REVIEW: NEUROLOGY IN MEDICINE

Neurology and the heart

Stephen M Oppenheimer, Joao Lima

In the past, considerable attention focused on the extracranial vasculature as a source of embolism to the brain. With the advent of transoesophageal echocardiography, it has become apparent that the heart is a much more important cause of stroke than previously suspected. In young patients with cryptogenic stroke, cardiac structural abnormalities are probably the principal source of cerebral emboli.¹ In these patients, there is often no atherosclerosis. On the other hand, even older patients with significant extracranial vascular disease may harbour a possible cardiac source of embolism. Thus between 15% and 35% of stroke patients with a significant (>60%) stenosis of the extracranial vasculature demonstrated by arteriography may also have a probable cardiac embolic source.^{2,3} Even lacunar infarcts (often thought to be secondary to disease of penetrating vessels in the brain as a result of hypertension) may be associated with potentially embolic cardiac pathology in 50% of cases.³ This review considers the currently debated cardiac issues faced by neurologists and cardiologists in the prophylaxis and management of stroke patients: anticoagulation for atrial fibrillation; incidence of cerebral haemorrhage and infarction, together with its prevention in infective endocarditis; and the cognitive and focal neurological consequences of cardiac surgery.

In addition to the increasing importance of the heart as a possible source of cardiac embolism there is recent evidence implicating the brain in the production of cardiac structural abnormalities and in cardiac dysrhythmogenesis. These effects are most often encountered after subarachnoid haemorrhage, but recent experimental and clinical findings imply that they may well occur after ischaemic stroke. The mechanisms involved are discussed at the end of this chapter.

Cardiac arrhythmias as a cause of stroke**ATRIAL FIBRILLATION**

Atrial fibrillation has the greatest documented potential of all cardiac arrhythmias to afford a milieu for cerebral embolisation. Chronic atrial fibrillation in the absence of rheumatic heart disease is associated with a fivefold increased incidence of stroke compared with the normal age matched population.⁴ Between 25-34 years, the incidence of atrial fibrillation is 2.6/1000 and rises to 38/1000 between 55-64 years.⁵ Wolfe *et al* showed that the stroke risk associated with atrial fibrillation was 0.2 per

1000 (in the age group 30-39 years), rising to 39/1000 (in the age group 80-89 years); 14.7% of all strokes were associated with atrial fibrillation ranging from 6.7% in patients aged 50-59, rising to 36.2% in patients aged 80-89.⁶ The risk of stroke in atrial fibrillation also depends on the length of time the patient had this arrhythmia.⁶

It is often difficult to identify whether or not a stroke is related to a cardiac source. A major problem with some earlier studies is the fact that the contribution of coincident extracardiac vascular disease may have been ignored. Many of the risk factors for atrial fibrillation also cause atherosclerosis. Thus Kanter *et al* reviewed the incidence of carotid stenosis >50% by ultrasound investigation in 676 patients in chronic atrial fibrillation.⁷ In patients older than 70 years of age, 12% had significant concomitant carotid stenosis which may have been the dominant influence on occurrence of stroke. Bogousslavsky *et al* also showed that 14% of stroke patients had other cardiac sources of stroke in addition to atrial fibrillation.⁸ In this study, 4% of patients in atrial fibrillation re-embolised within one month of their original stroke.

In the Oxfordshire Stroke Study 17% of all stroke patients were found to be in atrial fibrillation.⁹ The 30 day stroke recurrence rate as well as the annual recurrence rate were no greater in patients in atrial fibrillation than in those in sinus rhythm. Several other studies, however, have suggested otherwise. For example, Flegel and Hanley, in a retrospective study of 91 patients, indicated that the stroke risk was 8/100 person-years in patients in chronic non-valvular atrial fibrillation, a figure significantly higher than for the general population.¹⁰ However, if a previous stroke had occurred, these patients were twice as likely to have a second stroke. Other features predictive of recurrence were older age (more than 75 years of age) and increased systolic pressure.

Several studies have investigated whether any associated abnormalities may predict the potential for cerebral embolisation in patients in chronic atrial fibrillation. Petersen *et al* suggested that patients who were in atrial fibrillation and who also had heart failure or hypertension may be at increased risk of stroke.¹¹ Whether left atrial enlargement increases the stroke risk in patients in atrial fibrillation is still controversial. Shiveley *et al* measured blood flow velocity in different areas of the left atrium.¹² Stroke risk increased as the

**Departments of
Medicine (Cardiology)
and Neurology, The
Johns Hopkins
University School of
Medicine, Baltimore,
Maryland, USA**
S M Oppenheimer
J Lima

Correspondence to:
Dr Stephen M
Oppenheimer, Meyer 5-185,
Johns Hopkins Hospital, 600
N Wolfe Street, Baltimore,
Maryland 21287, USA.
Telephone 001 410 550
5356; fax 001 410 614 9807.

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velocity decreased below a cut off point of 14 cm/s. Patients who were particularly at risk of stroke during atrial fibrillation were those with left ventricular dilatation and decreased left atrial ejection fraction coupled with left atrial dilatation. Recently, Chimowitz *et al* have suggested that left atrial spontaneous echo contrast may be of importance in predicting those patients with atrial fibrillation who would be at risk of stroke.¹³ This phenomenon may indicate cardiac intracavitary blood stasis and coagulation. The relative risk of stroke in such patients was 27. This, however, was a retrospective study conducted on comparatively few patients.

In a review of the recent literature, Laupacis and Cuddy suggested that: (1) the risk of stroke in patients with chronic atrial fibrillation was about five times that of the normal population; (2) patients who were in lone atrial fibrillation (see below) had a comparatively low rate of stroke; (3) patients younger than 65 without diabetes, hypertension, a previous transient ischaemic attack or stroke, or heart failure had an annual stroke incidence of about 1%/year; (4) patients older than 65, with one or more of these factors, had a stroke risk of 4%/year.¹⁴

Atrial fibrillation may exist in many guises, such as lone atrial fibrillation and paroxysmal or chronic atrial fibrillation. Lone atrial fibrillation occurs in younger patients and is characterised by the absence of any associated cardiopulmonary or metabolic cause. Bogousslavsky *et al* have shown that the risk of recurrence of stroke is very low in this condition (<1/100 patient-years over a follow up period of 4.8 years).¹⁵ Paroxysmal or chronic atrial fibrillation is often associated with other cardiac abnormalities such as ischaemic heart disease and cardiomyopathy. However, Petersen *et al* suggested that the incidence of stroke in patients with paroxysmal atrial fibrillation is less than that of patients with chronic atrial fibrillation.¹¹ This may relate to differences in the cardiac intracavitary coagulability potential of the two conditions (see below).

