Progress in Cerebrovascular Disease

Management of Cerebral Embolism of Cardiac Origin

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SUMMARY The cardiac conditions most commonly associated with cerebral embolism are rheumatic heart disease (RHD), atherosclerotic heart disease (myocardial infarction and atrial arrhythmias) and other kinds of nonvalvular atrial fibrillation (AF). The natural history of cerebral embolism from these cardiac sources is reviewed. Virtually all rheumatic hearts producing embolus have mitral stenosis, but not all of them are in AF. Of patients with RHD, 10-20% will experience a systemic embolus, and approximately half will have a recurrence, usually early. Of patients with a myocardial infarction, 5-12% will have a clinically apparent systemic embolus, and one-third to one-half have a recurrence, usually early. As many as 10-20% of patients with non-rheumatic AF have a systemic embolus. Anticoagulation reduces systemic embolism to 10-20% of the natural incidence in RHD, and it reduces embolic recurrences to 10-20% of the natural recurrence rate. Anticoagulation diminishes the incidence of embolus in myocardial Infarction to 25% of the natural Incidence. It is not known what effect anticoagulation has on the incidence of embolism in nonrheumatic AF. The data regarding the effect of valvulotomy and prosthetic valve placement in RHD are briefly reviewed. Recommendations are made for the use and timing of anticoagulation based on the available data.

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I. Introduction

Cerebral embolism is a common cause of stroke yet it is usually not clinically possible to diagnose it with certainty. The diagnosis is frequently considered but a number of fundamental questions about cerebral embolism remain. Often a definite source for the embolus cannot be easily confirmed. There is uncertainty about the incidence of embolism in patients with non-fibrillating rheumatic heart disease (RHD), and in patients with fibrillating non-rheumatic heart disease. It is also not clear how likely a stroke is embolic in origin when it occurs in a patient with coronary artery disease but with no obvious evidence of a recent myocardial infarction. When the diagnosis of cerebral embolism is made, it is not certain whether anticoagulant therapy should be used and, if so, whether it should be given immediately or after a few weeks delay.

It has become clear that atherosclerotic disease in the extracranial cerebral arteries may act as a site of origin for material which can become emboli, and reach the retina and brain. While this kind of artery-to-artery embolism produces amaurosis fugax and, almost certainly, transient cerebral ischemic attacks, its role in producing sudden, major, completed strokes is less clear.

This review will examine the natural history of cerebral embolism associated with RHD and non-rheumatic heart disease and will review the effects of anticoagulant therapy and cardiovascular surgery on the morbidity and mortality in patients with cerebral embolism. Artery-to-artery embolism has separate treatment implications.

II. Natural History

A. Cardiac Source of Emboli

The criteria used for making a diagnosis of cerebral embolism vary. Clinically, the diagnosis is usually made when a patient with RHD, especially with atrial fibrillation (AF), or coronary artery disease with either AF or a recent myocardial infarction, has a stroke with an abrupt onset but without subarachnoid hemorrhage. More recently, the diagnosis is often considered in patients with chronic sinoatrial disorder and a prolapsing mitral valve. These criteria may exclude elderly patients with ventricular mural thrombi in whom a recent myocardial infarction cannot be demonstrated and they may include some elderly patients with non-rheumatic AF who actually have a thrombotic cerebral infarct. The criteria for diagnosing cerebral embolism in autopsy series usually includes the finding of an embolic source, the tendency to hemorrhagic infarction and multiple arterial occlusions.

The clinical features of cerebral embolism will be reviewed along with the autopsy, angiographic and surgical findings in the brain and in other organs.

1. Clinical Presentation

While the usual cerebral embolus manifests itself with the abrupt onset of focal cerebral dysfunction, approximately 13% of patients have vague prodromal symptoms in the minutes or hours preceding the embolism. These symptoms may include a "stuttering" focal neurologic deficit related to the cerebral territory of the subsequent infarct and may be due to one or more small preliminary emboli. Fisher suggested that the focal stuttering of symptoms may result from an incomplete vascular occlusion resulting in the...
3. Laboratory and Radiographic Findings

Lumbar puncture performed shortly following a cerebral embolism is nearly always normal. Wells states that of 21 patients, except for the patient with bacterial endocarditis, only 2 patients had more than 5 RBC or 5 WBC/cu mm in the cerebrospinal fluid (CSF). While the CSF is usually normal following a cerebral embolism, except when associated with bacterial endocarditis, Fisher and Adams state, "hemorrhage in the meninges in some, though not in every case, may be so extensive as to cause a moderately sanguinous cerebrospinal fluid (therefore, brain embolism should be included in the apoplectic disorders causing subarachnoid hemorrhage)."

