Topic 04 – Valvular heart disease and general cardiology

January 12th, Thursday 2012

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High levels of circulating lipoprotein-associated phospholipase A2, but not oxidized LDL, are associated with severe aortic stenosis; comparison with coronary artery disease

Jean-Christophe Chamiot [Orateur] (1), Randa Bittar (2), Jean-Paul Albertini (3), P Girard (4), C Cherfils (5), C Cosson (6), Erell Guillerm (5), Pascal Leprince (5), Iraj Gardjbakhch (5), Dominique Bonnefont-Rousselot (5)

(1) AP-HP, Hôpital Avicenne, Cardiologie, Bobigny, France  (2) AP-HP, CHU Pitié-Salpêtrière, Paris, France  (3) Hôpital Avicenne, Biochimie, Bobigny, France  (4) UMPC University Paris 06 UMR S 939 F, Paris, France  (5) AP-HP, CHU Pitié-Salpêtrière, Paris, France  (6) AP-HP, CHU Bicêtre, Biochimie, Le Kremlin-Bicêtre, France

Purpose: Aortic stenosis (AS) is a disease process akin to atherosclerosis and has been linked to several risk factors for coronary artery disease (CAD). Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an inflammatory biomarker secreted in the atherosclerotic plaque. We hypothesized a relationship between serum Lp-PLA2, plasma oxidized LDL (oxLDL) and AS, in contrast with CAD.

Methods: Between December 2009 and June 2010, from 494 subjects scheduled for diagnostic coronary angiography, we selected 234 patients (71.2% men) included into 2 groups: Group "CAD": patients with only CAD scheduled for diagnostic coronary angiography, we selected 234 patients (251.9±5.7 μg/L; p=0.03).

Results: In healthy controls, Lp-PLA2 was 163±43 μg/L (men: 166±45 μg/L; women: 159±39 μg/L; non significant). Lp-PLA2 were significantly higher in patients than in controls (219.2±49.1 vs 163.0±43.0; p=0.01). Lp-PLA2 increased in AS-patients, and were not significantly different than CAD-patients (217.3±44.5 vs. 220.4±51.9, respectively; NS). Moreover, Lp-PLA2 levels were similar in patients with single-vessel atherosclerosis (215.2±52.0) but significantly lower than in patients with three-vessel atherosclerosis (251.9±57 μg/L; p<0.03).

Conclusion: We report for the first time that high serum levels of Lp-PLA2 were associated with severe AS. This could have practical implications because statins and renin-angiotensin-aldosteron system inhibitors seemed to be a promising treatments of AS.

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Do you need to check systematically the INR during the RAMADAN’s fasting period?

Faouzi Addad [Orateur] (1), Majdi Amami (2), Rym Chrigui (2), Nadia Hammami (2), Samia Chirine (2), Sameer Darracki (2), Afef Ben Halima (2), Zied Bel Hadj (2), Ikram Kammoun (2), Salem Kachboua (2)

(1) EPS Fattouma Bourguiba, Cardiologie, Monastir, Tunisie  (2) CHU A. Afef Ben Halima (2), Zied Bel Hadj (2), Ikram Kammoun (2), Salem Kachboua (2), Afef Ben Halima (2), Zied Bel Hadj (2), Ikram Kammoun (2), Salem Kachboua (2), Afef Ben Halima (2), Zied Bel Hadj (2), Ikram Kammoun (2), Salem Kachboua (2)

(1) EPS Fattouma Bourguiba, Cardiologie, Monastir, Tunisie  (2) CHU A.

Introduction: During Ramadan, Muslims fast during the daylight hours for a month. A pharmacokinetic variability of several medications can occurred in this period. However, the effect of fasting Ramadan on INR (International normalized ratio) is unknown.

Aim of this study: was to evaluate the fasting Ramadan effect on the variability of the INR in patients treated at long term with oral anticoagulant.

