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Review

Out of proportion proximal aortic remodeling: A subclinical marker of early vascular ageing? A systematic review

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ABSTRACT

Introduction: Proximal aorta stiffens and dilates with aging. Aortic stiffening is a well known process, carrying prognostic implications. On the contrary, few data are available about proximal aorta dilatation. It is not known if "out of proportion" aortic remodeling, i.e. in excess for age, sex and body size, could be a marker of early vascular ageing; there is controversy on how it would be accelerated by classical risk factors or would associate with validated markers of cardiovascular organ damage.
Aim: We conducted a systematic review in order to evaluate the determinants of proximal aortic dimensions, focusing on the association with arterial hypertension, cardiovascular risk factors and markers of organ damage.
Determinants of proximal aorta remodeling: Age, gender and body size explain 40-50% of the variability of aortic dimensions; genetic predisposition accounts for nearly 20%. Among cardiovascular risk factors obesity and hypertension seem to be associated with faster outward aortic remodeling. Arterial hypertension would account for a 0.60-0.78 mm greater diameter at the ascending aorta. Moreover, in hypertension, left ventricular mass showed a strict association with aortic diameter in nearly all studies. Other classical risk factors for atherogenesis such as dyslipidemia and smoking showed a weak influence on proximal aortic dimensions. No study reported a greater aortic remodeling in diabetics.
Conclusions: "Out of proportion" proximal aortic remodeling, could represent a subclinical marker of early vascular ageing, describing the cumulative influence of genetic predisposition, arterial hypertension and obesity.

1. Introduction

Early vascular ageing (EVA) has been defined as an increased arterial stiffness for a specific age and sex [1]. Large arteries not only stiffen, but also dilate with ageing. "Out of proportion" aortic remodeling, i.e. abnormal diameter in relation to age, sex and body size, could represent the geometrical manifestation of early vascular ageing. Proximal aorta can be explored by routine transthoracic echocardiography. Even marked aortic remodeling is not an unusual event in arterial hypertension: estimated prevalence of aortic dilatation is about 9% in this population [2]. Cuspidi et al. recently showed an increased risk of cardiovascular events in hypertensive subjects carrying aortic root dilatation and left ventricular hypertrophy [3]. Controversies exist in literature about aortic remodeling determinants. Some studies suggest that arterial hypertension and obesity are associated with increased aortic diameter [4,5]. Proximal ascending aorta seems to be less prone to be involved by atherosclerosis than abdominal aorta [6]: sparse data in literature concern the influence of diabetes, dyslipidemia and smoking on ascending aorta. We ought to revise literature concerning determinants of physiological and "out of proportion" proximal aorta remodeling.

2. Methods

Medical literature was reviewed to identify articles evaluating determinants of proximal aorta diameter (echocardiography or II level imaging, Figs. 4 and 5). We searched for studies reporting: 1) evaluation of determinants of proximal aortic dimensions in multivariate analysis; 2) evaluating aortic remodeling at Sinus of Valsalva and/or ascending aorta. Studies involving subjects with genetic predisposition to aortic remodeling, or aortic syndromes were excluded. We conducted a computerized search using PubMed, OVID and ISI-Web of Knowledge databases from their inception through 2014.

Relevant data were extracted by two independent investigators (F.T. and D.L.), and controversies were resolved by a third

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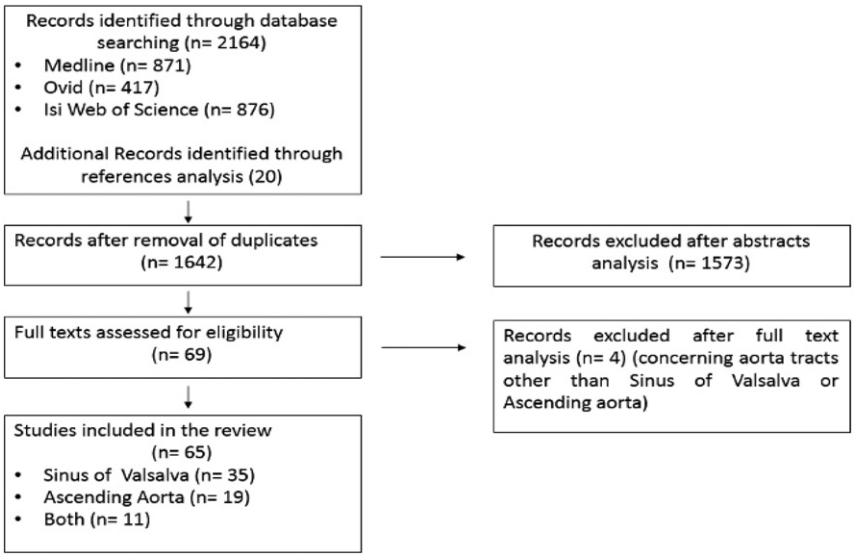

