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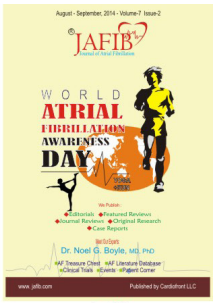

Control Of Hypertension Improves The Outcome Of Therapies For Paroxysmal And Persistent Atrial Fibrillation

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Abstract

Hypertension is known to increase the risk of atrial fibrillation. It has a role to play in atrial fibrosis and remodeling which tends to propagate further atrial fibrillation. Current anti arrhythmic therapy is unsatisfactory due to its toxicity. Management of hypertension offers an attractive target for improving therapy of atrial fibrillation. We examine the current evidence for anti hypertensive therapy in atrial fibrillation.

Background

Atrial fibrillation is the most common arrhythmia. Its prevalence in the population is around 1% but may be up to 9% in octogenarians.[1] The prevalence is increasing with the aging of the population. Left atrial size, coronary disease, valvular heart disease, congestive heart failure, height, BMI, age and systolic hypertension[2,3] have all been associated with an increased risk of developing atrial fibrillation.

Hypertension has been implicated in increases in left ventricular stiffness and hypertrophy which can lead to reduced coronary flow reserve, congestive heart failure, sympathetic activation and activation of the rennin angiotensin alderosterone system (RAAS) and increasing left atrial size.[4] It also has a role to play in left atrial fibrosis, increasing left atrial size.[5] and heterogeneity of left atrial conduction. All of these may lead to increasing incidence of atrial fibrillation.[4]

In an ovine model induced hypertension has been shown to increase left atrial pressure, atrial hypertrophy and left atrial dysfunction. Increased mean atrial refractory periods and inflammation were seen and AF inducibility was increased by 5 weeks. After 10 weeks of induced hypertension increased fibrosis and longer AF episodes were seen.[6]

Hypertension on its own increases the prevalence of atrial fibrillation approximately two fold.[4] It commonly co-exists with other conditions associated with atrial fibrillation. Due to the frequency of hypertension in the population, despite its modest increase in the risk of atrial fibrillation it contributes more to the incidence of atrial fibrillation than any other risk factor.[4]

Upstream management of hypertension can prevent much of the remodeling attributable to hypertension and hence should prove a suitable potential target for reducing new onset atrial fibrillation. Indeed post hoc analysis and case control studies have suggested a beneficial effect from upstream hypertension management.[7]

Once atrial fibrillation has developed a certain amount of atrial fibrosis and remodeling can be assumed to have already occurred bringing into question the value of antihypertensive therapies designed to prevent it.

The picture is further confused because when examining the effect of specific antihypertensive therapies it is difficult to discern the effect of the blood pressure reduction from intrinsic effects of the therapies themselves. This is especially true with regard to the antiadrenergic effects of beta-blockers and the effects of RAAS inhibition.

Atrial fibrillation is not a benign condition and although large studies have shown no mortality difference between rate and rhythm control, this is largely a commentary on the insufficiency of current rhythm control therapies rather than on the benign nature of atrial fibrillation itself. Indeed post hoc analysis of the AFFIRM study has shown that maintenance of sinus rhythm conferred a 47% mortality benefit over ongoing persistent atrial fibrillation.[8] Hence there is need for more benign therapies that contribute to maintenance of sinus rhythm. Hypertension management has the potential to fill part of the gap.

RAAS Inhibitors

The RAAS system provides an attractive target for the prevention of atrial fibrillation recurrences. Along side its role in generating hypertension and left ventricular hypertrophy. Angiotensin, production of which is promoted by atrial stretch has been implicated in proliferation of fibroblasts, induction of atrial fibrosis, stretch and remodeling precipitated by mitogen-activated protein kinase (MAPK) expression and reduction of collagenase activity.[9] This leads to increased conduction heterogeneity and may increase atrial ectopic activity[10] and propagation of atrial fibrillation.[11]

This effect has been shown to be reduced by co administration of captopril and candesartan and also by pretreatment with enalapril in experimental animals.[11]

Atrial fibrillation induced atrial stretch In 2009 Schneider et al conducted a meta analysis of 23 studies of renin angiotensin inhi-

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None.

