ISCHEMIC CEREBRAL VASCULAR DISEASE

AN OVERVIEW

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SUMMARY — The management of patients with cerebrovascular ischemic disease (ICD) is rapidly changing due to newer diagnostic approaches and therapies being developed. In the present article, the author reviews part of his experience in the clinical and basic fields of ICD which is the most common neurologic problem leading to acute hospitalization. Clinico-anatomic categories of ICD as well as prognosis and differential diagnosis are discussed. Data from basic and research are analysed with a main focus on their implications for clinical management.

Doença cerebrovascular isquêmica: uma avaliação

RESUMO — A doença cerebrovascular isquêmica (DCVI) representa a maior causa de hospitalização aguda por problemas neurológicos. Recentes avanços diagnósticos e terapêuticos, provenientes de pesquisa em áreas básicas, prometem modificar o atual panorama de desesperança terapêutica em curto prazo. No presente artigo, o autor revê parte de sua experiência no campo das DCVI e, com base em dados de pesquisa básica e clínica, discute aspectos essenciais de classificação, diagnóstico diferencial, prognóstico e tratamento, enfatizando o ponto de vista do clínico praticante à beira do leito.

Ischemic cerebral vascular disease (ICD) is the most common neurologic problem leading to acute hospitalization. Yet, ICD has typically not been managed in an intensive care unit unless extenuating circumstances prevailed. Circumstances such as impaired consciousness with or without cerebral edema, crescendo transient ischemic attacks or evolving stroke, major associated illness (myocardial infarction, sepsis, pulmonary embolism) or LCD in a patient already in an intensive care unit (ICD complicates 1 to 2 percent of patients with acute myocardial infarction) have led to acute management. In the future we can anticipate that many more patients with ICD will be managed in a general intensive care unit or a specialized unit dedicated to intensive stroke care. This change will occur as newer therapies directed at the metabolic consequences of acute focal brain ischemia and fibrinolysis of offending cerebral arterial thrombi are developed. The treatment of ICD in many cases will require prompt diagnosis and the institution of appropriate therapy based upon the stroke subtype. Many of the newer therapies to be discussed will need careful assessment for therapeutic efficacy and side effects, a situation which will probably require an increase in the intensiveness of medical and nursing care.

CATEGORIES OF ISCHEMIC CEREBROVASCULAR DISEASE

Defining and categorizing ICD is necessary for accurate diagnosis and appropriate therapy. Three *deggrees of completeness* can be recognized: transient ischemic attacks (TIA), stroke-in-evolution, and completed stroke i*. JIA is an episode of temporary focal cerebral dysfunction occuring on a vascular basis which evolves

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rapiply and then resolves within minutes to twenty-four hours. Stroke-in-evolution, a progressing stroke, is a neurovascular event that worsens over several hours although in the vertebral-basilar system, the progression may continue for two to three days. This category is imprecise, both in its definition and in the ability of clinicians to recognize it easily. A completed stroke is a neurovascular event in which the deficit has been stabilized for at least twenty-four hours in those portions of the brain supplied by the carotid artery and for seventy-two hours in those portions of the brain supplied by the vertebral-basilar system.

Two broad *clinical anatomic categories of I CD syndromes* are recognized, based upon the division of the vascular supply of the brain in those areas supplied by the carotid system and those supplied by the vertebral-basilar system **6.** The symptoms commonly encountered in carotid system disease include: mono or hemiparesis, mono or hemiparesthesias, monocular visual loss, homonymous hemianopsia, and various aphasic syndromes. The vertebral-basilar artery symptoms include binocular visual disturbance, vertigo, diplopia, ataxia, dysarthria, paresis, and paresthesias (frequently with involvement of one side of the face and the contralateral body). Loss of consciousness rarely occurs without other vertebral-basilar symptoms. Isolated symptoms such as vertigo, diplopia, amnesia, dysarthria, and lightheadedness cannot by themselves serve as a basis for the diagnosis of a vertebral-basilar event[16]. However, these symptoms together with other brainstem symptoms support the occurrence of a vertebral-basilar ischemic event. A small percentage of patients experience symptoms at different times in both the carotid and vertebral-basilar systems. In addition, some cerebrovascular symptoms cannot be adequately localized even by experienced clinicians.

