REPORT OF THE AMERICAN HEART ASSOCIATION'S 65TH SCIENTIFIC SESSIONS

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Introduction

This annual American Heart Association Scientific Sessions program was held in New Orleans from November 16 to November 19, 1992. It was attended by over 28,000 participants. The program provided three and one-half days of comprehensive educational experience in major facets of cardiovascular disease and stroke. The following is a brief summary of those current developments relevant to our geriatric practice, with comments added based on review of literature on related subjects.

Current approaches in atrial fibrillation

Atrial fibrillation (AF) is the most frequent disturbance of cardiac rhythm after multiple ectopic beats in the elderly. The Framingham Study showed that AF increased sharply with age. In USA, 5% of those over 65 years of age have AF. In patients with congestive heart failure, the risk of death is seven times higher for AF as compared to sinus rhythm. This is due to increased ventricular rate and reduced atrial contraction in patients with AF. The incidence of stroke is also higher in AF with an average rate of 5% per year.

The current view of the electrophysiological mechanism of AF is the formation of multiple wavelets of macro-reentrant circuits across atrium resulting from reduced conduction in atrium with heterogeneous refractory periods. The clinical implication is that atrial fibrillation can be terminated by increasing wavelength (wavelength = refractory period x conduction velocity). Class I anti-arrhythmics (eg. quinidine, procainamide) can terminate AF by increasing the refractory period, though the effectiveness is partially offset by an associated reduction in conduction velocity. Class III anti-arrhythmics (eg. amiodarone) are more effective in terminating AF as they allow selective increase in refractory period without any change in conduction velocity.

The objectives in management of atrial fibrillation are rate control, termination, prevention of recurrence and anti-embolic therapy. Digoxin is useful in slowing down the ventricular response, but is neither useful in termination nor prevention of recurrence. Although type I (eg. quinidine) and type III (eg. amiodarone) anti-arrhythmics are effective in preventing recurrence of AF, some studies have shown that the risk may actually outweigh the benefits in patients with congestive heart failure and AF. The Stroke Prevention Atrial Fibrillation (SPAF) study showed that for patients with congestive heart failure and AF, the relative risk of cardiac death is higher (4.7 vs. 3.7) in those treated with anti-arrhythmics to prevent AF recurrence. The Quinidine Meta-analysis revealed that the mortality was higher in the treated group (2.9% vs. control 0.8%). A recent audit[1] of the use of amiodarone in elderly patients detected a high incidence (24%) of adverse effects despite the majority were on the recommended maintenance dose of 200mg/day. Potentially dangerous dose-dependent symptomatic bradycardia also occurs more commonly in elderly subjects. A clear-cut indication for the use of amiodarone should therefore be established before it is prescribed and the lowest possible maintenance dose, probably 100mg/day, should be used in the elderly patient.

Atrial fibrillation and stroke prevention

AF is well recognized as an important risk factor for stroke in elderly people [2,3]. The Framingham study showed that chronic AF resulted in a fivefold increased risk of first stroke when compared with sinus rhythm. In elderly subjects aged over 80 years, AF was the only cardiovascular risk factor for stroke[3].

The following questions on stroke prevention in atrial fibrillation were discussed in a plenary session:

1. Does warfarin reduce the risk of stroke in AF and what is the risk of bleeding while on warfarin?

Five randomised controlled trials have studied the use of warfarin in the primary prevention of stroke in subjects with AF. The sample size varied from 400 to 12,000, length of follow-up from 1.2 to 2.2 years, international normalised ratio (INR) achieved was 1.5 to 3.0, and the outcome measures used were systemic embolisation/ strokes and intracranial bleeding. All the studies were stopped prematurely as warfarin was shown to reduce the risk of stroke in AF from 5% to 2%. The risk of bleeding complications was low at 0.5% per year.

2. Is the effect size clinically important?

The relative risk reduction is 60% while the absolute risk reduction is 3% per year. The number needed to treat to prevent one stroke is 33. For every 6 stroke prevented, there will be one with bleeding complication. Thus, the benefit of warfarin is clinically important. The limitation in these studies, however, is that stroke severity and mortality were not used as outcome measures.

3. Is the result generalisable?

As far as efficiency of treatment is concerned, the result is generalisable. As for side-effects, it is questionable whether the result can be generalised, because those at high risk of bleeding are not selected for trial. The trials

included only a 4-40% of screened patients with atrial fibrillation because of contraindications.

