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In chronic heart failure (CHF) patients, diuretic administration plays a key role in the control of congestion. However, high diuretic dose (HDD) has been also demonstrated to be associated with a worse prognosis. The aim of this study was to evaluate the factors independently associated to HDD and, in particular, the role of a marker of renal perfusion, the Renal Arterial Resistance Index (RRI).

We enrolled 250 outpatients (78% males, 64±13 years, NYHA class 2.2±0.8, left ventricular ejection fraction, LVEF, 34±10% with CHF (ESC criteria) due to left ventricular systolic dysfunction, in stable clinical conditions (> 1 month) and in conventional therapy. All patients underwent: a clinical evaluation to assess NYHA class; a routine chemistry to evaluate NT-proBNP and glomerular filtration rate (GFR) by creatinine (MDRD formula); an echocardiogram to evaluate LVEF and to estimate central venous pressure (CVP); a renal echo-Doppler in order to evaluate RRI. Peak systolic velocity and end diastolic velocity of segmental renal artery was obtained by pulsed Doppler flow and RRI was then calculated. RRI was positively and significantly correlated with furosemide equivalent dose (r= 0.33; p<0.001) and with HDD (r= 0.36; p<0.001). As shown in the table, RRI remained significantly associated with HDD in a multivariate logistic regression analysis including the other factors significantly correlated at univariate analysis.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDD</td>
<td>Age</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>NYHA class</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>CVP - 5 mm Hg</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>logNT-proBNP</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>GFR-MDRD</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>RRI</td>
<td>0.003</td>
</tr>
</tbody>
</table>

High diuretic dose was defined as Furosamide eq. dose >100 mg/die.

In conclusion, our findings help to better understand the wide variability of diuretic dosage, by demonstrating the independent influence of RRI, a parameter reflecting renal arterial resistance. These data could also represent the basis of future studies aimed to optimise therapeutic strategies by improving renal flow and, as a consequence, diuretic response.

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Structural abnormality of the hippocampus and depressive symptoms in a rat model of heart failure

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Purpose: Heart failure (HF) affects almost all organs in our body through reduced organ perfusion and resultant neurohumoral alterations. Major depression is more prevalent in HF patients as compared with normal subjects, suggesting the possible interaction between the heart and the brain in HF. However, the mechanism of depressive symptoms in HF remains largely unclear. Several reports showed the association between major depression and structural abnormality of the hippocampus such as grey matter reduction and decreased neurogenesis. In the present study, we thus investigated whether hippocampal grey matter reduction and decreased neurogenesis were observed in association with depressive symptoms in a rat model of HF using magnetic resonance (MR) imaging and histological analysis.

Methods: Male Wistar rats were divided into two groups: HF group with permanent ligation of the left coronary artery (n=28) and sham-operated control group (n=25). Four months after the procedure, the following two studies were performed. In the first study, the HF group (n=20) and the sham group (n=17) underwent behavioral tests (open-field test and elevated plus maze test) for assessment of depression and antidepressive effects. In the second study, MR images were analyzed to detect regional alterations in grey matter between the two groups as measured by grey matter probability values (a maximum value of 1). In the second study, brains of the both groups (n=8, each) were fixed for histological analysis of neurogenesis by counting the number of bromodeoxyuridine (Brdu)-immunopositive cells in the hippocampus.

Results: The HF group showed significantly greater depressive symptoms as compared with the sham group, including decreased time spent in the inner zone (HF group, 42.9±0.7% vs. sham group, 87.1±1.8%; P<0.05) in open-field test and decreased time spent in the open area (HF group, 2.5±0.6% vs. sham group, 6.6±1.5%; P<0.05) in elevated plus maze test. Analysis of structural brain MR images revealed grey matter reduction in the HF group than in the sham group in several brain regions including the bilateral hippocampus (HF group, 0.480±0.005 vs. sham group, 0.505±0.002; P<0.001). Moreover, the number of Brdu-immunopositive cells in the hippocampus was decreased in the HF group than in the sham group (HF group, 18.3±1.5 vs. sham group, 23.0±1.3; P<0.05).

Conclusions: The present study demonstrates for the first time that HF induces structural abnormality of the hippocampus such as grey matter reduction and decreased neurogenesis in association with depressive symptoms.

P639 | BEDSIDE

Longitudinal strain in Friedreich Ataxia: a potential marker for early left ventricular dysfunction


Background: Friedreich’s ataxia (FRDA) is a neurodegenerative disorder resulting from deficiency of frataxin, characterized by cardiac hypertrophy, heart failure and sudden cardiac death. However, the relationship between remodeling and novel measures of cardiac function such as strain, and time-dependent changes in these measures are poorly defined.

Methods and results: We compared echocardiographic parameters of cardiac size, hypertrophy and function in 50 FRDA patients to 50 normal controls. We quantified the following measures of cardiac remodeling and function: left ventricular (LV) volumes, LV mass, relative wall thickness (RWT), ejection fraction (EF) and myocardial strain. Linear regression was used to identify significant differences in echocardiographic parameters in FRDA compared to normals. In analyses adjusted for age, sex, and body surface area, significant differences were observed between parameters of remodeling (LV mass, RWT, and functions) and function in FRDA patients compared to controls. In particular, longitudinal strain was significantly decreased in FRDA patients compared to controls (<12.4% versus 16.0%, p<0.001), despite similar and normal LVEF. Over 3 years of follow-up, there was no change in LV size, LV mass, or LVEF among FRDA patients.
Conclusion: Longitudinal strain is reduced in FRDA despite normal LVEF, indicative of subclinical cardiac dysfunction. Given late declines in LVEF in FRDA, longitudinal strain may provide an earlier index of myocardial dysfunction in FRDA.

