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Intracranial Hemorrhage and Infarction in Anticoagulated Patients with Prosthetic Heart Valves

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SUMMARY In 1 year 6 patients with prosthetic heart valves (PHVs) treated with anticoagulants suffered intracranial hemorrhage. In 4, hemorrhage occurred into the site of a recent non-hemorrhagic infarction. In the others, both of whom had endocarditis, hemorrhages probably occurred as the result of rupture of a mycotic aneurysm. Five patients were treated with warfarin, 1 with heparin. In all patients the level of anticoagulant activity was greater than 1.5 times control. Five patients were in atrial fibrillation; 1 was hypertensive. The diagnosis of intracranial hemorrhage was made and its location and extent accurately determined by computed tomography

(CT). Three patients underwent surgery and 2 are alive with only minor neurological deficits. Among the 3 patients who did not undergo surgery 2 died and 1 is alive with a moderate neurological deficit. The management of PHV patients with use of anticoagulants is discussed in terms of the mechanisms involved in intracranial bleeding. Emphasis is placed on prevention of emboli, discontinuation of anticoagulants once non-hemorrhagic infarction has occurred and the primacy of CT scan in diagnosis when hemorrhage is suspected. The special problems of anticoagulation in the presence of endocarditis are also discussed.

A LARGE NUMBER of patients are now living with artificial non-organic prosthetic heart valves (PHVs). Although operative mortality and morbidity have been dramatically reduced, emboli and infection continue to be problems. In the absence of anticoagulants the frequency of

systemic and cerebral emboli is variable and has been related to the type of prosthesis, the covering of the prosthesis, and the cardiac rhythm.¹⁻⁷ After embolization serious disability and death frequently occur since the majority of symptomatic emboli lodge in the cerebral circulation.^{1, 2} At the N.Y.U. Medical Center the overall frequency of symptomatic emboli in 1,375 PHV patients in the 8 years between 1967 and 1975 was 11%. The overall frequency of fatal emboli was 1.5%.⁷ Anticoagulation has produced a marked reduction in the frequency of emboli

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from PHVs.¹⁻⁷ However, the therapy itself is often complicated by hemorrhage. Most of the bleeds are minor, involving the genito-urinary or gastrointestinal tract; serious or fatal intracranial bleeds represent the major therapeutic problem.^{4, 7-9} The development of intracranial bleeding has been related to the level of anticoagulant activity, concurrent or prior cerebral infarction, and arterial hypertension.¹⁰⁻¹⁷ An additional risk factor may be endocarditis.¹⁸⁻²⁰

We have encountered significant hemorrhage in 9.4% of patients treated with anticoagulants during an 8 year study period.⁷ The overall frequency of fatal hemorrhage was 1.0%. When cerebral hemorrhage occurs it must be differentiated from non-hemorrhagic infarction. While the patient with a hemorrhage is more likely to have a headache and become obtunded, variability in the mode of presentation requires laboratory confirmation. Cerebrospinal fluid examination by lumbar puncture traditionally has been the best available method for confirmation of intracranial bleeding. This technique will detect the presence of intracranial bleeding in 85% of patients.²¹ Lumbar puncture, however, carries a small but definite risk of transtentorial herniation in the presence of a unilateral mass lesion and raised intracranial pressure.^{22, 23} The anti-coagulated patient is also jeopardized by the additional risk of spinal epidural bleeding, sometimes with serious sequelae.^{24, 25} Once the diagnosis of intracranial bleeding has been made and surgical intervention is contemplated, further localizing information must be obtained.²⁶ Traditionally, this has required cerebral angiography, a procedure with intrinsic risks and an additional risk of significant bleeding at the arterial puncture site in the presence of anticoagulants.

The development of computed tomography (CT scan) has revolutionized the diagnosis of intracranial hemorrhage.²⁷⁻²⁹ Freshly extravasated blood is readily demonstrated on CT scan. After several days, however, there is clot resorption and one may no longer be able to discern the hemorrhage site. The majority of fresh hematomas have irregular and indistinct margins. They are usually associated with cerebral

edema and/or infarction manifested as a zone of decreased absorption surrounding the hematoma. Hematomas are often associated with a mass effect evidenced by ventricular compression and/or displacement of the pineal gland or choroid plexus. The CT scan is the first technique which is able, with 100% accuracy, to demonstrate the presence and extent of a fresh intracerebral hematoma during life.^{27, 29}

It is our purpose to present cases illustrating the variety of intracerebral bleeding encountered in patients with PHVs, to demonstrate the primary role of CT scanning in their diagnosis and to comment on their management.