Several studies have indicated that patients in atrial fibrillation may have coagulation abnormalities. Sohara *et al* identified significant increases in β -thromboglobulin, platelet factor 4, and other markers of platelet activation within 12 hours after the onset of paroxysmal atrial fibrillation when compared with values for the same markers after these patients had been in sinus rhythm for seven days.¹⁶ They concluded that atrial fibrillation itself enhanced platelet aggregation and coagulation, and that these effects were also influenced by the duration of atrial fibrillation. Gustafsson *et al* found a similar phenomenon: stroke patients in atrial fibrillation had an increased incidence of markers of coagulation and platelet aggregability compared with stroke patients in sinus rhythm.¹⁷ These findings are of importance in clarifying why it is that the different types of atrial fibrillation may have different prognostic relevance. Theoretically it might be expected that patients in paroxysmal atrial fibrillation would be at a higher risk of embolisation. Thrombus might form in a dysfunctional left

atrium, and then be dislodged when the atrium contracts normally during atrial systole once sinus rhythm is restored. On the other hand, several studies have indicated that risk of stroke is directly proportional to the period of time patients spend in atrial fibrillation. This may be reduced in patients with paroxysmal atrial fibrillation. In addition, activation of coagulation and platelet aggregability, although increased in patients with paroxysmal atrial fibrillation, may not be as pronounced as in patients in chronic atrial fibrillation. Possibly, to enhance these coagulation abnormalities engendered by atrial fibrillation, structural abnormalities of the heart should also be present. These are absent in lone atrial fibrillation; as a consequence the risk of stroke is less.

Several studies have shown that patients in atrial fibrillation have larger strokes and experience a higher stroke related mortality.^{9 14 18 19} It has been hypothesised that atrial fibrillation may decrease cardiac output and thus compromise viable tissue in the penumbra surrounding the stroke.

TREATMENT OF ATRIAL FIBRILLATION

The treatment of atrial fibrillation has been the subject of much recent investigation. In 1993, after consideration of the available studies, Boysen concluded that anticoagulation with coumadin was associated with a 65% risk reduction for stroke and a risk of intracerebral haemorrhage of only 0.3%/year.²⁰ The INR was maintained between 1.5–3. Anderson showed that patients treated with warfarin had a stroke rate of 1.6%/year compared with 8.3%/year in patients treated with a placebo.²¹ In the European study of anticoagulation in transient ischaemic attack or minor non-disabling stroke, the stroke risk was reduced from 12% to 4%/year in patients treated with warfarin.²² Aspirin was associated with a 15%/year stroke risk compared with a 19%/year stroke risk in patients treated with placebo.²² The bleeding complication rate was about 3% in patients on warfarin and about 1% in patients on aspirin. No intracranial bleeding was identified. It was concluded that aspirin might decrease the stroke risk in patients in chronic atrial fibrillation, and was generally safe, but was considerably less effective than warfarin. Miller *et al* also examined the efficacy of aspirin treatment in the Stroke Prevention in Atrial Fibrillation Study.²³ This therapy decreased the incidence of stroke in patients with non-valvular atrial fibrillation. However, the effect of aspirin was greatest in patients with a non-cardiac source of stroke. The implication here is that the primary influence of aspirin was on the extracranial vasculature and not on cardiac embolic sources. Table 1 shows a suggested paradigm for the prophylaxis of stroke for patients in atrial fibrillation.

OTHER CARDIAC ARRHYTHMIAS

The embolic potential of other cardiac arrhythmias such as supraventricular or ventricular bradycardias and tachycardias or heart blocks of various sorts has not been investigated. In general, the neurological problems faced by

Table 1 Suggested embolism prophylaxis regimens for patients in atrial fibrillation (the use of aspirin and warfarin implies no contraindication to its introduction) each case should be evaluated on an individual basis by a physician experienced in the treatment of such patients

Condition	Treatment
Lone atrial fibrillation. No extracranial vascular disease; no atherosclerosis risk factors (smoking; family history of myocardial infarction/stroke; hypertension; diabetes; hypercholesterolaemia)	Nil/aspirin (325 mg/ day)
Patients <65 years with chronic/paroxysmal atrial fibrillation and stroke risk factors, but a normal heart and no stroke/transient ischaemic attack symptoms	Aspirin (325 mg/day)
Atrial fibrillation associated with cardiac abnormalities (especially mitral stenosis, cardiomyopathy, previous myocardial infarction, dyskinetic or akinetic segments)	Warfarin (maintaining INR of 2–3)
Patients >65 years with chronic /paroxysmal atrial fibrillation and stroke risk factors but no significant cardiac disease	Warfarin (maintaining INR of 2–3)

patients with these disorders either relate to any underlying cardiac structural abnormality or the potential of these arrhythmias to be associated with appreciable or complete cessation of cardiac output. The consequences range from sudden cardiac death, to a global ischaemic encephalopathy and watershed infarction. The last occurs in cerebral border zone tissue at the intersection of the vascular supply from two major arteries and often involves brain supplied by both posterior and middle cerebral arteries. Cortical blindness can result as well as visual association and sensory modality infarction of the association cortex.

Endocarditis as a cause of stroke

There are three forms of endocarditis which may predispose a patient toward cerebral infarction. The most common, infectious endocarditis, is caused by the colonisation of an abnormal native valve or a valvular prosthesis with an infectious agent which may be bacterial, fungal, or occasionally viral. Infective endocarditis can also occur on a structurally normal valve usually secondary to an overwhelming septicaemia with an exceptionally virulent organism. The second form is marantic or non-bacterial thrombotic endocarditis, which usually occurs in a seriously debilitated patient. Under these circumstances a hypercoagulable state exists, resulting in the formation of platelet-fibrin excrescences on intact valves.²⁴ A third form of endocarditis occurs in the course of specific diseases. Possibly the best known is Libman-Sachs endocarditis associated with systemic lupus erythematosus.

