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Non-Coronary Artery Disease Scarring: Could it Serve as a Possible Biomarker for Atrial Fibrillation?

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Abstract

Background: In a series of patients with cerebrovascular disease, delayed enhancement cardiac magnetic resonance (DE-CMR) detected non-coronary artery disease (non-CAD) scarring in 15.3% of stroke patients and 4.8% in TIA patients [1]. One hypothesis for this trend was that high incidence of non-CAD scarring may be a result of small microemboli and a biomarker for atrial fibrillation [2]. If validated as a biomarker for non- CAD scarring, earlier diagnosis and treatment could potentially decrease the number of cryptogenic embolic strokes through earlier anticoagulation therapy and decrease the economic burden of stroke-related treatment and healthcare costs [3,4].

Methods: EPIC Slicer dicer was utilized to search for "stroke" and cardiac MRI". 87 patients' medical records were accessed in order to obtain information regarding the factors stated previously, the presence of atrial fibrillation, and cMRI results. Patients' medical histories were evaluated to see if there was an association between non-CAD scarring and atrial fibrillation. Factors such as gender, smoking, alcohol consumption, diabetes, hypertension, hyperlipidemia, renal disease, history of myocardial infarction (MI), seizures, and race was also analyzed to see if these factors had any effect on the prevalence of non-CAD scarring and atrial fibrillation.

Results: Large differences in the occurrences of non-CAD and CAD scarring were seen with gender, smoking, diabetes, hypertension, hyperlipidemia, renal disease, history of MI, and seizures in patients with no documented atrial fibrillation. There were more non-CAD and CAD scarring males with no atrial fibrillation compared to females and more non-CAD and CAD scarring occurrences when smoking, diabetes, or hypertension was present with no atrial fibrillation. Non-CAD and CAD scarring occurrences with no atrial fibrillation were more prevalent in the absence of renal disease, history of MI, and seizures; these trends with renal disease and seizures were unexpected.

Conclusion: Even though trends were observed with the various factors, scarring, and the presence or absence of atrial fibrillation, our study found no statistically significant evidence that suggests certain factors impact non-CAD or CAD scarring with and without atrial fibrillation. In this patient sample, we saw no association between non-CAD scarring and atrial fibrillation. Future studies could be conducted to explore the unexpected scarring trend seen with no renal disease or seizures present.

Keywords: Non-Coronary Artery Disease, EPIC Slicer dicer, Atrial Fibrillation, cMRI.

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Introduction

In 2013, approximately 6.5 million people worldwide died due to stroke, making stroke the fifth ranked global cause of death [3]. Several risk factors for stroke include Atrial Fibrillation (AF), hypertension, hyperlipidemia, smoking, and diabetes [5]. In addition to stroke, 17.3 million people worldwide died due to cardiovascular disease (CVD) [3]. Common outcomes of CVD include atrial fibrillation, heart failure, chronic kidney disease, and coronary artery disease (CAD), which can develop due to factors such as hypertension, dyslipidemia, smoking, or diabetes [6,7]. The number of stroke and CVD deaths per year continue to remain high as the prevalence of stroke risk factors and CVD related health issues continue to increase, especially atrial fibrillation [3,6]. Atrial fibrillation is the most common arrhythmia and increases the risk of stroke by five [8]. Detection rate of atrial fibrillation remains low with 0-25% of incidences detected by techniques such as in-hospital monitoring, Insertable Cardiac Monitors (ICMs), Serial Electrocardiography (ECG), and cardiac magnetic resonance imaging (cMRI) [2,4]. An effective biomarker is needed to increase the detection rate of atrial fibrillation and lead to earlier treatment and primary or recurrent stroke prevention. Unfortunately, nearly a third of patients who present with embolic strokes of unknown source are discharged on antiplatelet therapy, which is an ineffective regimen for paroxysmal AF.

A possible biomarker could be discovered using cMRI, an imaging technique that can detect cardiac pathologies such as heart arrhythmia and myocardial scarring - scar tissue that forms when muscular tissue of the heart dies due to myocardial infarction [2,9]. cMRI could be used to discover a possible biomarker of AF due to findings from a recently published 2014 study. Of 85 ischemic stroke and 21 Transient Ischemic Attack (TIA) patients in this study, non-CAD scarring was detected in 15.3% and 4.8% in stroke and TIA patients, respectively [2]. Since non-CAD scarring was approximately 3 times more prevalent in stroke patients than TIA patients, non-CAD scarring could possibly be linked to ischemic stroke [2]. Thus, non-CAD scarring could be a biomarker for atrial fibrillation, a risk factor for stroke and CVD. If non-CAD scarring is found to be a strong predictor for underlying atrial fibrillation, this would decrease the risk of stroke, the number of global stroke deaths per year, and the amount of money spent on stroke related healthcare [3,10].