Computed tomographic (CT) scanning may visualize the location and extent of cerebral infarction. The CT scan can support the clinical diagnosis of cerebral embolism by demonstrating hemorrhagic or multiple infarcts. However, embolic injury may appear as a single low density area compatible with pale infarction. Petechial hemorrhages within the area may not visualize as increased density tissue because when superimposed on the low density infarct the average tissue density is near that of normal brain.

4. Neuropathology

Fisher and Adams examined the pathology in 373 cerebral infarcts "with vascular occlusion" and 18% of them were hemorrhagic. They state that nearly 100% of the hemorrhagic infarcts were embolic in origin. Conversely, only 50% of embolic infarcts were hemorrhagic (if that many, since the etiology of the infarct was undetermined in one-third of cases). Adams and Vander Eecken later reported that 65% of embolic infarcts were hemorrhagic. Thus, nearly all hemorrhagic infarcts and many non-hemorrhagic infarcts are embolic in origin. The hemorrhages are usually petechial, involving primarily the grey matter of the cerebral hemisphere, but sometimes there is frank hemorrhage with hematoma formation extending into the white matter.

5. Source of Cerebral Emboli

Patients with RHD or atherosclerotic heart disease constitute the overwhelming majority of adults with cerebral emboli arising from the heart. Atrial myxoma, fat emboli, septic material, tumor, venous clots with a right-to-left cardiac shunt, congenital heart disease, cardiomyopathy, non-bacterial thrombotic endocarditis, mitral annulus calcification, and prolapsing mitral valves make up a small group. Idiopathic AF as an etiology for arterial embolization will be discussed with atherosclerotic AF. Emboli from prostatic heart valves and intraoperative emboli during cardiac surgery are special considerations.

a) Rheumatic Heart Disease. RHD has been reported as the predominant cause of cerebral embolism in the past. Most patients with rheumatic hearts have
mитral stenosis and some also have mitral insufficiency and aortic valve disease. The thrombi form in the left atrium, which is usually enlarged, but only half of the clots are in the atrial appendage. Occasionally, thrombi form on the valve itself.

Several authors report that only 55-82% of rheumatic hearts are fibrillating (or obviously changing rhythm) at the time of the embolization. Of Wells' 53 patients with cerebral embolism, half had normal sinus rhythm. However, 7 of these 25 had bacterial endocarditis as their embolic source, rather than a primary left atrial thrombus. Even so, AF is not the "sine qua non" for cerebral embolism. While as few as 55-82% of rheumatic hearts that produce emboli are fibrillating, a fibrillating heart has a several times greater chance of releasing emboli than one in normal sinus rhythm. These observations reflect the fact that the majority of rheumatic hearts with mitral stenosis are in normal sinus rhythm. The presence of AF and low cardiac output increase the risk of systemic emboli whereas the severity of mitral stenosis, as judged by valve area, may not correlate with the occurrence of emboli.

Systemic emboli occur in 9-49% of RHD patients followed over several years, with the average being 15-20%. The higher figures come from autopsy series in which a careful search was made for embolic infarcts. Twenty to 70% of these systemic emboli are cerebral, 40% being the average, with the higher figures coming from clinical series. Though many of the series reported are small and retrospective, it is clear that cerebral embolism is common in patients with RHD, even when they appear to be in a stable sinus rhythm.

b) Atherosclerotic Heart Disease. 1) Myocardial Infarction. It is well known that myocardial infarction causes ventricular mural thrombi to form which may then break away to become emboli in the arterial circulation. Cumulative data from a number of reports indicate that approximately 45% (with a range of 17-83%) of lethal myocardial infarctions have associated mural thrombi. These thrombi are most common when the infarct is large, when it involves the septum (particularly a through and through infarct) and when there is associated congestive heart failure. Juergens states that three-fourths of myocardial infarcts with ventricular aneurysm formation have thrombi in the aneurysm.

