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Editorial

Where are we with coronary artery disease for the cyanotic patient with congenital heart disease?

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We do not introduce new knowledge when saying that we currently have a growing congenital heart disease (CHD) population reaching adulthood. This statement also applies to those CHD patients presenting cyanosis. In 2006, Diller et al. reported that survival in the Eisenmenger population was significantly better than previously appreciated. They found that it was dependent on the underlying cardiac lesion, which was reflected by the fact that 50% of cyanotic patients with simple anatomy were alive at the age of 58 [1].

More recently, the group from Quebec (2011) studied their geriatric adult congenital heart disease (ACHD) cohort consisting of 3239 older adults aged over 65 and focused on mortality over a 15-year period. A minor proportion of cyanotic patients were included in the survey. They identified nine independent predictors for increased all-cause mortality: dementia, gastrointestinal bleed, chronic kidney disease, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, cancer, myocardial infarction and male sex. This highlights that in elderly patients with ACHD, acquired medical conditions have the highest impact on mortality [2].

In this regard, scientific research has recurrently revisited the prevalence of coronary artery disease (CAD) in the cyanotic congenital heart disease (cCHD) population showing a shift in trend over time. Initially, this very common life-style related disease was thought to rarely affect the cyanotic patient. The absence of coronary atherosclerosis in cyanotic adults was a striking finding in two remarkable papers in the early 20th century. First in 2005, Fyfe et al. studied a cyanotic cohort and showed atheroma-free coronaries in 59 coronary arteriograms (mean age 42 ± 4 years) and in 5 necropsy specimens [3]. Later in 2009, Giannakoulas et al. also addressed the prevalence of CAD in 250 ACHD patients, identifying a 9% burden in the overall population (mean age 51 ± 15 years). However, no cases were identified among the small proportion (7.2%) of Eisenmenger patients included in the study [4]. Conversely, when a year later the group from Toronto reported a prevalence of CAD of 1% (141 cases) among 12,124 ACHD patients, they identified 7 adults with CAD who presented Eisenmenger physiology. In this cohort, the mean age of the first CAD presentation was 56 ± 13 (overall), and 51 ± 12 in the Eisenmenger group [5]. In like manner, Tarp et al. have recently (2018) identified that among 74 cCHD patients (mean age 49.5 years), up to 21% had a coronary artery calcification (CAC) score > 0 as a marker for subclinical atherosclerosis, showing no differences when compared to matched controls (21% vs. 19%, respectively; $p = 0.8$) and therefore advocating for athero-preventive strategies to be applied to this population [6].

Perloff et al. reviewed this field in 2012 and the available studies back then. They considered that the main pathophysiological drivers for coronary artery disease present a favourable profile in the Eisenmenger patient. Firstly, histological findings in the Eisenmenger coronary arteries demonstrated loss of medial smooth muscle, increased medial collagen, and duplication of internal elastic lamina, which are reasons for their tortuosity and dilatation. Secondly, the basal flow through these vessels is increased while their potential for hyperaemia remains. This was considered to be due to higher nitric oxide (NO) and prostaglandin levels which are released in response to the increased shear-stress promoted by hyperviscosity, while reserve flow was assumed to be maintained because of the effects of NO and endothelial growth factor in the microcirculation. Additionally, they stated that hypocholesterolaemia, hypoxemia, upregulation of NO, hyperbilirubinemia, and low platelet count play an antiatherogenic role in the cyanotic setting [7].

However, the lipid profile in the adult cyanotic patient does not actually appear to be that favourable. Some previous studies found lower total-cholesterol levels in the cCHD population. However, when it comes to LDL-cholesterol, non-significant differences are seen between cyanotic and non-cyanotic individuals. More importantly, HDL-cholesterol levels are significantly decreased in cCHD patients [3,8,9]. In addition, Eisenmenger patients present increased levels of inflammatory markers which may promote the development of CAD [9].

Atherosclerosis may in fact affect other areas in addition to the coronaries. To better evaluate its impact in the Eisenmenger patient some studies have also assessed its burden at the carotid level. They used vascular ultrasound to detect plaques, stenosis and to measure carotid intima-media thickness (CIMT) as an early marker of atherosclerosis. Although Duffels et al. identified significantly lower CIMT among their 54 cyanotic patients (mean age 38, range 19–60), this has not been

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reproduced by Tarp et al. in their larger and older cohort (68 patients (56% median age: 50.0 years, range 23–78 years)). They have found that 19% of the cyanotic patients presented carotid plaques and no differences were seen in the CIMT between patients and controls [8,9].

In summary, surgical and medical advances have made possible that cCHD patients are reaching not only adulthood but also elderly years. Traditionally, it was suggested that these patients were somehow protected against atherosclerosis and therefore from CAD. However, this was based on small studies of an earlier era involving younger patients. As the cCHD population has aged and thus, older cCHD patients have become the subject of investigation, new studies have come to demonstrate that Eisenmenger patients may indeed be at the same risk of CAD as the normal population, if not more. Consequently, risk factors for atherosclerosis should be discussed and treated in a timely fashion to extend further quality of life and life expectancy in the Eisenmenger cohort.

Conflict of interest

There is no conflict of interest.

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