Cardiovascular Disease Supplements (2010) 2, 80-86

Topic 07 – Basic science

January 14th, Thursday 2010

247
Cardiac phenotype of familial amyloid polyneuropathy according to genotype

Vincent Algalarrondo [Orateur], Sylvie Dinanian, Christophe Juin, Soumiya Bennami, David Adams, Michel Siama
Hôpital A. Becleure, Cardiologie, Clamart, France

Introduction: Familial amyloid polyneuropathy (FAP) is an autosomal dominant disease due to the mutation in the transthyretin gene. The abnormal protein produced by the liver is responsible for polyneuropathy, autonomic dysfunction and cardiac involvement. Myocardial hypertrophy and conduction disturbances are the two major cardiac consequences in FAP. More than 100 mutations have been described; the substitution of methionine for valine at position 30 (Val30Met mutation) is the most common.

Methods: The aim of our study was to compare cardiac data of the Val30Met population to other FAP population. One hundred ninety four consecutive patients (pts) were referred to our department to have a cardiac evaluation after FAP diagnosis, 168 pts out of them were genotyped. Standard ECG, echocardiography and electrophysiological study were performed for each patient.

Results: Main results are shown in table 1. In patients carrying other mutations than Val30Met, cardiac hypertrophy was associated with a longer HV interval (p=0.0008). This association wasn’t found considering Val30Met patients.

Table 1: Main results

<table>
<thead>
<tr>
<th>Mean age</th>
<th>Gender % of male</th>
<th>Abnormal ECG %</th>
<th>Cardiac hypertrophy %</th>
<th>LW point (bpm)</th>
<th>HV interval (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val30Met</td>
<td>13</td>
<td>45</td>
<td>47</td>
<td>128±3</td>
<td>59</td>
</tr>
<tr>
<td>Other mutations</td>
<td>55</td>
<td>57</td>
<td>46</td>
<td>151±3</td>
<td>66</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td>0.04</td>
<td>NS</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abnormal ECG: RBB, LBB, abnormal axis or nodal AV block. Cardiac hypertrophy: interventricular septum thickness >12 mm. LW: luciani Wenckebach anterior point.

Conclusions: Demographic data and cardiac phenotype are significantly different according to the genotype between the Val30met and other mutations population. In pts carrying other mutation than Val30Met, cardiac hypertrophy and infra nodal block were more common and seemed to be related. Follow up and treatment must take into a count the genotype.

January 15th, Friday 2010

248
Ephrin-B1: a new ultrastructural protein of the cardiomyocyte

Céline Gales [Orateur], Gael Genet [Orateur], Benjamin Honton [Orateur], Céline Guilbaud-Frugier, Fabien Despas, Marie-Françoise Altie, Atul Pathak, Jean-Michel Senard
INSERM U858, Equipe 8 – Dpt Remodelage cardiaque/renal, Toulouse Cedex 4, France

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 adult remain unclear.

Aim: The aim of the present work is to characterize the cardiac phenotype of two-months old ephrin-B1 knockout mice.

Results: Western-blot analysis demonstrated specific expression of ephrin-B1 in total heart protein extracts from WT mice that was lost in KO mice. Further IF studies demonstrated broad expression of ephrin-B1 protein throughout all heart compartments (right ventricle, septum, left ventricle) with different cellular localizations (cardiomyocytes and micro/macrocirculation). HE stained-paraffin-embedded heart sections from KO mice revealed loss of organized cardiac tissue characterized by the presence of wavy cardiomyocytes in the myocardium from septum and right/left ventricles. Modification of cardiomyocytes’ morphology correlates with a loss of their apparent lateral junctions and a significant reduction in cytoskeleton proteins (α-actinin/β-actin levels), consistent with a reduced size of the myocytes. Ultrastructural analysis (electron microscopy) revealed significant loss of electronic density of Z-disks and a highly packed intercalated disk (ID) with no modifications in the ID space, probably as a consequence of myocytes’ lateral junction’s loss. Functional analysis of KO-mice with echocardiography revealed a significant increase in systolic and diastolic diameters of the left ventricle. Consistent with disruption of myocardial architecture, electrocardiograms demonstrated a first degree AV block together with a significant reduction of heart frequency.

Conclusion: This is the first report providing evidence for the presence of ephrin-B molecules in the adult heart tissue. This study using ephrin-B1 KO mouse identified ephrin-B1 as a new ultrastructural protein of the cardiomyocyte whose deletion leads to a dilated cardiomyopathy.

249
Diabetes Mellitus Abrogates Erythropoietin-Induced Cardioprotection against Ischemic-Reperfusion Injury by Alteration of the RISK/GSK-3β Signaling

(1) UPRES EA 3860, Protection et Remodelage du Myocarde, Université Angers, Angers, France – (2) Inserm U694, Université Angers, Faculté de Médecine, Angers, France – (3) Laboratoire de biochimie, CHU d’Angers, Angers, France – (4) INSERM U771, CNRS UMR 6214, Université Angers, Faculté de Médecine, Angers, France – (5) UPRES 3860, Université d’Angers et CHU d’Angers service de Cardiologie, Angers, France

Background: Recent studies using healthy animals have demonstrated cardioprotective effects of erythropoietin (EPO) against ischemic-reperfusion injury by up-regulation of the RISK pathway. Here, we sought to examine whether EPO-induced cardioprotection and activation of cardioprotective signaling is maintained in presence of type 1 diabetes mellitus or insulin resistance.

Methods: Isolated Langendorff-perfused hearts were obtained from 3 cohorts of Wistar rats: healthy adults; animals injected 4 weeks earlier with streptozotocin (STZ) to induce diabetes and rats fed for 4 weeks with a high fat diet (HFD) to induce insulin resistance. All hearts underwent 25min ischemia, and within each cohort, were assigned to receive either 2h reperfusion with no intervention or a single dose of EPO (1000 IU/kg) injected at the onset of reperfusion.

Results: In hearts from healthy rats: i) EPO was cardioprotective: infarct size was 14.36±10.66% vs 36.22±4.20% of the left ventricle (LV) in EPO-treated vs untreated healthy rat hearts; p<0.05; ii) EPO-induced cardioprotection was associated with significant increases in phosphorylated forms of Akt, ERK1/2 and GSK-3β, at 30min of reperfusion. At 4 wks post-STZ injection, rats displayed: i) inhibition of EPO-induced cardioprotection: infarct size was 32.05±2.38% vs 31.88±1.87% of the LV in EPO-treated vs untreated diabetic rat hearts; ii) no up-regulation of PI3K/Akt, ERK1/2 and GSK-3β signaling in response to EPO. In contrast, 4 weeks post-HFD, rats showed: i) cardioprotective effect of EPO: infarct size was 18.66±1.99% vs 34.62±3.41% of the LV in EPO-treated vs untreated HFD rat hearts; p<0.05; ii) up-regulation in PI3K/Akt, ERK1/2 and GSK-3β signaling in response to EPO, at 30min of reperfusion.