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Circulating endothelial microparticles are elevated in bicuspid aortic valve disease and related to aortic dilation

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ABSTRACT

Background/objectives: The mechanisms underlying aortic dilation in bicuspid aortic valve (BAV) disease are unknown. Circulating endothelial microparticles (EMPs) have emerged as biomarkers of endothelial damage. We sought to evaluate the relationships among EMPs, BAV disease, and aortic dilation.
Methods: Four evaluations were used. Circulating EMPs ($PECAM^+$, E-$selectin^+$) were compared between BAV patients and tricuspid aortic valve (TAV) control subjects. The variables related to circulating EMPs were investigated in BAV patients. Circulating EMP levels were compared between BAV and TAV patients with a dilated aorta. Finally, circulating EMPs in BAV patients were evaluated over time with respect to aortic valve surgery (AVS) or aortic surgery.
Results: We observed higher levels of circulating $PECAM^+$ EMPs in the BAV patients than in the control subjects (3.98 ± 0.2 vs. 2.39 ± 0.4 per log $PECAM^+$ EMPs/μl, $p = 0.001$). Aortic dilation was the most significant variable that correlated with the $PECAM^+$ EMP levels in the BAV patients ($\beta = 0.321$, $p = 0.008$). The BAV patients with aortic dilation exhibited higher $PECAM^+$ EMP levels than the TAV patients with dilated aortas, and this correlation was independent of aortic valve function. We observed a drastic decrease in the circulating $PECAM^+$ EMPs following AVS and aortic root replacement (4.27 ± 0.6 and 1.75 ± 0.3 per log $PECAM^+$ EMPs/μl, $p = 0.002$).
Conclusion: The observed pattern of higher circulating $PECAM^+$ EMP levels links BAV disease to endothelial damage and aortic dilation. Circulating $PECAM^+$ EMPs were identified as a biological variable related to aortic dilation in patients with BAV disease.

1. Introduction

A bicuspid aortic valve (BAV) represents the most common congenital cardiac malformation and is generally associated with the development of aortic valve dysfunction and the progressive dilation of the ascending aorta. The latter is associated with aortic regurgitation [1] and the risk of aortic dissection or rupture and often requires prophylactic aortic surgery [2–6]. The cause of ascending aorta dilation has been debated for several years and may be due to changes in the flow characteristics of the ascending aorta [7]. However, the mechanisms involved have not been fully elucidated. The aortic dilation observed in BAV disease may be related to endothelial dysfunction, as estimated by flow-mediated dilation [4]. Endothelial microparticles (EMPs) are small cell membrane vesicles, less than 1 μm in size, shed by endothelial cells upon activation, injury, or apoptosis [8]. The EMPs are characterized by the presence of endothelial-specific surface antigens, the composition of which is dependent on the cell origin of the microparticles and the generating process [9]. In this way, CD31 (PECAM) and CD62e (E-selectin) are markers of microparticles released from endothelial cells. The $PECAM^+$ EMPs have been related to apoptosis or endothelial damage and the E-$selectin^+$ EMPs to cellular activation [9]. The EMPs have been linked to inflammation, vascular injury, angiogenesis, and thrombosis and have emerged as markers of endothelial dysfunction [10]. They have also been linked to aortic valve disease [11]. However, the relationships among EMPs, BAV, and aortic dilation have not been extensively studied; thus, the aim of this study was to investigate these associations.

2. Methods

2.1. Study population

This study included a cohort of patients with BAV and patients with aortic dilation who were prospectively included and followed-up in our facilities. There were 185 patients with BAV and 125 patients with aortic dilation with tricuspid aortic valve (TAV). The participants were

Abbreviations: AVS, aortic valve surgery; BAV, bicuspid aortic valve; EMPs, endothelial microparticles; LV, left ventricular; TAV, tricuspid aortic valve; WSS, wall systolic stress.

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prospectively entered into a specific database and provided a blood sample upon enrolment and written acceptance. The samples were stored until needed in our biological samples bank (Biobanc IISPV — HUSJR). The diagnosis of BAV was made when two aortic leaflets were clearly visualized, with or without a raphe, on the parasternal short-axis view of a transthoracic echocardiogram [12], on a transesophageal echocardiogram [12], or by cardiac magnetic resonance [13]. A dilated aortic root or ascending aorta was diagnosed when the aortic diameter was ≥21 mm/m^2 [14]. Explorations were performed or supervised by the same observer (JMA). Our database and biobank also included a group of healthy controls. For this study, those individuals who met the characteristics to be included were selected. The participants were divided into different groups depending on the morphology of the aortic valve and the diameter of the aortic root (Fig. 1).

The design of the study included four evaluations to determine the possible factors related to the EMP circulation levels and BAV disease. First, the circulating EMP levels of the patients diagnosed with BAV (n = 60) were compared with those of the healthy TAV control subjects (n = 15), matched by age (ranging from 18 to 55 years) and sex. We excluded the BAV patients with evidence of significant left ventricular (LV) remodeling (LV end-diastolic diameter > 60 mm or LV end-systolic diameter > 45 mm) or LV dysfunction (LV ejection fraction < 50%) and individuals younger than 18 years or older than 55 years to reduce the possible confounding effects exerted by LV function and remodeling and age. Next, the effects exerted by aortic diameter on other variables potentially related to EMP levels were evaluated. The patients with BAV disease were within a defined age range (18–55 years) and had no restrictions pertaining to LV end-diastolic or end-systolic diameter or LV ejection. Patients were divided based on the presence or absence of aortic dilation, either at the level of the aortic root and/or the ascending aorta ($BAV_{non\text{-}dil}$ n = 32, BAV_{dil}, n = 39) or based on the dilation of the aortic root or the ascending aorta. The type of aortic dilation was categorized into two phenotypes, depending on the dilation pattern, as follows: an ascending phenotype ($BAV_{dil\_ascending}$, n = 25, dilation of the ascending aorta with either a normal aortic root or a less dilated aortic root) or a root phenotype (BAV_{dil_root}, n = 14, dilation in the aortic root with either a normal ascending aorta or a less dilated ascending aorta) [15].