Methods

EPIC Slicer dicer was utilized to search for “stroke” and “cardiac MRI” which gave yield to 87 patients. Each patient’s medical records were accessed in order to examine the studied factors (gender, smoking, alcohol consumption, diabetes, hypertension, hyperlipidemia, renal disease, history of Myocardial Infarction (MI), seizures, and race), the presence of atrial fibrillation, and cMRI results. CMRI results were analyzed to determine if the patient had CAD scarring, non-CAD scarring, or no scarring at all. Once data was gathered from all 87 patients, the following bar graphs were developed: occurrences of CAD scarring with and without atrial fibrillation in males and females, occurrences of non-CAD scarring with and without atrial fibrillation in males and females, occurrences of CAD scarring with and without atrial fibrillation in current and former smokers, occurrences of non-CAD scarring with and without atrial fibrillation in current and former smokers, occurrences of CAD scarring with and without atrial fibrillation in drinkers and non-drinkers, occurrences of non-CAD scarring with and without atrial fibrillation in drinkers and non-drinkers, occurrences of CAD scarring with and without atrial fibrillation in diabetics and non-diabetics, occurrences of non-CAD scarring with and without atrial fibrillation in diabetics and non-diabetics, occurrences of CAD scarring with and without atrial fibrillation in patients with and without hypertension, occurrences of non-CAD scarring with and without atrial fibrillation in patients with and without hypertension, occurrences of CAD scarring with and without atrial fibrillation in patients with and without hyperlipidemia, occurrences of non-CAD scarring with and without atrial fibrillation in patients with and without hyperlipidemia, occurrences of CAD scarring with and without atrial fibrillation in patients with and without renal disease, occurrences of non-CAD scarring with and without atrial fibrillation in patients with and without renal disease, occurrences of CAD scarring with and without atrial fibrillation in patients with and without history of MI, occurrences of non-CAD scarring with and without atrial fibrillation in patients with and without history of MI, occurrences of CAD scarring in patients with and without seizures, occurrences of non-CAD scarring in patients with and without seizures, occurrences of CAD scarring with and without atrial fibrillation in patients of white, African American, and Asian race, and occurrences of non-CAD scarring with and without atrial fibrillation in patients of white, African American, and Asian race. All data was then sent for statistical analysis to determine if any trends between the various bar graphs were statistically significant.

Results

From all 87 patients and 43 scarring occurrences, there was approximately double the percentage of CAD scarring occurrences with atrial fibrillation than non-CAD scarring occurrences with atrial fibrillation. The largest differences in scarring occurrences and similar patterned graphs were seen in factors with no atrial fibrillation. In our cohort, we noted a few trends with gender, race, diet, renal dysfunction, seizures and smoking when compared with scarring and CVD. In looking through the literature, there are a number of studies that have sought to try to explain the generally observed trends. The non-CAD and CAD scarring graphs for gender with no atrial fibrillation revealed that there were more males with scarring than females. The scarring trend observed in males is likely from differences in baseline risks. A 10-year study conducted in the US consisting of 1840 participants with no CVD discovered that 12.9% of men had myocardial scarring whereas the prevalence of scarring in women was 2.5% [11]. In yet another study of 1527 patients aged 20 years or older, fewer women had hypertension, more women had low triglycerides and higher HDL, and women were less likely to smoke [12]. These

disproportionate baseline factors could explain the trend observed in males that place them at a higher risk for CVD along with increasing their risk for developing CAD, which could potentially explain the higher CAD scarring in men. It is important to note, however, that this study also makes note that of all women, mostly non-Latino black women had a higher risk of hypertension and diabetes when compared with non-Latino white women, non-Latino white men, and non-Latino black men [12]. Considering that approximately 8 of the 36 females in our cohort are non-Latino black women and 25% of these women have CAD scarring, the trend might have shown a higher scarring occurrence with no atrial fibrillation for men than women due to the rather unequal proportion of non-Latino white women and non-Latino black women. If the proportion of non-Latino white women and non-Latino black women were approximately equal, the difference between scarring occurrences with no atrial fibrillation for men and women might have been smaller. The trend observed for gender in this study could have also been affected by depression. One study that analyzed the effect of depression on CVD risk factors discovered that women who were depressed had higher incidences of insulin resistance, low high-density lipoprotein (HDL), and high low-density lipoprotein (LDL) compared to women who were not depressed. This trend held true for men who were depressed who also had an increased likelihood of having hypertension and smoking compared to men who were not depressed [13]. Thus, if there were more depressed men than depressed women in our study, there is a possibility that the chances of developing CAD could have been higher. This in turn could have had an influence on the scarring trend.

