Hypertrophy is the mechanism by which muscle, any muscle, copes with persistent and repetitive overloads. Any increase in cardiac chamber radius ($r$) and/or pressure ($p$) will result in a proportional increase in total wall tension ($T$) according to the ideal Laplace formula, $T = pr$. The true load on the individual myocardial fibers can be appreciated by dividing the tension by the width of the chamber wall ($h$): $T_s = \frac{pr}{h}$. The result is the tensile stress (here, $T_s$), which is the force exerted across an area. With an increase in afterload (e.g. essential hypertension, aortic stenosis), the increase in the resultant wall tension and stress triggers almost immediately the synthesis of new contractile elements. The increase in wall thickness will then reduce wall stress towards normal while maintaining the increase in wall tension, although not without a price. The negative side is the associated increase in extracellular matrix and fibroblasts, the reduced coronary flow reserve, and increased chamber stiffness.

Until 1960, the major complications of the disease processes causing left ventricular hypertrophy (LVH) were related to the disease itself. In that year, the cornerstone study from Framingham demonstrated that LVH by ECG per se is an independent risk factor for cardiovascular morbidity and mortality, including sudden cardiac death (SCD). This was later reinforced by an extended study from the same group [1]. This independent risk was unrelated to the severity of the underlying disease causing LVH. Since then, it has been confirmed by numerous clinical studies [2]. What renders the patient with LVH susceptible to a several-fold increase in mortality including SCD? There are several potential factors involved.

(A) Electrophysiological alterations. These include prolongation of action potential duration, disturbed K ionic currents, early and late afterdepolarizations, slowing of conduction, and nonhomogeneous repolarization causing QT variability and dispersion of recovery [3,4].

(B) Anatomical changes. The stimulus for hypertrophy activates the genes responsible for the synthesis of collagen and extracellular matrix [5]. During the process of new collagen synthesis, cleaved peptide particles are released, and elevated levels have been demonstrated in the blood of patients with LVH [6]. The increase in connective tissue creates areas of conduction blocks, uncouples myocardial cells, and produces zigzag pathways, all of which become substrates for reentry.

(C) Sympathetic activity. There are indications that patients with LVH display abnormal heart rate variability pointing to increased sympathetic tone [7] and demonstrate increased levels of norepinephrine [8]. All the three groups of alterations associated with LVH may “join forces” and create serious and lethal arrhythmias. We can then claim that we understand why LVH is an independent risk for morbidity and mortality from cardiovascular causes.

Modern management of hypertension has drastically improved the prognosis of patients suffering from hypertension. Adequate control of blood pressure results in large and significant reduction in cerebrovascular accidents and cardiac morbidity and mortality including SCD. Large-scale clinical studies have demonstrated that the clinical improvement is associated with regression of the hypertrophy. This process involves also the regression of the excessive extracellular matrix [8]. The clinical observation of reduced incidence of ventricular arrhythmias and SCD upon control of blood pressure and anatomical regression of LVH [9] prompted studies investigating the possible regression of the functional abnormalities that were associated with LVH. Indeed, several studies have demonstrated the regression and eventual normalization of the LVH-associated electrophysiological abnormalities [10,11]. These studies, performed in cats and rabbits, suggested normalization of
membrane K+ ionic currents, of action potential duration, of dispersion of recovery, and of vulnerability to ventricular fibrillation. It should be stressed that these and other studies were performed on different animal models and with different research protocols. Also, the time periods of hypertrophy and regression differed. These results, however, did fall within the beneficial clinical observations associated with regression of LVH.

Do we then understand why regression is clinically beneficial? Botchway et al. [12] tell us “no” in this issue of the journal. They studied guinea pigs in which LVH was produced and where regression occurred following the release of the stimulus for hypertrophy. The electrophysiological alterations with hypertrophy were indeed as expected and were in line with previous studies, including action potential prolongation and slower conduction velocity. However, following 42 days of deconstriction, namely, removal of the stimulus for hypertrophy, the electrophysiological abnormalities did not regress, although anatomical regression did occur. So, the jury is called back to await further evidence and studies.

Why the conflicting results? There are several possibilities. Animal species differences, varying periods of hypertrophy and regression, and different research protocols may explain some of inconsistent results. For us clinicians, this is a disappointing scientific setback, proving again that biological research is difficult and correlating animal data with human biology is sometimes difficult if not impossible.

So where do we stand today? The clinical facts are clear. By treating our patients suffering from hypertension (the major cause of LVH) with angiotensin converting enzyme inhibitors, calcium channel blockers, beta-blockers, and diuretics, we improve their prognosis considerably. With diuretics, we improve their prognosis considerably. With regression did occur. So, the jury is called back to await further evidence and studies.

References