The other major division of acute ICD is the necessity to categorize the event into *large vessel atherothrombotic, small vessel,* or *cardioembolic type. A* fourth category of acute stroke, which must be differentiated, is primary intracerebral hemorrhage and this will be discussed in detail in a forthcoming paper. Large vessel atherothrombotic stroke related to atherosclerosis in the carotid or vertebral-basilar arteries is a common cause of ICD. The symptoms may develop abruptly or evolve as noted above. There are many different clinical syndromes which related to the particular vascular territory involved and the adequacy of collateral flow[19].

Compromise of small intracranial vessels such as the lenticulostriate arteries or basilar penetrators by microatheromata or lipohyalinosis leads to the development of small infarcts called *lacunae* (Fig. 1). If a lacune is strategically placed in the internal capsule, thalamus, or basis pontis, substantial neurologic deficits occur and these are termed «lacunar syndromes». The most common lacunar syndromes are pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, and clumsy-hand dysarthria syndrome[24]. Lacunar syndromes are truly syndromes because other pathogenetic mechanisms such as tumors, aneurysms, and large artery infarcts can cause the same clinical findings.

The final category of ICD is cardioembolic stroke and this ICD subtype has been recognized with increasing frequency as technology for the detection of underlying cardiac sources for emboli have improved. Cardioembolic strokes typically reach their maximal deficit at onset, although a small minority may have a stuttering course. Diagnostic difficulty may arise if patients have coexistent large arterial lesions and as many as one-third of patients with a cardiac source of emboli have another explanation for their stroke **2.** Therefore, it may be difficult to assign a precise subtype for an individual patient's stroke. The most common cardiac sources associated with cerebral embolic events are outlined in Table 1. Nonvalvular atrial fibrillation is associated with a stroke risk which approximates 4-5 percent/year and may vary with age, paroxysmal atrial fibrilation and left atrial size[1]. Patients with acute transmural myocardial infarction are at increased risk for embolic stroke, especially those with echocrdiographic evidence of ventricular thrombi. A major complication of mechanical cardiac valves is the development of cerebral emboli. The risk is higher in patients with co-existent atrial fibrillation and is lower with bioprosthetic valves. Patent right to left shunts in the heart have been recognized with increasing frequency in younger stroke patients by contrast echocardiography **22.** The direct relationship of this observation to ischemic stroke may be elusive.

Hemodynamic compromise secondary to cardiac arrest or systemic hypotension can lead to focal infarction and deficits in well circumscribed watershed patterns (Fig. 2)3. In the carotid circulation, watersheds occur between the middle cerebral artery and both the anterior and posterior cerebral arteries. The usual anterior infarction causes contralateral weakness and sensory loss sparing the face, while in posterior watershed infarcts, homonymous hemianopsia with little or no weakness is

