Adventures in Cardiovascular Research

Eugene Braunwald, MD, Harvard Medical School, Boston, Massachusetts, USA, described his early observations in cardiovascular (CV) research and related them to contemporary research. Dr. Braunwald has engaged in 5 areas of research since 1953: valvular heart disease, hypertrophic cardiomyopathy, heart failure, lipids, and myocardial ischemia.

In 1951, the age-adjusted CV mortality rate was 3 times the current rate. Pacemakers did not exist, and arrhythmias were treated with quinidine and digitalis. Echocardiography, nuclear imaging, coronary arteriography, and contrast ventriculography did not exist and only right heart catheterization was available. There were no cardiac care units, and the early acute myocardial infarction (AMI) mortality rate was 30%. Clinical trials, evidence-based medicine, hypothesis-based clinical investigation, and the concept of risk factors did not exist. Closed mitral valvotomy was available, but open-heart surgery was not. At the time, the 2 potential opportunities for advancing the field were cardiac catheterization and closed-cardiac surgery.

Dr. Braunwald's early work involved measuring the pressure gradient across stenotic valves and defining the natural history of aortic stenosis. In the late 1950s and early 1960s, he and his colleagues described techniques for left heart catheterization by the transbronchial and transseptal routes. By 1965, Dr. Braunwald demonstrated improved pulmonary vascular hemodynamics 6 months after mitral valve replacement. In 1968, he coauthored a paper that used post mortem data to describe the natural history of aortic valve stenosis in adults.

In 1959, Dr. Braunwald and Andrew G. Morrow, MD described hypertrophic cardiomyopathy, and in 1964 Dr. Braunwald and colleagues investigated the circulatory response of patients with hypertrophic cardiomyopathy to nitroglycerin and the Valsalva maneuver and described dynamic obstruction in this condition. They also studied inheritance patterns of and published reports on medical and surgical treatments. Recent genetic analyses have demonstrated that the gene for hypertrophic cardiomyopathy occurs in 1 of 500 births.

In 1962, Dr. Braunwald investigated neurohormonal abnormality in patients with heart failure (HF). He and his colleagues studied augmentation of the plasma norepinephrine response to exercise and catecholamine excretion and cardiac stores of norepinephrine in HF patients. They also described determination of left ventricular ejection fraction (LVEF) and ventricular end-diastolic and residual volumes, noting that "the estimations of the fraction of the LV end-diastolic volume that is ejected into the aorta during each cardiac cycle ... provides information that is fundamental to a hemodynamic analysis of LV function."

Thirty years later, Dr. Braunwald reported on the SAVE trial [Pfeffer MA et al. *N Engl J Med* 1992], in which mortality was significantly reduced in patients <10 days post-AMI with LVEF <40% who were treated with the angiotensin-converting enzyme inhibitor captopril. The 2011 CUPID trial [Jessup M et al. *Circulation* 2011] reported that intracoronary gene therapy with an adeno-associated virus in patients with advanced HF successfully upregulated intramyocardial calcium.

Dr. Braunwald chaired the CARE trial, which first demonstrated that statin therapy is beneficial in patients with average cholesterol levels [Sacks FM et al. *N Engl J Med 1996*]. The DEFINE trial [Cannon CP et al. *N Engl J Med* 2010] showed that the cholesterol ester transport protein inhibitor anacetrapib increased high-density lipoprotein cholesterol levels by 138.1% versus placebo ($p<0.001$) and decreased low-density lipoprotein cholesterol levels by 39.8% versus placebo ($p<0.001$). The REVEAL HPS-3 TIMI 55 trial [NCT01252953] is currently evaluating the effects of anacetrapib through lipid modification.

Dr. Braunwald's early work defined the determinants of myocardial oxygen consumption, leading to the concept of infarct size reduction and the "early open artery hypothesis." The TIMI research group has focused on secondary prevention following acute coronary syndrome, most recently finding, in the ATLAS ACS2-TIMI 51 trial, [Mega JL et al. *N Engl J Med* 2012] that the administration of low-dose rivaroxaban reduces CV and all-cause mortality.