Regional Myocardial Blood Flow and Coronary Reserve in Hypertensive Patients
The Effect of Therapy

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Summary

Patients with essential arterial hypertension demonstrate abnormal vasodilator capacity either during increased cardiac metabolic demand or during pharmacological vasodilation. Structural and functional damage to the coronary microcirculation has been proposed as one of the major causes of impaired coronary reserve in this disease.

To assess the role of microvascular impairment in regional myocardial blood flow (MBF), 27 patients with essential hypertension were evaluated by dynamic positron emission tomography (PET) at rest, during atrial pacing and after dipyridamole infusion and compared with 13 healthy subjects. All patients had normal coronary arteries, 17 had moderate to severe hypertension and 10 had mild hypertension. Baseline mean MBF of 0.97 ± 0.25 ml/min/g was significantly increased to 1.60 ± 0.38 during atrial pacing and 2.35 ± 0.95 after dipyridamole infusion (p < 0.01); however, mean flow during atrial pacing and after dipyridamole infusion was significantly lower than in healthy subjects (2.15 ± 0.73 and 3.71 ± 0.86 ml/min/g, p < 0.05 and p < 0.01, respectively). The MBF response to atrial pacing and dipyridamole infusion was similarly depressed in patients with mild and severe hypertension.

The study was repeated after 6 months of antihypertensive treatment with the calcium antagonist verapamil or the angiotensin converting enzyme (ACE) inhibitor enalapril in a subgroup of 20 patients as part of a randomised, single-blind clinical trial. This study is still in progress; the initial 16 patients treated with verapamil or enalapril showed an obvious improvement in MBF values during atrial pacing and after dipyridamole infusion after 6 months of therapy (mean MBF: 2.10 ± 0.64 and 2.99 ± 1.63 ml/min/g, respectively, p < 0.05 vs pretreatment values).

In conclusion, obvious impairment of MBF during atrial pacing and after dipyridamole infusion was observed in hypertensive patients with normal coronary arteries and this appeared unrelated to the severity of hypertension. Therapy with verapamil or enalapril improved coronary reserve and MBF response to an increase in myocardial oxygen demand.

Structural adaptations resulting from chronic pressure overload are represented by the development of left ventricular concentric hypertrophy (LVH), which leads to an increase in wall thickness and which may reduce the volume of the cardiac chamber. The thickening of the cardiac wall tends to normalise wall stress and preserve systolic shortening. If the degree of hypertrophy is insufficient, systolic wall stress may eventually increase, resulting in a reduction in systolic shortening with consequent ventricular dilation. Pressure overload, an increase in wall stress, and possible dilation of the cardiac chamber cause an increase in myocardial oxygen demand and, consequently, an increase in
tissue perfusion. These conditions may result in
subendocardial ischaemia secondary to an imbal­
ance between myocardial demand and supply.

Studies on coronary blood flow have shown im­
paired chronic vasodilating reserve in patients with
arterial hypertension with or without cardiac hy­
pertrophy (Marcus et al. 1982; Opherk et al. 1984;
Strauer 1979). Compromised subendocardial cor­
onary reserve may, in turn, provoke metabolic ab­
normalities that could impair diastolic function,
reduce ventricular compliance and increase myo­
cardial stiffness.

Thus, this complex interaction between arterial
pressure, perfusion, abnormal coronary reserve, and
alterations in diastolic relaxation and filling is the
cause of clinical events usually expected in hyper­
tensive patients and represented by myocardial is­
chaemia and cardiac failure.

1. Mechanisms Involved in the
Impairment of Coronary Reserve

The possibility that reduced coronary reserve
may be the mechanism responsible for angina pectoris in patients with arterial hypertension and nor­
mal coronary arteries was first suggested by Strauer
(1979). Since then, many clinical studies have es­
tablished the role of LVH as a cause of reduced
coronary reserve and the consequent clinical mani­
festation of ischaemia (Marcus et al. 1982; Opherk
et al. 1984). Although it has been documented that
myocardial reserve is reduced in hypertensive patients, the mechanism underlying such alteration has not been clarified. In fact, reduced coronary reserve may be the consequence of 1) an increase in resting coronary flow secondary to an increase in cardiac workload, 2) structural and functional alterations in the coronary microcirculation (microvascular disease), and 3) an increase in extravascular components of coronary resistance. It is conceivable that these 3 mechanisms, depending on when they occur and the degree of severity in­
olved, may impair coronary reserve. The diffi­
culty of measuring extravascular pressure and its
effect on coronary resistance in a clinical setting
preclude the conclusion that microvascular disease

is responsible for a reduced coronary reserve and
myocardial ischaemia in patients with hyperten­sion. Furthermore, an increase in ventricular wall
thickness may be responsible for a reduction in the
duration of diastolic relaxation and filling phase.
Several studies have shown evidence of an inverse
relationship between ventricular wall thickness and
diastolic relaxation (Eighorn et al. 1982; Shapiro
& McKenna 1984), while others emphasise the in­
ability to normalise systolic wall stress, via the
compensatory mechanism of hypertrophy (after­
load mismatch), as being a cause of impairment in
the diastolic phase in hypertensive patients (Han­
rath et al. 1980; Inouye et al. 1984). During the last
few years, myocardial ischaemia has been impli­
cated as an important cause of diastolic impair­
ment in patients without coronary atherosclerosis
(McLaurin et al. 1973; Paulus et al. 1982). Vatner
et al. (1990) recently showed the importance of im­
paired coronary reserve in the subendocardial lay­
ers as a mechanism responsible for the diastolic
dysfunction observed in the hypertrophied heart
exposed to stress. Finally, the role of impaired dia­
stolic filling in systolic function in patients with
essential hypertension associated with cardiac hy­
pertrophy has been investigated. Studies of left
ventricular function, under basal conditions and
during exercise, have demonstrated that abnormal
left ventricular ejection fraction in hypertensive
patients is correlated with impaired diastolic fill­
ing, leading to an inadequate increase in end-dia­
stolic volume during exercise (Cuocolo et al. 1990).
This diastolic mechanism seems to be involved in
systolic dysfunction during exercise in patients with
arterial hypertension and left ventricular hyper­
trophy.

1.1 The Calcium Hypothesis

Cardiac hypertrophy may be associated with
biochemical alteration that is intrinsic to the
cytoplasmic transport of calcium and that may mod­
ify diastolic relaxation. Experimental studies have
emphasised the importance of calcium disregula­
tion by the sarcoplasmic reticulum as the principal
biochemical mechanism responsible for diastolic