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COMMENTARY

Sympathetic nerve activity and endothelial function

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METHODOLOGICAL DIFFERENCES IN TESTING FOR ENDOTHELIAL FUNCTION

Endothelial function has intrinsic biological variability, unlike other vascular tests for measuring the structure of the vessel wall (Table 1). Therefore, endothelial dysfunction, characterized by the loss of nitric oxide (NO) bioavailability, is the key component in the pathogenesis of atherosclerosis and has a prognostic value in patients with atherosclerosis who are also at high cardiovascular risk.[1,2] The significance of endothelial dysfunction has been confirmed in clinical studies showing that it precedes clinical and morphological atherosclerotic changes.[3] Endothelial dysfunction is also linked to risk factors for cardiovascular diseases.[4] However, there is currently no simple and optimal method to assess the vascular risk.

Deanfield *et al.*[5] described the differences in the methods used for the clinical assessment of the endothelial function, and the flow-mediated dilation (FMD) of the brachial artery has been the standard measure over the last two decades based on the evidence supporting its association with cardiovascular outcomes and the atherosclerotic progression of IMT.[1,2,6,7] The procedure is technically difficult to perform and requires technical proficiency and a novel method for assessing endothelial function that is easily utilized with an automated, reproducible end point has been highly anticipated.

Recently, peripheral arterial tonometry (PAT) has come to be available. PAT is also a noninvasive technique that utilizes fingertip plethysmography to measure the changes in pulse-volume amplitude to reactive hyperemia (RH) compared with the baseline value. PAT signals are normalized to the measurements from the contralateral arm as non-endothelial-dependent systemic effects to avoid the fluctuations in sympathetic nerve outflow that may induce changes in the peripheral arterial tone that are superimposed on the RH response. This phenomenon has been shown to be NO dependent, and PAT is independent of the operator, making it a potentially convenient measure of the endothelial function.[8] Because PAT measurement simply requires insertion of two fingers into thimble-like peripheral arterial tonometers, in contrast to measuring the FMD, which requires a trained examiner to obtain accurate and reliable serial images of the brachial artery during the test. Therefore, PAT is thought to provide the measurements of NO-mediated endothelial response with good reproducibility, which may correlate with the findings of FMD obtained by brachial artery ultrasound.

Indeed, small studies have demonstrated that PAT measurements correlate with the FMD and the PAT hyperemic ratios are lower in patients with increased cardiac risk factors, and in patients with coronary artery disease. A linear relationship has been described between PAT and brachial artery FMD measurements in a population of patients with a range of traditional cardiovascular risk factors.[9] However, there have been few large-scale studies relating PAT to other established measures of endothelial function. The possible differences in the target for vascular territories with regard to the endothelial function remained unsolved.

AUTONOMIC NERVE ACTIVITY AND ENDOTHELIAL FUNCTION

These two tests are non-invasive evaluations of the endothelial function. However, clamping the forearm for 5 min at over 200 mm Hg to induce ischemia is painful and the sympathetic tone of the cardiovascular system may be increased by the pain and the mental stress. Most of the previous studies lacked careful consideration of the impact of the autonomic nervous system. This may be because it is still difficult to evaluate sympathetic nerve activity directly and easily. There are a few available methods to evaluate autonomic nervous function including 1) direct recording of the muscle sympathetic nerve activity (MSNA), 2) blood sampling to measure the levels of catecholamines (CA), and 3) analyzing the heart rate variability (HRV). MSNA correlates plasma level of catecholamine, however, direct recording of the nervous activity is not easy because of the required body position (at rest in a recumbent position), accessibility and invasiveness. The plasma levels of CA may provide the total result of high sympathetic nerve activation, however, it cannot reflect the rapid changes in nerve activity.

Tomiyama *et al.*[10] used HRV to evaluate the autonomic function in the study, and it is also used as an indirect method to reflect the outflow of the autonomic nerve activity. It was previously used with Holter ECG monitoring; however, it is now possible to evaluate the real-time HRV in response to rapid changes of the HRV beat-by-beat for a short period. Therefore, it is a reasonable way to evaluate the autonomic function. They also demonstrated the effects of rapid sympathetic nerve activation during brief forearm clamping on the endothelial function examined by different two methods in hypertensive patients, and suggested that the vascular system and structure (which autonomic nerves mediate) probably was responsible for the differences among the findings in this manuscript.[10] As mentioned in their manuscript, endothelial function tests may be influenced by SNA, and examiners need to take into account the fact that sympathetic nerve activation affects the results of

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Table 1 The characteristics of tests to evaluate the peripheral endothelial function

	FMD	*PAT*	*Strain-gauge plethysmography*
Vascular system	Large conduit arteries (brachial artery)	Small (digital) arteries Microcirculation (fingertip)	Small arteries Microcirculation (in whole forearm)
Method	Ultrasound	Plethysmography	Plethysmography
Evaluation	Incremental diameter of an artery in response to RH	Pulse volume amplitude in response to RH	Incremental volume in response to local agonist (ACh, SNP)
	NO dependent	NO dependent	NO independent
Advantage	Repeatable	Repeatable	Accurate
	Short test time	Short test time	Plentiful evidence (association with the CV prognosis)
	Plentiful evidence (association with the CV prognosis)		
Disadvantage	Requires training	Few studies on the correlation with the CV prognosis	Invasive

Abbreviations: ACh, acetylcholine; CV, cardiovascular; FMD, flow-mediated dilation; NO, nitric oxide; PAT, peripheral arterial tonometry; RH, reactive hyperemia; SNP, sodium nitroprusside.

endothelial function tests performed under various situations and using different methods.

The Japanese Circulation Society published the 'Guidelines for non-invasive vascular function test' in 2013. Only a Japanese version is currently available; however, it is the most up-to-date and comprehensive guideline for vascular testing, including FMD, PAT, ABI (Ankle-Brachial Index), PWV (Pulse Wave Velocity) and the CAVI (Cardio-Ankle Vascular Index). These tests are widely used in accordance with the worldwide prevalence of atherosclerosis and novel findings, and acknowledge that the improvements in vascular tests and endothelial function tests are accumulating every year.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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