Methods: 67 fasting patients (aged 60±11.4 years) treated at long term by acenocoumarol in the evening who fasted during Ramadan participated in this open, prospective and single center study. Venous blood samples were taken 1 week before Ramadan (INR1), on the 15th (INR2) and 29th days (INR3) of Ramadan. Exclusion criteria was an INR<1.7 or INR>4.5 before Ramadan and patient taking twice daily dose.

Results: Compared before Ramadan, the mean INR2 was significantly increased during the 15th days of Ramadan, 4.1±1.7 vs 2.9±0.8, respectively (p<0.001). A Vitamin K antagonist overdose (INR2>5) was obtained in 19 patients (28.4%). The mean variation of INR during this first period was +46.5% (+33%, +56.4%). We excluded for the third measure all patients with an INR2>5. The mean INR3 (n=42 pts) was significantly higher than the INR2. 3.4±0.88 vs 2.9±0.6 (p=0.0001). Compared to INR2, the mean variation of INR3 during this second period was +16.1% (+29.6%, +114.4%). Finally during Ramadan a VKA overdose was noted in 31.3% of cases. By multivariate analysis we found two independent predictors factors linked to a high INR during Ramadan: an initial INR>3 before Ramadan (OR=3.57; p=0.037) and a dose of acenocoumarol ≥4 mg (OR=3.5; p=0.041).

Conclusions: At our knowledge this is the first study demonstrate that intermittent fasting led to increase significantly the level of anticoagulation during this holy period. After this pilot study, we recommend checking systematically the INR before and during this period in order to reduce the INR around 2.

Impact of chronic obstructive pulmonary disease on long-term prognosis in coronary artery disease


(1) CHU Toulouse, Cardiologie A, Toulouse, France  (2) CHU Toulouse, Épidémiologie, Inserm U1027, Toulouse, France  (3) CHU Toulouse, Épidémiologie, Inserm U1027, Toulouse, France  (4) CHU Rangueil, Cardiologie B, Toulouse, France  (5) CHU Rangueil, Cardiologie B, Toulouse, France

Purpose: We aimed to assess the long term prognosis associated with COPD in a contemporary large cohort of pts with established CAD.

Methods: 783 consecutive male pts hospitalized in 2001-2004 for coronary artery disease were considered. The median follow-up was 7.17 years. Total mortality was predicted with a Cox proportional hazard model.

Results: Mean age (SD) was 60.2 (8.1). 144 pts (18.4%) were diabetic, mean glycemia was 5.9 mmol/L (2.1), 155 pts (19.8%) were smokers, mean blood pressure was 139 (20)/84 (11) mmHg and median heart rate was 61 bpm [Interquatile range (IQR)] [57-70]. Mean HDL cholesterol was 43 mg/dl (11), mean LDL cholesterol 124 mg/dl (39) and median triglycerides were 147 mg/dl [IQR: 109-197]. Mean Cockcroft-Gault creatinine clearance was 87 ml/min and 11 pts (1.4%) had a severe chronic renal failure (lower than 30 ml/min). Mean left ventricular ejection fraction was 0.53 (0.13). 88.5% were on antiplatelet therapy, 75.2% on beta-blocker, 66% on statin therapy and 54.8% on ACE inhibitors or ARB.

A previous history of COPD was present in 3.5% of pts; 37% of them had a beta-blocker therapy. The cumulative seven-year total mortality rate was 17.9% in the whole sample (51.8% in pts with COPD and 16.7% in those without, p<0.001). Among COPD pts with beta-blocker therapy, the mortality rate was 30% while mortality reached 64.7% in COPD pts without beta-blocker (p=0.08).

After multivariate adjustment for age, diabetes, tobacco consumption (none, ≤40 pack-years, >40 pack-years), heart rate, left ventricular ejection fraction (>0.55, ≤0.5 and >0.35, ≤0.35), duration of CAD, ankle-brachial index (>0.9; ≤0.9 and >0.6; ≤0.6), history of stroke, statin therapy and coronary revascularization, hazard ratio for all-cause death was 2.22 (95% CI [1.15; 4.26]) p=0.016) in pts with COPD compared to those without.
**Conclusion:** Presence of a chronic obstructive pulmonary disease is associated with a doubling risk of all-cause death in CAD pts.

