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Review Article

Association of Coronary Artery Disease and Abdominal Aortic Aneurysm – A Narrative Review

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Abstract

Studies have shown a strong association between coronary artery disease (CAD) and Abdominal Aortic Aneurysm (AAA). CAD is an independent predictor for developing AAA. The strong risk factors which were associated with the development of AAA were older age, male sex, hypertension, smoking, dyslipidemia, respiratory disease, cerebrovascular disease, claudication, and renal insufficiency in predicting the development of AAA. The prevalence of AAA among patients with angiography-verified CAD was higher in men. It also increased to 8.6% in men aged above 65 years. They also found that 2.5% of patients with normal coronary profile, 4.3% of patients with single vessel disease, 5.7% of patients with double vessel disease and 14.4% of patients with triple vessel disease on angiogram had AAA. The Pathological features like chronic inflammation, degradation of the extracellular matrix and apoptosis of the vascular smooth muscle cells are common to both CAD and AAA. The vascular Smooth Muscle Cell (VSMC) plays an important role in the pathogenesis of coronary artery disease and aortic aneurysms. Another mechanism identified in these VSMCs is the role of ubiquitin-like containing PHD and RING finger domains 1 (UHRF1) as the epigenetic master regulator of VSMC plasticity. Large symptomatic AAA with significant CAD, a combined procedure should be the preferred approach. Asymptomatic AAA and CAD, a staged approach of CABG followed by AAA repair within two weeks should be performed to minimize the risk of AAA rupture. A one-time ultrasound screening for AAAs in men or women 65 to 75 years of age with a history of tobacco use, in first-degree relatives of patients who present with an AAA, in men or women older than 75 years with a history of tobacco use is recommended.

Introduction

Abdominal aortic aneurysm (AAA) is defined as an abnormal permanent dilation of the abdominal aorta reaching a diameter of 3 cm or more [1]. In 2013, Li et al reported that the pooled prevalence of AAA was 4.8% with the highest in Australia (6.7%) and the lowest in Asia (0.5%) [2]. However this may not be a true reflection of the actual situation in the Asian countries as a study by Saw et al found a relatively higher prevalence of undiagnosed AAA of 1.1% [3]. It generally has a higher prevalence in males than females and appearing a decade later in women than men [4]. AAA remains asymptomatic in most people until it ruptures. The risk for rupture of the AAA varies according to the aneurysm size and it has been reported that the risk of death following rupture maybe even as high as 81% [5]. Early detection of AAA followed by its corrective repair is the best strategy currently available for preventing death due to rupture of the AAA.

Risk Factors

Multiple epidemiologic studies and meta-analyses have reported that older age, male sex, and smoking history are strong risk factors for predicting the development of AAA [2, 4-6]. Other studies have also reported atherosclerosis, coronary artery disease and hypertension can lead to the development of AAA [7]. Hernesniemi et al brought out a strong association between coronary artery disease (CAD) and AAA. They showed, using pooled data from multiple studies, that CAD was associated with a higher occurrence rate of subclinical AAA (OR: 2.38; 95% CI: 1.78-3.19). They also showed that the pooled prevalence of AAA among patients with angiography-verified CAD was also higher in men [8].

Durieux et al found that 4.2% of patients undergoing a coronary angiogram had an AAA. This prevalence increased to 8.6% in men aged above 65 years. They also found that 2.5% of patients with normal coronary profile, 4.3% of patients with single vessel disease, 5.7% of patients with double vessel disease and 14.4% of patients with triple vessel disease on angiogram had AAA. By multivariate analysis, they found that CAD was an independent risk factor for AAA ($p < .0001$), but the association with AAA was only statistically significant for the three-vessel disease subgroup ($p < .001$, OR = 10.5; 95% CI: 2.72 - 40.1) [9]. A meta-analysis by Altobelli et al used data from 5 studies to report that CAD lead to an increase in the development of AAA, OR = 2.29 (95% CI: 1.75 – 3.01), $p < 0.0001$ [10].