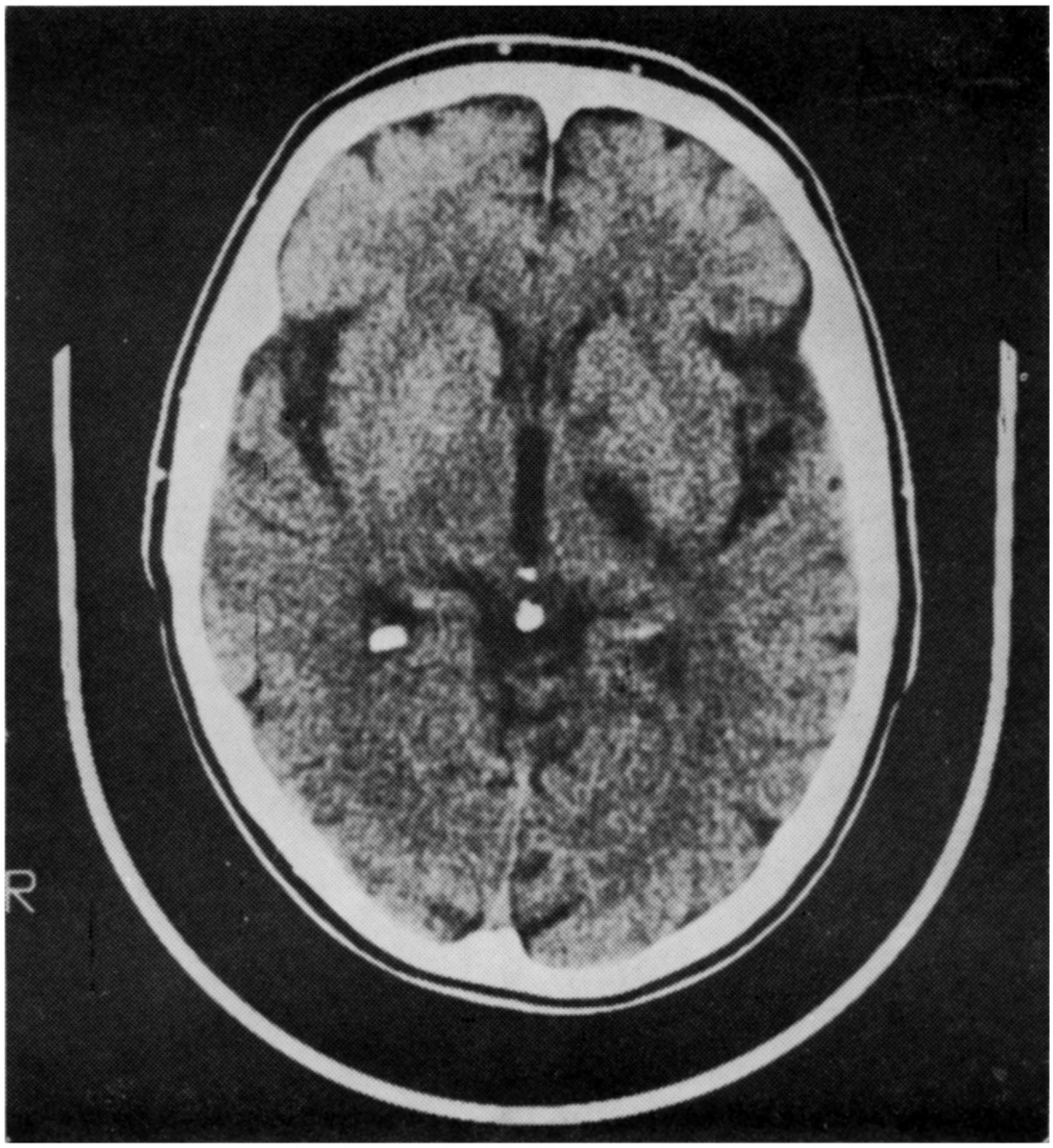

Fig. 1 — A CT example of a large lacunar infarct in the posterior limb of the left internal capsule.

Common
Non-valvular atrial fibrillation
Acute anterior wall myocardial infarction
Ventricular aneurysms and dyskinetic segments
Rheumatic valvular disease
Prosthetic cardiac valves
Right-to-left shunts
Bacterial endocarditis
Less Common
Mitral valve prolapse
Cardiomyopathy
Bicuspid aortic valve
Atrial myxoma
Nonbacterial endocarditis
Mitral annulus calcification
IHSS
Atrial septal aneurysm

Table 1 — Cardiac sources for cerebral emboli.