Methods

Between 1967 and 1975 a total of 1,375 patients underwent 1 or more cardiac valve replacements at the N.Y.U. Medical Center. There were 602 aortic valve replacements (AVRs) including AVRs combined with coronary bypass or mitral commissurotomy. There were 773 patients with mitral valve replacements (MVRs) including MVRs combined with AVRs or tricuspid valve replacements or coronary bypass. The 602 patients with AVRs were analyzed separately from the 773 patients with MVRs in regard to the development of emboli and hemorrhages. There were 188 operative deaths among the 1,375 patients with operative mortality falling from 16.5% in 1968 to 9.6% in 1975.

The Starr Edwards cloth-covered metallic ball valve prosthesis was used and updated as newer models became available. Between 1967-70 anticoagulation was begun employing heparin for 4 days after operation and continued with warfarin titrated to 1½ times the control prothrombin time or to less than 20 seconds. During this period the incidence of emboli was approximately 2% a year among the patients with AVRs and approximately 3% a year among the patients with MVRs. In December, 1970, terminating anticoagulation was tried, stopping it 1 year following MVR and 3 months following AVR. After 18 months this resulted in an impressive increase in emboli in the patients with

TABLE 1. Intracerebral Hemorrhage in Anticoagulated Patients with PHVs

Patient	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	Mean
Age (yrs.)	51	58	68	79	63	55	61 yrs.
Valve	Aortic	Aortic	Mitral	Mitral	Mitral	Mitral Aortic	
Time from surgery (mos.)	23	7	54	8	36	2	22 mos.
Rhythm	AF	NSR	AF	AF	AF	AF	
PT*	3.6	2.1	2.4	1.7	Heparin	2.5	2.5
PTT*	4.7	2.3	1.9	1.5	Heparin	1.7	2.4
History of hypertension	No	Yes	No	No	No	No	
Endocarditis	No	No	No	No	Yes	Yes	
Recent infarct	Br. stem-cbll.	R. Occip.	R. Cb.	L. Cb.	L. Cb.	L. Cb.	
Days from infarct	3	1	6	1	60	6	3 dys.†
Location hemorrhage	Cbll.	R. Occip.	R. Frontal	L. Frontal	L. Frontal	L. Frontal-Parietal	
Hemorrhage related to infarct	Yes	Yes	Yes	Yes	No	Yes	

*PT; PTT expressed as multiples of control.

†Mean for the 5 infarcts thought to be causally related to the hemorrhage.

MVRs (22% a year). Consequently, in June, 1972, anticoagulation was resumed in MVR patients. The increase in emboli in non-anticoagulated patients with AVRs was less apparent; therefore, these patients were not treated with routine anticoagulation until 1975 at which time the benefits from anticoagulation were appreciated in all PHV categories.

During 1967–1975 among the patients with MVRs there were 60 non-fatal emboli; 43 occurred in the absence of anticoagulant therapy, 16 in association with anticoagulant therapy. In 1 patient the status of anticoagulation was uncertain. Additionally, there were 10 fatal emboli; all occurred in patients whose anticoagulation status was unknown. In the same period among patients with AVRs there were 37 non-fatal emboli: 26 occurred in patients not receiving anticoagulants; 8 occurred during anticoagulant therapy. In 3 patients the status of anticoagulation was uncertain. In addition, 6 fatal emboli afflicted patients in whom the status of anticoagulation was unknown.

During 1967–1975 a total of 1,187 patients were placed on anticoagulants. There were 111 non-fatal hemorrhages: 19 of these were major gastrointestinal, retroperitoneal or intracranial bleeds and 92 were minor bleeds (none intracranial). There were also 13 fatal intracranial hemorrhages. No intracranial hemorrhages occurred in non-anticoagulated patients.

The overall frequency of endocarditis was 5.7% with an approximately equal number of infections among patients with AVRs and MVRs. In these patients, in the absence of recent infarction, anticoagulation was continued when benefits were thought to exceed risks.