P640 | BENCH
Long-term therapy with Bendavia (MTP-311), a novel mitochondria-targeting peptide, reverses mitochondrial abnormalities in left ventricular myocardium of dogs with advanced heart failure

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Background: Mitochondria (MITO) of failed human hearts and hearts of dogs with experimental heart failure manifest functional abnormalities characterized by reduced state-3 respiration, reduced membrane potential (△ψm) and increased opening of mitochondrial permeability transition pores (mPTP). These abnormalities lead to reduced ATP synthesis that adversely impacts LV function. Bendavia (MTP-311), a novel, first in class, MITO-targeting peptide, has been shown to improve LV systolic function in dogs with chronic heart failure and to improve ATP synthesis in multiple organs including heart, kidney and skeletal muscle in other animal models of disease. The present study tested the hypothesis that long-term therapy with Bendavia reverses functional MITO abnormalities in dogs with chronic heart failure.

Methods: Studies were performed in cardiomyocytes isolated from LV myocardium of 14 HF dogs produced by intracoronary microembolizations (LV ejection fraction <30%). Dogs were randomized to 3 months monotherapy with subsequent addition of Bendavia (0.5 mg/kg once daily, n=7) or saline (Control, n=7). MITO state-3 respiration was measured using a Clark electrode. △ψm was measured using the dye JC-1 and mPTP was measured based on the rate of calcine exit from MITO. MITO ATP synthesis was measured using the bioluminescent ApoSENSORTM ATP assay.

Results: Compared to Control, Bendavia significantly improved MITO state-3 respiration, increased △ψm, decreased the rate of calcine exit from MITO thus decreasing mPTP opening and increased ATP synthesis (Table).

Table: Indexes of mitochondria function

<table>
<thead>
<tr>
<th>MITO State-3 Respiration (ng atoms of oxygen consumed/mg protein/min)</th>
<th>Control</th>
<th>Bendavia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Fluorescence (% of Maximum)</td>
<td>54.3±3.5</td>
<td>66.0±4.8 (p&lt;0.05)</td>
</tr>
<tr>
<td>ATP synthesis (RLU/min/protein)</td>
<td>447±80</td>
<td>506±14 (p&lt;0.05)</td>
</tr>
</tbody>
</table>

P: probability vs. Control; RLU, relative light units; ATP, adenosine triphosphates.

Conclusions: Therapy with Bendavia reverses abnormalities of MITO function in LV myocardium of dogs with chronic heart failure and increases ATP synthesis. The latter can explain the observed improvement of LV systolic function following long-term therapy with Bendavia in dogs with HF.

HEART FAILURE CARE AND QUALITY OF LIFE

P642 | BEDSIDE
Quality of life and heart rate according to the presence of sinus rhythm or atrial fibrillation in heart failure patients

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Introduction: Heart failure (HF) is one of the most important chronic diseases that cause quality of life (QoL) impairment. Among other clinical parameters, QoL has been related to heart rate in patients with HF.

Objective and methods: To assess the relationship between heart rate determined at first visit and QoL assessed by the Minnesota Living with Heart Failure Questionnaire (MO) and degree of depression, (Wessagow’s Geriatric Affective Scale (YS)) were measured and compared pre and 3 months post NEI. NEI consisted of four weekly consecutive sessions with brochures and audio-visual support that included topics as promoting self-care, recognition of alarm signs and symptoms, flexible diuretic regimen, diet/exercise aspects, pharmacological treatment, importance of psychological aspects etc.

Results: From 428 patients visited in our HFU during this time, 107 patients (26%) were included in our NEI. 74% were men, mean age was nearly 70 years (range 43-89 years). Mean left ventricle ejection fraction was 31±8%, 91% were on NYHA class II-III and 97% were on ECA-inhibitors/ARB. Included patients were mostly independent in daily living (Barthel mean score (MS): 88±5.8), without significant cognitive impairment (Pfeiffer’s test MS: 94±0.5) and moderate degree of co-morbidities (Charlson co-morbidity index MS: 5.27±2.27). After NEI, our patients showed a statistically significant improvement in quality of life (MO MS reduction: 3.79, p<0.001), a better self-care (ESS MS reduction: 6.12, p<0.001) and lesser degree of depression (YS MS reduction: 3.36, p<0.001).

Conclusions: NEI improved self-management, quality of life and depression symptoms in patients with Chronic HF. This is an important benefit for the special, high-mortality, easily-decompensated population that can suppose an economical cost-reduction for health-care systems. NEI should be promoted to benefit these patients.

P644 | BEDSIDE
Disease management program in implementing the guidelines of heart failure

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Introduction: Heart Failure (HF) is a public health problem around the world with a fast growing prevalence. Optimized treatment has proven to be effective in reducing morbidity and mortality. HF Registers have demonstrated a heterogeneity regarding the application of the Guidelines. Specialized HF clinics results in a improvement of quality of life due to better adherence to the treatment. Regarding hospitalized patients there is no evidence of the benefit of management programs. Our hypothesis is that a hospital management program has a key role in better adherence to current Guidelines. Objective: Evaluate the role of Management Program in HF treatment in hospitalized patients.

Material and methods: We evaluated 418 patients with HF and ventricular fibrillation function (LVEF<45%), divided in two groups: G1=258 hospitalized patients treated in 2010, before the adoption of the program, and G2=160 patients including 346 hospitalization, hospitalized after the implementation of the Program. The Program consist in a trained and specialized multidisciplinary team work-