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Review Article

The height as an independent risk factor of atrial fibrillation: A review

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ABSTRACT

Atrial fibrillation (AF) is characterized by abnormal heart rhythm. Among other well-known associations, recent studies suggest an association of AF with height. Height is related to 50 diseases spanning different body systems, AF is one of them. Since AF, a heterogeneous disease process, is influenced by structural, neural, electrical, and hemodynamic factors, height alters this process through its contribution to increasing atrial and ventricular size, leading to altered conduction patterns, autonomic dysregulation, and development of AF. Multiple underlying mechanisms associate height with AF. Apart from these indirect mechanisms, genome-wide association studies suggest the involvement of the same genes in AF and growth pathways. Tall stature is independently associated with a higher risk of AF development in healthy individuals. Since adult height is achieved much earlier than the onset of AF, protective measures can be taken in individuals with increased height to monitor, manage, and prevent the progression of AF.

1. Introduction

Atrial fibrillation (AF), a major form of supraventricular tachycardia (SVT), is characterized by an abnormally rapid and irregular heart rhythm due to electrical disruption in the atria of the heart. It is the most common cardiac arrhythmia that comes across in routine clinical practice. AF can be classified into various types. One of such classification classifies AF into three main types: paroxysmal, persistent, and permanent. Paroxysmal AF usually self-resolves within 24 h and in some cases may last up to a week. On the other hand, persistent and permanent types of AF last for more than a week and require medical treatment to reset heart rate and rhythm back to normal.[1] Atrial remodeling, caused by preexisting heart disease or altered function and/or expression of cardiac ion channels, leads to the advancement of AF from paroxysmal to persistent to permanent form.[1] AF is the most common type of sustained arrhythmia which has a marked effect on the morbidity and mortality of older adults.[2,3] With a global prevalence of 33 million, as reported by AFGen Consortium, AF is the leading cause of a stroke as well as a risk factor of heart failure and dementia.[4]

The prevalence of AF is on the rise due to an aging population and has been projected to increase 2.5-fold in the next 50 years.[5] Often regarded as a nongenetic disease due to its strong relationship to age, recent studies suggest that a positive family history of AF has also been discovered in 5% of all patients with AF and 15% of patients with idiopathic AF, indicating the presence of a genetic component.[2] Among well-known associations with cardiac and extracardiac diseases such as hypertension (HTN), valvular heart diseases, and hyperthyroidism, recent studies suggest an association of AF with height, with height being an individual risk factor of AF in older adults, European and Chinese patients, and those with left ventricular failure.[3,6]

One study explored the relationship of adult height with 50 diseases spanning different systems of the body, such as gastroesophageal reflux disease (GERD), diaphragmatic hernia, AF, venous thromboembolism (VTE), and intervertebral disc disorder, using epidemiological (increase in height) and genetic (genetically determined height) approaches. This study found out the inverse epidemiological associations of increased height with stroke, HTN, peripheral vascular disease (PVD), aortic stenosis (AS), coronary artery disease (CAD), and heart failure (HF), whilst analysis of genetics showed an inverse association for CAD and HTN only. On contrary to these inverse association, taller height was directly linked with increased risk of VTE and AF in both genetic and epidemiological analyses, the latter proving un-confounded associations and possible underlying mechanisms.[7] Height has a life-

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long effect in the development of AF as final adult height is attained long before AF is likely to develop.[8,9]

This article focuses on how variability in height of a person and the possible underlying mechanisms, linking height with AF, can contribute to the development of AF and thus be regarded as an independent risk factor of it.