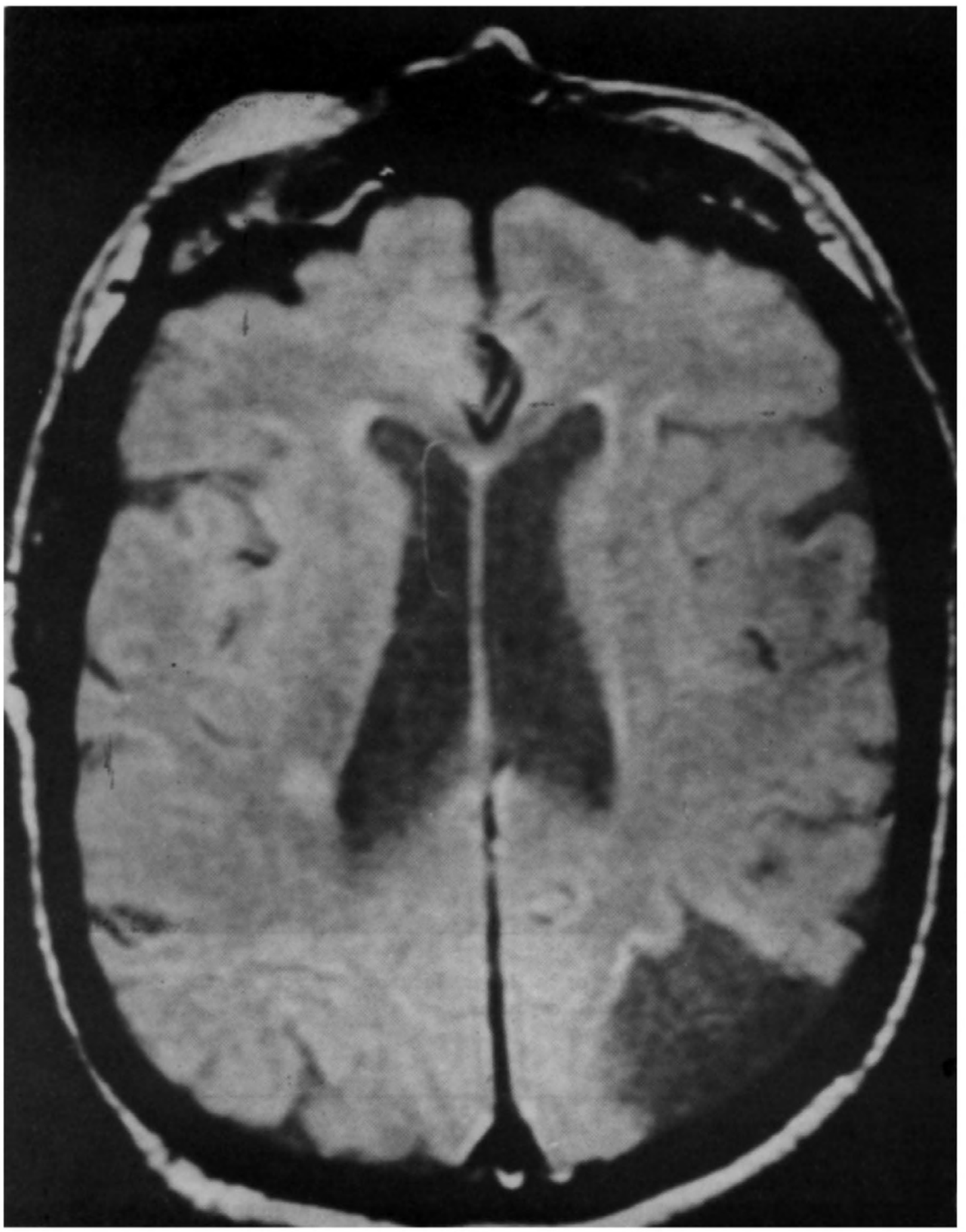

Fig. 2 — A head MRI demonstrating an infarction in the watershed territory between the middle cerebral and posterior cerebral arteries.

most common. Quadriparesis, cortical blindness, or bilateral arm weakness may also be seen in other vascular territory watershed infarcts.

PROGNOSIS

The prognosis of completed ICD in either the carotid or vertebral-basilar distributions cannot be predicted with certainty during the initial phase of the ictus. The overall mortality from recent series approximates three to twenty percent in both vascular distributions **8.** However, patients manifesting either coma or an altered level

of consciousness have a significantly greater mortality than patients who remain alert. A dense hemiplegia and conjugate eye deviation are other early signs that point toward a poor prognosis at least in carotid system strokes.

Functional outcome also varies widely, with a favorable outcome observed in twenty to seventy percent of cases'*. Patients with lacunar syndromes have a very-low one month mortality (approximately one percent) and good functional recovery in that seventy-five to eighty percent are in this category one to three months after their event. In one large series, thirty-four percent of patients with large artery atherothrombotic strokes had a progressive or fluctuating course, while eighteen percent of cardioembolic patients followed a similar pattern **4.** In thirty-seven patients with veretbral-basilar symptoms, forty-three percent were observed to have progressive course[18].