In a 1-year period (1975) 6 patients with PHVs all treated

with anticoagulants suffered intracerebral hemorrhages. No patients in this group received concurrent treatment with platelet inhibitor drugs. Only 1 patient of the 6 had pre-existing hypertension. Two patients had AVRs, 3 had MVRs. One had both an AVR and an MVR. The clinical course was complicated by endocarditis in 2.

Patient Number 1

A 51-year-old, right-handed female received an aortic valve replacement with a cloth-covered Starr Edwards prosthesis two years prior to admission (pta). She was in good health until 3 days pta when she developed vertigo, nausea and vomiting without headache. Symptoms disappeared the next day. However, on the day of admission similar symptoms reappeared and she developed a severe headache. There was no history of hypertension or previous cerebral infarction. On admission the patient was afebrile; blood pressure was 160/110 torr; she was drowsy but followed simple commands; the eyes exhibited dysconjugate movements; pupils were small and reactive. There was marked truncal ataxia; the patient was unable to stand or sit without support. Plantar responses were extensor bilaterally. An ECG showed atrial fibrillation (AF) with a rate of 110/min. Prothrombin time (PT) was 44.2 seconds with a control of 12.4 seconds. CT scan demonstrated an intracerebellar vermian hematoma (fig. 1). The hematoma was removed in surgery and the patient completely recovered.

Patient Number 2

A 58-year-old, right-handed male underwent an aortic valve replacement with a cloth-covered Starr Edwards prosthesis seven months pta. He was well until one day pta when he noted an inability to see parts of objects and words in his left visual field. He did not complain of headache. There was a history of mild systolic hypertension. Examination on admission revealed the patient to be afebrile; BP was 160/90 torr. He was awake and alert. On confrontation he had a partial left homonymous visual field deficit. There was no facial or extremity paresis. There was no nuchal rigidity. An ECG revealed normal sinus rhythm. PT was 24.8/11.9 seconds. Six hours after admission he complained of a severe headache and became drowsy. On re-examination he now had a dense left homonymous hemianopsia, a moderate left hemiparesis and nuchal rigidity. A CT scan revealed a large hematoma with surrounding edema and/or infarction involving the right occipital lobe with extension to the parietal lobe. The ventricles were compressed and shifted (fig. 2). Right carotid angiography failed to reveal an aneurysm. The hematoma was removed through a right occipital lobectomy. Postoperative examination revealed only a homonymous hemianopsia.

Patient Number 3

A 68-year-old female had rheumatic fever as a child and later developed mitral and aortic insufficiency. Nine years pta she suffered a right cerebral infarction from which she made a complete recovery. Four years pta an MVR was performed using a cloth-covered Starr Edwards prosthesis. She was in good health until 6 days pta, when she developed the