INFECTIOUS ENDOCARDITIS

Neurological complications are not infrequent after infective endocarditis. The presentation may be focal (due to cerebral infarction or haemorrhage) or diffuse. Embolisation from valvular vegetations, or the rupture of an artery secondary to infective arteritis can occur producing focal effects. Inflammation within the artery to which septic material has embolised may cause the formation of a mycotic aneurysm which can subsequently rupture. Diffuse neurological manifestations (alterations in the level of consciousness or a toxic confusional state) may be consequent on mul-

tiples small microemboli lodging in the distal cerebral vasculature. Multifocal petechial haemorrhages may occur as a result of disseminated intravascular coagulation producing generalised neurological impairment without focal findings. Other causes for altered levels of consciousness and non-focal neurological findings may include the metabolic derangements that can occur as a result of organ failure—including renal insufficiency—which are not infrequent in this condition.

Several studies have investigated the incidence of neurological abnormalities in infective endocarditis. Most of these have confirmed the relative rarity of intracerebral haemorrhage in this disease and that treatment with antibiotics rather than with anticoagulants provides optimal prophylaxis of embolism. Corr *et al* reported 14 patients with neurological sequelae.²⁵ Four presented with subarachnoid haemorrhage; five had intracerebral haematomas; four presented with cerebral infarction, and one with seizures. All underwent arteriography. Ten of the 14 (71%) had a single aneurysm, and four (29%) had multiple aneurysms. Two thirds of the aneurysms were located in the peripheral cerebral vasculature, the most common site being in the distal middle cerebral artery. Patients were treated with antibiotics and 33% showed complete resolution of their aneurysms after six weeks of treatment. Of the remaining aneurysms, a third showed no change in size, 17% decreased in size, and 17% showed an increase in size. No new aneurysms were detected. However, in a meta-analysis of available studies, Hart *et al* showed that aneurysms occurred in only 1.6% of 1284 patients in recent patient series and were associated with streptococcal infections.²⁶ It was indicated that many of these mycotic aneurysms, if unruptured, heal with antibiotic therapy and therefore do not require investigations to detect their asymptomatic presence.

The incidence of embolism during the course of infective endocarditis was investigated in a retrospective study by Davenport *et al*; 18% of such patients presented with an embolic stroke.²⁷ This usually occurred within three days after the diagnosis and the start of antimicrobial therapy. There was a low incidence of stroke recurrence (9%) once antibiotic treatment was started. Bioprosthetic valves were associated with a lower stroke risk than mechanical prostheses. Anticoagulation did not confer any benefit to recurrence of embolism once antibiotics were started. A brain haemorrhage was the presenting neurological event in 8% of patients. Anticoagulation therapy was not associated with an increased risk of cerebral haemorrhage.

The timing of surgical intervention in those patients with infective endocarditis who developed neurological complications was studied by Eishi *et al*.²⁸ Of 181 patients in this retrospective analysis who underwent surgery, 10% had preoperative cerebral complications (ischaemic stroke, intracerebral haemorrhage, or cerebral abscess). The preoperative mortality associated with these neurological conditions was 11%. If surgical intervention

Table 2 Incidence of neurological events after cardiac surgery (data from studies reviewed in the text)

Neurological event	Incidence (%)
Persistent cognitive deficits	20–40
Reversible encephalopathy	3–12
Stroke	3–6
Seizures (in children)	3

occurred within four weeks of the cerebral event, there was a very high rate of mortality or debilitating stroke (varying from 70% on the first day to nearly 20% at the fourth week). After this time mortality and morbidity were significantly reduced (7%).

Hart *et al* analysed the cause of intracranial bleeding in 17 patients with infective endocarditis and suggested that anticoagulation treatment was a major contributing factor.²⁹ Nearly two thirds of these haemorrhages occurred within 48 hours of admission. In this study, anticoagulation was considered to have contributed to intracranial haemorrhage in 24% of these patients whether or not the haemorrhage was symptomatic. Proved mycotic aneurysms were found in only 12% of haemorrhages. The authors suggested that mycotic aneurysms were uncommon and underlay only a fraction of intracranial haemorrhages. Masuda *et al* suggested that most haemorrhages occurred in an area of antecedent cerebral infarction.³⁰ They concluded that the likely mechanism was rupture of a vessel inflamed by septic arteritis, the infected embolic material having initially caused an ischaemic infarct. Salgado *et al* studied 68 patients with infective endocarditis presenting with a mycotic aneurysm and 147 patients with endocarditis without mycotic aneurysm.³¹ Over an average of 40 months of follow up, no rupture of mycotic aneurysms or subarachnoid haemorrhage occurred in 121 patients discharged after a full course of appropriate antibiotic therapy. They concluded that the risk of rupture of a mycotic aneurysm (suspected or unsuspected) was low after an adequate course of antibiotic therapy. However, they suggested that arteriograms should be performed in all patients with infective endocarditis who experienced a focal neurological syndrome even if associated with good recovery.

The effect of antibiotics on the natural history of infective endocarditis and the incidence of vegetations was reviewed by Hart *et al*; 212 patients were studied, of whom 21% developed a stroke during the course of their illness. Intracerebral haemorrhage occurred in 7%²⁶; 113 patients underwent transthoracic echocardiography of whom 53% were found to have identifiable vegetations. The presence of vegetations did not correlate with the risk of embolisation. This lack of association might have been different if patients had been studied with transoesophageal echocardiography. Nearly 75% of strokes occurred before the start of antibiotic therapy. Stroke recurrence was 0.5%/day, usually in the context of uncontrolled infection. Cerebral haemorrhage in this group of patients was more often encountered in intravenous drug misusers and was associated with *Staphylococcus aureus* infection. It was

concluded that recurrent embolisation was rare once the infection was controlled with antibiotics, and that surgery or the introduction of anticoagulant therapy was not warranted to prevent recurrent embolisation. *Staphylococcus aureus* infection was also more often associated with neurological complications than other infective agents. Transient ischaemic attacks occurred in 8% of the patients.

