1030-10 The Severity of Left Ventricular Hypertrophy is Greater in Patients with Hypertrophic Cardiomyopathy Due to Malignant Mutations

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Genotype-phenotype correlation studies have shown that β myosin heavy chain (βMHC) mutations are determinants of prognosis in patients with hypertrophic cardiomyopathy (HCM). While $Arg^{719}Trp$ mutation is associated with a high incidence of sudden cardiac death (SCD) and an average life expectancy of 38 years, the $Val^{606}Met$ mutation is associated with a near normal life expectancy in the families studied here. However, it is unknown whether the prognostic significance of HCM mutations correlates with the degree of left ventricular hypertrophy (LVH) associated with each mutation. Accordingly, we determined the left ventricular mass index (LVMI) and the extent of LVH in 12 patients with the $Arg^{719}Trp$ mutation and five patients with the $Val^{606}Met$ mutation. Left ventricular mass was derived by the area-length method using 2-D echocardiograms and indexed for body surface area (BSA). Extent of LVH was determined using a semi-quantitative point score method that takes into account the extent of involvement of the septum, apex, and lateral wall of the left ventricle. The mean LVMI was 147.0 ± 36 g/m^2 in patients with the $Arg^{719}Trp$ mutation and 111.7 ± 19 g/m^2 in patients with the $Val^{606}Met$ mutation ($p = 0.020$). Similarly the extent of hypertrophy was greater in patients with the $Arg^{719}Trp$ mutation than in those with the $Val^{606}Met$ mutation (5.92 ± 2.3 vs. 3.2 ± 1.5, respectively, $p = 0.015$). The mean septal thickness was also greater in patients with the $Arg^{719}Trp$ mutation than in those with the $Val^{606}Met$ mutation, however, this was not statistically significant (2.03 ± 0.7 vs. 1.62 ± 0.26, $p = 0.095$). There was no difference in the mean BSA, age, or gender among the two groups of patients. In conclusion, HCM patients, due to a malignant mutation such as the $Arg^{719}Trp$, have greater LVH than patients with a benign mutation such as the $Val^{606}Met$. These results indicate the grave prognosis of HCM mutations are associated with expression of greater hypertrophy. This provides an easily detectable clinical parameter to further stratify patients at risk of sudden death that are candidates for invasive interventions such as implantation of cardiac defibrillators.

1030-11 Ventricular Myocytes in Culture Express Endothelin-1 (ET-1) mRNA but not ET-2 mRNA or ET-3 mRNA in Response to the Hypertrophic Agonists Phenylephrine and ET-1

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Background In addition to its potent vasoactive properties, endothelin-1 (ET-1) has powerful effects on cell growth and may be involved in the process of myocardial hypertrophy. The roles of ET-2 and ET-3 in this process are unknown. We have investigated the effects of exogenous ET-1 and the α-adrenergic agonist phenylephrine (PEP) on levels of ET-1, ET-2 and ET-3 mRNAs in myocytes.

Methods Neonatal rat ventricular myocytes were stimulated with ET-1 or PEP. Quantitative ribonuclease protection assay and laser densitometry were used to assay levels of the mRNAs for ET-1, ET-2 and ET-3, and constitutive GAPDH.

Results ET-1 mRNA was present in unstimulated myocytes. ET-2 and ET-3 mRNAs were not detectable in control or stimulated myocytes. ET-1 and PEP caused a dose-dependent increase in myocyte [ET-1 mRNA] relative to [GAPDH mRNA] within 1 hour. [ET-1 mRNA] remained elevated to 24 hours:

Myocyte [ET-1 mRNA], optical density units

	time (hours)				
	0	0.5	1	6	24
Control	0.07 ± 0.03	0.18 ± 0.02	0.06 ± 0.03	0.17 ± 0.09	0.19 ± 0.10
ET-1, 0.1 μM		0.22 ± 0.07	0.66 ± 0.18*	0.87 ± 0.20*	0.97 ± 0.18*
PEP, 100 μM		0.13 ± 0.04	0.59 ± 0.12*	0.94 ± 0.09‡	0.89 ± 0.21*

means ± sem, n = 3, *$p < 0.05$, ‡$p < 0.005$ relative to control

Conclusions Ventricular myocytes produce ET-1 mRNA but not ET-2 or ET-3 mRNAs. PEP and ET-1 increase ET-1 mRNA levels in myocytes. PEP-induced hypertrophy may be mediated at least in part by ET-1 generation from myocytes.

