Hypertension, one of the most important risk factors for cardiovascular diseases, is associated with both left ventricular hypertrophy and endothelial dysfunction. Both have been recently recognized as independent predictors of clinical events in different groups of patients. In fact, a dysfunctioning endothelium loses its antiatherosclerotic and antithrombotic action, and, therefore, promotes the atherosclerotic process. Similarly, cardiac hypertrophy is recognized as a powerful and independent risk factor for cardiovascular morbidity and mortality because it predisposes to arrhythmias and maximizes the consequences of acute myocardial ischemia. Recently, an evident interaction has been demonstrated between endothelial dysfunction and left ventricular mass. In particular, the coexistence of both left ventricular hypertrophy and endothelial dysfunction almost doubles the risk for future vascular events in hypertensives. Thus, in hypertensive patients, it is clinically useful to choose an aggressive therapeutic strategy—to reduce left ventricular mass and to improve endothelial function.

Introduction
Blood pressure is a quantitative trait with a normal, continuous distribution in the general population. Blood pressure has both genetic and environmental components, which defines it as a multifactorial trait. Arterial hypertension is a clinical definition of the upper end of the blood pressure distribution. High blood pressure is a chronic clinical condition that affects almost 25% to 30% of the adult population, and it appears to be even more prevalent in the elderly subjects. Diseases related to the cardiovascular system are the most common cause of morbidity and mortality in the industrialized countries. Arterial hypertension is one of the most important risk factors for cardiovascular diseases and clinical outcomes; the magnitude of this risk is further increased, in a multiplicative fashion, by the coexistence of some other conditions, such as diabetes or insulin resistance, dyslipidemia, smoking, and left ventricular hypertrophy (LVH) [1,2].

It is clearly demonstrated that high blood pressure is associated with a significant reduction in life expectancy as the result of the appearance and progression of both the atherosclerotic process and organ damage. Data from the Framingham Heart Study found hypertensive patients to have a seven-fold greater rate of stroke, a fourfold increase of congestive heart failure, a threefold higher incidence of coronary artery disease, and a doubling of peripheral arterial occlusive disease compared with normotensive subjects [2,3]. All of these clinical conditions are attributable to vascular damage that starts with endothelial dysfunction. In keeping with this, it has been consistently demonstrated that endothelium-dependent vasodilation is impaired in essential hypertension, as a result of a diminished bioavailability of nitric oxide (NO) [4].

Endothelium and Atherosclerosis
Atherosclerosis is a progressive process that initially involves endothelial dysfunction and the accumulation and peroxidation of intimal lipids followed by the release of inflammatory cells and growth factors, resulting in vascular smooth muscle cell proliferation and collagen matrix production. The normal endothelium—an autocrine, paracrine, and endocrine organ—plays a key role in preventing atherosclerosis because it possesses various vasoprotective effects, such as vasodilation, inhibition of platelet aggregation, suppression of adhesion of leukocytes and monocytes on the endothelial surface, and inhibition of migration and proliferation of vascular smooth muscle cells [5,6]. These protective effects of the endothelium are regulated by NO, a short-lived molecule produced by the endothelial enzyme NO
synthase (eNOS) from the amino acid L-arginine [7]. Traditional and emerging cardiovascular risk factors induce both coronary- and brachial-artery endothelial dysfunction because of a decreased bioavailability of NO, suggesting that endothelial cells may be both targets and mediators of atherosclerosis. This condition, which occurs early in vascular damage, may be caused by various mechanisms, including decreased NO synthesis due to a specific defect in the phosphoinositol pathway, leading to activation of eNOS, to increased NO degradation due to oxidative stress, or to reduced smooth muscle cells sensitivity to NO [8,9]. With regard to the first mechanism, the activity of eNOS may be inhibited also by endogenous analogues of L-arginine, such as asymmetric dimethylarginine (ADMA) [10], which has been shown to increase in patients with chronic renal diseases [11], in familial hypercholesterolemia, and in a variety of clinical settings [12], including essential hypertension [13]. A dysfunctioning endothelium loses the ability to exert a protective effect on the vascular system by reducing its potent anti-atherosclerotic and antithrombotic action and playing, therefore, a key pathophysiologic role in the appearance and progression of the atherosclerotic process [6].

