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Specific Features of Target Organ Damage in Patients with Arterial Hypertension and Coronary Artery Disease

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1. Introduction

Worldwide, nearly 8 million premature deaths, 54% of stroke cases and 47% of ischemic heart disease cases were attributable to high blood pressure (BP >115 mm Hg systolic) (Ruilope, 2011). It is widely known that arterial hypertension has effects on target organs like the brain, the heart and the kidney. Now a large body of evidence on the crucial role of subclinical organ damage in determining cardiovascular risk in individuals with and without high blood pressure is available. New evidence showed that inflammation and activation of immunity are central features in the pathogenesis of atherosclerosis and also in hypertension-induced target organ damage. Recent studies have demonstrated that macrophages and various T-cell subtypes play a pivotal role in the regulation of blood pressure and target organ damage (Muller, 2011). A powerful promoter of inflammation and one of the major mediators of hypertension-induced target organ damage is also Angiotensin (Ang) II (Kvakan, 2009). European guidelines for the management of arterial hypertension from 2007 defined target organ damage by the presence of any of the following:

- electrocardiographic left ventricular hypertrophy (LVH) (Sokolow–Lyon > 38 mm; Cornell >2440 mm x ms)
- echocardiographic LVH (left ventricle mass index in men ≥ 126 g/m^2 and in women ≥ 110 g/m^2)
- carotid wall thickening (IMT > 0.9 mm) or plaque
- ankle/brachial index <0.9
- slight increase in plasma creatinine
- males: 115–133 µmol/l (1.3-1.5 mg/dl)
- females: 107–124 µmol/l (1.2-1.4 mg/dl)
- Low estimated glomerular filtration rate (< 60 ml/min/1.73 m^2) or creatinine clearance < 60 ml/min
- Microalbuminuria 30-300 mg/24 h or albumin–creatinine ratio: ≥22 (males); or ≥31 (females) mg/g creatinine

Since then, other studies proposed *home blood pressure* to be as reliable as ambulatory monitoring in predicting hypertension-induced target-organ damage, because it is superior to carefully taken office measurements (Viazzi, 2002; Stergiou, 2007). Marinakis et al. have demonstrated a relationship between heart rate variability and TOD, thus highlighting its importance in the genesis of subclinical cardiovascular disease (Marinakis, 2003). Recently, inflammation, and in particular tumor necrosis factor-α (TNF-α), has been implied in the cascade leading to TOD in patients with essential hypertension (Navarro-Gonzalez, 2008). Another study proposed the maximum value of home blood pressure to be a novel indicator of target organ damage in hypertension (Matsui, 2011).

Remodeling of small resistance arteries is also considered an early sign of target organ damage in hypertension (Cheng, 2010). The microcirculation is recognized as the site where the earliest manifestations of cardiovascular disease, especially inflammatory responses, that may play a pivotal role in driving the atherosclerotic process in conduit vessels, occur (Lockhart, 2009). Endothelial dysfunction is a predictor of a series of cardiovascular diseases (Heitzer et al, 2001; Halcox et al, 2002), although data on hypertension are still scarce (Taddei et al, 2002). Furthermore, techniques available for investigating endothelial response to various stimuli are invasive, laborious and time consuming. Finally, methods are not yet standardized and no certainty exists, that endothelial function assessed in an organ is representative of other vascular territories. However, current studies on circulating markers of endothelial activity and on endothelial cell progenitors are promising (Werner et al, 2005). This could facilitate evaluation of their prognostic role on a larger scale for more widespread clinical use. Although not traditionally considered a target organ, arterial blood vessels represent the site for the development of the atherosclerotic process that causes cardiovascular events.