NON-BACTERIAL THROMBOTIC ENDOCARDITIS

The neurological presentation of non-bacterial thrombotic endocarditis is very similar to that of infectious endocarditis and occurs often as a terminal event in patients debilitated by malignancies or AIDS. However, the incidence of primary intracerebral haemorrhage is less. The emboli themselves may contain tumour particles, the heart being a not infrequent site of metastases. Often, these patients have a hypercoagulable state which, when combined with dehydration, metabolic abnormalities, and inactivity, can lead to vegetations containing platelet fibrin being deposited on native valves. Acquired deficiencies of the antithrombotic cascade can also be seen in patients with malignancies. A large Japanese study of 3408 consecutive necropsied elderly patients identified 86 cerebral infarcts of cardiac origin.³² Of these, 11% were attributed to non-bacterial thrombotic endocarditis. Graus *et al* identified non-bacterial thrombotic endocarditis in 18.5% of necropsied cancer patients with neurological complications.²⁴ The clinical presentation was most often a diffuse encephalopathy rather than a focal abnormality such as ischaemic stroke or intracerebral haemorrhage.

Neurological complications of cardiac surgery

The neurological complications of cardiac surgery can be considered as either focal or global, and in both cases may be either transient or permanent. Focal neurological complications include transient ischaemic attack and stroke, but may also encompass cerebral abscesses and focal infections of the nervous system in immunosuppressed patients with cardiac transplants. The most frequent neurological presentation is as a decline of cognitive function (table 2). This may have many causes, including cerebral hypoperfusion, systemic infections, metabolic abnormalities, medications, and possibly some aetiopathological phenomena specific to cardiac surgery. The last may include focal microdilations of arterioles identified within the brains of patients dying after coronary artery bypass grafting and thought to be caused by air or fat microembolisation after the release of aortic cross clamping.

The incidence of neurological complications is difficult to assess. This is particularly true of cognitive decline. The neuropsychological examination and instruments used vary from institution to institution and may have a wide range of specificities and sensitivities dependent on their nature, how they are administered, and by whom. The same is also true of the diagnosis of perioperative stroke.

In the study of Egloff *et al* of 3593 patients undergoing open heart surgery, 2% suffered focal strokes, of which nearly 25% were fatal.³³ The principal aetiologies were: (a) an embolus from the ascending aorta; (b) embolisation from the ascending aorta or a cardiac valve; (c) left ventricle or left atrial thrombus; (d) air embolus; (e) cardiac arrest; (f) cerebral haemorrhage; (g) unknown but possibly related to a high grade ipsilateral internal carotid artery stenosis, or a 50% stenosis of both internal carotid arteries.

Hupperts *et al* explored the possibility that global cerebral hypoperfusion might be responsible for the postoperative complications of cardiac surgery.³⁴ They reasoned that if this were the case, then these patients would be more likely to show neurological abnormalities on CT in a watershed distribution. Of 37 patients who sustained perioperative strokes after surgery, about one third developed watershed regional infarcts. However there was no difference in the perioperative and intraoperative haemodynamic status between the groups with watershed infarction and focal strokes in other locations. They concluded that cerebral hypoperfusion was not a frequent cause of stroke in such patients. Recently Redmond *et al* prospectively followed up 1000 patients undergoing cardiac operations and bypass, of whom 71 had a previously documented stroke.³⁵ They found a significantly higher incidence of focal neurological signs in such patients. These deficits included a new stroke in 8.5%, the re-emergence of a previous deficit in 26.8%, and worsening of previous deficits in 8.5%. The last two presentations were not associated with new neuroimaging abnormalities. The one month mortality rate was greater in patients with a previous stroke (7%) compared with those without such a lesion (0.7%).

The nature of the cardiac surgery has been correlated with the likelihood of a neurological complication: Cernaianu *et al*³⁶ suggested that the lowest stroke rate occurred with aortic valve replacements (0.9%). Interestingly, severe aortic atherosclerosis with calcinosis was identified in 43% of patients who developed neurological complications, but in only 5% of patients who did not. This would suggest embolisation of atherocalcareous debris in the aetiology of strokes in these patients. About 14% of patients who developed perioperative cerebral infarction had also had a previous stroke. The aortic cross clamping time was almost twice as long in patients with postoperative stroke compared with those who remained neurologically pristine. Bypass time was also about one third longer. Surgery for congenital heart conditions, whether in children or in adults, has been associated with a comparatively low incidence of neurological sequelae: Litasova *et al* found an incidence of 3.5% in 3141 patients.³⁷ Application of Luria's tests identified cognitive abnormalities in 15% of patients. These neurological complications were not associated with the time of circulatory arrest, but rather fluctuations in blood pressure. However, the patients in this study underwent perfusionless deep hypothermia, and therefore it may not be pos-

sible to extrapolate these findings to the general population of patients undergoing cardiac surgery. Kuroda *et al*³⁸ found that the incidence of neurological complications was higher in patients with coronary artery bypass grafting (11%) than in patients who underwent valve surgery (7%). The factors predictive of CNS complications included: previous stroke and the length of time on bypass. However, patients undergoing coronary artery bypass grafting were older and had a significantly greater incidence of hypertension, diabetes, and previous stroke.

Seizures are the most common neurological complication in children undergoing cardiac surgery. Usually these are benign and transient. In a retrospective study, Fallon *et al* reported that neurological events (coma, seizures, encephalopathy, and focal neurological changes) occurred in 31 of 523 children who had undergone corrective cardiac surgery for the treatment of structural cardiac lesions.³⁹ The information was gathered from analysis of the senior registrar's discharge summary. Seizures occurred in 16 of 31; postoperative pyramidal signs were found in 11 of 31, and extrapyramidal signs in eight of 31. The highest incidence of neurological abnormalities was seen after repair of aortic arch abnormalities (17%). A significant association was found between neurological abnormalities and the duration of bypass and low perfusion pressure.

