Another case where bigger is not better 1

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Santiago, Chile. Over the past year, resident in medicine, Nicole Hernandez-Chamorro, had become quite fascinated with myocardial hypertrophy, particularly since it held important inferences for public health. Left ventricular hypertrophy is a major prognosticator for adverse cardiovascular events in both the general population and individuals with hypertension. In the past year alone, Nicole had come to care for patients with either LVH or biventricular hypertrophy and to address the relative importance of circulating substances, hemodynamic factors and signals generated de novo within cardiac tissue in modifying growth and behavior of the heart’s constitutive cell population 1,2.

On Monday, December 2, 1991, she had seen 58-year-old Mr. D. in follow-up. It had been a year since she diagnosed his acromegaly due to pituitary adenoma and despite trans-sphenoidal surgery, he continued to note excessive perspiration and headache. Mr. D. had never been hypertensive or diabetic. Particularly troublesome to him were breathlessness and fatigue on exertion that compromised his duties as a bus driver and his quality of life in general. Serologic studies today gave evidence of growth hormone (GH) and insulin growth factor-1 (IGF-1) hypersecretion that did not suppress after glucose administration. Echocardiography demonstrated increased right and left ventricular wall thickness with normal end-diastolic dimensions and increased calculated right and left ventricular mass in keeping with biventricular hypertrophy. In addition, parameters of diastolic function, including isovolumic relaxation time and early filling velocities, were delayed for each ventricle while their systolic function (or ejection fraction, EF) was preserved. Such biventricular hypertrophy, thought Nicole, had not enhanced cardiac function, but rather was linked with ventricular diastolic dysfunction. Moreover, cardiovascular risk is increased in acromegalic heart disease. Like a myocardial infarction, she mused, this is another case where bigger is not better. She immediately conferred with her supervising attending in endocrinology, Dr. G. Together they elected to begin octreotide, a cyclic peptide analog of somatostatin, in hopes of interfering with GH secretion from what must be remnant pituitary tumor tissue.

Summer was in full session when Mr. D. returned to her continuity clinic on Monday, February 3, 1992. He noted less sweating and headache and his echocardiogram now demonstrated a regression in wall thickness and calculated myocardial mass with improved diastolic dysfunction; EF remained stable. Importantly, he noted improved exercise tolerance. Plasma GH and IGF-1 levels had fallen. Gratified, Nicole shared this information with Dr. G., who suggested she present Mr. D.’s case at conference in the morning and that she invite cardiologist, Dr. J. to provide a multidisciplinary perspective to the discussion. Nicole enthusiastically prepared her conference materials Monday evening. She chose to make the session provocative by posing questions she found particularly vexing.

First, did Mr. D.’s recent echocardiographic findings indicate a true reduction in cardiac myocyte size? Wall thickness, used in the calculation of ventricular mass, must be influenced by several factors.

Second, anabolic properties of GH would enhance protein synthesis of cardiac muscle cells. Could this raise their energy requirements and contribute to increased risk for adverse cardiovascular events that often complicate acromegalic heart disease?

Third, and according to the somatomedin hypothesis, GH stimulates endogenous production of IGF-1 and it is the endocrine properties of this circulating peptide that determines myocyte growth and widespread visceromegaly. Does IGF-1 lead to cellular hypertrophy alone or is there also DNA activation? Would the latter not
enhance the mitogenic potential of presumptively postmitotic muscle cells allowing them to re-enter the cell cycle thereby promoting hyperplastic growth? Is there not also an increased potential for neoplasia in other tissues? Would answers to these questions not only reside in the acromegalic heart but also following administration of recombinant GH to patients with hypopituitarism?

Fourth, and given that bigger is not better, should administration of octreotide be considered in regressing myocyte mass in patients with hypertrophic cardiomyopathy?

Answer

Drs. G. and J. were quite pleased with Nicole’s presentation at Tuesday’s conference. She had stimulated each of them and the audience by her thoughtful questions. Dr. J. noted that cardiac myocyte hypertrophy is an integral feature of the biventricular hypertrophy found in acromegalic heart disease, but there also exists an interstitial fibrosis that surrounds myocytes and which may influence the potential for a regression in myocyte size. Interstitial edema and a lymphocytic infiltration can also be found. A reduction in wall thickness must therefore take all these factors into consideration. Myocyte size, however, is the dominant factor. Dr. G. indicated that it is via somatomedins that GH: increases protein synthesis by enhancing amino acid uptake and accelerating transcription and translation of mRNA; decreases protein catabolism; and mobilizes fat as an efficient fuel source. GH therefore has a protein-sparing effect that promotes cell growth and which should not in and of itself adversely affect energy requirements of the myocardium. Dr. J. pointed out that other conditions that can be associated with acromegaly, including hypertension, atherosclerotic coronary artery disease and diabetes mellitus, may contribute to adverse cardiovascular risk in these patients, as well as the adverse structural remodeling found in the myocardium.

IGF-1, a somatomedin synthesized in the liver, is the driving principle to somatic growth noted Dr. G. It promotes cellular hypertrophy and hyperplasia. Recent evidence in man and animals indicates cardiac myocytes retain their capacity to synthesize DNA and re-enter the cell cycle throughout life and that they are not terminally differentiated. This growth reserve mechanism appears to be modulated by IGF-1. Whether myocyte proliferation occurs in patients receiving GH for their hypopituitarism is unknown. Certain tumor cells express somatomedin genes and requisite receptors and this autocrine behavior could promote carcinogenesis. Octreotide has proven useful in the treatment of various malignancies, particularly neuroendocrine tumors of the gastrointestinal tract.

Finally, the use of octreotide in regressing cardiac myocyte size in hypertrophic cardiomyopathy has been suggested, noted Dr. J., but remains to be systematically evaluated. The converse, he suggested, has attracted recent interest. Sacca and co-workers have reported on the clinical utility of using GH to promote cardiac and skeletal muscle growth in patients with dilated cardiomyopathy.

References