DIFFERENTIAL DIAGNOSIS

An attempt can be made at the bedside to differentiate between the three major subtypes of ICD based upon the history and neurological examination. Although, in some cases this task may not be possible without laboratory investigation. It is important to differentiate ICD patients from those with primary intracerebral hemorrhage. Hemorrhage patients typically have a progressive course with the evolution of symptoms over hours **25.** Early obtundation or even coma is much more common in intracerebral hemorrhage than in ICD because of mass effect upon the deep arousal system, which occurs rapidly with hematomas. Seizures, headache, and emesis are also much more common in patients with intracerebral hemorrhages. If the diagnosis is suspected, early imaging with either a CT or MRI scan is imperative.

Other conditions besides cerebral vascular events can occasionally cause acute focal neurologic deficits and must be considered. Patients with primary or metastatic brain tumors can rapidly develop focal neurologic signs either related to hemorrhage or by other mechanisms (Fig. 3). Subdural hematomas can rarely present with rapid development of focal neurologic deficits and must be considered in elderly patients who have no history of head trauma. Patients with migraine commonly develop focal neurologic symptoms either before or during the early phase of their headache. Rarely these deficits may persist and are associated with frank areas of infarction on imaging studies. Such an event is termed a migrainous stroke **26.** Patients with focal seizures may develop sensory and aphasic symptoms which can mimic ICD, although they are usually stereotyped, transient, and march in a pattern not typically seen with ICD. Occasionally, these focal neurologic deficits seen with seizures may persist for twenty-four hours or longer, a so called Todd's paralysis.

LABORATORY AND RADIOLOGICAL EVALUATION

The necessity for early imaging in most ICD patients is apparently based upon differential diagnostic considerations and possibly the need for therapeutic intervention. Both CT scanning and MRI studies are reliable and sensitive measures for differentiating between ICD, hemorrhage and other mass lesions. MRI scanning may be more sensitive for the identification of brain tumors and subdural hematomas than CT. MRI will identify areas of focal ischemic infarction at an earlier stage (within twelve to twenty-four hours**)2i.** However, the most important reason for early imaging is to differentiate between infarct and hemorrhage and the two imaging techniques are of relatively equal sensitivity in this regard. An electrocardiogram should be obtained to look for underlying cardiac rhythm disturbances or ischemic changes. Confusion may rise because morphologic and rhythm disturbances may occur secondary to the cerebral ischemic event. Echocardiography and prolonged EEG monitoring should not be performed routinely because of the relatively low yield. These studies should be considered in younger ICD patients or in those with a significant cardiac history, abnormal cardiac examination, or abnormal baseline electrocardiogram (Fig. 4). A multiple profile blood chemistry screen, chest X-ray, erythrocyte sedimentation rate, syphilis serology, complete blood count, partial thromboplastin time and urinalysis should be obtained in *all* patients. Other blood studies including anticardiolipin antibodies, clotting studies, serum viscosity, serum protein electrophoresis, fibrinogen, and lipid studies, may be needed in some patients. The need for a lumbar puncture