In a retrospective study, Furlan *et al* detected an ipsilateral stroke incidence of 1% during coronary artery bypass grafting in patients with 50%-90% carotid stenosis.⁴⁰ In patients with more than 90% stenosis, the stroke rate rose to 6.2%. In a small recent study, Hertzler *et al* showed that 8.7% of 23 patients who underwent coronary artery bypass surgery and who were also known to have >70% stenosis of the carotid arteries sustained a stroke in the perioperative period.⁴¹ However, whether these strokes occurred principally within the territory of the stenotic vessel was not discussed.

The best method of treatment of patients with severe coronary artery disease and stenosis of the extracranial vasculature has yet to be decided. In some centres, simultaneous carotid endarterectomy and coronary artery bypass grafting are performed. Alternatively a staged procedure may be contemplated in which the extracranial vessel with the highest degree of stenosis is surgically treated first. As yet there is no conclusive evidence whether any of these interventions, or indeed no intervention at all, is the best course to pursue. Klima *et al* performed simultaneous carotid endarterectomy and open heart surgery in 89 patients.⁴² These patients either had symptomatic carotid artery disease or asymptomatic haemodynamically relevant stenosis of 50%-60%. Neurological complications occurred in five of 89, four of whom had had previous strokes. They considered that the perioperative neurological complication rate in these patients undergoing simultaneous procedures was about 5%.

The risk of cardiac surgery in patients who have had recent strokes is unclear. Maruyama

Figure 1 Transoesophageal echocardiogram showing a large thrombus attached to the lateral wall of the left atrium and a second one attached to the left atrial ceiling (underneath the aortic root). Intra-atrial thrombus formation is particularly common in patients with severe left ventricular dysfunction with enlarged left atria and diminished transmitral flow, causing intra-atrial blood stasis characterised as spontaneous echocardiographic contrast. Patients with such abnormalities are at a high risk of cerebral embolic ischaemic events.

et al studied 14 patients with acute cardiogenic stroke who required cardiac surgery for infective endocarditis or other reasons within a mean of 5.3 days from stroke onset; two patients developed a severe and fatal cerebral haemorrhage and four patients deteriorated (of whom three developed septic emboli in the perioperative period).⁴³ They suggested that patients who had had a large cardiogenic cerebral infarction were the most likely to develop severe perioperative neurological events.

Atrial fibrillation may contribute to the incidence of perioperative stroke. This arrhythmia is common after cardiac surgery, occurring in about 5%-40% of patients. Several authors have identified a three to fivefold increase in stroke risk in such patients.⁴⁰ However, the Cleveland Clinic experience has not shown any significant increase in the incidence of perioperative stroke in patients who developed atrial fibrillation compared with those who did not.⁴⁰

Mills has investigated the incidence of neurocognitive abnormalities after coronary artery bypass grafting and reported an incidence varying from 60%-80% one week after surgery, to 20%-40% two months after operation.⁴⁴ The incidence of severe diffuse encephalopathy after open heart surgery may vary from 3% to 12%, but subtle and persistent cognitive abnormalities may be identified at a later stage in up to 30% of patients undergoing coronary artery bypass surgery.⁴⁰ Moody *et al* identified intracerebral arteriolar dilatations in patients who died during or shortly after coronary artery bypass surgery.⁴⁵ These were thought to represent gas or fat emboli and may contribute to cognitive impairment. Others have suggested that the impairment relates to reduction in cerebral blood flow. Although various authors have indicated that cerebral autoregulation is disturbed during open heart surgery, as yet there is no convincing evidence that clinical outcome relates to a reduction in intraoperative cerebral blood flow. However, it is likely that the cerebral metabolic rate for

oxygen decreases during bypass inducing a concomitant physiological decrease in cerebral blood flow, thus confounding the interpretation of blood flow measurements in these conditions. Newman *et al* showed that patients who undergo a cognitive decline after open heart surgery may have a significant genetic predisposition.⁴⁶ A significant association between the occurrence of postoperative cognitive decline and the finding of the apolipoprotein E ϵ 4 allele was found in a multivariate analysis of patients with and without cognitive decline. The allele has recently been associated with both genetic and sporadic forms of Alzheimer's disease.

Structural heart disease and stroke

The risk of cerebral vascular embolism increases with progressive loss of ejection fraction in patients with left ventricular dysfunction caused by acute myocardial infarction.⁴⁷ Similarly, patients with primary cardiomyopathies are known to be at an increased risk for cardioembolic events as left ventricular function deteriorates from moderate to severe in magnitude (left ventricular ejection fraction <40%).⁴⁸ In both groups of patients, intraventricular thrombus formation is enhanced by blood stasis and possibly by loss of the dense subendocardial trabeculation which is characteristic of the normal heart (fig 1). This is particularly true in the case of left ventricular aneurysms formed as a consequence of acute myocardial infarction. The network of subendocardial trabeculae may function as many small compartments able to produce high levels of intracavitary force during systole, propelling blood away from the endocardial surface during left ventricular contraction. The development of endocardial damage in addition to ventricular dilatation further enhances the favourable environment for endocardial thrombus formation and peripheral embolism. However, acute myocardial infarction, even without significant global systolic dysfunction, can often lead to intraventricular thrombus formation because of the associated loss of trabeculation. This is particularly true when infarction is localised to the anteroapical segments of the left ventricle, secondary to occlusion of the left anterior descending coronary artery.⁴⁹

Progressive left atrial enlargement with atrial fibrillation can result from chronic mitral valve disease. Rheumatic mitral stenosis is well known for its accompanying risk of cerebral embolisation. Unfortunately, in many cases cerebral infarction is the mode of clinical presentation in patients with mitral stenosis.⁵⁰ In moderate or severe mitral stenosis left atrial dilatation is common with accompanying enlargement of the left atrial appendage. This structure is particularly prone to serve as a nidus for thrombi in patients with mitral stenosis, because of concomitant blood stasis which appears in the echocardiogram as spontaneous echocardiographic contrast (fig 2). Even before atrial fibrillation develops, patients with mitral stenosis with enlarged left atria are at an increased risk for stroke.⁵¹

Figure 2 (A) Transoesophageal echocardiogram from a 72 year old woman with thrombus which was mobile during the examination. (B) As the transducer is rotated from right to left, the lateral aspect of the left atrial appendage is seen entirely filled by the thrombus.

