplasia/Cardiomyopathy (ARVD/C) is based on International Task Force Criteria (ITFC). But the diagnosis remains challenging especially in the early course of the disease.The purpose of this study was to assess if the RV 2D strain analysis could be an accurate tool to detect RV abnormalities in patient with suspicion of ARVD/C.

Methods: We enrolled 95 patients with suspicion of ARVD/C referred to our institution. ECG, SAECG, echocardiography and RV angiography were performed in all patients. Based on ITFC and a final experts'agreement, the patients were classified as follows: affected ARVD/C (n=50), borderline ARVD/C (n=9) or normal (n=36). In addition, RV longitudinal strain was measured in 6 RV segments obtained from the RV focused apical 4-chamber view. Analysis was performed offline and blinded of the final diagnosis.

Results: Compared to normal, affected patients had only a mild decrease in RV fractional area change (FAC)(37±9% vs 44±7% p=0.0002) and an mild increase RV outflow tract diameter (RVOT)(35±6mm vs 32±5mm, p=0.002). Borderline had normal FAC and increase RVOT. Affected patients displayed a reduced global RV strain (RV-GS)(-20.8± 4.8% vs-24.8±3.3% p<0.0001). Segmental strain analysis showed the reduction was major in the lateral-basal segment (RV-LBasS), the lateral-mid segment (RV-LMidS) and the septum-basal segment (RV-SBasS). Bordeline's patients had no significant altered RV strain compared to normals or affected patients.

Conclusion: RV 2D strain is significantly lower in affected ARVD/C patients compared with normal normal, but not with borderline, especially in mid lateral and basals segments. The presence of a RV strain impairment may be useful for the diagnosis of ARVD/C in the early course of the disease.



*p<0,006 ARVC/D vs normal (borderline ns)
**p<0,0001 ARVC/D vs normal (borderline ns)

Figure – Results

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Congestive heart failure in type 2 diabetes: about 324 Tunisian patient

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Objective: To estimate the prevalence and incidence of congestive heart failure (CHF) in populations with and without type 2 diabetes and to identify risk factors for diabetes-associated CHF.

Research design and methods: We searched the inpatient and outpatient electronic medical records of 324 individuals diagnosed with type 2 diabetes

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