Though some authors report the incidence of peripheral emboli following acute myocardial infarction as low as 2-3%, and cerebral emboli in 10-90% of them, other studies from autopsied patients with myocardial infarction have shown peripheral infarcts, presumably embolic, in from 45% to 60% with approximately half of them being cerebral. Although the very high incidence reported by some authors occurred in patients who died and in whom the diagnosis was made by a careful search for infarcts at autopsy, it is clear that the incidence is substantial in this very common cardiac disease. Asymptomatic emboli must be common, perhaps 2-3 times as common as symptomatic ones.

In a recently reported clinical series of 783 consecutive patients with myocardial infarction, 1.7% had a stroke. However, the stroke rate was 4.7% for the third of patients with the largest infarcts as evidenced by cardiac enzyme elevation in the plasma. Fulton and Duckett suggest identifying patients at risk for thromboemboli by monitoring plasma fibrinogen concentration. Additionally, the use of 2-dimensional echocardiography to demonstrate ventricular mural thrombi in patients following myocardial infarction may prove useful in identifying patients at risk for systemic emboli.

Of considerable importance is the time of occurrence of cerebral emboli after an acute myocardial infarction. Bean found that 11% occur in the first week after the infarction, 33% in the second week and 16% in the third week. The fact that nearly two-thirds occur in the first 3 weeks has clear therapeutic implications. Another 24% occur in the fourth week, 6% in the second month and 8% in the third month. This latter group of patients with "delayed" emboli may have little or no residual evidence of their myocardial infarction even with a history suggesting an embolic event.

2) Atrial Fibrillation. A matter of some importance and controversy is the issue of whether thrombi are prone to form in the left atrium of patients with AF not due to RHD or other identifiable valvular disease. Friedberg states that emboli are rarely caused by a fibrillating heart without RHD and he advises against anticoagulating such patients. Beer reported 295 autopsies of patients with a clinical diagnosis of atherosclerotic heart disease without obvious myocardial infarction. He found evidence of peripheral emboli in 0.8% of those patients known to have been in normal sinus rhythm and in 2.0% in those known to have been in AF (i.e., 2 emboli in 243 patients without fibrillation and one embolus in 52 with fibrillation). He concluded that peripheral embolization is uncommon in patients with atherosclerotic heart disease without myocardial infarction, regardless of the cardiac rhythm. This author excluded another 8 emboli from an atrial source because he discovered atrial infarction or abnormal heart valves. These patients should not be discarded from the overall statistics when one is managing patients only with clinical data, that is, with a clinical diagnosis of non-rheumatic AF. There is other evidence to suggest that "arteriosclerotic" and idiopathic AF may cause systemic emboli. Aberg reported an autopsy study of 506 patients with AF but no valvular disease or congenital heart lesions. Half of them had myocardial infarction and the other half had other manifestations of atherosclerotic or hypertensive heart disease, or some other illness. Of these patients 13.7% had left atrial, not ventricular, thrombi. Systemic emboli were found in 41.7%, half of these to the brain. Thus, 20% of these patients with AF and no valvular disease had cerebral emboli. Darling et al. reported a clinical series of 260 consecutive patients with arterial emboli of whom 97 had arteriosclerotic AF. One-third of these 97 patients had associated myocardial infarction and two-thirds...
had only atherosclerotic heart disease and fibrillation. Thus, nearly 20% of all systemic emboli occurred in patients with atherosclerotic heart disease with AF but without myocardial infarction. They noted that about 70% of their patients had AF, with atherosclerosis being the most common cause. It is surprising that they had no patients with RHD and normal sinus rhythm. This may mean that some of their “arteriosclerotic fibrillators” in fact had RHD with left atrial thrombi. Nevertheless, these patients were in the atherosclerotic age group (average age 72 years) and clinically they had arteriosclerotic AF.

In an autopsy study of 333 patients with AF, Hinton and co-workers found embolism to be nearly as common without RHD (59 of 171 or 35%) as with mitral valve disease (29 of 70 or 41%). In 20% of the non-RHD patients they found thrombus in the left atrium.

Wolf and colleagues recently provided valuable prospective epidemiological data from the Framingham Study assessing the risk of embolic stroke in patients with chronic AF. While AF with RHD had a 17-fold increased risk of stroke, compared to the general population, chronic idiopathic AF had a 5.6-fold increase.

Fogarty found that among 300 consecutive patients with systemic emboli, 183 had arteriosclerotic AF as the source. That is, 61% of all emboli were due to arteriosclerotic AF. The basis for his statement is not clear, however.