2. Height and atrial fibrillation: is there a direct correlation?

While height has been considered an individual, non-modifiable risk factor of AF, it rarely has been the focus of the studies. The whole rationale of the previous studies and this review is to acknowledge and identify the parameter of height as a new risk factor, segregate individuals that may be at a higher risk of AF than others, and by such an identification plan, implement an intervention that will reduce the burden, morbidity, and complications associated with AF.[2,3,6–10]

Studies carried out to assess the relationship of height and its impact on AF have implicated that mean height in prevalent cases of AF was higher in comparison with participants free from it and taller height was an individual risk factor of AF in healthy individuals, independent of sex.[2,5] One of those conducted from 1972-1995, on Swedish men, with no history of cardiovascular diseases, with a median age of 18.2, observed a strong positive association of AF with taller height. This association was attenuated with adjusting weight to it, which also showed an individual increased risk of AF but to a much lesser extent than height. In comparison to the above-mentioned study which only included men, another study of Sweden included 1,522,329 women with a mean age of 28.3 years, found the same association of height with AF, further eliminating the sex predilection.[11,12] A cohort done in the United States of America analyzed older adults and came to the same conclusion that in both genders, the increase in height was similarly associated with increased AF risk.[6]

A large Korean cohort study which analyzed data from the Korean National Health Insurance Service–National Sample Cohort (NHIS–NSC) from 2002 to 2015 included over 300,000 individuals that had a medical check-up between 2006 and 2009 while excluding those who were diagnosed before 2006 and those with other valvular and vascular diseases. They performed the multivariate statistical analysis and after adjusting data for the various confounders still found that an increment of 5 cm in height increased the risk of AF 1.22 times.[13] Schmidt and associates conducted a 36-year cohort study for men born between 1955 and 1965 by obtaining data from the Danish National patient registry, started follow-up of patients from their 22nd birthday from 1977 to an eventual outcome of either death, emigration, or till the 21st December 2012. They correlated height with various variables including myocardial infarction, heart failure, angina pectoris, and AF and found that tall people had a higher risk for AF than people with a shorter stature.[14]

One possible explanation found in these studies, relate cardiac output and stroke volume with increased height, weight, body mass index (BMI), and body surface area, and suggested that higher volume output could mediate and enhance the risk of developing AF. This explanation is congruous with multiple studies that observed a higher risk of AF amongst high endurance athletes that also have a high-volume load because of excessive training.[12] While being a risk factor for ischemic heart disease and premature death, shorter height was found to be a protective factor for people suffering from AF.[14] A study conducted in Copenhagen, in which four cross-sectional examinations were carried out from the year 1976 till 2003 and included a total of 18,852 people who did not have AF at the start of the study, concluded that with each 10 cm difference in height, risk of AF increased by 35–65%, with males gaining an average 3.3 cm height and females 2.1 cm between initial and the final examination, yielding an 11–18% and 6–11% rise in the risk of AF incidence in males and females, respectively.[9] The hazard ratio (HR) between AF and height as reported by Rosenberg MA *et al* for women per 10 cm was 1.32 [confidence interval 1.16–1.50, $P < 0.0001$); and in men per 10 cm was 1.26 (Confidence interval 1.11–1.44, $P < 0.0001$].[6] This is supported by various experimental and observational studies in animals that suggested the relationship between the total size of their body and the development of AF. Larger animals such as horses have a higher prevalence of AF than smaller animals like swine, and much higher than mice, in which, it is impossible to induce AF.[3,8] This is likely due to decreased left atrial (LA) size in smaller animals.[8]

3. Increasing height alters atrial dimensions and conduction pathways: a possible mechanism for developing atrial fibrillation

Studies suggest a direct correlation of height with atria and ventricular size, making them important parameters for the increased risk of AF due to height.[6,10] This correlation was confirmed by a study which reviewed echocardiographic data of patients and suggested that the population whose height was greater than the median by gender, detected larger mean LA diameter. This applies to both males and females.[8] Another study used regression analysis to invent height- and sex-specific reference limit for LA size and other cardiac M-mode measurements in a reference sample and then classifying those measurements according to increasing deviation from the sex- and height-specific reference limits and 95th, 98th, and 99th percentile values for the broad sample, which was then used to study relation, between different cardiovascular diseases and those measurements. It proposed that an increase of 1.6 fold in the incidence of AF was associated with an increase in the category of LA size.[15] Rosenberg MA *et al* found no difference in the association of height and AF in either gender. Furthermore, either sex was not a predictor of the incidence of AF. LA size, which is commonly thought to be the primary mediator of height-induced AF, was not significantly associated with height and did not change the HR significantly for the association of height with AF.[6]

