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Letters

Atrogin-1 Pathway Activation in Cushing Syndrome Cardiomyopathy

Cushing syndrome (CS) may associate with a cardiomyopathy whose substrate is poorly understood. A total of 8 of 473 consecutive patients with dilated cardiomyopathy (DCM) (1.6%, 4 male, 4 female, mean age 61 ± 4.9 years) had CS due to adrenal adenoma. Diagnosis of CS was supported by typical clinical signs of hypercortisolism including moon face, central obesity, skeletal muscle atrophy, hyperglycemia, and increased blood and urine cortisol levels. A cortisol-secreting adrenal adenoma was identified in all patients by hormonal dynamic tests and magnetic resonance imaging. Patients had noninvasive and invasive cardiac studies including endomyocardial biopsy (EMB), after written informed consent, at baseline and, in 3 patients, also 1 year after adrenal adenoma removal. Echocardiographic left ventricular end-diastolic diameter (LVEDD), ejection fraction (EF), and maximal wall thickness (MWT) were assessed.

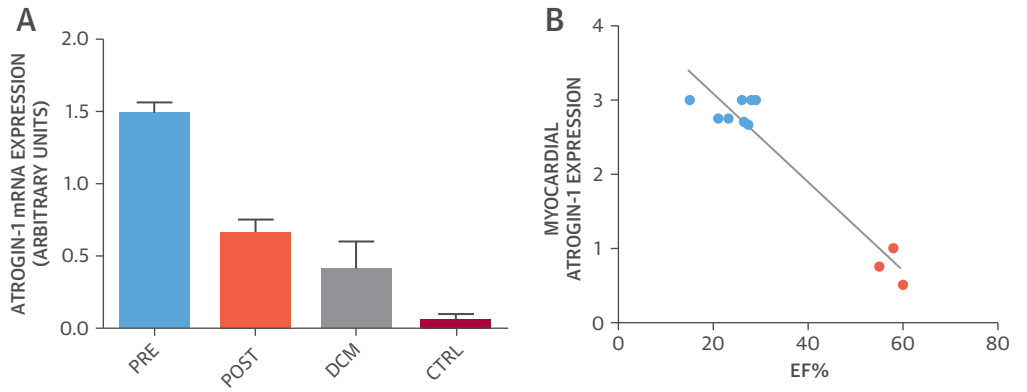
EMB with assessment of cardiomyocyte diameter and percent myofibrillolysis area, myocardial fibrosis, and cell death by apoptosis and necrosis was obtained. Myocardial atrogin-1 was evaluated by immunohistochemistry, real-time polymerase chain reaction, and western blot analysis. Intensity of immunostaining was semiquantitatively evaluated as absent (grade 0), mild (grade 1), moderate (grade 2), and intense (grade 3). Controls were EMB from 10 patients with idiopathic DCM matched for age, sex, and severity of LV dilation and dysfunction, as well as surgical LV samples from 10 patients with mitral stenosis and normal LVEDD and EF.

At presentation, the LV was hypertrophied, dilated, and severely hypokinetic in all (EF <30%). After adrenalectomy, LVEDD reduced on average from 69.0 ± 3.5 mm to 50.0 ± 3.5 mm, maximal wall thickness reduced from 12.8 ± 1.2 mm to 8.6 ± 0.8 mm, and LVEF rose from 25.0 ± 3.2% to 53.0 ± 3.3% ($p < 0.001$). Cell diameter reduced from 28.7 to 15.7 μm ($p < 0.01$), myocardial fibrosis declined from 11.5% to 3.1%, and myofibrillolysis area reduced from 61% to 22% ($p < 0.001$). Immunohistochemistry showed a significant increase in atrogin-1 expression in CS cardiomyopathy compared with idiopathic DCM and normal control samples (2.8 ± 0.15 vs. 0.79 ± 0.30; $p < 0.001$, and vs. 0.15 ± 0.30; $p < 0.001$, respectively). Atrogin-1 messenger ribonucleic acid was at presentation >28 fold higher than normal control samples and >3.5 fold higher than idiopathic DCM (**Figure 1A**); levels normalized after adrenalectomy and inversely correlated with LVEF (**Figure 1B**). Western blot analysis confirmed the overexpression of atrogin-1. Cell death was comparable to idiopathic DCM and increased compared with normal control samples.