Fisher reported 100 patients with AF and cerebral embolism. The underlying heart disease was non-valvular in 83. He also described another group of 48 unselected patients with AF, though it is not clear how many had non-valvular disease, who were followed prospectively for 4 years. Thirty-five percent of them suffered a typical embolic stroke. Friedman and associates also showed that “...atrial fibrillation in the absence of myocardial infarction, congestive heart failure, or rheumatic heart disease was strongly associated with stroke.”

Fairfax and associates described 100 patients with chronic sinoatrial disorder. Sixteen of them had evidence of systemic emboli and multiple episodes occurred in 6. Fifteen of the 16 patients had the bradycardia-tachycardia syndrome. An additional 41 patients with chronic ventricular bradycardia and atrial flutter or fibrillation had an embolic prevalence of 7.3%. These authors believe that “impaired atrial function appears to be a key factor in predisposing to intracardiac thrombosis, and paroxysmal supraventricular tachycardia increases the risk of subsequent embolization.”

All things considered, AF without obvious RHD is a major source of cerebral emboli.

Systemic embolism is a particular risk when the atrial rhythm is changing. One to two per cent of patients undergoing cardioversion for AF will experience an embolus in the first few days. The risk exists whether the AF is rheumatic or idiopathic in origin. Bjerkelund and Orning noted fewer emboli in those patients anticoagulated at the time of cardioversion. Other investigators cite the low incidence of cardioversion associated emboli and recommend anticoagulating only high risk patients.

Mitrail Valve Prolapse. Recently, several workers described the neurological disturbances in several patients with a prolapsing mitral valve and the data to support their belief that the abnormal valve was the source of emboli. Whether this common disorder is a substantial cause of cerebral embolism is not yet known but it is worth consideration, particularly in young patients without another obvious source of ischemic stroke.

Cardiomyopathy. Cardiomyopathy may be associated with systemic emboli particularly if there is associated congestive heart failure or cardiac arrhythmia. Emboli are more common in those patients with idiopathic or alcoholic cardiomyopathy where from 35–100% of patients at autopsy have mural thrombi present. Because of the risk of systemic emboli, long-term anticoagulation should be considered in patients with moderate or severe cardiomyopathy.

6. Evaluation

The nature and extent of the cardiac evaluation in a patient with cerebral infarction is largely determined by the degree of suspicion that cardiogenic embolism may have occurred. Every patient with a stroke should be carefully questioned for a history suggesting RHD, cardiac arrhythmia and myocardial infarction. Examination of the heart should concentrate on auscultation for abnormal heart sounds. A chest x-ray will determine the heart size and configuration and an electrocardiogram will identify rhythm and conduction abnormalities.

A more extensive cardiac evaluation should be undertaken in patients in whom the suspicion of embolism is high. They include the young, those with a history of heart disease, those with evidence of multifocal or hemorrhagic infarcts and those with seizures at onset. Continuous electrocardiographic monitoring may demonstrate an intermittent arrhythmia and an echocardiogram may disclose mitral valve disease, an intracardiac thrombus or tumor and akinetic segments of myocardium.

In patients with myocardial infarction, the clinical and electrocardiographic findings, along with the results of cardiac enzyme determinations, fluoroscopy and radionuclide scanning, may identify those patients with large infarcts, ventricular aneurysms, congestive heart failure and other factors which predispose to peripheral embolism.

7. Prognosis and Embolism Recurrence Rate

The immediate mortality from cerebral embolism is about 25–35% and the immediate morbidity in survivors is approximately the same. Thus, approximately 50–70% of patients die or suffer major morbidity immediately. The need to identify and treat prophylactically those patients at risk for cerebral embolism is obvious. Though it is often stated that one-
half to two-thirds of all patients with cerebral embolism will die within one year, largely because of their serious primary cardiac disease, this estimate is not well-documented. However, in Daley’s long-term follow-up study,44 half of the patients with RHD without bacterial endocarditis ultimately died of cerebral embolism. Wells noted that advanced age, prodromal symptoms, loss of consciousness and/or seizures at onset, and failure to improve within 48 hours, were factors that correlated with a “poor outcome.”

a) Recurrence Rate of Embolization in RHD. The natural recurrence rate of cerebral and systemic embolization is from 30–75% in patients followed for varying periods of time.34, 40, 43, 47, 48, 54 The 75% comes from Carter’s clinical series with the longest follow up, from 6 to 12 years.49 Approximately one-half to two-thirds of recurrent emboli occur in the first year and Szekely noted that 40% occurred in the first month.44 Darling,43 in his 10 year follow up study, noted a 56% recurrence rate for systemic embolism: 16% in 2-4 days and 18% in 5-14 days. Thus, one-third of recurrences occurred within 2 weeks of the initial embolism.