AF is a diverse disease process that is governed by structural, neural, electrical, and hemodynamic factors. Height alters this mechanism through its participation in increasing atria and ventricular size leading to abnormal conduction patterns, autonomic dysregulation, and development of AF.[1,10] In the pursuit of finding more pathophysiological relations between height and AF, Kofler T *et al*, measured genetically determined height with abnormal electrophysiology of heart in young and healthy individuals. They calculated that an escalation of 4.33 m/s in the PR interval and 2.57 m/s in QRS duration was affiliated with an enlargement of 10 cm in genetically determined height. However, this calculation was not linked to the QTc interval. These findings emphasize a different pathway other than increased LA dimensions that could potentially open a new understanding of increased height with electrophysiological dysfunction of the heart.[16] From these parameters, the PR interval can be defined as the time needed to conduct electrical impulses from the sinoatrial node to the atrioventricular node, and its prolongation has been related to the remodeling of atria and thus with an increased incidence of AF.[17] One of the new predictors of new-onset AF was demonstrated by a meta-analysis study. They observed that individuals who have frequent premature atrial contractions recorded by Holter monitoring or 12-lead electrocardiogram were at a 3-fold greater risk of new-onset AF than individuals without premature atrial contractions. To identify the determinants of premature atrial contractions

(PACs) that would eventually lead to AFs, a fascinating study was recently published which claimed that a taller height and increasing age were one of the positive determinants of PACs explaining yet another linkage between taller height and AF.[18,19] From different complications of AF, the most feared one is an ischemic stroke which renders the patient in lifetime rehabilitation, so early diagnosis and treatment of silent AF could potentially be lifesaving to patients. To make it clinically relevant, a group of researchers evaluated intra atrial conduction time, that has been proven to be linked with silent AFs using transthoracic echocardiographs, by dividing the sample size into two groups, one with a normal population and the other one with ischemic stroke. After comparing these groups and adjusting confounding variables, they found out that the group with ischemic stroke patients had increased LA size, increased height, and increased intra atrial conduction time than the normal population, providing a simple and non-invasive technique for clinicians to adopt and treat silent AFs.[20] Increase left atrial size is an established risk factor for AF development and various studies have found a positive correlation between LA size and AF. However, the process of measuring and reporting atrial size with adjustment for body size has been less straight forward.[21–23]