Remodeling of large arteries during essential hypertension is also an early sign of organ damage. There are a number of noninvasive screening tests to identify structural and functional abnormalities of large arteries in arterial hypertension. By the time symptoms develop or clinical signs of atherosclerosis can be detected in conduit vessels, the disease process is already at an advanced stage (McVeigh, 2004; Lockhart, 2009). Remodeling of large arteries is characterized by an increase in intima-media thickness (IMT) aimed for maintaining circumferential wall stress, lumen enlargement of proximal elastic arteries, and no change in the lumen diameter of distal muscular arteries. Measurement of IMT by ultrasound examination of carotid arteries, and identification of atherosclerotic plaques, are predictors of both stroke and myocardial infarction (Salonen et al, 1993, Bots et al, 1997; Hodis et al, 1998, O`Leary et al, 1999). There is evidence that in untreated hypertensive patients without target organ damage, these alterations are common and therefore carotid ultrasound examination can detect structural damage at an early stage by routine examination. The relationship between increased carotid IMT and cardiovascular events is known, and value of IMT in the common carotid artery > 0.9 mm is considered the cut-point to emphasize the existence of structural abnormalities also in coronary arteries (Graf, 2009). Increased carotid IMT may be related to intimal or medial hypertrophy or both, and may be an adaptive response to changes in flow, wall tension, or lumen diameter (Vaudo, 2000). It is likely that ultrasound examination limited to the common carotid artery measures vascular hypertrophy only, while the evaluation and examination of bifurcation atherosclerosis and/or internal carotid artery, where plaques are most common, are more reliable for IMT

estimation. The presence of atheromatous plaques can be identified by the presence of focal increased thickness of 0.5 mm or 50% of the surrounding IMT (Zanchetti et al, 2002; Zanchetti et al, 2004).

Low ankle-arm index below 0.9 indicates the presence of peripheral arterial disease and, in general, advanced atherosclerosis (Feringa et al, 2006), while the measurement of carotid IMT can detect early changes (Zanchetti et al, 2002). However, a low ankle-arm index correlates with further development of angina, myocardial infarction, heart failure, need for coronary bypass's, stroke, need for carotid surgery and peripheral vascular level (Hiatt et al, 2001, Vogt et al, 1993) and in patients with multivessel coronary involvement it confers additional risk (Burek, 1999).

In the last 10 years, a large amount of data has been accumulated on large artery compliance and pulse wave reflection phenomenon, which have been identified as the most important pathophysiological determinants of isolated systolic hypertension and increased pulse wave velocity (Safar et al, 2003). Measurement of arterial compliance by vascular diameter changes in relation to changes in blood pressure is complex and unsuitable for clinical use. On the other hand, pulse wave velocity measurement between femoral-carotid arteries provides detailed non-invasive assessment of arterial compliance, which is simple and rigorous enough to be considered a procedure (Laurent et al, 2006). This determination is an independent predictor for overall mortality and cardiovascular morbidity, coronary events and strokes in patients with uncomplicated essential hypertension (Laurent et al, 2001, Boutouyrie et al, 2002, Laurent et al, 2003; Willum-Hansen et al, 2006). Although the relationship between aortic stiffness and coronary events is continuous, a threshold value > 12 m/s for pulse wave velocity suggests significant alterations of aortic elastic function in middle-aged hypertensives (Mancia, 2007).

Several methods for detecting vascular lesions cannot be clinically used for a variety of reasons. An elevated media-to-lumen ratio of small resistance arteries dissected from gluteal subcutaneous tissue is an indicator of increased cardiovascular risk (Rizzoni et al, 2003). These measurements can demonstrate early changes in diabetes and hypertension (Korsgaard et al, 1993, Park et al, 2001; Rizzoni et al, 2001, Schofield et al, 2002) and have predictive value for cardiovascular morbidity and mortality (Rizzoni et al, 2003), but the invasive character of the method makes this approach unsuitable for general use. Increased calcium content in coronary arteries, measured by high resolution cardiac CT was also validated by prospective studies as predictor of cardiovascular disease but its availability is limited due to high costs (Greenland et al, 2003).

Other diagnostic procedures such as magnetic resonance, cardiac scintigraphy, coronary angiography and exercise testing are reserved for specific indications. Chest X-ray can be a useful additional diagnostic method, when dyspnea is the main symptom or when looking for information on large intrathoracic arteries of the pulmonary circulation.
In recent years, an increased interest was given to assessment of cardiac fibrosis. Basic techniques have used echoreflectivity (Ciulla et al., 1997; Hoyt et al., 1984). Reversed dispersion method (backscattering signal) may reflect to some extent the contractile properties of the myocardium more than collagen content, while echoreflectivity more directly correlates with histologically measured fibrosis. Echoreflectivity showed that left ventricular hypertrophy may vary and that drugs that promote its regression may differ in

reducing fibrosis (Ciulla et al, 2004). Now, the most accurate method of assessing cardiac tissue composition is nuclear magnetic resonance, whose cost, however, prevents its widespread use. Also, tissue collagen component markers are currently under investigation (Ciulla et al, 2004), but they have been shown to only partially derive from cardiac tissue.