Daley42 reported 194 patients with RHD without bacterial endocarditis and 115 of them had a total of 201 recurrent emboli. Thirty-two occurred in the first week and 41 occurred between the second and fourth week. Thus, one-third of the total recurrences occurred in the first month.

b) Recurrence Rate of Emboli in Atherosclerotic Heart Disease. Davies and Pomerance40 reported 74 patients at autopsy with chronic AF, 62% of whom had thrombi in the left atrial appendage. While they didn’t analyze this group of 46 patients by specific diagnosis, they did state that only 18 of the 74 patients had RHD. That is, most of the patients with atrial appendage thrombi had some form of heart disease with AF other than RHD.

1) Myocardial Infarction. As noted previously, Bean40 reviewed a number of reports in the literature which showed that approximately 45% of patients who die following a myocardial infarction have thrombi in the left ventricle. Of the 300 patients in Bean’s series, 60 had 78 systemic emboli, of which only 8% were cerebral. That is, 20% of his patients with myocardial infarction had a systemic embolus and one-third of those had a recurrence. He states that an additional 38 instances of “thrombotic” infarction occurred. Forty-four percent of the emboli occurred in the first 2 weeks following the myocardial infarction and the number had risen to 60% by the end of the third week and to 84% by the end of the first month.

Darling49 reported that in 28 patients with systemic emboli following myocardial infarction, in 7 (25%) subsequent emboli occurred, with 5 of the 7 (71%) recurrences within 14 days of the preceding embolism. If the patients who had AF with their myocardial infarction were added to the myocardial infarction only group, the recurrence rate for the total group was 21 of 52 patients, or 40%. Half of these recurrences occurred within 14 days of the initial embolus.

2) Arteriosclerotic Atrial Fibrillation (without myocardial infarction). Darling49 reported that in 59 patients with systemic emboli, twenty-five (42%) had subsequent emboli. Of the recurrences, 48% occurred within 2 weeks, 24% between 2 weeks and 4 months, and 28% between 4 months and 5 years.

Therefore, not only do non-rheumatic fibrillators embolize, but they have a 42% chance of recurrent embolization, usually early.

III. Treatment

A. Anticoagulation

Anticoagulation has been found to be a highly beneficial treatment in the prevention of systemic, including cerebral, emboli in patients with a cardiac source for emboli.47, 48, 52-54 Some of the data supporting this treatment are derived from prospective studies in patients without a previous embolus and some from the effect of anticoagulation on prevention of recurrence of emboli. In RHD, the natural recurrence rate of approximately 50% is reduced to 5-25%.44 In patients with lethal myocardial infarction, the 45% natural occurrence of mural thrombi is halved by anticoagulation and the incidence of clinical cerebral embolism is diminished to approximately one-fourth of the natural incidence.45-47 Although there is still controversy about the overall efficacy of anticoagulation in the acute phase of myocardial infarction,48 there is general agreement that the risk of cerebral embolism is greatly reduced by this therapy. While the effect of anticoagulation in patients with non-rheumatic AF is not known, in part because these patients are usually not given anticoagulants, 40% of Darling’s patients with arteriosclerotic AF and systemic emboli, had atrial thrombi present at autopsy.49 This observation suggests that these patients also may benefit from anticoagulation. While there is little question about the efficacy of anticoagulation in the prevention of cerebral embolism in “at risk patients,” there is considerable debate about when anticoagulation should be initiated and how long it should be continued. Because it was recognized that cerebral embolism often produced hemorrhagic infarcts, many clinicians feared that early treatment with anticoagulant would result in grossly hemorrhagic infarcts with worsening of the morbidity and mortality. In 1956, Symonds stated that, “anticoagulant drugs should not be used in case of cerebral embolism, for in these cases hemorrhage into the area of infarction often occurs, probably as the result of displacement or fragmentation of the embolus . . . .”43 He gave no evidence, however, to support his view.

