As compared to patients of Group 1, those of Group 2 were younger (47±14 vs 41±15 years, p<0.001), and showed less advanced LV dysfunction (EF 28±9 vs 35±9%, p<0.001) and remodelling (end-diastolic diameter index 38±7 vs 35±7 mm/m², p<0.001) at the time of diagnosis. Most patients of Group 1 and 2 were treated with ACE-I (93% and 88%, p=NS) and BB (83% and 74%, p=0.05).

Five and 10-year transplant-free survival was respectively 73 and 57% in Group 1 vs 93 and 86% in Group 2, while hospitalisation-free survival was 47 and 32% in Group 1 vs 70 and 88%, p=NS) and BB (83% and 74%, p<0.05). The long-term progression of HF symptoms and LV dysfunction was similar in asymptomatic patients of Group 2a and 2b and not significantly different to that of patients of Group 1.

Even though asymptomatic DC patients receiving an optimal medical treatment are characterized by low rates of death or heart transplant, nevertheless during a long-term follow-up they frequently worsen as well as develop new features or different clinical conditions. Our data suggest that in these patients an early and aggressive BB strategy should be carefully considered in order to counteract as much as possible the long-term progression of the disease.

**Functional Significance of Myocyte Endothelin-1 in Experimental Chronic Chagasic Cardiomyopathy**

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**Background.** Trypanosoma cruzi, the etiologic agent of Chagas' disease, is an important cause of chronic cardiomyopathy. Endothelin-1 (ET-1) has been implicated in the pathogenesis of chronic chagasic heart disease, possibly due to its effect on the coronary microcirculation. Among the peptide’s actions is the role of ET-1 in the pathogenesis of chronic chagasic cardiomyopathy, we infected ET-1 (foxfox);EtMc-cre(+) (ETKO) mice, in which the ET-1 gene has been deleted from cardiac myocytes, with 10⁴ trypomastigotes of T. cruzi (Brasil strain). We injected infected (foxfox);Cre(+) (FLOX) mice. Uninfected littermates of both groups served as controls. All mice (n=28) survived and were evaluated at 160-170 days post infection by transthoracic echocardiography. Septal and posterior wall thickness (RWT), and fractional shortening (FS) were measured. Right ventricular (RV) size was assessed using a section of area = 3.3. Results compared with their respective, uninfected controls. Both infected FLOX and ETKO mice had increased LV EDD [(3.8±0.3 v 2.7±0.1mm, FLOX) and (3.0±0.1 v 2.6±0.1mm, ETKO), both p<0.05], along with reduced LV FS [(40±5 v 53±1%, FLOX) and (47±2 v 56±2%, ETKO), both p<0.05] and RWT [(0.4±0.0 v 0.5±0.0, FLOX) and (0.5±0.0 v 0.6±0.0 ETKO), both p<0.05]. However, the magnitude of these changes was attenuated in the infected ETKO group as compared with the infected FLOX group (p<0.05 for LV EDD, RWT, and FS). Similarly, RV was larger in infected FLOX compared with ETKO (2.5±0.3 v 1.6±0.3mm, respectively, p<0.01). Conclusions: These data provide support for the role of ET-1 in pathogenesis and progression of chronic chagasic heart disease and indicate that the cardiac myocyte is an important source of ET-1 in this disease.

**Mitochondrial Respiratory Abnormalities in Ventricular Myocardium of Patients With End-stage Congenital Heart Disease**


Background. Nitric oxide (NO) binds to mitochondrial cytochrome oxidase to decrease myocardial oxygen consumption (MVO₂). This regulation is disrupted in end-stage heart failure in part due to reduced NO availability. We compared NO-mediated regulation of MVO₂ in patients with end-stage congenital heart disease (CHD) vs cardiomyopathy (CMP) undergoing cardiac transplantation.

Methods. MVO₂ was measured in vitro using a Clark type oxygen electrode in LV muscle segments obtained from explanted failing human hearts at heart transplantation. This included 7 pts with complex CHD (mean age 11±10 years) and 14 pts with dilated CMP (mean age 25±10 years). We compared the effect of increasing doses (10⁻⁷-10⁻³M) of the following NO agonists on MVO₂ - amloidipine, ramiprilat, bradykinin - all of which cause independent NO production, and exogenous NO donors, S-nitroso-N-acetyl-penicillamine (SNAP) and nitroprussin (NTG). MVO₂ was measured with and without addition of NO donors. All pts were treated with L-NAME (10⁻⁴ M), NO synthase inhibitor. Results: All drugs caused a significant dose-dependent decrease in MVO₂ in both groups. However, myocardium from CHD pts showed a smaller decrease in MVO₂ in response to NO agonists compared to CMP pts. Changes in MVO₂ at highest dose in CHD vs CMP were: amloidipine, -5±7% vs -29±6%, (p<0.001); ramiprilat, -17±8% vs -26±2%, p=0.05; and bradykinin, -22±7% vs -30±5%. NO donors, SNAP and NTG also caused smaller decreases in MVO₂ in CHD vs CMP (SNAP -37±4% vs -49±3% and NTG, -16±6% vs -37±4%, p<0.05). Therefore, NO donors were unable to completely reverse altered regulation of MVO₂ in CHD suggesting abnormal mitochondrial function. L-NAME. NO inhibitor, attenuated the effect of amloidipine, ramiprilat and bradykinin but not of SNAP and NTG. Conclusion: Abnormal regulation of MVO₂ in end-stage heart failure may be secondary to reduced NO availability and can be reversed by use of NO donors. In end-stage CHD, however, this abnormality may be related at least in part to abnormal mitochondrial function.