2. Hypertension-induced retinal damage

Hypertension, if not controlled, causes injuries to blood vessels and thereby causes alterations also in the retinal microcirculation. Advanced retinopathy is nowadays confirmed as hypertension-induced target organ damage (Cohuet, 2006). Signs of hypertensive retinopathy are frequently seen in adults 40 years and older, and are predictive for stroke, congestive heart failure, and cardiovascular mortality—independently from traditional risk factors (Wong, 2007). Mild hypertensive retinopathy signs, such as generalized and focal retinal arteriolar narrowing and arteriovenous kinking, are weakly associated with systemic vascular diseases. Moderate hypertensive retinopathy signs, such as isolated microaneurysms, hemorrhages and cotton-wool spots, are strongly associated with subclinical cerebrovascular disease and predict incident clinical stroke, congestive heart failure and cardiovascular mortality, independent from blood pressure and other traditional risk factors (Wong, 2005). Clinically, signs of hypertensive retinopathy were classified into four grades of increasing severity (Keith, 1974). The correlation between retinal vascular modifications and the severity of hypertension supports the importance of using fundus oculi to improve the diagnosis and to predict future cardiovascular events (Porta, 2005). In fact, assessment of hypertensive retinopathy signs for risk stratification is supported by international hypertension management guidelines, including the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the British Society of Hypertension (Williams, 2004; Chobanian, 2003).

The pathophysiological mechanism of hypertensive retinopathy is not completely established. It seems that elevated blood pressure and other pathogenic mechanisms may be involved, such as increased oxidative stress or low-grade inflammation. Retinopathy lesions have been associated with hyperglycemia, hypertension, endothelial dysfunction and inflammation in different studies (Wong, 2007). Many studies have linked signs of hypertensive retinopathy with cognitive decline, cerebral white-matter lesions identified by cerebral MRI, lacunar infarctions, cerebral atrophy, and stroke mortality (Wong, 2002; Kwa, 2002; Wong, 2003; Mitchell, 2005; Wong, 2007). Today, retinal examination offers an excellent way to study non-invasively the effects of common vascular risk factors on small vessels and possibly for gaining a better understanding of the pathophysiological processes involved in cerebral small vessel disease (Doubal, 2009).

3. Hypertension-induced cardiac damage

Electrocardiogram is part of all routine assessment of subjects with arterial hypertension. Left ventricular hypertrophy (LVH) is one of the earlier manifestations of TOD and constitutes a powerful predictor of cardiovascular events (Agabiti-Rose, 1998). This simple test provides useful information on conduction disturbances and ischemic heart disease, conditions that might urge the performance of additional investigations and influence the choice of antihypertensive drugs. A main advantage of ECG is to allow the detection of left

ventricular hypertrophy (LVH) (Larsen, 2002; Alfakih, 2006; Waeber, 2009). Sensitivity for identifying left ventricular hypertrophy is increased but still Sokolow-Lyon index (SV1 + RV5-6 > 38 mm) or the product of QRS duration times Cornell voltage (with adjustment of 6 mm in women and a partition value of > 2440 mm × ms) are independent predictors of cardiovascular events (Levy et al, 1994). Their use as markers of cardiac damage or regression induced by treatment appears to be valuable, at least in patients over 55 years (Okin et al, 2004, Fagard et al, 2004). ECG can also be used to detect patterns of ventricular overload (indicating a severe risk) (Levy et al, 1994), ischemia, conduction disturbances and arrhythmias, including atrial fibrillation, not rare in elderly hypertensive patients. Holter electrocardiographic monitoring is indicated to detect hypertension when arrhythmias or ischemic episodes exist. It may also provide evidence of reduced heart rate variability, which can occur in severe hypertension (Mancia et al, 1983). However, its negative prognostic significance is not established, although it has been demonstrated for heart failure and post infarction (Kleiger et al, 1987, Bigger et al, 1992, La Rovere et al, 2003).