Li et al reported a varying profile of risk factors for AAA from different regions. In Europe, the risk factors were hypertension, smoking, coronary artery disease, dyslipidemia, respiratory disease, cerebrovascular disease, claudication, and renal insufficiency. In America, the risk factors were smoking and coronary artery disease while in Australia, smoking, diabetes mellitus, coronary artery disease, dyslipidemia and respiratory disease were the risk factors for AAA. In Asia, however, only hypertension and smoking were found to be risk factors for AAA [2]. In a study from the Middle East, only 0.5% of patients were found to have AAA. 36% of patients with AAA also had CAD. They were generally older males with multiple other risk factors also.

In addition there was a higher mortality among persons with CAD and AAA when compared to persons with AAA but not CAD (47% vs 26%) [11]. In a study from Malaysia, the prevalence of undiagnosed AAA was 1.1% (95% CI 0.2–3.1). In patients with high-risk CAD, (defined as three vessels with ≥ 70% stenosis or two vessels with ≥ 70% stenosis including the proximal left anterior descending artery, or stenosis of ≥ 50% in the left main artery), the prevalence of undiagnosed AAA was 1.7% (95% CI 0.3–4.8). he studies also found that in patients having significant CAD, the prevalence of sub aneurysmal aortic dilatation (2.5 – 2.9 cm) was higher at 6.6% (95% CI 3.9 – 10.2). Most of the patients were younger than 65 years suggesting the need for earlier screening in Asian populations [3]. The variations in the prevalence of the AAA and the associated risk factors can also be sometimes attributed to a variation in the definition of AAA among various studies.

In a case control study conducted in 2008 among 1714 patients (899 patients with AAA and 815 controls), the lead single-nucleotide polymorphism, rs1333049, on chromosome 9p21 was genotyped. The frequency of the C (risk) allele of rs1333049 in their control group was found to be 0.471 and there was a significant association between the C allele and AAA (odds ratio, 1.22; 95% confidence interval, 1.06 to 1.39; P=0.004) [12]. This locus was identified in previous studies as a strong factor for the genetic predisposition of coronary artery disease [13-15].

Pathogenesis

Atherosclerosis and aortic aneurysms share similar risk factors. Pathological features like chronic inflammation, degradation of the extracellular matrix and apoptosis of the vascular smooth muscle cells are common to both the processes [16, 17]. However there exist certain differences that might suggest the role of other factors in the pathogenesis of both the diseases. For example, diabetes mellitus is known to increase the risk of atherosclerosis but has been experimentally proven to protect from aortic aneurysms [18, 19]. This has been postulated to be due to the protective effect of hyperglycemia on degradation of the tunica media [20]. This is further highlighted by the fact that in a study by Shathikumar et al, the prevalence of diabetes in patients with AAA was only 6%–14% while in control patients without AAA, prevalence of diabetes was higher at 17% to 36% [21].

At a cellular level, the vascular Smooth Muscle Cell (VSMC) plays an important role in the pathogenesis of coronary artery disease and aortic aneurysms. α-smooth muscle actin (SMA), encoded by the acyl-coenzyme A (CoA): cholesterol acyltransferase 2 (ACTA2) gene, is an isoform of smooth muscle cells (SMCs), typically expressed in VSMC. Mutations of the ACTA2 gene have been demonstrated in aortic aneurysms and dissections and coronary artery diseases [22]. In a normal individual, VSMCs of the aorta demonstrate a well-differentiated, contractile state; in atherosclerosis, the VSMCs expressed increased amount of the α-smooth muscle actin (SMA) indicating a shift toward the synthetic phenotype leading to a narrowing in the lumen. In patients with aortic aneurysms, VSMCs expressed decreased amount of the α-smooth muscle actin (SMA) indicating a severe SMC degeneration or a switch between the contractile and synthetic phenotype of SMCs, which may be even beneficial because of the production of an extracellular matrix that is necessary for healing of the vascular wall [23].