4. How does aspirin compare to warfarin?

Regarding efficacy, the evidence for aspirin is not as compelling as for warfarin both in terms of size and consistency. The risk of serious bleeding is about the same. The "nuisance factor" is better for aspirin.

5. Can we identify subgroups with a low or a high risk of stroke?

Studies have attempted to identify which at risk subgroup to select for anticoagulation. Younger patients (aged below 65) with no clinical heart disease and normal echocardiogram form a low risk subgroup. For those aged over 65, there is lack of agreement on risk factors probably because of the small number studied. Some have identified previous myocardial infarction and age over 70 as clinical risk factors; while others have identified left atrial enlargement, mitral calcification, and left ventricular dysfunction as echocardiographic risk factors. In the SPAF study, the risk factors used are history of hypertension, recent congestive heart failure, previous thrombo-embolism, and global left ventricular dysfunction. The risk of stroke is shown to be 0.01, 0.06, and 0.09 for none of these risk factors, 1 or 2 risk factors, and 3 or more risk factors respectively.

6. Will there be more data available?

Further data will soon be available from the following studies: the Boston Area Anticoagulation Trial for AF investigators, SPAF II (Stroke Prevention AF II study comparing aspirin with warfarin), EAFT (European AF Trial on secondary prevention), and a Dutch study using warfarin at 2 different intensities of anticoagulation (INR 2.5 - 3.2, 1.1 - 1.6) and comparing with aspirin 150 mg qd.

In summary, warfarin has clinically important effect in the prevention of stroke in patients with atrial fibrillation. Careful monitoring of anticoagulation is required. The benefit of aspirin is not that established as that of warfarin. Patients aged below 65 with no clinical heart disease and normal echocardiogram should not be anticoagulated because of low risk of embolisation. However, such low risk subgroup represents only a small percentage of the total requiring anticoagulation. The majority of those with atrial fibrillation at high risk of stroke are aged over 65.

A study in U.S.A.[4] has highlighted that many doctors remain reluctant to prescribe warfarin for their older patients despite the published trials of the efficacy of oral anticoagulant therapy in the primary prevention of stroke in individuals with AF. Fear of haemorrhagic complications and the erroneous belief of a lack of efficacy of warfarin in primary prevention were the principal reasons for such negative attitudes. Although age over 65 has been implicated as a risk factor for anticoagulant-induced haemorrhage, other studies[5] have shown no age-related increase in haemorrhagic complications. Knowledge of a greater sensitivity to warfarin in elderly subjects is important in minimising the haemorrhagic complications. One study[6] has revealed that by the age of 70, the dose required to maintain a given degree of anticoagulation has fallen by a quarter to a third when comparison is made with a 30-year-old. However, the variation between individuals of the same age is much greater than the variation associated with age. Provided that patients without known contraindications to anticoagulation are chosen and, regular monitoring is undertaken then anticoagulant therapy is not contra-indicated by age alone.[7]

So far, the efficacy of warfarin in reducing stroke in AF is demonstrated only for primary prevention, i.e. before a stroke has ever occurred. The roles of warfarin in acute ischaemic stroke and in secondary prevention of stroke remain to be answered by current international trials.[8] In the Oxfordshire community stroke project[9], patients with acute stroke and AF had a higher early mortality than patients in sinus rhythm (23% vs. 8%). It might be due to the association of atrial fibrillation with occlusion of the middle cerebral artery by large fibrin rich emboli from atrial thrombi. If that is the case, prompt treatment with fibrinolytic agents, or antiplatelet, or anticoagulant might decrease the early mortality in acute stroke with AF by reducing thrombotic extension or recurrence of thromboemboli; a hypothesis which is being tested in current trials. The Oxfordshire project also revealed that some strokes in people with AF are due to primary intracerebral haemorrhage and are unrelated to AF, making computed tomography of the brain to exclude haemorrhage mandatory before any antithrombotic treatment. As for secondary prevention of stroke, aspirin in a dose of 75-300mg[8] is currently the recommended regimen for patients with previous ischaemic stroke irrespective of rhythm. The efficacy of warfarin as compared to aspirin in secondary prevention of stroke in AF will soon be answered by current trials.