Moyes et al.44 and Wood et al.44 have presented experimental evidence related to this problem. Both studies involved the injection of vinyl acetate into the carotid artery of dogs followed by anticoagulation with warfarin derivatives. Moyes reported that 25% of control animals, and 50% of anticoagulated animals, die in the first 30 hours. Total occlusion of the internal carotid artery was common and the control animals had no grossly hemorrhagic infarcts. Even though
these animals were excessively anticoagulated, this report is evidence for avoiding anticoagulant in acute cerebral infarction but the pathogenesis clearly relates more to cerebral thrombosis than cerebral embolism. Wood’s findings were very similar. In an experiment perhaps more analogous to the human embolism situation, Sibley produced embolic cerebral infarcts in 36 dogs by injecting homologous clot fragments into the internal carotid artery. Six animals from both the control and anticoagulated groups died in the first 24 hours following the embolism and the infarcts were pathologically identical in the 2 groups. Only one of the 12 survivors in the control series died more than 24 hours later. Most of these animals were anticoagulated 24 hours prior to producing embolism. Also, the prothrombin time was more than 3 times the control value in 3 of the 4 late deaths and approximately 5 times control in the fourth. Sibley concluded that anticoagulant should be avoided in the treatment of patients who have suffered recent cerebral infarction due to embolism. He also suggested that the prothrombin time should be returned to normal as soon as possible in patients who have a cerebral embolism on anticoagulant. Wright and McDevitt, on the other hand, reported no excess of hemorrhage or mortality with anticoagulation.

Carter, in 1957, reported on 29 patients with RHD and showed that anticoagulation was clearly beneficial and that early treatment was desirable. He also showed that those patients on anticoagulant who died had “no sign of intracranial bleeding, and the infarcted areas were surrounded by the usual small area of hemorrhage.” In 1965, Carter updated his findings in a report of 130 patients with 176 episodes of cerebral embolism. He confirmed his previous view that “treatment with anticoagulants has significantly improved the prognosis of cerebral embolism in relation to immediate outcome, late survival and recurrence”. Also, Fleming and Bailey noted only 5 systemic emboli in their 217 patients treated with long-term anticoagulation, for an embolus rate of 0.8% per patient-treatment year.

Our interpretation of these data is that anticoagulant in experimental animals probably makes cerebral infarcts more hemorrhagic but probably doesn’t affect mortality; meager human studies appear to show a beneficial effect on both morbidity and mortality when anticoagulant is used immediately following the cerebral embolization, in spite of anecdotal reports of patients on anticoagulant dying with grossly hemorrhagic infarcts.

However, on the issue of immediacy of anticoagulation, Carter concluded that “the results show no significant gain from the immediate use of anticoagulants in patients whose neurological lesion is persistently complete. If anticoagulants are to be used in these patients an interval of three weeks should elapse before commencing treatment.” This view does not seem well founded and is of considerable clinical importance. Carter appears to have based his view on the following: “Wells (1959) found an increased number of red cells in the CSF of some patients treated with anticoagulants within 48 hours of their cerebral embolism and noted that in these the results ‘were bad.’ Similar reports of serious bleeding after anticoagulation came from de Morsier and Tissot and Ushiro and Schaller; it seemed likely that, if a major infarction of the brain had occurred after the embolic episode, it was probably of the hemorrhagic type, and unlikely to be helped by anticoagulation.” In fact, Wells’ data support immediate anticoagulation and only suggest that anticoagulants might be avoided if the CSF is hemorrhagic. Ushiro and Schaller supply no evidence that anticoagulation was detrimental for cerebral embolism. In addition, because of this concern Carter avoided immediate anticoagulation whenever it seemed likely that a major infarction of the brain had occurred and he therefore supplied no evidence of his own to support or refute his view.

Since Carter found “the survival rate improved significantly in patients with incomplete or fluctuating lesions (in whom ischemia is more likely than infarction) when anticoagulants were used in the early stages,” and “in all patients the recurrence rate was high immediately after the initial cerebral embolism,” we conclude, as did Marshall, that immediate anticoagulation should be initiated in all patients with cerebral embolism in whom the CSF is not hemorrhagic and the neurologic deficit is not massive and persistent beyond 24 hours.