Fig. 1. Flow chart of the selection of the articles included.

investigator (A.M.). Fig. 1 shows flow chart for selection of included papers. (Table 2, see online Supplemental Digital Content (SDC)).

3. Main determinants of aortic remodeling

Age, body size and gender are the main determinants of aortic diameters (Figs. 2-3): in healthy subjects multivariate analysis including only these factors accounted for 40-58% of the variability of aortic root dimensions [6–10,53–58] and explained 31-55% of the variance of ascending aorta diameter [6,9–11] (Table 2, SDC). "Out of proportion" aortic remodeling refers to the difference between observed and expected proximal aortic diameter, indicating the variability of aortic dimensions not explained by age, sex and body size.

3.1. Ageing

Longitudinal data inferred by the Framingham study demonstrated a progressive enlargement of aortic diameters with ageing (0.7-0.9 mm per decade) in agreement with previously reported evidences [4,7,12]. In our analysis, the great majority of studies evaluating in multivariate analysis ageing and aortic root dimensions found a significant relation (Figs. 1 and 2): ageing alone accounted for 13-19% of the variability of aortic root diameter [8,11] and for the 28-38% of such variability in ascending aorta dimensions [11].The ascending tubular tract of proximal thoracic aorta, carrying distinct histological and geometrical features from aortic root (e.g. a greater content of elastic lamellae [13]) might deserve particular attention from the ageing point of view: II level imaging studies highlighted an even more marked effect of ageing at this level [6,10,14,15].

3.2. Genetic influence, foetal programming and body development

There is an important non-syndromic genetic predisposition to aortic remodeling in general population: inheritance explains up to 26% of the variability in aortic diameter in studies based on homozygotes twins [15,16]. There could be factors with a lifelong influence

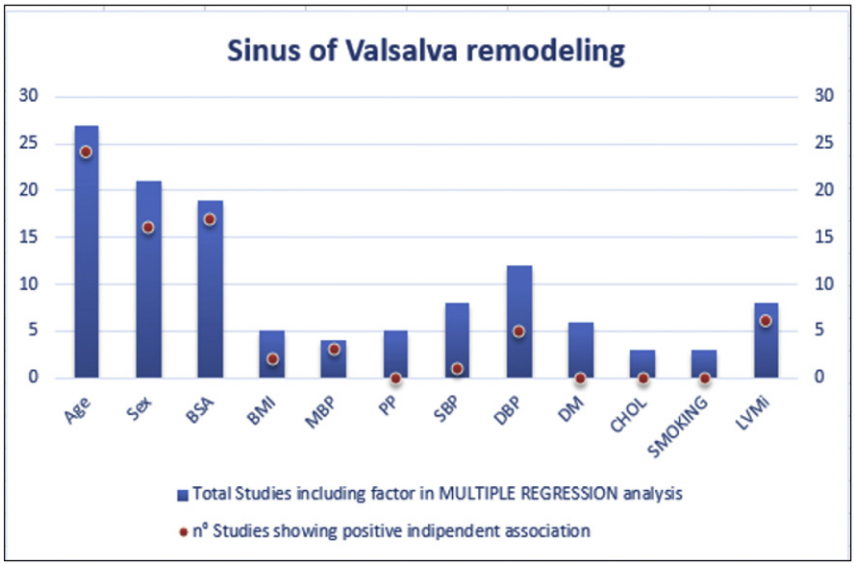

Fig. 2. The number of studies including determinant factors in multiple regression analysis (bars) and the number of studies showing positive indipendent association (red circles) beetween determinant factors and Sinus of Valsalva remodeling. BSA, Body Surface Area; BMI, Body Mass Index; MBP, Mean Blood Pressure; PP, Pulse Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; DM, diabetes mellitus; CHOL, cholesterol; LVMI, Left Ventricular Mass index.