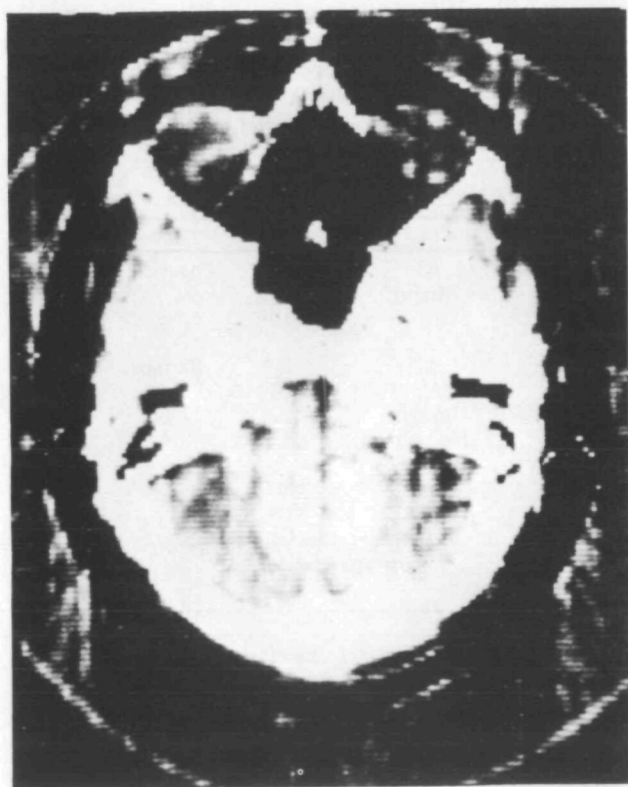


FIGURE 1. Intracerebellar vermian hematoma

sudden onset of headache, nausea and vomiting. Symptoms subsided after 3 days. However, on the day of admission the patient became confused and drowsy. There was no history of hypertension; the patient was afebrile; BP was 140/110 torr; she was confused but followed simple commands. There was a left central facial paresis. ECG revealed AF with a rate of 60. PT was 31.3/12.8 seconds. Within a few hours she became unresponsive and developed a left hemiparesis. CT scan demonstrated a dense, slightly mottled lesion without sharp margins surrounded by a zone of lucency in the right frontal lobe with right to left shift of the ventricles and the pineal gland (fig. 3). A right carotid angiogram failed to reveal an aneurysm. The hematoma was evacuated and initially after surgery the patient was awake. Anticoagulants were resumed. Twenty-four hours later the patient rebelled and died.

Patient Number 4

A 79-year-old, right-handed female had rheumatic fever in childhood and developed mitral stenosis. Four months pta she developed intractable congestive heart failure and underwent an MVR with a cloth-covered Starr Edwards prosthesis. She was well for 4 months. On the day prior to admission her daughter noted during a telephone call that the patient's speech was aphasic. This episode cleared and later the patient was noted to speak clearly. The next morning the patient was found in her apartment mute with a right hemiparesis. Examination on admission revealed a temperature of 37.8°C; BP was 130/60 torr. The patient was awake but did not speak or respond to verbal commands. She had a complete right hemiplegia. An ECG revealed AF; PT was 20.6/11.8 seconds. CT scan revealed a large homogenous density surrounded by an area of infarction and/or edema involving the entire left frontal lobe from the pole to the body of the lateral ventricle. There was intraventricular extension of the hemorrhage. There was no shift of midline structures. The lesion was considered inoperable. Anticoagulation was discontinued. The patient was given supportive care only. Over the course of a month she made a satisfactory recovery. She regained her ability to speak spontaneously, to follow complex commands and to use her right arm and leg.

Patient Number 5

A 62-year-old, right-handed female developed mitral and tricuspid insufficiency with atrial fibrillation 31 years pta. Twenty-four years pta she suffered a right cerebral infarction from which she made a complete recovery. Three years pta an MVR was performed using a cloth-covered Starr Edwards prosthesis. She was placed on warfarin but this was discontinued later because of hepatitis. She was well until two months pta when she suffered a left cerebral infarction. Anticoagulation was reinstituted. In the month pta she developed fever, malaise, and a new aortic murmur was heard. There was no history of hypertension. Examination on admission revealed a temperature of 38.3°C; BP of 120/50 torr. There was a residual right hemiparesis. ECG revealed AF with a rate of 84. On heparin PT was 15.5/12.2 seconds. Anticoagulation was continued. One blood culture was positive for *Staphylococcus aureus* and was begun on

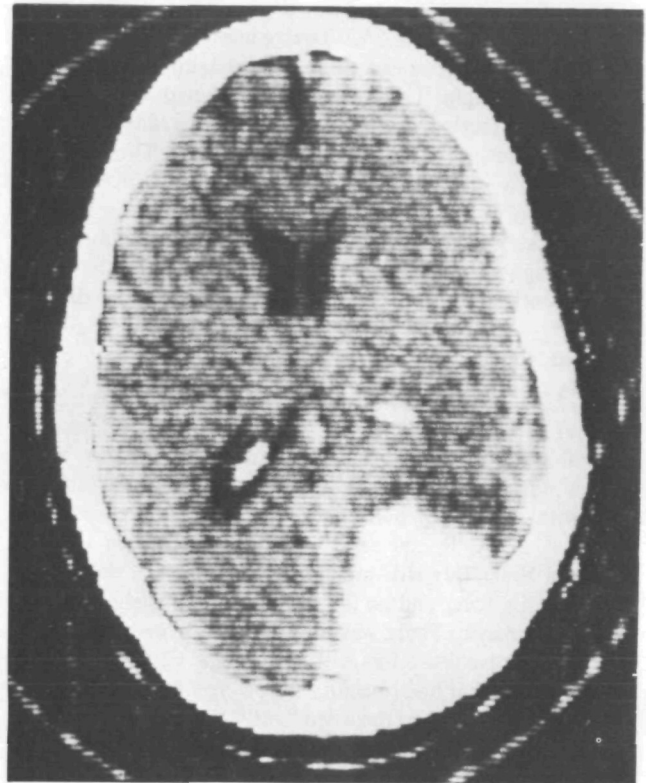


FIGURE 2. Right occipital hematoma partially surrounded by edema and/or infarction. The right choroid plexus is displaced anteriorly and the pineal gland is shifted from right to left.