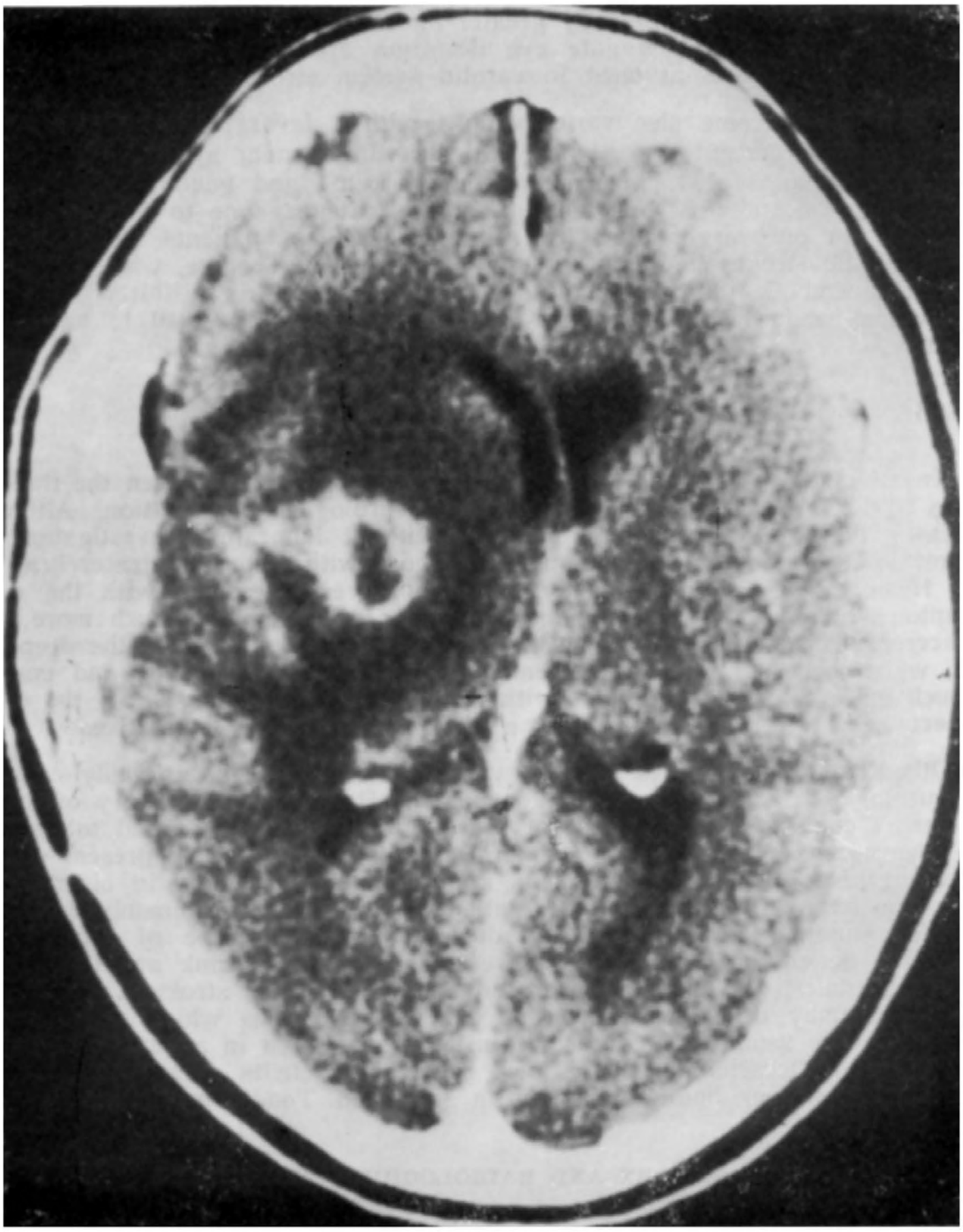

Fig. 3 — A large glioma which preesnted with symptoms of pure motor stroke as seen on CT scan.

has diminished with the availability of imaging studies to reliably diagnosis hemorrhage. A lumbar puncture should be performed if meningitis is suspected or subarachnoid hemorrhage is a consideration with a negative imaging study. Electroencephalography is rarely helpful, except when associated seizure activity is suspected.

Noninvasive studies of the carotid arteries such as B mode and Doppler ultrasound can be a useful and safe method for assessing the status of the extracranial vessels in ICD patients. These studies should be considered in most ICD patients with carotid territory infarcts. Even patients with lacunar infarcts or cardiac sources for stroke may be appropriate candidates because carotid artery narrowing leading to embolus formation may be the source of the former and coexistent carotid disease is not uncommon in patients with potential cardiac sources for emboli. Transcranial Doppler ultrasound is now widely available and can provide information about the Status of the intracranial vessels both in the carotid and vertebral-basilar territories **9,**

