JAFIB
Journal Review
Journal of Atrial Fibrillation
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Supraventricular Ectopic Activity: When Excessive it is not all Benign!

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Introduction

Stroke is a significant cause of mortality and disabling morbidity. The major subtypes of stroke are divided into thrombo-embolic, haemorrhagic and cryptogenic, with each having different predisposing risk factors and management strategies. Atrial fibrillation (AF) is the commonest arrhythmia predisposing to thrombo-embolic stroke. The incidence of AF increases with age, affecting up to 5% in the elderly population.[1-2] Electrophysiology studies have implicated that spontaneous atrial ectopic beats that originate in or near pulmonary veins adjacent to the left atrium, may initiate paroxysms of AF.[2-3] Supraventricular ectopy can be a manifestation of hypertensive heart disease or other structural heart disease, resulting in left atrial enlargement and increased wall stress, that could be associated with subsequent development of AF.[4]

Binici et al. in their recent article entitled " Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke" in Circulation 2010, had conducted a population based cohort study of Danish individuals from the Copenhagen Holtor study, evaluating the hypothesis that excessive supraventricular ectopy would predispose to a higher incidence of thrombo-embolic stroke, death and AF.[4] The population sample consisted of 678 Caucasian subjects (41.4 % females) aged 55-75 years (mean 64.5 ± 6.8 years), and who otherwise had no previous history of stroke or heart disease. The participants were followed up for up to 7 years (median of 6.3 years).

The enrolled subjects had 48 hour ambulatory Holtor monitoring whereby supraventricular arrhythmias were identified. The observed arrhythmias were divided into isolated supraventricular ectopic complexes (SVEC) and runs of ≥ 3 SVEC. There were no previous definitions to determine the frequency of "excessive" supraventricular ectopy; hence the investigators used an arbitrary cut-off value being the top 10th percentile for both frequency and length of the runs of SVEC. Excessive supraventricular ectopic activity (ESVEA) was thereby defined as ≥ 30 SVEC per hour or any episodic runs of ≥ 20 SVEC. In the 678 subjects recruited, 99 had ESVEA, 70 had SVEC > 30/hour and 42 had runs of ≥ 20 SVEC (13 had both).

At baseline, the ESVEA positive group were older (67.6 ± 6.3 years vs 63.9 ± 6.7 years; $p < 0.0001$), had higher systolic and diastolic blood pressure, and higher N-terminal prohormone B-type natriuretic peptide levels from multivariable logistic regression analysis.

The primary endpoint (a composite of thrombo-embolic stroke and death), was significantly higher in the ESVEA group on univariate analysis ($p<0.0001$), and remained significant in this group after adjustment of conventional risk fac-

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tors: smoking, systolic blood pressure, diabetes mellitus, cholesterol, sex and age (Hazard ratio [HR] = 1.64; 95 % confidence interval [CI], 1.03-2.60; p=0.036). Furthermore, subjects with ESVEA had significantly more hospital admissions for AF, from both univariate and age/sex adjusted Cox regression models (p=0.011 and p=0.035 respectively). Episodes of SVEC, as a continuous variable, also correlated with a significant increase in the primary endpoint of stroke or mortality on univariate analysis (HR=1.46; 95% CI, 1.22-1.73; p<0.0001 for SVEC; HR=1.13; 95% CI, 1.05-1.21; p=0.0007 for runs of SVEC), whilst multivariate analyses was significant for SVEC only (HR 1.27; 95% CI, 1.05-1.53; p=0.013 for SVEC; HR=1.06; 95% CI, 0.98-1.15; p=0.14 for runs of SVEC).

The presence of ESVEA, SVEC and runs of SVEC showed a significantly higher risk of all cause mortality (secondary endpoint) on univariate analysis (HR=2.12; 95% CI, 1.30-3.47; p=0.003; HR=1.49; 95% CI, 1.24-1.79; p<0.0001; and HR =1.12; 95% CI, 1.03-1.21; p=0.006 respectively). However on multivariate analysis, only SVEC was significant, while ESVEA or runs of SVEC were non-significant. Strokes occurred in only 27 patients (10 patients with ESVEA and 17 patients without ESVEA) during follow-up, with only ESVEA being significantly higher in both univariate and adjusted models, while SVEC or runs of SVEC were non-significant.

One of the main limitations as outlined by the authors was that the cohort recruited only middle aged Caucasian subjects; hence these results may not be applicable to other age groups and ethnicities. There was also a potential underestimation of AF reporting, in particular those with asymptomatic AF. Possible hospital admissions for AF may have been prevented by outpatient treatment, especially if symptoms were not severe. Given the small patient numbers and low event rates, the study was possibly underpowered to show statistically significant results with the multivariate models.

Discussion

Excessive supraventricular ectopic activity was associated with significantly increased risk (>60%) of mortality and stroke. A 2.7 fold increase in rate of AF was also observed during follow up. A stepwise increase in the risk of the primary endpoint by 27% and risk of AF by 50% was noted for each increase of 10 SVEC per hour.

The association between paroxysmal atrial ectopy and stroke has been supported by several studies in the literature. Todo et al, retrospectively examined the Holtor results from a Japanese cohort presenting with thrombo-embolic strokes.[5] The results suggested more frequent SVEC in the groups with pre-existing AF and an undetermined aetiology for stroke. An early report from Engström et al, examined prospectively a cohort of "Men Born in 1914" registry from Sweden.[6] This revealed a significant association between frequent SVEC and the development of ischaemic stroke, independent from other major cardiovascular risk factors. SVEC progressing to AF was further characterised by a small prospective study by Wallmann et al, who reported that patients with more frequent SVEC's were at higher risk of developing AF (OR of 9.3, p = 0.01) than those with less frequent supraventricular ectopy.[7] Left atrial size was also significantly larger in the group developing AF compared to those remaining in sinus rhythm.

Although a simple investigative tool, ambulatory Holter monitoring is generally insensitive in detecting occult supraventricular arrhythmias given the limited recording time. Implantable devices can be utilised for longer periods of continuous cardiac monitoring. Ziegler et al described supraventricular ectopy, detected from implantable pacemakers and defibrillators, occurring in 28% of subjects with previous thrombo-embolic cerebrovascular events [8]. Implantable loop recorders are being utilised in a current trial, the CRYSTAL AF trial, to prospectively evaluate the long term detection of AF following cryptogenic stroke [9].

The findings of the current study raises questions about consideration for early implementation of anti-arrhythmic therapy and anticoagulation in those with increased SVEC and other risk factors for thrombo-embolism from AF. Currently there are no studies that explore this clinical scenario. In addition, further investigations to correlate increased SVEC with parameters of atrial volumes and function would be beneficial. Echocardiographic studies have demonstrated that left atrial enlargement in those with chronic and paroxys-

mal AF predicted a higher incidence of stroke [10-11]. Even in those in sinus rhythm, increased left atrial volumes have been associated with increased incidence of stroke, AF and other cardiovascular events [12-13]. Therefore, combining left atrial volume and function with increased SVEC may provide useful prognostic information in individuals at risk of future onset of AF and stroke. In turn, this may facilitate earlier initiation of both anti-arrhythmic and anticoagulant treatment in the prevention of adverse cardiovascular outcomes.

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