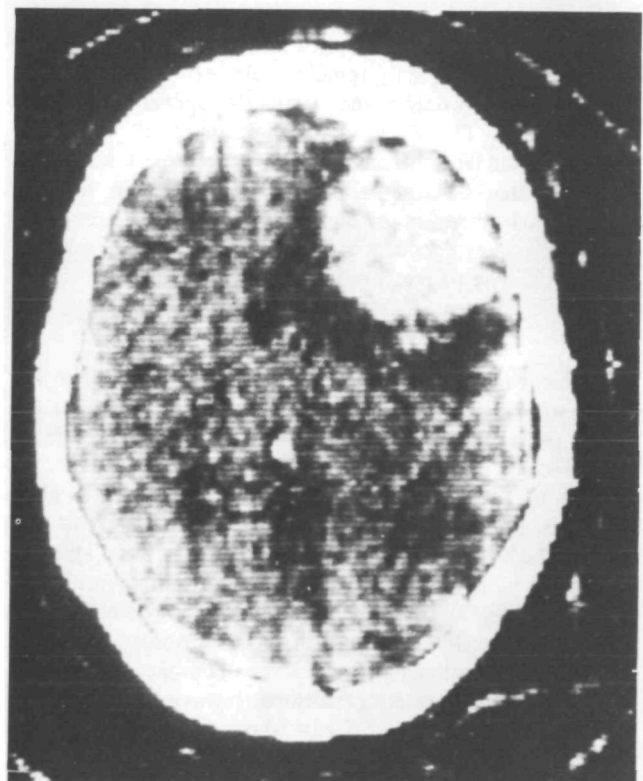


FIGURE 3. Right frontal hematoma surrounded by edema and/or infarction with right to left shift of the ventricles and pineal gland.

appropriate antibiotics. Two days after admission her temperature rose to 45.5°C. Twelve hours later she suddenly became unresponsive and exhibited fixed, dilated pupils, left greater than right. The patient was intubated and placed on high dose methylprednisolone (1,000 mg/day) therapy. Pupillary responsiveness to light returned. The CT scan revealed a non-homogeneous irregularly marginated hematoma in the left frontal lobe with extension into the ventricles. There was compression of the left and dilatation of the right lateral ventricle. Shortly thereafter she developed ventricular tachycardia and hypotension and died.

Patient Number 6

A 55-year-old, right-handed female presented with a history of rheumatic fever. She subsequently developed mitral and aortic insufficiency with atrial fibrillation. Three years pta she suffered a right cerebral infarction which left her with a mild left hemiparesis. Two months pta she underwent an AVR and an MVR, both employing a cloth-covered Starr Edwards prosthesis. One day pta the patient developed a fever and on the day of admission she suddenly became aphasic. There was no history of hypertension. Examination revealed a temperature of 38.8°C; BP was 90/60 torr. The patient had difficulty following simple commands. Speech was limited to the word "yes". She did not complain of headache. There was a right homonymous hemianopsia and a right central facial weakness. Her neck was supple. An ECG revealed AF with a rate of 120/min. A CT scan was normal. PT was 28.7/11.6 seconds. A lumbar puncture revealed normal opening and closing pressures with clear acellular fluid containing normal levels of protein and sugar. Blood and cerebrospinal fluid cultures revealed no growth. A presumptive diagnosis of endocarditis was made and the patient was placed on antibiotics; coumadin therapy was discontinued. PT and PTT remained elevated 3 days. On the day after admission the patient's speech improved dramatically. The visual field cut disappeared. Two days later she suddenly became unresponsive. A CT scan now demonstrated a large inoperable hematoma in the left fronto-parietal region surrounded by an extensive area of infarction and/or edema with a marked left to right ventricular shift. The patient expired shortly thereafter.

Results

Three patients underwent surgery and two of these are alive with minor neurological deficits but one died. Of the three patients who did not have surgery two died and one survived.