4. Genetic pathway linking height and atrial fibrillation

As it is a well-known fact that South Asians have a higher prevalence of cardiac and extracardiac diseases such as HTN, CAD, and diabetes mellitus (DM), they interestingly have a decrease incidence of AF.[24,25] In conquest to find out the underlying mechanism behind it, a comparative study among 200 healthy volunteers of South Asian and Caucasians aged 18–40 years was published in 2019 which observed that South Asians had a lean body mass and were of smaller height as compared to Caucasians, which corresponds to small atrial size resulting in reduced P wave dispersion and a lower burden of supraventricular ectopy. These findings may explain the less incidence rate of AF among South Asians despite having an increased prevalence of known AF risk factors.[25] In the middle-aged population, the pathogenesis of AF is driven by a direct relationship of LA and ventricular size with lean body mass, this, however in the elderly population, is driven by the relationship to body height than lean body mass per se.[26,27] However, these relations contribute minor risk attributable to height, suggesting other possible underlying mechanisms for height-mediated increased AF risk.[6] One such mechanism was derived in the results from genome-wide association studies (GWAS), which suggests an involvement of similar genes in AF, naming the pituitary homeobox 2 gene (PITX2) and the zinc-finger homeobox 3 gene (ZFHX3), as involved in the growth pathways.[2,6] *Pitx2* is a developmental left-right asymmetric (LRA) homeobox gene that positively regulates micro RNAs to repress the sinoatrial node genetic program, and if deficient or inactivated, predispose mice to different arrhythmias that increases the risk for developing AF in humans.[28] This is partly due to loss of function of *Pitx2c*, an isoform of the *Pitx2* homeobox gene, which promotes ectopic automaticity in left atria by *Shox2*-mediated mechanism, leading to increased susceptibility of developing AF.[29] A study conducted to show the linkage between the *Pitx2* homeobox gene and AF in humans identified that levels of *Pitx2c* were significantly decreased in patients with sustained AF.[30] In the hope to understand more about the importance of the genetic pathway between height and AF, Yuliya mints and colleagues demonstrated common allele variation near the *Pitx2* locus on chromosome 4q25 and its association with increased LA volume (LAV) in AF patient. They found that homozygous polymorphism at the T allele at SNP rs10033464, but not rs2200733, near the *Pitx2* locus on chromosome 4q25, is correspondent with higher LAV and this correspondence was unrelated to left ventricular ejection fraction and AF duration.[31] As for height, *Pitx2* deletion in thyrotropes of mice leads to mild growth reduction which can be due to low growth hormone secretion, as growth hormone transcription is regulated by thyroid hormones.[32] This, however, is an unlikely mechanism, and studies must be conducted to show how the involvement of *Pitx2* homeobox gene alters height.[32] *Pitx2* also regulates the activity of several growth pathway genes including *Cyclin D1*, *Cyclin D2,* and *c-MYC*, in response to *WNT/B-catenin* induced pathway.[33] Another example suggesting the role of *Pitx2* in growth pathways comes from a study conducted on mice to see the contribution of *Pitx1* and *Pitx2* genes in the development of hindlimb buds. It was suggested that both *Pitx1* and *Pitx2* homeobox genes are required for sustained hindlimb bud growth and formation of hindlimbs, although *Pitx2* is not expressed in limb bud mesenchyme itself.[34]

Research targeted a new avenue of relating height with AF. This time maternal height was considered as a risk factor for the increased risk of developing AF in offspring later in life. Also included in this study were other early factors of life such as socioeconomic status, placental size, and body size at birth. Early-onset AF (<65.3 years) among offsprings were related to taller maternal height. However, it was not allied with later onset AF. These outcomes were dissociated with the incidenceof CAD, HTN, and/or DM. Perhaps, this relation could be described by the aforementioned genetic pathways as maternal height genes are transferred to the offspring, but also indicate maternal lifelong nutrition linking a common pathway between maternal height and offspring AF.[35]

5. Increasing height: a dilemma for future generations

According to an epidemiological survey of over 100 years, adult height is stagnating or declining in developing countries especially in Africa, but people of developed countries have been observed to have increased height than their previous generations. This finding can be explained by better nutrition, higher socioeconomic status, and less disease prevalence than poor countries.[20] Taking consideration of this fact, we can predict that in near future more people will likely be taller as countries and non-profited organizations such as United Nations are working toward eradicating poverty and developing more advanced health care systems which would also increase the incidence of AF.

It is now imperative for researchers to further understand this correlation, its underlying mechanisms, and to develop screening parameters for taller people to prevent and manage AF and its complications before its occurrence. In a series of possible mechanisms, one study suggested an area of exploration, associating height with the anatomy of the pulmonary vein, as it is a well-known fact that pulmonary veins are a major trigger of AF and a target of therapy.[2]

As discussed throughout this review, to the best of our knowledge all those researches on this association showed a positive correlation and none have discussed or indicated a negative one. Further work must be done to clearly and directly link height with AF.

6. Conclusion

Tall stature is a nonmodifiable risk factor of AF in healthy individuals, independent of sex. Multiple underlying mechanisms such as increased atrial size, volume overload, and abnormal electrical conduction in cardiac tissue associate height with AF. Apart from these indirect mechanisms, GWAS suggests the involvement of identical genes in AF as involved in the growth pathways, but this remains a focus of interest for future researches. Since adult height is achieved much earlier than the onset of AF,

and itself is nonmodifiable, its clinical utility is limited to protective measures that can be taken in individuals with increased height to monitor, manage, and prevent the progression of AF.

Declaration of competing interest

The authors have no financial or proprietary interest in the subject matter of this article.

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