Advances in the Management of Heart Failure

There is a shift of emphasis from the traditional haemodynamic hypothesis (Figure 1) of heart failure to a neuroendocrine perspective (Figure 2). Several studies have shown that patients with heart failure exhibit activation of the sympathetic nervous system and the renin-angitoensin-aldosterone system, and an elevation of circulating arginine vasopressin. The authors of the SOLVD trial concluded that "neuroendocrine activation appears to precede overtly symptomatic heart failure and therefore may contribute to its development."[10] It may be that the critical event triggered by myocardial injury is not peripheral vasoconstriction, but activation of vasoactive neurohormones. Increased neuroendocrine activity may lead to progression of the syndrome of heart failure through multiple mechanisms on the intrinsic function (contractile proteins, excitation-contraction coupling) and the stimulated function (regulated sarcoplasmo-reticular function, adenyl-cylase pathway and beta-adrenoceptors with $ß_1$-downregulation, $ß_2$-uncoupling and increased G inhibitory proteins). Such neurohormonal activation results in calcium overload and secondary toxic damage to the heart, and maladaptive compensatory responses.

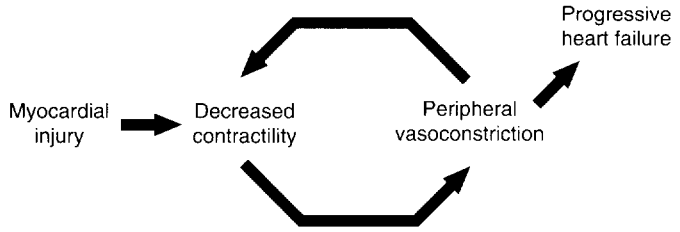

Figure 1. Haemodynamic hypothesis of heart failure

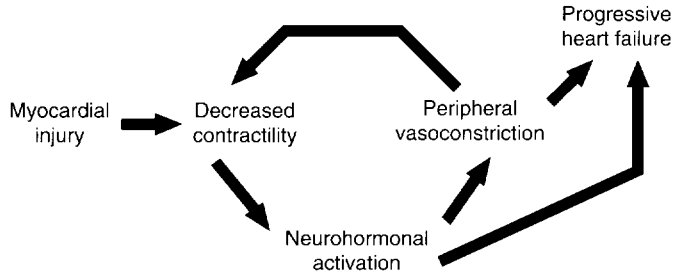

Figure 2. Neuroendocrine hypothesis of heart failure

Angiotensin converting enzyme inhibitors (ACEI) produce haemodynamic improvement in the failing heart by reducing left ventricular preload and afterload. They accomplish this by interfering with the activated neurohormonal systems that produce vasoconstriction and fluid retention. Inhibition of the renin-angiotensin-aldosterone system results in vasodilation and promotes salt and fluid excretion. Furthermore, since angiotensin-II modulates sympathetic nervous system activity and vasopressin secretion, activity of these deleterious systems is also inhibited. A number of studies have shown improvements in survival, symptoms and exercise tolerance in patients with congestive heart failure when ACEI are added to diuretics and digoxin or to diuretics alone. There is suggestive evidence that the early use of ACEI might prevent heart failure in patients with hypertension and myocardial infarction. It is found that an ACE gene (producing higher tissue ACE levels) is a risk factor of myocardial infarction and it might be possible that ACEI has a beneficial effect on patients with this genotype.

Blood pressure and renal function must be monitored carefully after the initiation of ACEI in congestive heart failure patients. This is particularly important for the elderly patients. Severe hypotension after the first dose of ACEI[11] is a cause for concern in the elderly, in whom baroreceptor reflexes may be impaired. ACEI can impair renal function as can both ageing and heart failure. In an evaluation of the safety of enalapril in treating heart failure in the very old [12], only 11 out of 17 elderly patients (mean age 83) tolerated the introduction of enalapril in doses equal to or less than the 2.5mg currently recommended. The adverse reactions in the 6 patients included hypotension , acute renal failure, acute confusional state, ataxia and acute mesenteric ischaemia. All but one of the adverse drug reactions occurred 8h or more after the first dose. It was suggested therefore that aged patients started on ACEI should be observed in hospital until stabilized on a maintenance dose. Of the 10 patients followed up with 5mg or 10mg maintenance doses, enalapril was withdrawn in 3 because of symptoms of mesenteric ischaemia and in 4 because of dramatic deterioration of renal function (which returned to baseline after withdrawal of enalapril). One of the latter was found subsequently to have severe bilateral atheromatous renal artery stenosis. Continuing monitor of adverse effects is thus essential in elderly patients with severe heart failure, and the risk of occult renal artery stenosis requires regular biochemical screening during follow up. It was postulated that the benefit to cost ratio of ACEI might be improved in elderly patients with heart failure by using them at an earlier stage, when perfusion of essential organs is not grossly impaired.