The CT scan accurately localized hematomas in all 6 patients. In 3 of these patients the hematomas were at surgically accessible sites: cerebellum (patient 1, fig. 1); right occipital lobe (patient 2, fig. 2); and right frontal lobe (patient 3, fig. 3). In patient 5 the hematoma was considered accessible, i.e. left frontal with intraventricular extension, however, the patient died of cardiac complications before surgery could be safely performed. Intraventricular extension was also noted in patient 4 who stabilized without surgery but was left with a moderate neurological deficit.

Prior to the development of the CT scan intraventricular bleeding had been considered invariably fatal. The fallacy of

this concept has been demonstrated by our own experience in this case and that of others.²⁹ In the last patient the inoperable hematoma was associated with extensive edema and/or infarction. Among the three patients who underwent surgery anticoagulants were not resumed in the two with AVRs. They are being treated with aspirin and dipyridamole; after 2 years both are doing well, however, aspirin had to be discontinued (patient 2) because of gastrointestinal bleeding. Anticoagulants were not resumed in patient 4 who suffered a left fronto-parietal hemorrhage and did not undergo surgery. She has been treated with aspirin and dipyridamole. Anticoagulation with heparin was resumed within 24 hours in patient 3 with an MVR who underwent craniotomy. Within 24 hours rebleeding occurred and the patient died.

Discussion

Successful management of hemorrhage in the patient with PHVs receiving anticoagulants requires an understanding of the mechanisms involved in intracranial bleeding. The majority of hemorrhages in these patients arise when bleeding occurs in previously infarcted brain. The mechanism of these hemorrhages differs from that associated with hypertension. The latter are believed to be secondary in most cases to rupture of microaneurysms of small intraparenchymal arteries. The distribution of these hemorrhages, predominantly within the central gray^{28, 30-32} and parallel to the known locations of microaneurysms, differs from the more randomly distributed post anticoagulation hemorrhages.⁸⁻¹⁶ The primacy of infarction in the pathogenesis of anticoagulant hemorrhage is illustrated by patients 1, 3, 4, and 6. In these 4 the original neurological deficit cleared, strongly suggesting non-hemorrhagic infarction. This was followed by neurological deterioration related to bleeding occurring in the area of recent infarction. The non-hemorrhagic nature of the original infarction was confirmed by lumbar puncture and CT scan in patient 6 and the development of hemorrhage into the area of recent infarction was confirmed by post-mortem examination in patient 3. The same mechanism of non-hemorrhagic infarction followed by hemorrhage was probably involved in patient 2, although there was no clearing of the initial deficit. In this patient the rapid onset of a restricted neurological deficit without headache suggested non-hemorrhagic infarction while its evolution 1 day later to complete hemianopsia with hemiparesis suggested subsequent hemorrhage into the site of recent infarction. This mechanism is less applicable to patient 5. Here the initial infarct occurred 2 months prior to the hemorrhage. Though the patient did develop a hemorrhage at or near the site of the initial infarct, the rapid neurological deterioration in the presence of endocarditis was more suggestive of ruptured mycotic aneurysm. Such a rupture may also have occurred in patient 6.

Although hemorrhagic infarction may occur in the absence of anticoagulants the role anticoagulants play in converting a non-hemorrhagic into a hemorrhagic infarction has been amply demonstrated experimentally.^{33, 34} Our data from 1967-1975 also illustrate the role anticoagulants play in intracranial hemorrhage. Thus, intracranial hemorrhage occurred only among patients who were treated with an-

ticoagulants. Since there were fewer intracranial emboli with infarctions among the anticoagulated patients, the data imply that a large number of these initially non-hemorrhagic infarctions became hemorrhagic because of the administration of anticoagulants.

Infarction in patients with PHVs is secondary to embolization. The emboli arise from deposits of platelets and fibrin on the valves. Emboli arise more frequently from mitral than aortic prostheses probably because the velocity of blood flow is less resulting in greater deposition of platelets and fibrin on the mitral valve. These emboli may initially lodge in and occlude a major artery with subsequent infarction. Within a few hours to a week the embolus may fragment and migrate distally with restoration of arterial patency and flow.³⁵⁻³⁸ Such restoration of flow exposes the infarcted tissue to the full force of arterial blood with resulting hemorrhage from damaged capillaries.³⁹⁻⁴² Hemorrhage is likely to be enhanced in the presence of anticoagulants.^{33, 34} Once bleeding has occurred the blood acts as a mass compressing surrounding tissue and resulting in additional infarction with shift of midline structure and compromise of vital brainstem structures. Thus, the most important step in management is prevention of the initial embolus.