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**Brain natriuretic peptide in asymptomatic degenerative mitral regurgitation: determinants and impact on outcome**

Julien Magné [Orateur] (1), Haïfa Mahjoub (2), Kim O’Connor (1), Luc A. Piérard (1), Patrizio Lancellotti (1), Philippe Pibarot (2) (1) CHU St-Tilman, Cardiologie, Liège, Belgique (2) Centre de recherche de l’Hôpital Laval, Québec, Canada

**Introduction:** In degenerative mitral regurgitation (MR), brain natriuretic peptide (BNP) is a surrogate biomarker of the consequences of MR on the left ventricle (LV) and left atrium (LA). LV global longitudinal strain (GLS), quantified by 2-D speckle-tracking imaging (2DSI) improved the detection of subclinical LV dysfunction. We aimed evaluating the impact of BNP on outcome and its relationship with GLS, in asymptomatic patients with degenerative MR.

**Method and results:** Comprehensive transthoracic echocardiography including of BNP quantification was performed in 135 consecutive asymptomatic patients with moderate to severe degenerative MR and preserved LV function. BNP was correlated with age (r=0.28, p=0.009), indexed LV end-systolic diameter (r=0.30, p=0.006), indexed LA volume (r=0.51, p<0.0001), E/Ea ratio (r=0.33, p<0.0001), systolic pulmonary pressure (r=0.24, p=0.006) and GLS (r=-0.45, p=0.0001). On multiple regression analysis, only indexed LA volume and GLS were independently associated with BNP (β=1.1±0.4, p=0.002 and β=–6.6±1.4, p<0.001, respectively). According to the median of BNP, patients with high BNP level had significant reduced event-free survival (21±8% vs. 75±6%, p<0.001). A GLS<23% was also associated with lower event-free survival (85±6% vs. 33±7%, p<0.0001). In Cox multivariate analysis, after adjustment for age, sex, E/Ea ratio and indexed end-systolic diameter, only indexed LA volume (hazard ratio [HR]=1.01, 95% confidence interval [CI]: 1.03–1.0, p=0.036), GLS<23% (HR=3.3, 95% CI: 1.1–9.9, p=0.03) and BNP<41 pg/ml (HR=3.5, 95% CI: 1.7–7.2, p=0.001) were independent determinants of cardiac event-free survival.

**Conclusion:** In asymptomatic degenerative MR, LV longitudinal function and LA volume are the main determinants of BNP release. BNP is a powerful independent predictor of cardiac events. Assessment of plasma BNP level, LA volume, and LV longitudinal function may help to improve risk stratification and the management of these patients.

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**Prognostic value of brain natriuretic peptide in elderly patients with aortic stenosis**

Claire Cimadevilla [Orateur], Caroline Cuffe, Nadia Berjeb, Bernard Iung, Alec Vahanian, David Messika-Zeitoun

AP-HP, CHU Bichat-Claude-Bernard, Cardiologie, Paris, France

**Background:** Detection of high-risk patients is an important issue for the management of aortic valve stenosis (AS). Previous studies have shown that plasma levels of BNP increases with AS severity and may provide prognostic information. However, these studies were impeded by selection bias and inclusion of relatively young patients, or their small sample sizes. In addition, a wide overlap of BNP values between symptomatic and asymptomatic patients was observed. Thus, the aim of the present study was to evaluate the prognostic value of BNP in a cohort of elderly patients with AS.

**Method:** NT-proBNP was measured at entry in the study and patients were prospectively followed on a yearly basis. Inclusion criteria were age ≥70 years, at least mild AS, absence of symptoms, and absence of significant renal insufficiency.