Isolated mitral regurgitation is associated only rarely with intra-atrial thrombus formation. Severe mitral regurgitation is often complicated by pronounced left atrial dilatation with accompanying enlargement of the left atrial appendage. However, because the regurgitant jet produces constant motion of blood inside the chamber, the chances of thrombus formation are greatly reduced. After mitral valve replacement or even repair, the atrium remains dilated and blood flow is generally reduced in most cases, leading to an increased risk of cerebral embolism.⁵² The presence of mechanical as opposed to bioprosthetic artificial valves increases manifold the risk of thromboembolic events in patients with mitral valve replacement, requiring continuous and strict anticoagulation. Chronic therapy with warfarin is mandatory in these patients (INR levels should be maintained around 3 units at all times).

Recently, some interest has been expressed in the addition of aspirin to warfarin in the prevention of embolisation from prosthetic heart valves. The hypothesis is that the two agents affect different clotting mechanisms and when combined have an additive effect significantly reducing embolisation. Turpie *et al* investigated the long term effects of this combined therapy in a randomised placebo controlled trial of the addition of 100 mg aspirin or placebo to warfarin (INR maintained between 3 and 4.5) in patients with either mechanical heart valves or bioprosthetic valves plus atrial fibrillation or a history of thromboembolism.⁵³ They showed that the combination therapy significantly reduced the incidence of major systemic embolism or death from any cause (relative risk reduction of 65% from 11.7% to 4.2%) over an average follow up period of 2.5 years. As expected there was a significant increase in major bleeding episodes in the combination therapy group (relative risk increase of 27% from 10% to 13%). They concluded that the combination therapy under these circumstances reduced mortality, especially from vascular causes and that this offset the morbidity from major bleeding episodes.

Mitral annulus calcification is a common finding in elderly hypertensive patients or patients with chronic renal disease. The presence of this abnormality has been corre-

lated with an increased risk of stroke.⁵⁴ However, its value as an independent predictor of cerebrovascular embolism is difficult to show because of its frequent association with other known determinants of stroke such as atrial fibrillation, left atrial enlargement associated with diastolic dysfunction, and arterial hypertension. However, anecdotal documentation of an intra-atrial thrombus attached to a severely calcified mitral annulus is not rare in a busy transoesophageal laboratory.

Other mitral valve anomalies have a more tenuous aetiological relation with stroke. Mitral valve strands have been postulated as a source of cardiogenic cerebral embolism, but the strength of this relation is still unknown. Myxomatous degeneration of the mitral valve (often associated with mitral valve prolapse) has often been cited as a cause of stroke and equally contested in the literature.⁵⁵ Partly, the problem is due to the frequent finding of this anomaly in the normal, asymptomatic population as well as in stroke patients. Although it is possible that patients with severe mitral myxomatous changes are at a slightly increased risk for stroke, the association is weak. In addition, patients with this condition who develop severe mitral regurgitation due to chordal rupture are unlikely to develop intra-atrial thrombi because of the protective effect of the regurgitant stream of blood which leads to high intra-atrial blood flow.

Aortic valve diseases themselves, except for the case of aortic valve vegetations (see above) or the much rarer aortic valve elastic tumours, are rarely the source of cerebral embolism. Calcific embolisation in the setting of chronic calcific aortic stenosis has been reported but is uncommon. Left atrial myxomas are also rare but may embolise to the brain or peripherally. Embolic events due to other cardiac tumours are exceedingly rare.

Congenital cardiac defects can be associated with paradoxical cerebral embolism as a consequence of peripheral venous thrombi or right sided cardiac thrombi passing across inter-atrial or interventricular communications as well as aortic-pulmonary windows. This may occur with atrial septal defects because the flow across them is commonly bidirectional. Paradoxical embolisation across ventricular septal defects is less common unless Eisenmenger

Figure 3 Cross sectional echocardiogram of the descending aorta immediately below the aortic arch obtained by the transoesophageal approach. The aorta has severe atherosclerosis with mobile debris reflecting ruptured atherosclerotic plaque with superimposed thrombus formation. This aortic lesion represents a potential source of peripheral embolism and when located in the ascending aorta or aortic arch is associated with an increased risk of cerebral embolism and infarction.

physiology is present (pulmonary hypertension increasing intrapulmonary vascular resistance and favouring flow from the right to the left side of the heart). This is now rare given the improvements in pediatric care. The emboligenic role of paradoxical embolisation across a patent foramen ovale is also controversial.⁵⁶ It is most likely that a patent foramen ovale is a risk factor for stroke when accompanied by pulmonary hypertension (particularly when caused by pulmonary embolism), right ventricular dysfunction due to myocardial infarction, cor pulmonale, or left heart failure with secondary pulmonary hypertension. It is also very likely that a patent foramen ovale represents the mechanism of stroke in the presence of venous thrombosis and the demonstration of intracardiac right to left shunting by contrast echocardiography at rest or during manoeuvres induced to cause simultaneous oscillation in right and left atrial pressures such as coughing and the Valsalva manoeuvre. However, the importance of paradoxical embolisation through a patent foramen ovale in stroke patients without venous thrombosis or right sided disease is less clear. Patent foramina ovals are common in many healthy people and thus, its importance as an isolated risk factor for stroke is still under intense investigation.