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Mechanisms by which hypertension can increase atrial fibrillation
Increased LA size
Increased LA Stiffness
LA stretch
RAS overactivity related to LA stretch
Fibrosis and increased conduction heterogeneity
MAPK overactivity (and increased conduction hetrogeniety)
Vagally induced increased refractory period
Sympathetic surges
Increased activity of LA(especially pulmonary vein) triggers
Increased LA chimase activity
Increased intra cellular calcium
Reduction of collagenase activity

bition in atrial fibrillation.[12] This covered 87048 patients across a spectrum of primary and secondary prevention, hypertension, left ventricular hypertrophy, left ventricular failure and post MI. In secondary prevention it covered both those cardioverted and managed medically principally with amiodarone. Atrial fibrillation was significantly reduced across the secondary prevention spectrum by 45% in the cardioversion studies and 68% in the medical trials. In the ablation era there are 2 studies looking at RAS inhibition post ablation. In 2010 Tayebjee et al performed a retrospective analysis of 419 patients who had undergone ablation 222 for paroxysmal and 197 for persistent AF. The patients taking RAS blockade were older, more likely to suffer from hypertension, diabetes, coronary disease, or left ventricular impairment but even with propensity analysis there was no significant difference between the groups.[13] However in 2012 Takigawa et al conducted a retrospective analysis of 292 ablation patients. RAS inhibition was associated with a reduction of atrial fibrillation recurrences in those without a dilated left atrium (< 0.4cm) HR 0.3 P 0.003 but not in those with a dilated left atrium[14] implying that there is greater benefit to be gained by RAS inhibition and hypertension management earlier in the course of the disease.

In the J Rhythm II study[15] comparing candesartan vs. amlodipine in 318 patients with atrial fibrillation associated with hypertension there were similar events in the 2 groups despite a larger blood pressure reduction with amlodipine, suggesting that ace RAS inhibition may have an extra effect beyond blood pressure reduction.

Alderesterone antagonists have not been studied in this context in man. However pre treatment with spironolactone in a dog atrial fibrillation model reduced the amount of atrial fibrosis and inducibility of atrial fibrillation.[4]

Beta-blockers

Beta-blockers are in common use in persistent atrial fibrillation for control of heart rate and this can confuse the picture to an extent.

They reduce adrenergic surges and hence reduce episodes of adrenergic driven shortening of the atrial action potential which could precipitate atrial fibrillation,[16] they may also reduce the activity of pulmonary vein triggers.[17] Both of these could lead to action over and above their effect on blood pressure. Indeed in groups where the adrenergic surges are likely to be of most importance, heart failure and post bypass surgery, they have been shown to reduce atrial fibrillation episodes. In heart failure a large meta analysis has shown benefit[18] while post CABG beta-blockers have been shown to be equivalent (with a trend towards superiority) to amiodarone.[19]

However a study by Van Nord et al[20] of 162 patients post cardioversion found that at one month, only in the hypertensive (defined as >160/95) cohort had the beta-blockers increased the maintenance of sinus rhythm from 28% to 65%. Although in the non-hypertensive cohort beta blockade did reduce the number of relapses within 3 days. Small numbers and a non-randomized recruitment design limited this study.

A further study by Kuhlkamp et al[21] randomized 394 post cardioversion patients to either metoprolol or placebo. Metoprolol significantly decreased the rate of relapse into atrial fibrillation from 60% to 48% (p0.005). 47% of the patients were noted to be hypertensive although this was not further defined and the mean blood pressure overall was only 132/81. Unfortunately the authors did not break down the results based on the presence or absence of hypertension at baseline. Beta blockade has been shown equivalent to sotalol (although the sotolol dose used of only160mg /day has almost exclusively beta blocker activity) but less successful than amiodarone at maintaining sinus rhythm post cardioversion.[22,23]