Aside from the concern about converting a white infarct into a hemorrhagic one, bleeding is a risk and occurs in as many as 20% of patients on prolonged therapy. While it is usually minor or transient, especially with short-term therapy, several studies report a mortality rate of 0.5–1.0%.

B. Cardiac Surgery

The role of cardiac surgery in the prevention of arterial embolization is becoming clearer. Several authors provide evidence to indicate that valvulotomy protects against later arterial embolization and in a follow-up period of "a few months to four years," Belcher reported late emboli in only 1% of his 430 patients after operation. Other investigators on the other hand, present data indicating that valvulotomy provides no protection against subsequent emboli. The operative mortality for the valvulotomy itself is in the range of 3–9% and another 6–20% if so of patients suffer an intraoperative arterial embolism. Also of note is the belief of some that atrial appendagectomy at the time of valvulotomy is beneficial in preventing subsequent emboli, at least if the appendage is large. Others believe that appendagectomy is of limited or no value.

It therefore seems that when the operative morbidity and mortality are added to the equivocal benefit of the surgery, mitral valvulotomy cannot be generally recommended for the prevention of arterial embolization.
While newer valves and techniques have resulted in low operative mortality, recent studies of mitral valve replacement showed an overall hospital mortality of 5-22%. In addition to the operative mortality there is a significant incidence of arterial embolism in the late post-operative period. Some studies show that the rate of occurrence of embolism is highest in the early months and years after valve placement. Starr reported an occurrence rate of 7% in a 3 year follow up, with half in the first month and the other half in the first year. Friedli reported a 16% occurrence of emboli in 170 patients followed a mean of 26 months after valve placement with a decreasing incidence of emboli with time. Others have shown that the incidence is significantly higher in the longer term follow up studies. Fishman, for example, reported that 22% of patients had an embolus in 5 years of follow up. The use of new model valves results in embolic rates of 5% over 3 years. Thus, it appears that mitral valve replacement cannot be generally recommended as a treatment for the prevention of arterial emboli even though recent technical improvements are diminishing the operative and postoperative mortality and morbidity associated with this surgery.

**IV. Conclusions and Recommendations**

Cerebral embolism producing the abrupt onset of a major, focal neurological deficit usually has its thrombus source in a diseased left heart. Headache, seizures and transient loss of consciousness in this setting increase the likelihood of cerebral embolism over cerebral thrombosis. There is usually no blood in the CSF as occurs with ruptured aneurysms and vascular malformations and with most intracerebral hemorrhages.

The most common kinds of heart disease associated with cerebral emboli are rheumatic and atherosclerotic (i.e., coronary artery disease). The rheumatic heart with a left atrial thrombus invariably has mitral stenosis, the atrium is commonly enlarged and 1/2 to 2/3 are fibrillating or changing rhythm. The chances of emboli are several times higher with AF than with normal sinus rhythm. Approximately 15-20% of patients with non-rheumatic AF will have emboli. Additionally, risk factors may include atrial enlargement, the bradycardia-tachycardia syndrome and congestive heart failure. Among those patients who have emboli, 1/3 to 1/2 will have a recurrence, half of them within the first 2 weeks. We believe that the senile and coronary artery diseased heart without valvular disease is underestimated as a cause of cerebral embolism.

Anticoagulation reduces systemic embolism to 10-20% of the natural incidence in RHD. It also reduces embolic recurrences to about 10-20% of the natural recurrence rate.

Anticoagulation diminishes the incidence of emboli in myocardial infarction to 25% of the natural incidence.

It is not known what effect anticoagulation has on the incidence of embolism in non-rheumatic AF.

We agree with Marshal, based on the evidence available, that any patient with a probable cerebral embolism from any cardiac source should be anticoagulated immediately, provided bacterial endocarditis is unlikely and there is no blood in the CSF and no hematoma on CT scan. This recommendation is based on the high probability of a second embolus occurring, very likely in the next 1-3 weeks. This can be accomplished by immediate heparin or warfarin administration. We give 7,500 units of heparin intravenously followed by 1,000-2,000 units per hour by intravenous drip infusion monitored to maintain the activated partial thromboplastin time at twice normal. This regimen is maintained for the first several days during which the patient is monitored for hemorrhagic complications and evaluated. Then, a warfarin derivative can be administered and when the prothrombin time is 2 to 2-1/2 times normal, the heparin is discontinued.