In the third step, the influence of valve morphology on EMP levels was evaluated among the patients with aortic dilation and compared with the previously described control subjects (defined in the first step) and BAV_{dil} (defined in the second step, n = 67), as well as a third group composed of TAV patients with a dilated aorta (TAV_{dil}, n = 19). Due to the older ages of the TAV patients with a dilated aorta included in our database, no restrictions regarding age range were applied to this step although age was analyzed as a possible confounding factor. Patients with Marfan syndrome were excluded. Finally, circulating EMPs were analyzed for BAV patients over time with respect to aortic valve surgery (AVS). New blood samples were obtained periodically, and the effect of AVS was evaluated in the BAV patients by measuring the EMP levels from blood samples obtained before and 6 months after the surgery (BAV pre- and post-AVS, respectively, n = 10).

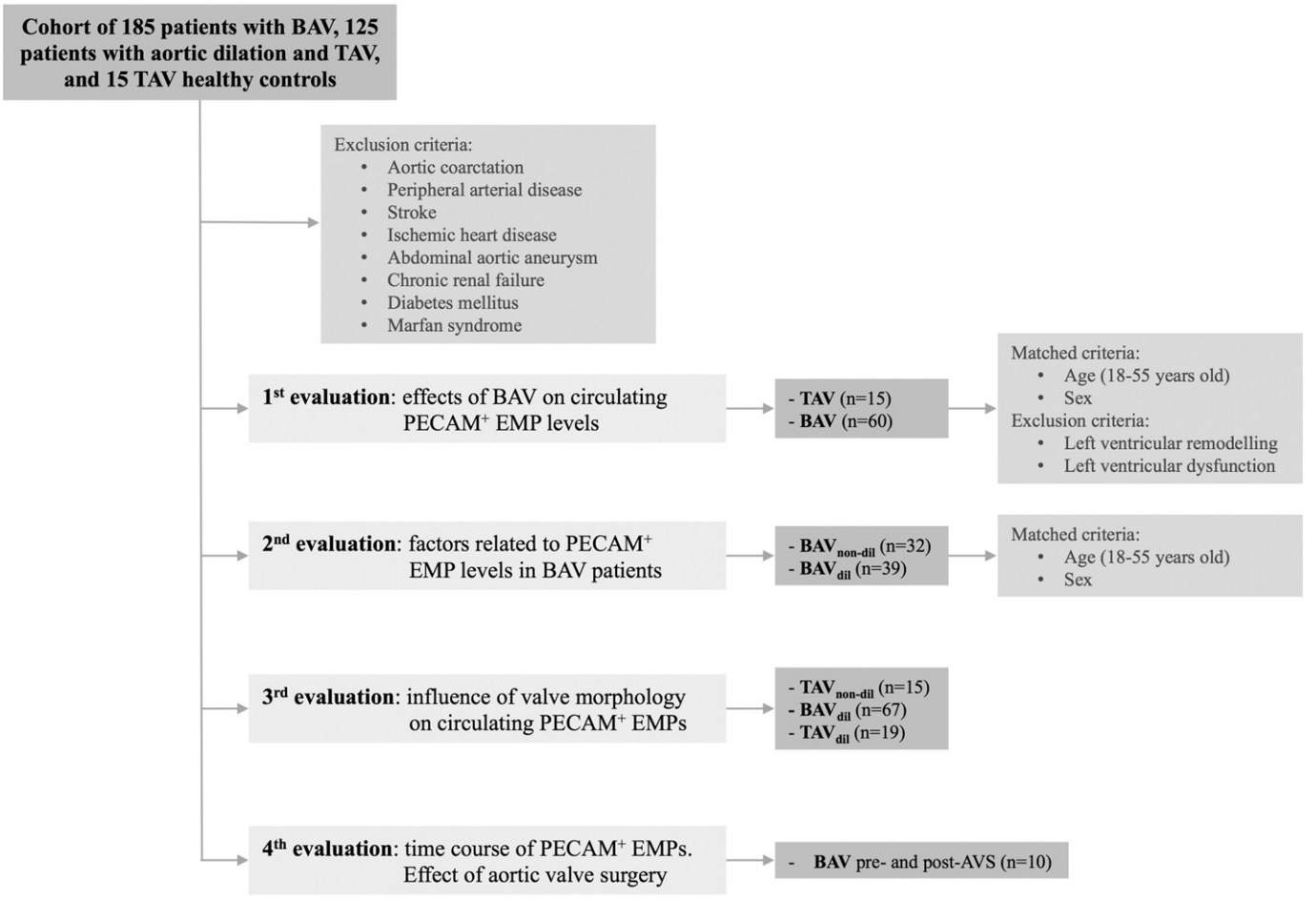

Fig. 1. The participants were divided into different groups based on the morphology of the aortic valve and the diameter of the aortic root for each of the four evaluations used. In the first evaluation, the circulating PECAM$^+$ EMPs were compared between BAV patients and tricuspid aortic valve (TAV) control subjects. In the second evaluation, the variables related to circulating PECAM$^+$ EMPs were investigated in BAV patients. The third evaluation compared the circulating PECAM$^+$ EMP levels in BAV and TAV patients with a dilated aorta. Finally, circulating EMPs in BAV patients were evaluated over time with respect to aortic valve surgery (AVS) or aortic surgery in the fourth evaluation.