Calcium Channel Blockers

Calcium channel blockers of the phenylalkylamine variety and to a lesser extent of the, benzothiapine variety reduce calcium influx within the heart which may be responsible for some of the atrial remodeling that perpetuates atrial fibrillation,[24] thus they may have an anti arrhythmic effect beyond the anti hypertensive effect. These agents are commonly used in atrial fibrillation to regulate the heart rate. Verapamil has been studied post cardioversion. In the verapamil plus other antiarrhythmics study (VEPARAF)[25] 363 patients post cardioversion were randomized to either amiodarone or flecainide plus or minus verapamil. Verapamil reduced recurrences in both groups significantly. Similar effects were seen in the PAFAC trial[26] of 848 patients post cardioversion treated with sotalol, quinidine verapamil or placebo. The three drugs had similar effects and all were superior to placebo. Dihydropyridine calcium channel blockers are more frequently used for hypertension management alone. Studies for this group of drugs compared with placebo are lacking. However in the J rhythm II study[15] patients treated with amlodipine had similar rates of atrial fibrillation recurrence to those treated with candesartan, although amlodipine had a larger effect on blood pressure. In 2002 Fogorri et al reported on a study of 391 hypertensive patients with paroxysmal atrial fibrillation randomized to amlodipine, ramipril or telmisartan. There were similar blood pressure reductions between the groups. However there were significant differences in recurrences of atrial fibrillation, 49% in the amlodipine group, 25.5% in the ramipril group and 12.9% in the telmisartan group. The authors suggested that the differences may be explained partly by RAS inhibition, partly by ARB blockade of Ang II activity produced by left atrial chimase and partly by telmisartan specific HKv 1.5 potassium channel. Channels highly expressed in the atria.[27]

Other Anti Hypertensive Drugs

The effect of other anti hypertensives on secondary prevention of atrial fibrillation has not to my knowledge been investigated. There are suggestions of possible benefit in that in the management of hypertension hydrochlorothiazide reduced left atrial size more than captopril, atenolol or diltiazem.[28]

Renal Ablation Therapy

Ablation of the sympathetic plexus adjacent to the renal arteries has been shown to have significant effects on resistant hypertension. On average reducing office blood pressure by around 30mmhg and

ambulatory blood pressure by 10mmhg.[29] Renal sympathetic stimulation induces both renin and noradrenaline release and increases circulating levels of Ang II,[30] which increases atrial intracellular calcium concentration. Thus renal artery denervation could potentially reduce atrial fibrillation burden both by effects on blood pressure and on the RAAS system.

Atrial fibrillation may be triggered by autonomic dysbalance and renal denervation partially negates this. In a porcine model of obstructive sleep apnoea, simulated by tracheal occlusion, it has been shown that renal denervation reduced the vagally mediated atrial refractory period shortening induced by tracheal occlusion more successfully than atenolol,[31] thus confirming that autonomic dysbalance must play a role. Renal denervation also mitigated post apnoic blood pressure rise whereas Atenolol did not.[31]

A recent small study of 27 patients with refractory symptomatic atrial fibrillation and resistant hypertension randomized them to either PVI only or PVI + renal artery denervation. In the renal denervation group there was a mean reduction of arterial blood pressure of 25/10 and a significant (p=0.033) reduction in atrial fibrillation recurrences at 12 months from 69% to 29%.[32] However the poor results on blood pressure control from the recent blinded SYMPLICITY HTN3 trial[33] make success with this technique less likely.

Conclusion:

Conclusions regarding the reduction of atrial fibrillation by managing hypertension are limited for a number of reasons. The first is that most of the agents used for hypertension management have modes of action that in themselves have plausible reasons for reducing atrial fibrillation outside of their effect on hypertension. Often patients with atrial fibrillation have other indications for some of these therapies such as ventricular failure, coronary heart disease, or rate control. Trials performed are mostly trials of a particular agent, which has antihypertensive properties, and in some the authors have not characterized their results based on the initial presence or absence of hypertension. The second is that hypertension management, with most current agents, has such clear benefits outside of atrial fibrillation management, that a placebo-controlled trial can only be contemplated in those without hypertension. Comparisons based on success of antihypertensive therapy have too many confounders.

Despite all the above there does appear to be some reduction in atrial fibrillation episodes in both paroxysmal atrial fibrillation and persistent atrial fibrillation post cardioversion. It would also appear that targeting the RAAS system either pharmacologically or mechanically offers the most rewards.

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