In the 1970's it was shown that intravenous **vasodilators** can improve left ventricular performance of the failing heart by reducing afterload and preload. In the 1980's it was found that orally active vasodilators (hydrallazine, isosorbide dinitrate) could improve cardiac function in patients with heart failure similar to the intravenous agents. However in the 1990's two findings modify the role of vasodilators in heart failure. First, not all vasodilators are clinically useful. Though prazosin, minoxidil, diltiazem and other calcium channel blockers produce haemodynamic benefit, no clinical benefit is obtained with regard to symptoms, exercise tolerance and survival. One possibility of such discrepancy between haemodynamic and clinical benefit is that such direct acting vasodilators tend to increase neurohormonal activation leading to the development of tolerance. Tolerance to nitrates develops in direct proportion to increases in plasma renin activity and heart rate. Second, ACEI reduced mortality more than vasodilators. Thus instead of using vasodilators alone, studies have been going on to see whether the addition of vasodilators to ACE inhibitors reduce symptoms and prolong life. The results will be ready by 1994. Newer vasodilators, flosequinan and epoprostenol (a prostacyclin), are currently also being investigated.

Chronic sympathetic stimulation on the failing heart is potentially deleterious, resulting in arterial and venous constriction, adverse electrophysiologic effects, renin production, increased myocardial hypertrophy and possible direct myocardial toxicity. There is a renewed interest in the role of **beta-blockers** in heart failure. In ischaemic cardiomyopathy, beta-blockers reduce total cardiac death by reducing energy consumption of the failing heart, allowing better relaxation and diastolic filling and optimising myocardial tension. Sudden death is also less because of reduction in automaticity and re-entry. Beta-blockers can prevent the progression of congestive heart failure by improving glucose and free fatty acid utilization and by possibly blocking autoantibodies directed against beta-receptors. Beta-blockers potentiate ACEI in improving cardiac function in

ischaemic cardiomyopathy. In dilated cardiomyopathy, beta-blockers improve the quality of life.

There are factors for and against the use of **positive inotropic agents** in heart failure. Positive inotropic agents support pump function, but tend to be arrhythmogenic, have adverse effect on energetics, impair relaxation and accelerate the progression of disease. However, their mechanisms of action are different. The following classification was used in the conference:

I. Increased intracellular cyclic AMP

Phosphodiesterase inhibitors (eg. amrinone, milrinone) and **beta-adrenergic agonists** (eg. xamoterol, prenalterol, denopamine) belong to this class. They show lack of efficacy and have safety concern with increased mortality up to 20% for the phosphodiesterase inhibitors.[13]

II. Action on sarcolemmal ion pumps/ channels

Digoxin belongs to this class. Digoxin inhibits the membrane-bound Na, K-ATPase, and the resulting increase in intracellular sodium facilitates the exchange of sodium for calcium, resulting in higher intracellular calcium levels and thus improved contractility and increased ejection fraction. Although over the years there has been some controversy about the clinical efficacy of digoxin in patients in normal sinus rhythm, many studies over the past decade have confirmed that digoxin decreases symptoms, improves exercise tolerance and reduces cardiovascular morbidity in patients with heart failure. The difference in clinical performance between digoxin and the class I positive inotropes may be explained by their opposite effects on neurohormonal activation, the former decreases it while the latter increases it. The neurohormonal effect of digoxin is distinct from its inotropic effect, may occur at doses lower than inotropic doses, and may be an important contributing factor to clinical benefits. In the 1970's digitalis intoxication was thought to be the most frequent adverse drug reaction in clinical practice. The incidence of digoxin toxicity has been falling in the 1980's because of several factors. First, physicians have increased awareness of conditions that increase susceptibility to digoxin (eg. ageing, impaired renal function, electrolyte imbalances, and drug interactions). Second, assays for digoxin serum concentrations have become widely available. Third, digoxin is currently used at lower doses than were used in the 1970's. Fourth, digoxin is often used in combination with other therapies, allowing lower doses of each of the components.

III. Intracellular calcium mechanisms

The mechanisms of this class involve release of sarcoplasmo-reticular calcium and increase sensitivity of contractile proteins. No clinically useful drugs of this class are available now.

IV. Mixed action

Examples of this class are the newer agents pimobendan (type I and III actions) and vesnarinone. They are currently under investigations.

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