Finally, the presence of significant atherosclerosis in the ascending aorta and aortic arch represents a potential source of cerebral embolism. Patients undergoing cardiac surgery are at a particularly high risk of stroke from aortic atherosclerotic disease because aortic cannulation is often performed during cardiopulmonary bypass. The magnitude of aortic atherosclerosis has been directly related to the risk of developing cerebral embolism with the presence of mobile aortic arch emboli as the most significant lesion predicting cerebral ischaemia (fig 3).⁵⁷

Neurocardiology: brain-heart interactions

Much emphasis has been placed on the heart as a possible cause of neurological disease either as a source of focal embolisation or as a result

of global hypoperfusion. Recent attention has been paid to the mechanisms whereby brain pathology could influence cardiac function. There has been considerable evidence over the past 50 years to suggest that patients with acute stroke may develop various cardiac abnormalities.⁵⁸ These include left axis deviation, and various repolarisation abnormalities including QT interval prolongation, septal U waves, and ST segment changes.⁵⁸ The incidence of these abnormalities is highest after intracerebral haemorrhage, particularly subarachnoid haemorrhage, in which they may be seen in 60%-70% of patients; after ischaemic stroke the abnormalities may be seen in about 15%-20% of patients.⁵⁸ Evidence suggests that these changes (which persist for a variable period of several days to possibly even a few months) are not due to coexistent coronary artery disease, but possibly to a neural mechanism. Recent attention has shifted to the insular cortex as a possible cortical site of generation of some of these changes. For example, the ECG changes can be mimicked in experimental models of middle cerebral artery occlusion including the insula.⁵⁹ In addition, prolonged insular stimulation may also simulate these changes.⁶⁰ Our recent investigations in the rat suggest that the left insular cortex is primarily concerned with parasympathetic cardio-motor control and that the right insula is concerned with sympathetic vasomotor and cardiac control.⁶¹ It is suggested that damage to the left insular cortex is particularly associated with cardiac sympathetic neural upregulation. In this regard, a recent study of patients with acute stroke has shown that lesions predominantly confined to the left insula area may be particularly prone to produce these ECG abnormalities and an increase in cardiac sympathetic nerve activity (assessed by spectral analysis).⁶² Such shifts towards increased cardiac sympathetic dominance are strongly predictive of sudden cardiac death after myocardial infarction and may contribute to the excess cardiac mortality which comprises the major cause of death after stroke.⁶³

Conclusion

Recent advances in cardiac imaging including the wider application of transoesophageal echocardiography have shown that the heart and the aorta can be important sources of cerebral emboli in many stroke patients. Even in those with significant extracranial vascular disease structural cardiac lesions may be identified, making the decision regarding the cause of stroke and its treatment an increasingly complex problem. In addition, recent research has confirmed the anecdotal reports that acute intracerebral lesions including stroke may affect cardiac structure and function. The recognition of these important interactions between the heart and the brain has generated recent studies investigating the optimum management of patients with cardiogenic stroke as well as the clinical relevance of stroke effects on the heart and how this may influence subsequent outcome and prognosis. This promises to be a fascinating area of multidisciplinary

research in which we can expect to see important new developments with major impact on the prophylaxis of stroke and care of our stroke patients.

