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

1 A brief mystery which sets the stage for the accompanying mini-review, seeking to integrate basic laboratory and clinical sciences and diverse expressions of disease, while highlighting the role of the generalist (that is, the integrator).
enhance the mitogenic potential of presumptively postmi-
totic muscle cells allowing them to re-enter the cell cycle
dthereby 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 acrome-
galic heart but also following administration of recombi-
nant 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 cardiomyopa-
thy?

Answer

Drs. G. and J. were quite pleased with Nicole’s pre-
sentation 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 acrome-
galic 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 so-
matomedins that GH: increases protein synthesis by en-
hancing 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 dis-
ease 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 pro-
motes cellular hypertrophy and hyperplasia. Recent evi-
dence 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 neu-
roendocrine 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. Saccà and co-workers have reported on the clini-
cal utility of using GH to promote cardiac and skeletal
muscle growth in patients with dilated cardiomyopathy.

References

[1] Weber KT. Gateways, gangways, getaways and the one-trick dog