1030-12 The Action of a Specific Natriuretic Peptide Receptor Antagonist (HS142-1) Upon Basal Coronary and Renal Vascular Resistances

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While the natriuretic peptides, ANP (atrial), BNP (brain), and CNP (C-type), mediate potent endothelial-independent vasorelaxing actions in vitro, the role of the endogenous natriuretic peptide system in vascular regulation in vivo remains unclear. HS142-1 is a novel natriuretic-peptide receptor antagonist derived from a fungus named Aureobasidium sp. which selectively blocks particulate guanylate cyclase-linked natriuretic peptide A and B receptors which bind ANP, BNP and CNP and thus attenuates the generation of cGMP. To characterize the vascular actions of the endogenous natriuretic peptide system in the control of basal coronary and renal vascular tone, six normal male mongrel anesthetized dogs were studied while a second group of six dogs served as control. HS142-1 was given as an intravenous bolus at 3 mg/kg and five 20 minute periods were studied.

No significant change after HS142-1 was observed in MAP, HR, CO, PAP, PCWP, renal blood flow (RBF) or renal vascular resistance (RVR) compared to baseline. In contrast, a significant increase in coronary vascular resistance (CVR) and decrease in coronary blood flow (CBF) was observed which was different from the control group.

	C1 (base line)	C2 (20 min)	C3 (40 min)	C4 (60 min)	C5 (80 min)	C6 (210 min)
CBF	52 ± 10	41 ± 10	41 ± 9	37 ± 9*	33 ± 10*	32 ± 10*
RBF	258 ± 40	266 ± 46	251 ± 42	249 ± 40	242 ± 37	241 ± 38
CVR	2.1 ± 0.5	3.0 ± 0.7*	2.9 ± 0.5*	3.5 ± 0.8*	3.9 ± 0.8*	4.0 ± 0.9*
RVR	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1

CBF, RBF = ml/min, CVR and RVR = RU. Data are Mean ± SE. *denotes $p < 0.05$

These studies demonstrate that HS142-1 produces potent vasoconstriction in the coronary but not renal vascular circulation. We therefore conclude that the endogenous natriuretic peptide system which is of cardiac and endothelial cell origin is an important regulator of basal coronary vascular tone.

1030-13 Alterations in Endothelial Cell Adenosine Receptors Mediate Endothelium-Dependent Vasoconstriction in Experimental Vein Grafts

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Adenosine is a potent endogenous vasodilator which mediates its action through A1 and A2 receptor subtypes located on both vascular endothelial and vascular smooth muscle cells (SMC). Adenosine-mediated relaxation in vein grafts has not been examined. This study assesses the in vitro isometric tension responses to specific adenosine receptor agonists (A1: R-phenyl-isopropyl-adenosine and A2: CSG-21680; 10–9 to 10–4 M) of common carotid external jugular vein bypass grafts (VG) in New Zealand White rabbits. These responses were compared to those obtained in the external jugular vein (JV) and in the common carotid artery (CA). All vessels were precontracted with prostaglandin F2a (10–5 M). Endothelialized and de-endothelialized vessels were examined. The A1 mediated relaxation in JV was endothelium-independent, whereas A2 mediated relaxation was endothelium-dependent. In CA, A1 mediated relaxation was partially endothelium-dependent, while A2 mediated relaxation was endothelium-independent. In VG, A1 activation induced endothelium-dependent vasoconstriction. Endothelial denudation restored A1 mediated relaxation, but reduced compared to that of JV (max. 19 ± 9%). A2 relaxation in VG was endothelium-independent (max. 39 ± 4%). Primary cultures of arterial and vein graft SMC expressed both A1 and A2 receptors on northern blot analysis. There was, however, a marked reduction in the A1 affinity of the SMC from the VG compared to the arterial SMC (40.9 ± 1.3% arterial binding). This study, therefore, demonstrates that there is a substantial change in the adenosine mediated vasoreactivity in VG compared to JV, due to a change in endothelial A1 receptor mediated response from relaxation to constriction, coupled with a decreased affinity of the A1 receptors on the VG SMC. The adenosine responses of the VG are also different from CA. Therefore, the endothelial cells of VG appear to be unique, in that functionally they neither maintain a venous phenotype nor acquire an arterial phenotype in response to adenosine.