Cushing Syndrome Cardiomyopathy
Clinicopathologic Impact of Cortisol Normalization

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Endogenous Cushing syndrome (CS) is associated with systemic manifestations including abnormalities in glucose and lipid metabolism, alterations in coagulation factors, hypertension, cardiovascular disease, depression, and impaired health-related quality of life.

Dilated cardiomyopathy is rarely associated with CS, with only few single cases previously reported in English literature. Histological changes and molecular pathways involved in CS-dilated cardiomyopathy are poorly understood, whereas structural outcome after cardiac recovery is unknown.

We reported a research case of CS dilated cardiomyopathy in which noninvasive and invasive cardiac studies at baseline and follow-up were obtained after written patient consent.

A 63-year-old woman had CS caused by adrenal adenoma. Echocardiographic left ventricular (LV) end-diastolic diameter, ejection fraction and maximal wall thickness, endomyocardial biopsy with assessment of cardiomyocyte diameter, % myofibrillolysis area, myocardial fibrosis and cell death, and myocardial atrogin-1 were evaluated at presentation and after 1-year cortisol normalization with adrenalectomy. At presentation, LV was hypertrophied, dilated, and severely hypokinetic (ejection fraction <24%; Movies I and II in the Data Supplement). After adrenalectomy, LV end-diastolic diameter reduced from 61 to 51 mm, maximal wall thickness from 12 to 8 mm, whereas LV ejection fraction rose from 24% to 50% (Figure 1; Movies III and IV in the Data Supplement). Cell diameter reduced from 28.5 to 15.5 μm, myocardial fibrosis declined from 11.7% to 3.0%, and myofibrillolysis cell area reduced from 60% to 21% (Figure 2). Cell death was comparable with idiopathic dilated cardiomyopathy. Atrogin-1 mRNA was at presentation 30× higher than normal controls, normalized after adrenalectomy and correlated inversely with LV ejection fraction.

The present report comparing histological, ultrastructural, and molecular parameters in endomyocardial biopsy samples from a patient 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 (Figure 2). 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 >30× control values during failing state and normalizes after cardiac recovery being associated to decrease of myofibrillolysis cell area from 60% to 21%. In humans, these data confirm the atrophic effects of glucocorticoids on skeletal2 and cardiac3 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.

Myocardial fibrosis derives from a direct glucocorticoid stimulation of fibroblast activity, likely through Smad and transforming growth factor β-1 pathway, and reducing in our CS patient from 11.7% to 3.0% after adrenalectomy confirming the data obtained by speckle tracking echocardiography.4

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

Disclosures

None.

References


Ken Woots: cardiomyopathy, dilated ▪ Cushing syndrome ▪ cardiomyopathies ▪ endomyocardial fibrosis ▪ pathology

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**Figure 1.** Patient 1 with Cushing syndrome (CS) cardiomyopathy: electrocardiographic (A and B), echocardiographic (C and D), and left ventricular (LV) angiographic changes (E-H) at presentation and after 1-y adrenalectomy. It is shown a reduction of heart rate and QRS voltages with normalization of ventricular repolarization, a reduction of LV wall thickness, and a complete recovery of cardiac volumes and function.

**Figure 2.** Effects of glucocorticoid withdrawal on optical and ultrastructural morphology of myocardium after 1-y cortisol normalization with adrenalectomy. A and B, Paraffin-embedded, Masson-stained endomyocardial biopsy samples before (A) and after (B) adrenal adenoma removal. A remarkable decrease of myocyte size is evident in B when compared with A. C and D, Epon resin-embedded, basic fucsin-stained thin sections from endomyocardial biopsy samples. Cell swelling, myofibrillolysis, and partial disorganization of sarcomeres are appreciable in C. An advanced recovery of cell volume, cytosol density, and sarcomeric organization is evident in D. E, Myofibrillolysis, sarcomeric disorganization, and cytosol dilution are evident, which completely recover after adrenalectomy (F). Bar, 2 mm for E and F. G and H, Paraffin-embedded, immunohistochemistry for atrogin-1 samples before (G) and after (H) surgical removal suprarenal adenoma. A remarkable increase of atrogin-1 expression is evident in failing state samples (G; immunoperoxidase ×20).
Supplemental Material

Movie Legends

Movie 1. 2D echocardiographic movie (2 chamber view) at baseline showing severe mitral regurgitation associated with LV dysfunction.

Movie 2. LV angiography at baseline showing severe dilation and dysfunction.

Movie 3. 2D echocardiographic movie (4 chamber view) at follow-up showing remarkable reduction of mitral incompetence with decrease LV wall thickness and recovery of cardiac function.

Movie 4. LV angiography at follow-up showing reduction of LV dimension and increase of LV function.