If the embolic source is self-limited or treatable, anticoagulation should be discontinued when the high risk period has passed. For myocardial infarction this is after about 3 months. For a treatable cardiomyopathy it may be several weeks after cardiac function is normal. Following conversion of non-valvular AF it may be a few weeks after sinus rhythm appears to be successfully maintained.

If the embolic source cannot be eliminated, anticoagulation should generally be continued indefinitely. This includes any patient with RHD, even if the mitral valve is replaced or the AF is successfully converted to normal sinus rhythm. It also includes the patient with non-valvular AF, persistent cardiomyopathy and possibly mitral valve prolapse, who has had one or more systemic emboli.

The role of anticoagulation in the prevention of emboli in the at risk patient with no prior history of embolism is less clear. In myocardial infarction, the risk of systemic embolism increases with increasing infarct size, congestive failure and ventricular aneurysm formation. Consequently, patients with large infarcts should be started on warfarin and anticoagulation should be maintained at least during the 3 month high risk period. Those with echocardiographically dem-
onstrated mural thrombi should be heparinized and then converted to warfarin.

All patients with prominent RHD are at risk for systemic embolism and should be anticoagulated with warfarin indefinitely. This includes patients with obvious mitral stenosis, a large left atrium, congestive heart failure, AF, and echocardiographically demonstrated atrial thrombi. Whether the benefit of long-term anticoagulation outweighs the risk in patients with lesser degrees of RHD is unclear. The role of long-term anticoagulation in patients with non-valvular AF with no evidence of systemic embolism also is unclear. However, these patients are clearly embolus prone and if there are no significant contraindications we favor anticoagulation for an indefinite period.

The best treatment for cerebral embolism is prevention and, therefore, we believe that more vigorous treatment of patients with thrombus-prone heart disease is indicated. Virtually all patients with moderate to severe RHD, large myocardial infarcts and many patients with nonvalvular AF should be prophylactically anticoagulated.

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Summary of 12th Conference on Cerebrovascular Disease

Williamsburg, Virginia, March 2–4, 1980

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THE 12TH CONFERENCE on Cerebrovascular Disease was held in Williamsburg, Virginia, March 2–4, 1980. The first session of the Conference was devoted to a review of functional imaging of the brain with in vivo biochemistry and perfusion studies.

The initial presentation was "Scanning Systems and Analytical Methods using Positron Emission Tomography" given by Dr. Marcus E. Raichle of the Washington University School of Medicine, St. Louis MO. He described current detector isotope strategy mentioning that oxygen-15, nitrogen-13, carbon-11 and fluoride-18, which have half-lives of 2, 10, 20 and 110 minutes respectively, were the radioactive substances currently in use. The detector resolution capability is about 6.0 mm at present and the theoretical lower limit of resolution is about 1.5 mm. Sodium iodide detectors are commonly used but more sensitive detectors, such as those made with bismuth germanate and cesium fluoride, are being developed.

Dr. Raichle reported that brain blood volume, cerebral metabolism, tissue chemical composition, cerebral blood flow and the permeability of the blood-brain barrier can be measured by positron emission tomography. He reviewed the details of measurement of cerebral blood flow with a PET scanner and showed examples of scans using H2O18 in patients with stroke.

He reported that there are now available many radio-labeled pharmaceuticals whose action and localization can be traced through the central nervous system. Utilization and consumption of metabolites can be measured using radioactive oxygen in water or in carbon dioxide.

Functional mapping of metabolism in the brain using positron emission tomography in animals was discussed by Dr. Martin Reivich of the University of Pennsylvania. He commented that there are very tight spatial links between function and anatomy in the rat; stimulating one whisker can cause a localized increase in blood flow and cerebral metabolism as demonstrated by the autoradiographic appearance of the rat brain. Dr. Reivich discussed his experience using fluorodeoxyglucose to study visual, tactile and auditory stimuli and their effect on local cerebral metabolism in man. In 6 human subjects, visual stimuli were applied to the left visual field which immediately produced a higher metabolic rate in the right visual cortex and when the right visual field was stimulated, the left visual cortex showed increased blood flow and metabolism. Tactile stimuli to one hand was accompanied by an increase of blood flow and metabolism in localized areas of the cerebral cortex in the contralateral sensory areas. Auditory
Management of cerebral embolism of cardiac origin.
J D Easton and D G Sherman

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