DCM is a clinical entity characterized by progressive cardiac dilation and dysfunction that has various etiologies and mechanisms of damage. Among endocrine disorders, hypothyroidism, hyperthyroidism, pheochromocytoma, acromegaly, and growth hormone deficiency have been associated with DCM. DCM has also been reported as a predominant or presenting feature of CS. In this setting, descriptions are mostly limited to single case reports, and the structural myocardial changes as well as the molecular pathways involved are still poorly understood.

The present report comparing histological, ultrastructural, and molecular parameters in EMB samples from 8 patients with CS cardiomyopathy, before and after cortisol normalization, shows that cardiomyocyte hypertrophy, myofibrillolysis, and myocardial fibrosis are the main structural abnormalities and that they revert completely at 1 year follow-up from adrenalectomy. Mechanisms involved in cell hypertrophy include pressure overload, a glucocorticoid-mediated increase of angiotensin-II, and an enhanced responsiveness of cardiomyocytes to angiotensin-II. Cell myofibrillolysis strictly correlates with myocardial expression of atrogin-1, which is increased >28 fold control values during the failing state and normalizes after cardiac recovery, associated with a decrease of myofibrillolysis cell area from 61% to 22%. These data confirm in humans the atrophic effects of glucocorticoids on skeletal (1) and cardiac (2) muscle obtained in experimental models. The molecular pathway involved includes activation of Foxo transcription factors, overexpression of atrogin-1, and ubiquitin promoting proteasome proteolysis of endogenous contractile elements.

FIGURE 1 Myocardial Atrogin-1 Expression in Cushing Syndrome Cardiomyopathy



(A) Myocardial atrogin-1 messenger ribonucleic acid (mRNA) expression in Cushing syndrome cardiomyopathy before and after adrenalectomy, in idiopathic dilated cardiomyopathy (DCM) and control (CTRL) biopsy samples. **(B)** Inverse correlation between myocardial atrogin-1 and left ventricular ejection fraction (EF). **Blue circles** indicate failing state; **orange circles** indicate recovery state.

Myocardial fibrosis derives from a direct glucocorticoid stimulation of fibroblast activity, likely through Smad and the transforming growth factor beta-1 pathway, and was reduced in our CS population from 11.5% to 3.1% after adrenalectomy, confirming the data obtained by speckle tracking echocardiography (3).

Along with CS, chronic steroid administration may result in cardiac arrhythmias, remodeling, and dysfunction that reflect a direct detrimental action on cardiomyocyte structure and function. Patients on steroids who manifest with cardiomyopathy should consider drug discontinuation.

In conclusion, CS cardiomyopathy is a reversible entity induced by high levels of glucocorticoids, characterized by cell hypertrophy, myofibrillolysis, and myocardial fibrosis that revert after adrenalectomy. Atrogin-1 activation has a major pathogenetic role.

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Time Course of Change in Ectopic Fat Stores After Bariatric Surgery

More than body mass index (BMI), adiposity distribution in visceral area and in ectopic sites likely plays an important role in the obesity-related risk. Ectopic fat accumulation in the heart, the liver, and the pancreas, namely steatosis, could induce accumulation of toxic lipid intermediates leading ultimately to organ dysfunction. Whether ectopic fat stores are subjected to modification through intervention approaches is therefore crucial. The development of noninvasive imaging has made it possible to quantify ectopic fat stores with accuracy. Myocardial triglyceride content (MTGC), hepatic triglyceride content (HTGC), and pancreatic triglyceride content (PTGC) can be measured in humans by proton magnetic resonance spectroscopy (1). We previously demonstrated