Echocardiography is more sensitive than electrocardiography in diagnosing left ventricular hypertrophy, in cardiovascular risk prediction and may help stratify global cardiovascular risk more precisely and establish therapy, although it has some technical limitations (differences between operators, poor image quality in obese patients and in patients with obstructive lung disease) (Reichek et al, 1981; Levy et al, 1990). A proper assessment includes measuring the dimensions of interventricular septum, posterior wall thickness and left ventricular end diastolic diameter of left ventricular to left ventricular mass calculation according to Devereux formula (Devereux et al, 1986). Although the relationship between left ventricular mass index and cardiovascular risk is linear, the estimates of left ventricular hypertrophy are widely used: > 134 g/m^2 for men and > 110 g/m^2 for women (Hammond, 1986). Concentric hypertrophy (increased left ventricular mass and relative wall thickness ratio >0.45), eccentric hypertrophy (relative wall thickness ratio < 0.42, with increased left ventricular mass) and concentric remodeling (relative wall thickness ratio ≥ 0.42, with normal left ventricular mass), are predictors for increased incidence of cardiovascular disease, but concentric hypertrophy is shown to provide the most cardiovascular risk increase (Jennings et al, 1997; Muiesan et al, 2004). A major advantage of echocardiography compared with ECG is better sensitivity, enabling the detection of milder degrees of LVH (Waeber, 2009). In addition, echocardiography provides a method to assess left ventricular systolic function. Ejection fraction, fractional shortening as medio-parietal endocardial and were proposed as possible additional predictors of cardiovascular events (De Simone, 1996; Aurigemma, 2001). Left ventricular diastolic filling (a measure of so-called "diastolic function") can be assessed by measuring the ratio wave Doppler E/A of transmitral blood flow, time to relax, protodiastolic pulmonary venous flow and left atrial enlargement (Swedberg, 2005). Useful information can be obtained by tissue Doppler at the mitral ring (Ogunyankin, 2006). All these determinations arouse great interest at present, because a considerable proportion (50%) of heart failures can be explained by "diastolic dysfunction" with an impaired systolic minimum and that the so-called „diastolic heart failure "is a condition with adverse prognosis. Alterations in diastolic function are common in hypertensive and elderly subjects with hypertension, at least one in four patients may be affected (Zanchetti, 2006). These changes may occur in the absence of systolic function alterations and even without left ventricular hypertrophy. There is evidence that diastolic dysfunction increases the

risk of atrial fibrillation (Tsang, 2004). Furthermore, two studies have reported that diastolic dysfunction is predictive factor for subsequent heart failure (Aurigemma, 2001) and is associated with an increased incidence of mortality (Redfield, 2003), although in another study it was shown that this combination is not independent (Bella et al, 2002). Echocardiography provides information about the presence and degree of left atrial dilation, which correlates with risk of atrial fibrillation, cardiovascular disease and death (Laukkanen, 2005; Verdecchia, 2003; Kizer, 2006). Also, data can be obtained by kinetic abnormalities of left ventricular segmentation, due to ischemia or previous infarction. A regression of left-ventricular hypertrophy on electrocardiography is indicative of substantial clinical benefit and should be an important objective of treatment (Devereaux, 2004; Okin, 2004).

4. Hypertension-induced renal damage

Diagnosis of hypertension-induced renal damage is based on the discovery of a reduced renal function and/or increased urinary albumin excretion detection (Stevens et al, 2006). Renal failure is now classified according to glomerular filtration rate, calculated by MDRD formula that includes age, gender, and race and serum creatinine of the patient (Hallan, 2004). Glomerular filtration rate values below 60 ml/min/1,73 m^2 indicate chronic kidney disease stage 3, while values below 30 ml min/l,73 m^2 indicate chronic kidney disease stage 4, and values below 15 ml/min/l,73 m^2 indicate chronic kidney disease stage 5 (Moe, 2005). Cockroft-Gault formula estimates creatinine clearance and is based on age, sex, weight and patient's serum creatinine (Cockroft and Gault, 1976). This formula is used for values > 60 ml/min, but it overestimates creatinine clearance in chronic kidney disease stage 3-5 (Moe et al, 2005). Both formulas are helpful in the detection of renal function slightly altered, where serum creatinine is still within normal limits (Moe et al., 2005). Reduced glomerular filtration rate and increased cardiovascular risk are also suggested by elevated levels of cystatin C (Shlipak, 2006). A slight increase in serum creatinine (up to 20%) can sometimes occur when initiating or changing antihypertensive therapy, but it should not be considered as a sign of progressive renal damage. Hyperuricemia is common in untreated hypertensives and has been shown to correlate with decreased renal flow and the presence of nephrosclerosis (Viazzi, 2007). While serum creatinine concentration increased or decreased estimated glomerular filtration rate shows a decrease in glomerular filtration rate, increased urinary excretion of albumin or protein indicates deterioration in the permeability of the glomerular filtration barrier.