**Results:** 346 patients were included. Mean age was 79±6 years. 225 had severe AS and 196 were symptomatic. NT-proBNP increases with NYHA class and hemodynamic parameters (p<0.0001). However, NT-proBNP values were widely scattered with a large overlap between symptomatic and asymptomatic patients. Consequently, NT-proBNP had poor sensitivity and specificity for the detection of patients with severe symptomatic AS (ROC curve = 0.73, sensitivity=47%, specificity=85%). Among the 150 asymptomatic patients, 12 underwent a prophylactic surgery and follow-up was in 126 (91%). Patients with NT-proBNP<300 pg/ml had a better outcome than patients with NT-proBNP between 300 and 700 pg/ml, or >700 pg/ml (99% vs. 90% and 86% event free survival at one year, p=0.004). However, NT-proBNP was not an independent predictor of outcome after adjustment for valve area, age and gender (p=0.30).

**Conclusion:** Our study is the first to enhance the limits of NT-proBNP for the evaluation of AS patients. Our data show that NT-proBNP is not an independent prognostic factor of outcome and raises caution regarding a patients’ management based on BNP value especially in the elderly population.

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**TFPI-2 expression in diseased aortic valves**

Alexia Jadot (1), Christophe Zawadzki (1), Francis Juthier (1), Carlo Banfi (1), Delphine Coseaux (1), Nadia Bouabdallaoui (1), André Vincentelli (1), Thierry Le Tourneau (2), Brigitte Jude (1), Eric Van Belle (1), Sophie Susen (1), Joke Breyne [Orateur] (1)

(1) Université Lille Nord de France, UDSL, IRF114, EA-2693, Faculté de Médecine, Lille, France (2) Inserm UMR915, Université de Nantes, CHU Nantes, Institut du Thorax, Nantes, France

**Objectives:** The human matrix associated serine protease inhibitor “tissue factor pathway inhibitor-2” (TFPI-2) is known to have inhibitory activity towards matrix metalloproteases (MMPs), which play an important role in the process of aortic valve stenosis (AS). Reduced synthesis of TFPI-2 has been related to numerous pathophysiological processes such as atherosclerosis. Since AS is an atherosclerosis-like process, we hypothesized that TFPI-2 might play a protective role in the progression of AS.

**Methods:** Calcified aortic valves (n=28) were obtained from patients undergoing aortic valve replacement (16 men; 68±2.2 years; indexed aortic valve area 0.42±0.3 cm²/m²). Valvular expression and localization of TFPI-2 and other components of atherosclerosis were evaluated by immunohistochemistry. TFPI-2 expression was further analyzed using a home-made ELISA and by Western blot. Finally, we evaluated TFPI-2 expression in primary valve myofibroblast cultures obtained from explanted valves after collagenase digestion (n=12).

**Results:** We demonstrated TFPI-2 expression in aortic valves, which was found to be significantly lower in the calcified regions as compared to non calcified zones (1705±266 vs 2997±433 pg/mg; p=0.001). In contrast, there was an overexpression in calcified regions as compared to non calcified zones of pro-atherosclerotic factors (tissue factor (837±131 vs 476±95 pg/mg; p=0.01) and MMP9 (97±46 vs 38±7 pg/mg; p=0.04)) and pro-calcifying proteins (osteonectin (46±11 vs 46±1.3 ng/mg; p=0.0005)). Finally we showed that cultured valve myofibroblasts express variable amounts of TFPI-2, inducible by IL-1β or TNF-α stimulation. Baseline TFPI-2 expression seemed to be inversely correlated to the degree of calcification of the valves.

**Conclusion:** We showed here for the first time, the presence of TFPI-2 in calcified human aortic valves. The inverse correlation between TFPI-2 expression and valve calcification might suppose a protective role for TFPI-2 in aortic valve disease.

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**Long-term efficacy of percutaneous mitral commissurotomy for restenosis after previous mitral commissurotomy**


AP-HP, CHU Bichat-Claude-Bernard, Cardiologie, Paris, France

**Purpose:** Whether surgical or percutaneous, mitral commissurotomy is hampered by late mitral restenosis. Percutaneous mitral commissurotomy (PMC) can be used to treat restenosis. Series with long-term follow-up are necessary to evaluate the usefulness of PMC in deferring surgery.

**Methods:** We studied 163 patients (pts) who underwent PMC because of restenosis a mean period of 16±8 years after previous commissurotomy.