It has been shown that anticoagulation is the best means of reducing embolization.¹⁻⁷ Additionally, it has been shown that the platelet inhibitor, dipyridamole,⁴³ combined with warfarin, may further reduce the incidence of embolization. At the present time treatment for certain high risk patients, i.e. patients with a history of infarction despite anticoagulation with warfarin, should consist of the addition to warfarin of aspirin, dipyridamole or both. In the future, treatment may involve the use of glutaraldehyde-preserved porcine valves where the rate of embolization is under 2.0% without anticoagulants in all patients.⁴⁴

Once embolization with infarction has occurred, attention should be directed toward prevention of hemorrhage. Prosthetic heart valve patients with cerebral infarcts, where facilities are available, should have a CT scan to confirm the non-hemorrhagic nature of the infarct. Where CT scan is not available, lumbar puncture remains a relatively safe diagnostic tool. Prior to performance of a lumbar puncture care must be taken to reverse anticoagulant activity. Once the non-hemorrhagic nature of the infarction has been established anticoagulants should be discontinued for at least 10 days. It is unlikely that after 10 days there will be additional migration and/or fragmentation of the embolus with the attendant risk of hemorrhage. If embolization leading to a transient ischemic attack occurs and the CT scan is normal, anticoagulants may be continued in certain high risk patients if benefits are thought clearly to outweigh risks.

Once hemorrhage has occurred, anticoagulation should be reversed as soon as possible. If bleeding is thought to be secondary to a surgically repairable ruptured aneurysm, angiography should be performed. The feasibility of surgical intervention is determined by the patient's clinical status and the location and extent of the hemorrhage.²⁶ If an intracerebral hematoma is evacuated anticoagulants should probably not be resumed for several days in order to allow any surgically induced intracranial bleeding to cease. Resumption

of anticoagulants in the immediate postoperative period in a patient at high risk for embolization was probably contributory to the rebleeding in patient 3.

Special problems are associated with the use of anticoagulants in patients with PHVs who develop endocarditis. These patients continue to remain at risk of non-septic embolization from the prosthesis as well as septic embolization. In a recent study anticoagulants were shown to decrease the risk of major intracranial complications including embolic infarction and hemorrhage in PHV patients with endocarditis.²⁰ The decrease in intracranial hemorrhage reflected the decrease in embolization with subsequent infarction.

While the incidence of intracranial complications in patients with PHV endocarditis is less in patients receiving anticoagulants, it has also been well documented that massive and fatal cerebral hemorrhage may occur when anticoagulants are used in the presence of endocarditis.^{18, 19} Most of these bleeds appear to be secondary to rupture of a mycotic aneurysm.⁴⁶⁻⁴⁹ Mycotic aneurysms develop when bacteria invade and inflame the walls of cerebral arteries. However, statistics on the incidence of hemorrhage secondary to rupture of mycotic aneurysm vary. One group reported 5 instances of hemorrhage from mycotic aneurysm in 130 cases of endocarditis (4.6%) in a 12-year period;⁴⁶ while another reported a 10% incidence.⁴⁹ Neither report states how many bleeds occurred in patients with PHVs or how many patients with PHVs were on anticoagulants. A third group reviewed 953 patients with PHVs and reported 12 cases (1.3%) of endocarditis.⁵⁰ Ten of these patients were on anticoagulants; 2 of these suffered intracerebral hemorrhages; 1 of these was fatal. Thus, although rupture of an aneurysm may have grave consequences in patients treated with anticoagulants, it has not been established that anticoagulants *per se* cause aneurysmal rupture in patients with endocarditis.

In any patient with PHV endocarditis on anticoagulants the risk of hemorrhage complicating a septic or non-septic infarction and the risk of spontaneous rupture of a mycotic aneurysm must be weighed against the risk of embolization in the absence of anticoagulants. Our own data indicate that particularly in high risk patients (MVRs) the risks of embolization are greater than the risk of hemorrhage. In these patients continuation of anticoagulants is indicated unless there has been recent cerebral infarction.

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