Microalbuminuria was associated with a cluster of metabolic and nonmetabolic risk factors, suggesting that it might indicate the presence of generalized microvascular damage in patients with essential hypertension (Pontremoli, 1998). It was shown that microalbuminuria is also a predictor of diabetic nephropathy development in type 1 and 2 diabetes (Parving, 1996), while the presence of proteinuria indicates, in general, the existence of renal parenchymal lesions. In diabetic and non-diabetic hypertensive patients, microalbuminuria is a good predictor of cardiovascular events. It has been reported in some studies a linear relationship between non-cardiovascular mortality and cardiovascular and urinary protein ratio/creatinine > 3.9 mg/g in men and 7.5 mg/g in women. Thus the term microalbuminuria may be misleading (for falsely suggests a minor injury) and should be replaced with "low degree of albuminuria." Microalbuminuria can be measured by urinary

albumin concentration reporting urinary creatinine concentration (urine samples per 24 hours or the night should be discouraged because of lack of accuracy), type dipstick tests detect albuminuria above 300 mg/g creatinine and positive dipstick test for microalbuminuria in values above 30 mg/g creatinine. Microalbuminuria assessment is now recommended at the initial evaluation of a patient with hypertension. Two first-morning voided urine samples should be tested for the albumin/creatinine ratio (Redon, 2008). Microalbuminuria assessment is now recommended in a risk stratification strategy for hypertension management, since its presence indicates early organ damage and, rarely, a clustering of cardiovascular risk factors (Mancia, 2007).

5. Hypertension-induced brain damage

Until now, preclinical hypertensive lesions in the brain have not been well characterized. Microcirculation dysfunction may explain the deterioration in cognitive functions in hypertensive subjects (Cohuet, 2006). Cognitive deterioration and its end point overt dementia are, in brief, to be characterized by progressive memory loss, disorientation in time and space, loss of autonomy, and ultimately, depersonalisation/alienation (Birkenhäger, 2006). Consensus criteria recognize various syndromes, including multiple cerebral infarcts (large vessel infarcts), single infarcts, small vessel disease (multiple lacunes dementia), global hypoperfusion, and hemorrhagic dementia in the pathogenesis of vascular dementia (Cohuet, 2006). Silent brain infarction, which is cerebral target organ damage of hypertensive microangiopathies, is frequently seen in hypertensive patients (Kwon, 2007). Indeed, the degree of risk for hypertension-induced cerebrovascular disease increases progressively with the rise in BP levels (Wolf, 1991). An increased risk for cerebrovascular events in uncomplicated patients with hypertension and LVH diagnosed using both electrocardiography and echocardiography was demonstrated in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study (Verdecchia, 2001). A close association has also been shown between silent stroke (evidenced by cerebral white matter lesions) and echocardiographic LVH in 62 asymptomatic middle-aged patients with hypertension (Sierra, 2002). Many epidemiologic studies have indicated a correlation between blood pressure level and cognitive decline or dementia later in life (Starr, 1993; Seux, 1998; Postner, 2002; Hanon, 2003; Piguet, 2003; Whitmer, 2005). The importance of lowering blood pressure in hypertensive subjects is well-known, but the relationship between hypertension and cognitive function is still controversial. It is believed that atherosclerosis resulting from long-standing hypertension, and cerebral hypoperfusion secondary to severe atherosclerosis may be major biological pathways linking both high blood pressure in midlife and low blood pressure in late-life to cognitive decline and dementia (Qiu, 2005).

6. Conclusion

Signs of target organ damage (TOD) should be carefully detected in all hypertensive patients because the likelihood of identifying high-risk individuals increases. Detection of any subclinical target organ damage in the coronary, peripheral, cerebral, and renal arterial beds requires therapeutic objectives and strategies in order to induce regression and improve patient prognosis.

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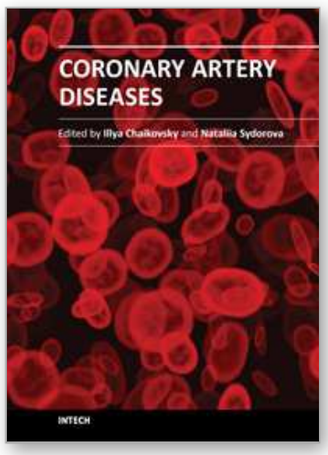

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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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