- 1 Bevan H, Sharma K, Bradley W. Stroke in young adults. *Stroke* 1990;21:382-6.
- 2 Gagliardi R, Benvenuti L, Frosini F, et al. Frequency of echocardiographic abnormalities in patients with ischemia of the carotid territory—a preliminary report. *Stroke* 1985;16:118-20.
- 3 Albers GW, Comess KA, De Rook FA, et al. Transesophageal echocardiographic findings in stroke subtypes. *Stroke* 1994;25:23-8.
- 4 Wolf PA, Dawber TR, Thomas HE, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973-7.
- 5 Kannel WB, Abbott RD, Savage DB, et al. Epidemiologic features of chronic atrial fibrillation. *N Engl J Med* 1982;306:1018-22.
- 6 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med* 1987;147:1561-4.
- 7 Kanter MC, Tegeler CH, Pearce LA, et al. Carotid stenosis in patients with atrial fibrillation. Prevalence, risk factors, and relationship to stroke in the stroke prevention in atrial fibrillation study. *Arch Intern Med* 1994;154:1372-7.
- 8 Bogousslavsky J, Van Melle G, Regli F, et al. Pathogenesis of anterior circulation stroke in patients with non-valvular atrial fibrillation: the Lausanne Stroke Registry. *Neurology* 1990;40:1046-50.
- 9 Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influences on early and long term prognosis (Oxfordshire community stroke project). *BMJ* 1992;305:1460-5.
- 10 Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with non-rheumatic atrial fibrillation. *Stroke* 1989;20:1000-4.
- 11 Petersen P. Thromboembolic complications in atrial fibrillation. *Stroke* 1990;21:4-13.
- 12 Shively BK, Geland EA, Crawford MH. Regional left atrial stasis during atrial fibrillation and flutter: determinants and relation to stroke. *J Am Coll Cardiol* 1996;27:1722-9.
- 13 Chimowitz MI, De Georgia MA, Poole RM, et al. Left atrial spontaneous echo contrast is highly associated with previous stroke in patients with atrial fibrillation or mitral stenosis. *Stroke* 1993;24:1015-9.
- 14 Laupacis A, Cuddy TE. Prognosis of individuals with atrial fibrillation. *Can J Cardiol* 1996;12(suppl A):14-16.
- 15 Bogousslavsky J, Adnet-Bonte C, Regli F, et al. Lone atrial fibrillation and stroke. *Acta Neurol Scand* 1990;82:143-6.
- 16 Sohara H, Amitani S, Kurose M, et al. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1997;29:106-12.
- 17 Gustafsson C, Blomback M, Britton M, et al. Coagulation factors and the increased risk of stroke in non-valvular atrial fibrillation. *Stroke* 1990;21:47-51.
- 18 Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. *Stroke* 1985;16:182-8.
- 19 Candelise L, Pinardi G, Morabito A. Mortality in acute stroke with atrial fibrillation. The Italian Acute Stroke Study Group. *Stroke* 1991;22:169-74.
- 20 Boysen G. Anticoagulation for atrial fibrillation and stroke prevention. *Neuroepidemiology* 1993;12:280-4.
- 21 Anderson DC. Progress report of the stroke prevention in atrial fibrillation study. *Stroke* 1990;21:12-17.
- 22 EAFT study group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-62.
- 23 Miller VT, Rothrock JF, Pearce LA, et al. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. *Neurology* 1993;43:32-6.
- 24 Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine* 1985;64:16-35.
- 25 Corr P, Wright M, Handler LC. Endocarditis-related cerebral aneurysms: radiologic changes with treatment. *AJNR Am J Neuroradiol* 1995;16:745-8.
- 26 Hart RG, Foster JW, Luther MF, et al. Stroke in infective endocarditis. *Stroke* 1990;21:695-700.
- 27 Davenport J, Hart RG. Prosthetic valve endocarditis 1976-87. Antibiotics, anticoagulation, and stroke. *Stroke* 1990;21:993-9.
- 28 Eishi K, Kawazoe K, Kuriyama Y, et al. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. *J Thorac Cardiovasc Surg* 1995;110:1745-55.
- 29 Hart RG, Kagan-Hallet K, Joerns SE. Mechanisms of intracranial hemorrhage in infective endocarditis. *Stroke* 1987;18:1048-56.
- 30 Masuda J, Yutani C, Waki R, et al. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. *Stroke* 1992;23:843-50.
- 31 Salgado AV, Furlan AJ, Keys TF. Mycotic aneurysm, subarachnoid hemorrhage, and indications for cerebral angiography in infective endocarditis. *Stroke* 1987;18:1057-60.
- 32 Yamanouchi H, Tomonaga M, Shimada H, et al. Non valvular atrial fibrillation as a cause of fatal massive cerebral infarction in the elderly. *Stroke* 1989;20:1653-6.
- 33 Egloff L, Laske A, Siebenmann R, et al. Cerebral insult in heart surgery. *Schweiz Med Wochenschr* 1996;126:477-82.
- 34 Hupperts R, Wetzleer W, Heuts-van Raak L, et al. Is haemodynamic compromise a specific cause of border zone brain infarcts following cardiac surgery? *Eur Neurol* 1995;35:276-80.
- 35 Redmond JM, Greene PS, Goldsborough MA, et al. Neurologic injury in cardiac surgical patients with a history of stroke. *Ann Thorac Surg* 1996;61:42-7.
- 36 Cernaianu AC, Vassilidze TV, Flum DR, et al. Predictors of stroke after cardiac surgery. *J Card Surg* 1995;10:334-9.
- 37 Litasova EE, Lomivirov VN, Borbatich JN, et al. Deep hypothermia without extracorporeal circulation in surgery of congenital cardiac defects. *J Cardiovasc Surg* 1994;35:45-52.
- 38 Kuroda Y, Uchimoto R, Kaieda R, et al. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. *Anesth Analg* 1993;76:222-7.
- 39 Fallon P, Aparicio JM, Elliott MJ, Kirkham FJ. Incidence of neurological complications of surgery for congenital heart disease. *Arch Dis Child* 1995;72:418-22.
- 40 Furlan A, Sila C, Chimowitz M, et al. Neurologic complications related to cardiac surgery. *Neurol Clin* 1992;10:145-66.
- 41 Hertzner NR, Loop FD, Beven EG. Surgical staging for simultaneous coronary and carotid diseases: a study including prospective randomization. *J Vasc Surg* 1989;9:455-63.
- 42 Klima U, Wimmer-Greinecker G, Harringer W, et al. Surgical management of coronary heart disease and simultaneous carotid artery stenosis. *Wien Klin Wochenschr* 1993;105:76-8.
- 43 Maruyama M, Kuriyama Y, Sawada T, et al. Brain damage after open heart surgery in patients with acute cardioembolic stroke. *Stroke* 1989;20:1305-10.
- 44 Mills SA. Cerebral injury and cardiac operations. *Ann Thorac Surg* 1993;56(suppl):S86-91.
- 45 Moody DM, Bell MA, Challa VR. Brain microemboli during cardiac surgery or aortography. *Ann Neurol* 1990;28:477-86.
- 46 Newman MF, Croughwell ND, Blumenthal JA, et al. Predictors of cognitive decline after cardiac operation. *Ann Thorac Surg* 1995;59:326-30.
- 47 Loh E, StJohn Sutton M, Wun CC. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;336:251-7.
- 48 Kyrle PA, Kornringer C, Gossinger H. Prevention of arterial and pulmonary embolism by oral anticoagulants in patients with dilated cardiomyopathy *Thromb Haemost* 1985;54:521-6.
- 49 Hellerstein HK, Martin JW. Incidence of thromboembolic lesions accompanying myocardial infarction. *Am Heart J* 1947;33:443-6.
- 50 Jordan RA, Scheifley CH, Edwards JE. Mural thrombosis and arterial embolism in mitral stenosis; a clinicopathological study of fifty-one cases. *Circulation* 1951;3:363-77.
- 51 Hwa JJ, Li YH, Lin JM, et al. Left atrial appendage function determined by transesophageal echocardiography in patients with rheumatic mitral valve disease. *Cardiology* 1994;85:121-8.
- 52 Harker LA. Antithrombotic therapy following mitral valve replacement. In: Duran C, ed. *Recent progress in mitral valve disease*. London: Butterworths, 1984:340-8.
- 53 Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;329:524-9.
- 54 Benjamin EJ, Plehn J, D'Agostino R, et al. Mitral annular calcification and the risk of stroke in the elderly. *N Engl J Med* 1992;327:374-9.
- 55 Wolf PA, Sila CA. Cerebral ischemia with mitral valve prolapse *Am Heart J* 1987;113:1308-12.
- 56 Haussman D, Mugge A, Becht I, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992;70:668-72.
- 57 Davila Roman VG, Phillips KJ, Daily BB. Intraoperative transesophageal echocardiography and epiaortic ultrasound for assessment of atherosclerosis of the thoracic aorta. *J Am Coll Cardiol* 1996;28:942-7.
- 58 Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. *Neurological Clinics of North America* 1992;10:167-76.
- 59 Hachinski VC, Cechetto DF, Guiraudon C, et al. Asymmetry of the cardiovascular consequences of stroke. *Arch Neurol* 1992;49:697-702.
- 60 Oppenheimer SM, Wilson JX, Guiraudon C, et al. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? *Brain Res* 1991;550:115-21.
- 61 Kulshreshtha N, Zhang ZH, Oppenheimer SM. Effects of insular lesions on the rat baroreceptor reflex. *Society for Neuroscience Abstracts* 1996;22:157.2.
- 62 Oppenheimer SM, Martin WM, Kedem G. Left insular cortex lesions perturb cardiac autonomic tone. *Clin Auton Res* 1996;6:131-40.
- 63 Bigger J, Fleiss K, Steinman R, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164-71.