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Original article

Advanced peripheral microvascular endothelial dysfunction and polyvascular disease in patients with high cardiovascular risk☆

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ABSTRACT

Background: Polyvascular disease (PolyVD) refers to the coexistence of coronary artery disease (CAD), peripheral arterial disease (PAD), and/or cerebrovascular disease (CVD), and carries a high risk of cardiovascular mortality. Endothelial dysfunction plays a crucial role in cardiovascular pathophysiology. This study investigated the association between PolyVD and the presence of microvascular endothelial dysfunction.

Methods: Consecutive stable patients ($n = 533$) with diabetes mellitus and/or multiple cardiovascular risk factors were enrolled. Peripheral microvascular endothelial function in the finger microvasculature was assessed using the reactive hyperemia peripheral arterial tonometry index (RHI), and ankle-brachial index was measured for diagnosis of lower-extremity PAD prior to coronary angiography. Diagnosis of CVD was based on clinical symptoms, carotid ultrasound, and magnetic resonance imaging. PolyVD was defined as two or more coexisting vascular diseases from CAD, lower-extremity PAD, and CVD.

Results: Natural logarithmic transformations of RHI (Ln-RHI) were significantly attenuated in 93 patients with PolyVD (0.44 ± 0.20) compared with those in 440 patients without PolyVD (0.56 ± 0.19; $p < 0.001$) or in 299 patients with a single vascular disease (0.54 ± 0.19; $p < 0.001$). There was an independent correlation between Ln-RHI (per 0.1) and the presence of PolyVD in all high-risk patients [odds ratio (OR): 0.724; 95% confidence interval (CI): 0.610–0.859; $p < 0.001$] and one or more vascular diseases (OR: 0.724; 95% CI: 0.605–0.867, $p < 0.001$). Receiver-operating characteristics curve analysis showed that Ln-RHI correlated significantly with PolyVD (area under the curve, 0.682, 95% CI: 0.625–0.740, $p < 0.001$). The optimum cut-off point of Ln-RHI for the existence of PolyVD was 0.479.

Conclusions: Microvascular endothelial dysfunction is significantly associated with the presence of PolyVD. Severe impairment of endothelial function in peripheral microvasculature may be an important pathophysiological component of PolyVD.

Introduction

Atherosclerosis is a systemic and progressive condition that can lead to coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD) [1]. Atherothrombotic disease can frequently be found in different vascular beds in high-risk patients, resulting in polyvascular disease (PolyVD) [2]. PolyVD is defined as the presence of more than one affected vascular bed in the coronary, cerebrovascular, or peripheral arterial systems, and is associated with a higher risk of death and cardiovascular

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morbidity [3,4]. This may be a consequence of the greater burden of atherosclerotic plaques in the whole arterial tree, more complex coronary lesions, or greater inflammatory activity in patients with PolyVD than in those with CAD alone [5–7]. However, the precise pathophysiological condition and mechanisms underlying PolyVD are still not fully understood.

The crucial role of endothelium in the pathogenesis of atherosclerosis and cardiovascular disease is well established, and individuals with endothelial dysfunction are at an increased risk of cardiovascular events [8]. Reactive hyperemia peripheral arterial tonometry (RH-PAT) is a relatively straightforward and automated means of evaluating peripheral microvascular endothelial function that is not affected by operator variability [9,10]. A device used to measure RH-PAT and thereby assess endothelial function, the Endo-PAT2000 (Itamar Medical Ltd., Caesarea, Israel), has received clinical approval by the Food and Drug Administration in the USA and the Ministry of Health, Labour and Welfare in Japan [9,11]. We have previously reported that RH-PAT was a clinically useful means of identifying high-risk patients among women with ischemic heart disease [12], and in heart failure patients with normal left ventricular ejection fraction [13].

In this cross-sectional study, we hypothesized that the extent of microvascular endothelial dysfunction as volumetrically measured by RH-PAT might be associated with the presence of PolyVD in stable patients with multiple coronary risk factors or diabetes mellitus (DM).

Materials and methods

An expanded Materials and Methods is presented in the online-only Data Supplement.

Study population

Consecutive, stable, high-risk patients (n = 596) with multiple conventional coronary risk factors or DM were recruited. It is recognized that certain underlying diseases can influence the results of endothelial function tests. We excluded patients with cardiomyopathy, severe valvular disease, heart failure (New York Heart Association class III/IV and/or left ventricular ejection fraction <40%), cancer, end-stage renal dysfunction with hemodialysis, critical limb ischemia, and systemic illness. Details of medical history and symptoms of vascular diseases, such as myocardial infarction (MI), angina, stroke, transient ischemic attack (TIA), and intermittent claudication, were recorded. We measured the RH-PAT index (RHI) and ankle-brachial index (ABI) before coronary angiography (CAG). Patients with PolyVD were defined as those with two or more of CAD, lower-extremity PAD, and CVD. Comparisons of RHI were made between patients with no vascular disease, individual vascular disease, or PolyVD (Fig. 1A).