Another mechanism identified in these VSMCs is the role of ubiquitin-like containing PHD and RING finger domains 1 (UHRF1) as the epigenetic master regulator of VSMC plasticity. It is usually not expressed much in normal cells but is expressed more in damaged vascular cells. It causes the VSMCs to dedifferentiate in response to extracellular cues such as vascular damage and inflammation. Dedifferentiated VSMCs are proliferative, migratory, less contractile, and can contribute to vascular repair as well as to cardiovascular pathologies such as intimal hyperplasia/restenosis in coronary artery and arterial aneurysm. Elia et al demonstrated the role of UHRF 1 in VSMC proliferation [24].

Allara et al conducted a systematic investigation of causal relationships between circulating lipids and cardiovascular outcomes using a Mendelian randomization approach. They evaluated the effect of lipid and triglyceride lowering on non-coronary cardiovascular diseases. From a meta-analysis of 188 577 participants, and genetic associations with cardiovascular outcomes from 367 703 participants (Global Lipids Genetics Consortium), they found independent associations of genetically predicted LDL-cholesterol with abdominal aortic aneurysm (OR, 1.75 [95% CI, 1.40–2.17]). This demonstrated the possible benefit of lipid lowering on the reduction of abdominal aortic aneurysm in addition to the lowering of atherosclerosis linked CAD [25].

Screening

The 2019 US Preventive Services Task Force Recommendation statement on screening for Abdominal Aortic Aneurysm suggested routine screening by ultrasound for men aged 65 – 75 years who have smoked and a selective screening in men aged 65 – 75 years who have not smoked. It did not recommend routine screening in women [26, 27]. The American College of Cardiology and the American Heart Association recommended a one-time screening for AAA with physical examination and ultrasonography in men aged 65 to 75 years who have ever smoked or in men 60 years or older who are the sibling or offspring of a person with AAA. They do not recommend screening in men who have never smoked or in women [28]. The Society for Vascular Surgery recommends a one-time ultrasound screening for AAAs in men or women 65 to 75 years of age with a history of tobacco use, in first-degree relatives of patients who present with an AAA, in men or women older than 75 years with a history of tobacco use and in otherwise good health who have not previously received a screening ultrasound examination [29]. However more studies from Asian countries and Latin American countries may be needed to provide more country specific recommendations and treatment guidelines.

Treatment

Coronary artery disease is a major cause of morbidity and mortality among patients undergoing repair of an abdominal aortic aneurysm. In patients with a large symptomatic AAA with significant CAD, a combined procedure should be the preferred approach. Concomitant repair in patients with impaired left ventricular and pulmonary function is better because survival after two separate procedures is less certain than after a single procedure. In patients who have asymptomatic AAA and CAD, a staged approach of CABG followed by AAA repair within two weeks should be performed to minimize the risk of AAA rupture. In all patients who are suitable for minimally invasive procedures like PCI and Endovascular Aneurysmal Repair, these procedures can be used. [28, 29]. In a meta-analysis done by Takagi et al, it was found that statin therapy reduced the rate of growth of AAAs, especially when their size is above 3.5cm [30].

Another meta-analysis showed the long-term outcome benefit of stain therapy in patients with AAA without any significant impact on peri operative mortality [31]. This was also observed in another study done by Liao et al [32]. This benefit is derived due to the reduction in the inflammatory markers and the levels of the matrix metalloproteinases [33]. The studies on role of antibiotic therapies and ACE inhibitors in medical management of AAA have not yielded much benefit [34]. The only randomized trial in patients with AAA using propranolol was stopped early due to the unfavorable outcomes [35].

Conclusion

CAD is associated with increased risk of subclinical AAA and in developing AAA-related adverse events in the future. The risk estimate seems to depend on the diagnostic criteria of the coronary disease and population characteristics. Among angiography-verified CAD patients, the prevalence of AAA is consistently high, and the prevalence is higher among patients with more severe CAD. Screening with ultrasound among CAD patients especially in patients with risk factors could possibly benefit survival and in predicting the risk of adverse events. Despite advances in reduction in risk factors for coronary artery disease, the prevalence of AAA has not decreased by much. This probably indicates the need for further research in this area.

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