Furthermore, a recent study looking at diet trends indicated that vegetable variety could affect CAD [14]. This study that included 38,981 adults showed that there was an inverse relationship between vegetable variety and the prevalence of CAD [2]. The study also revealed that smokers did not tend to eat vegetables of a wide variety [2]. Thus, the high scarring trend seen with smokers could potentially have been affected by vegetable variety. Yet another study looking at diet trends conducted in Western India found a higher prevalence of CVD risk factors when they skipped breakfast [15]. Those that skipped breakfast had the highest odds of developing diabetes, followed by hypertension and smoking as a habit [15]. Although certainly a stretch, it is possible that if the people in our study skipped breakfast on a regular basis, then they could have had a higher chance of developing CVD, then CAD, and possibly CAD scarring; this would have impacted the high scarring trend seen with smokers compared to former smokers, diabetics compared to non-diabetics, and people with hypertension compared to people without hypertension. The trend in the CAD scarring with no atrial fibrillation graph for hyperlipidemia could also have been affected by the depression study that could have impacted the gender-scarring trend. Since high cholesterol is a CVD risk factor, if there was a large number of depressed women in the current study, they could have had low HDL and high LDL, which might have increased their chance of developing CAD, as well as CAD scarring [3,13].

Both the non-CAD and CAD scarring graphs for smoking, diabetes, and hypertension with no atrial fibrillation had larger scarring occurrences when the factor was present. The scarring graphs for hyperlipidemia with no atrial fibrillation partially exhibited the same trend as the smoking, diabetes, and hypertension graphs. The CAD scarring graph of hyperlipidemia with no atrial fibrillation showed that there was more CAD scarring occurrences with the factor present. However, the non-CAD scarring graph of hyperlipidemia with no atrial fibrillation showed that there was an equal number of occurrences when the factor was present and absent.

For the patients with renal disease, history of MI, and seizures without atrial fibrillation, the occurrences of both non-CAD and CAD scarring were higher when the factor was not present; this is the opposite trend seen with those patient's hat have history of smoking, diabetes, and hypertension. Several past studies do not appear to support the trend observed with both the non-CAD and CAD scarring graphs with no atrial fibrillation for renal disease. A retrospective study involving 491 adults from the United Arab Emirates (UAE) discovered that men and women with chronic kidney disease stages 3-5 also had diabetes, hypertension, dyslipidemia, as well as another CVD risk factors [1]. Since this study indicated that there may be an association with chronic kidney disease stages 3-5 and several CVD risk factors, one would predict that there were would be more instances of CAD and CAD scarring for people with chronic kidney disease stages 3-5 compared to those with no kidney disease. Interestingly, within our study population, we found a higher incidence of CAD scarring in people with no renal disease. Moreover, another study investigating CAD in renal transplant recipients discovered that CAD was most severe in people on chronic dialysis, followed by renal transplant patients, and lastly people without existing renal impairment [16]. One could, based on prior studies, theorize that there would be less CAD scarring instances with those who have no chronic kidney disease. Again, surprisingly, this was not observed with the renal disease CAD scarring graph in patients without atrial fibrillation. Our study certainly has limitations, and sampling bias could have also impacted the scarring trend. Patients with renal disease of a certain severity are not able to have cMRI's performed, thus, this study likely could have excluded a large amount of people who could have had CAD or non-CAD scarring.

Similarly, to what we found in patients with renal disease, patients with history of seizure with non-CAD and CAD scarring, but without atrial fibrillation had the opposite trend of what is reported in recent studies. One study, consisting of 677 patients with seizures, found that 3.4% of these patients had diffusion hyperintense lesions (DHLs) in the perforating arteries [17]. These patients also had a higher likelihood of developing possible outcomes of CVD, specifically atrial fibrillation and CAD, than patients without DHLs [17]. Since this study indicates that there might be an association between DHLs and two specific possible outcomes of CVD, patients in our study who had seizures may not have had DHLs and CAD. This in turn could have impacted the low

occurrences of CAD scarring in patients without atrial fibrillation in those with a history of seizures. Finally, as for the expected low number of scarring occurrences in those without history of MI and atrial fibrillation, a similar trend was observed in our cohort. We were not surprised given that myocardial scarring generally forms when cardiac muscle cells die in the setting of ischemia as seen with myocardial infarction [12].

Discussion

Although our results suggest that the presence of certain factors could be related to CAD or non-CAD scarring and not having atrial fibrillation, we found no statistical significance between atrial fibrillation in direct relationship with CAD scarring. Additionally, our cohort failed to find a link between non-CAD scarring and atrial fibrillation. The need for a biomarker for atrial fibrillation has a significant potential for benefit in primary and secondary stroke prevention. Larger, more focused, randomized controlled studies are needed to better test for these possible biomarkers. Additionally, subgroups such as ours with renal dysfunction, seizure, or specific demographic factors which had a trend to correlation with scarring, warrant further review.

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