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## Editorial

# The Correlation Between Arterial Hypertension and Endothelial Function

## Editorial

Arterial hypertension is defined by a stable increase in systemic arterial blood pressure (BP) values, i.e. systolic value of 140 mmHg or more and/or diastolic one of 90 mmHg or more. Its prevalence is about 30–45% of the general population; representing a well-known cardiovascular (CV) risk factor [1]. In addition to BP values, the assessment of target organ damage has a pivotal role in stratification of total CV risk of patients. Current guidelines for the management of arterial hypertension suggest several tools for evaluating hypertension-related asymptomatic organ damage, such as electrocardiography, echocardiography, vascular ultrasound examination (carotid wall thickening or plaque, carotid-femoral pulse wave velocity, ankle-brachial index), and estimated glomerular filtration rate and microalbuminuria for study of renal function. However, these techniques are able to detect a already established structural lesion, while, on the other hand, the evaluation of early phases of atherosclerosis is crucial in primary CV prevention. Endothelial dysfunction represents the earliest stage of atherosclerosis, occurring before the evidence of morphological vascular alterations at Doppler ultrasonography and angiography [2]. Its impairment is able to significantly predict CV events independently of traditional risk factors [3], as well as the recovery of endothelial function predicts the increase in CV event-free survival [4].

Flow-mediated vasodilation (FMD) is a non-invasive methods able to assess endothelial dysfunction. This technique measures the percentage increase in diameter of a conduit artery, i.e. brachial artery, respect to the baseline after the application of a pressure stimulus [5].

At this purpose, well known is the relationship between endothelial function and arterial hypertension, this latter an established risk factor for atherosclerosis.

Several evidences show, in fact, an impaired vasodilator response to acetylcholine and bradykinin, endothelium-dependent vasodilators, in patients with essential hypertension due to a generalized endothelial damage rather than to a reduced bioavailability of a specific intracellular mediator of vasorelaxation [6]. Besides, endothelial dysfunction involves the total systemic

arterial bed, as shown by a study performed in hypertensive patients in which abnormal brachial artery FMD was correlated with in vitro maximal response to acetylcholine in subcutaneous small resistance arteries and, on the other hand, FMD was independently related to the impaired small artery vasodilation [7]. Moreover brachial artery FMD correlates with the severity of hypertension: patients with uncontrolled resistant hypertension have, in fact, a greater impairment in endothelial function compared to controlled resistant hypertension ones, and this result is related to non-dipping BP pattern [8]. Furthermore, a study performed in treated hypertensive subjects showed that nocturnal systolic and diastolic BP mainly affected FMD of the brachial artery rather than insulin sensitivity [9].

Lower brachial artery FMD was also related to increased risk of CV events during a 95 months-follow-up in 172 uncomplicated hypertensive patients [10].

Endothelial dysfunction associated to arterial hypertension shows, however, of being a reversible alteration: six months of antihypertensive therapy improve brachial artery FMD in postmenopausal women and reduce CV events during a mean follow-up of 67 months compared to women in which FMD did not change during treatment [11]. Among the antihypertensive drugs nebivolol ameliorates vasodilatory response to acetylcholine [12], while renin-angiotensin system blockers [13] and combination of perindopril/indapamide [14] FMD values in hypertensive subjects.

Inflammation appears to underlie the link between high blood pressure and endothelial dysfunction. In fact, a systemic inflammatory status induces endothelial dysfunction also in non-hypertensive patients [15], and in addition, circulating levels of C-reactive protein, a marker of inflammation, may independently predict the development of arterial hypertension [16]. Furthermore, also oxidative stress, a well-known determinant of endothelial dysfunction, plays a role in pathogenesis of hypertension through a vicious cycle involving inflammation [17].

The severity of endothelial dysfunction is correlated with serum levels of inflammation markers and antioxidant substances also in relatively young subjects affected by essential hypertension [18]. Moreover, in hypertensive patients higher levels of the plasma inflammatory cytokine neopterin are associated with impaired brachial FMD, and, after 3 months of antihypertensive treatment, the decrease in neopterin levels was correlated with the improvement in FMD and the reduction in blood pressure values [19].

As others CV risk factors, hypertension injures endothelium,

causes its dysfunction and promotes atherosclerotic process [20]. In male subjects elevated systolic BP in adolescence can predict the reduction of FMD 21 years later independently of other CV risk factors [21]. These studies suggest that hypertension may cause endothelial dysfunction, but since both conditions share some pathogenetic mechanisms, it is interesting to highlight whether the impaired endothelial function precedes the development of hypertension or viceversa.

Some evidences support the role of endothelial dysfunction in promoting the onset of arterial hypertension. In offspring of essential hypertensive patients a reduced vasorelaxant response to acetylcholine was found compared with that of offspring of normotensive subjects [22]. In a cohort of 952 healthy postmenopausal women with normal BP levels an increase in the risk of developing arterial hypertension, correlated with the grade of endothelial dysfunction, was demonstrated, independently of age and baseline pressure values. In particular, a 16% increase in the relative risk of hypertension for each unit decrease of FMD was found [23]. However, a study carried out in 3500 participants from the Multi-Ethnic Study of Atherosclerosis did not show a role of endothelial dysfunction assessed with FMD as independent risk factor for hypertension [24]. Although results are conflicting and this issue remains open, these data suggest that endothelial dysfunction is a consequence of arterial hypertension rather than a primary abnormality. Further studies are needed in order to better understand this relationship.

In the future, the knowledge of exact mechanisms underlying such a linkage may lead to new insights, i.e. in the drug development, offering to patients more effective treatments for management of arterial hypertension. As an early marker of atherosclerosis it is desirable that the assessment of endothelial function may be widely used by physicians as screening tool for identify subjects with asymptomatic and initial arterial damage at higher CV risk. Finally, future studies aimed to highlight whether the recovery of endothelial function is associated with better prognosis of hypertensive patients are warranted.

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