RH-PAT examination

The principle and details of RH-PAT have been described previously [9]. RH-PAT was evaluated automatically using the Endo-PAT2000 device. We used a natural logarithmic transformation of the RHI values to calculate the Ln-RHI [12,14].

Coronary artery disease

Based on quantitative CAG analysis (CAAS; Pie Medical Imaging, Maastricht, The Netherlands), we defined CAD as the presence of >50% narrowing of coronary artery diameter (equating to 75%

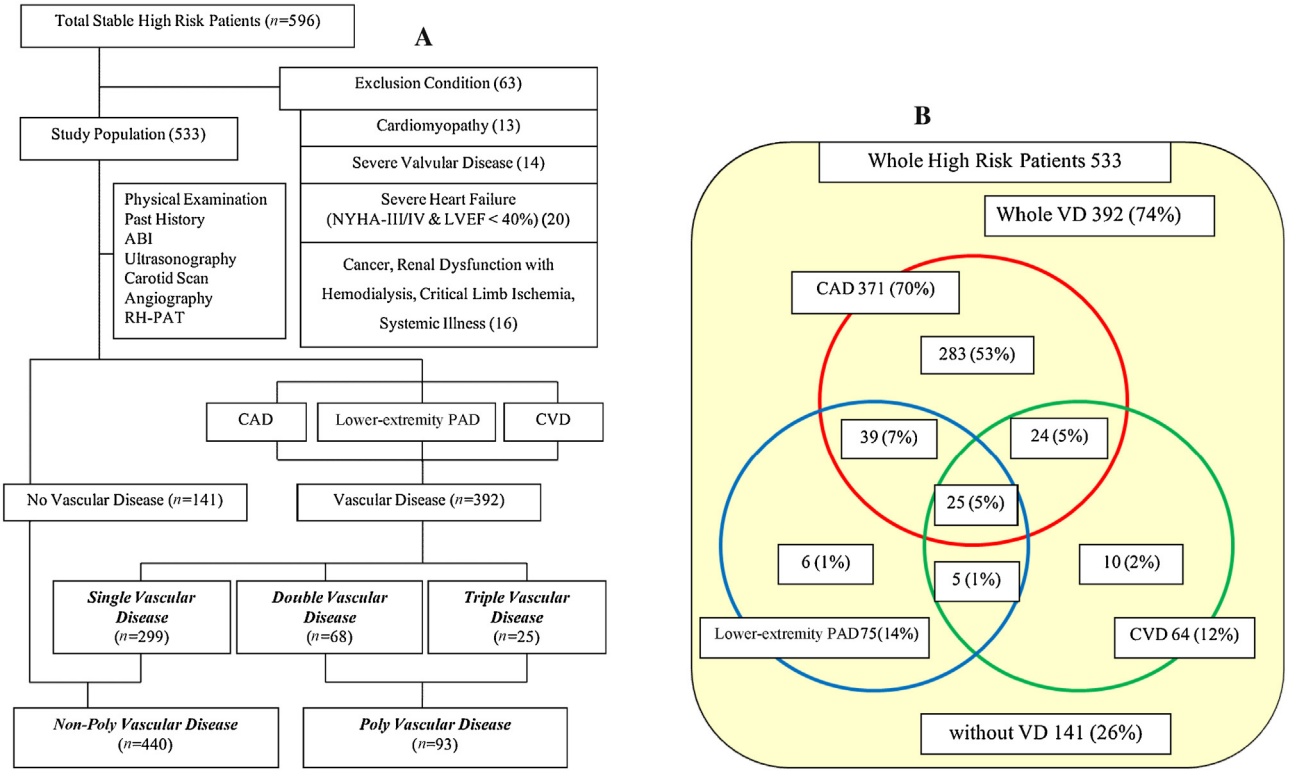

Fig. 1. (A) Flow chart showing the protocol used for enrollment of patients with PolyVD. Enrollment and screening for PolyVD in high-risk patients. We recruited 596 consecutive, stable high-risk patients and excluded those with cardiomyopathy, severe valvular heart disease, heart failure (NYHA-III/IV and LVEF <40%), and systemic illness. (B) Prevalence of vascular diseases within the study cohort. Of 533 high-risk patients, 141 had no vascular disease, 392 had any vascular disease, and 93 had PolyVD. Among CAD patients, the prevalence of PolyVD was 24%. ABI, ankle-brachial index; CAD, coronary artery disease; CVD, cerebrovascular disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease; PolyVD, polyvascular disease; VD, vascular disease; RH-PAT, reactive hyperemia peripheral arterial tonometry.