Endothelial function is most commonly measured as the vasodilating response to physical (shear stress) or pharmacologic stimuli (acetylcholine, bradykinin, thrombin, substance P, and serotonin) that act through a cellular membrane receptor, with the signal transduction operating through the G-protein system. Recently, it has been demonstrated that depressed coronary endothelial function in humans may be associated with myocardial ischemia. Furthermore, cholesterol-lowering agents significantly reduce cardiovascular outcomes in secondary as well as in primary prevention, suggesting the possibility that these beneficial effects may be mediated, at least in part, by an improvement of endothelial dysfunction [14]. In keeping with this, more recently it has been reported that both coronary [15] and forearm endothelial vasodilator dysfunction [16••] predict long-term atherosclerotic disease progression and cardiovascular event rates, providing important diagnostic and prognostic information in patients who are at risk for future vascular disease. On the basis of these findings, it is possible to observe the systemic nature of endothelial dysfunction, even if the question whether peripheral endothelial dysfunction may be considered a surrogate marker of coronary vascular dysfunction remains unanswered. However, several studies clearly demonstrated that endothelial dysfunction, detected on both peripheral and coronary arteries, can be considered a useful and reliable prognostic marker in patients with vascular disease [17]. Therefore, the prognostic value of peripheral endothelial dysfunction is to facilitate the stratification of global cardiovascular risk in patients who are at risk for future cardiovascular events; however, before a routine clinical application can be established, the methodologies for peripheral endothelial function testing must be standardized and reproducible.

The hypothesis that a primary dysfunction of the endothelial cells is the initial occurrence in atherogenesis is, therefore, particularly attractive, because it is capable not only of explaining atherogenesis through pathologic damage but also of conceptually integrating an age-related, physiologic dysfunction of the endothelial cells.

**Hypertensive Heart Disease**

The cardiac consequences of chronically elevated blood pressure are hypertrophy of the heart, cardiac dilation, and congestive heart failure. Furthermore, essential hypertension is a substantial cofactor in the development of coronary artery disease. Left ventricular mass shows a continuous distribution in the general population [18], whereas LVH is a conventional categorization that defines the upper end of cardiac mass distribution [2,3,19]. Echocardiographic LVH is generally found in 20% to 30% of subjects with mild-to-moderate essential hypertension [20], and its prevalence varies according to the selected cut-off value [21] and population selection. Cardiac modifications are characterized by an increase in cardiac mass with or without cavity dimension increase contributing to the development of concentric or eccentric LVH. Generally, concentric LVH occurs predominantly as a pressure-loading effect, whereas eccentric LVH is due to a volume-loading effect.

Several stimuli, such as increased afterload that characterizes the hypertensive status, initiate a cascade of biologic events leading to increased cardiac growth. The mass increase, due to hypertrophy of myocytes rather than hyperplasia, is initially compensatory to sustain a high stroke volume and/or to normalize systolic wall stress. Generally, the load is expressed on the basis of the Laplace relation, in that the tension generated within the wall of the heart (T) is directly related to the pressure (P) times the radius of the ventricular cavity (r) and inversely related to two times the wall thickness (h)—that is, \( T = P \times r/2h \). In particular, the degree of LVH seems to be strongly correlated with the magnitude of pulsatile hemodynamic load rather than with that of the steady hemodynamic load; precisely, it is strongly correlated with the impedance of the aorta, with the arterial compliance, and with pulse-wave velocity, components that characterize the pulsatile hemodynamic load [22]. High blood pressure also influences left ventricular structure. In fact, echocardiographic evaluations of left ventricular mass and relative wall thickness identify a spectrum of cardiac adaptations, including concentric and eccentric LVH, normal ventricular geometry, and concentric left ventricular remodeling [3,23].

Standard measurements of cardiac function in patients with high blood pressure show that ejection fraction is preserved but that diastolic filling, as assessed