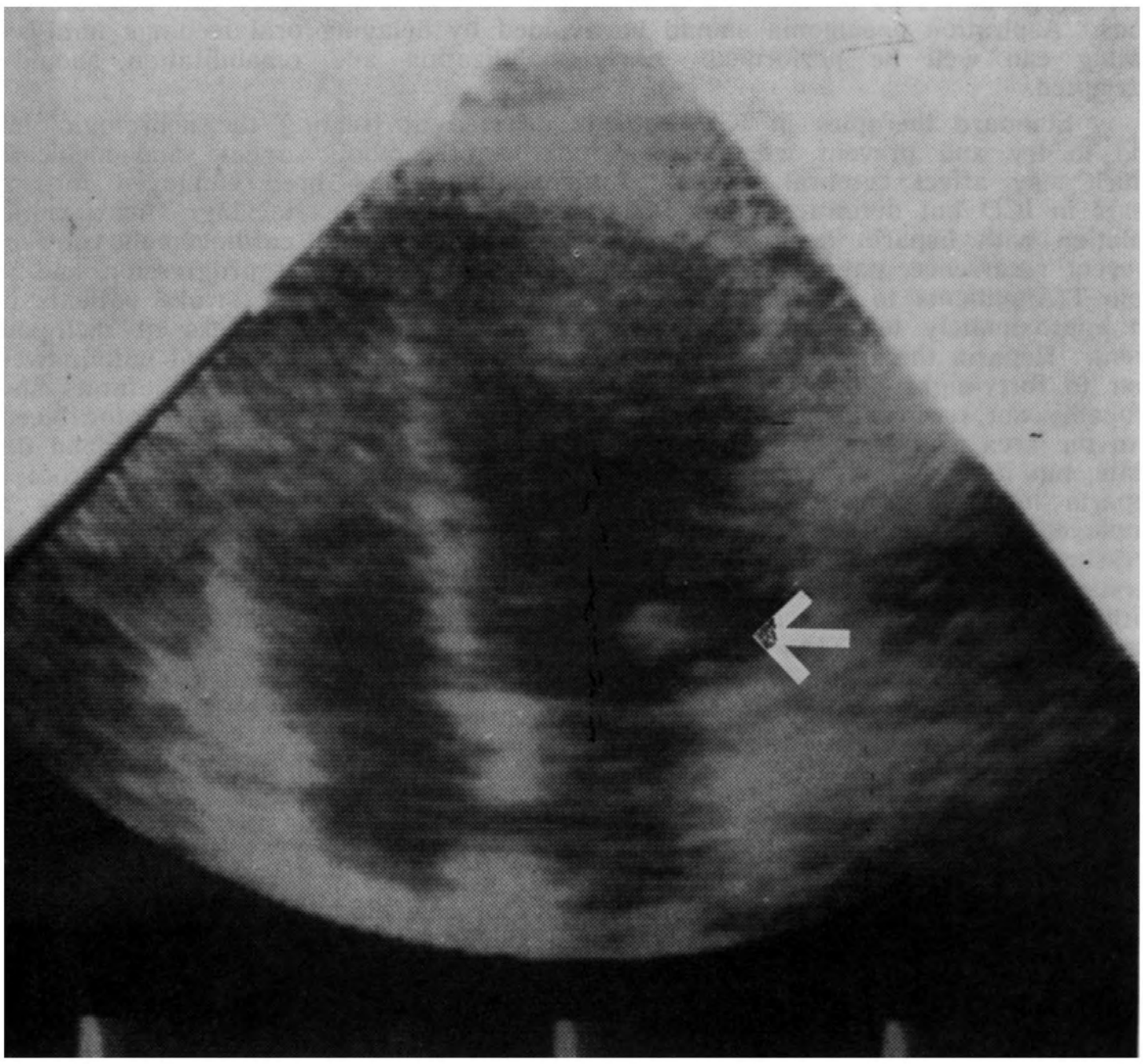

Fig. 4 — A large vegetation on the mitral valve (arrow) demonstrated by echocardiography in a patient with cardioembolic stroke.

Atherosclerotic narrowing of the middle cerebral or basilar arteries can be identified as can embolic occlusions. The information obtained from these techniques may add to our ability to more accurately diagnose and more effecttively manage patients with selected ICD types.

THERAPY

The treatment of ICD can be divided into four major categories: preventive, supportive, standard interventions and newer experimental approaches. Stroke prevention has been possible as risk factors have been identified and treated[11]. The treatment of hypertension, a primary stroke risk factor, has been clearly identified as a mechanism to reduce ICD risk. Smoking is another risk factor which can be ameliorated. The treatment of diabetes and hyperlipidemia are of less obvious benefit. Aggressive, supportive therapy for ICD patients is imperative when inpatient hospitalization begins **23.** in most cases, blood pressure elevations should be observed for at least four to six hours before acute anti-hypertensive therapy is initiated, unless malignant hypertension with focal signs is diagnosed. The blood pressure will typically return to baseline with bedrest, but should be carefully lowered by no more than twenty-thirty percent of the mean arterial pressure, if it remains substantially elevated. Subcutaneous heparin therapy should be considered in immobilized ICD patients to reduce the risk for pulmonary emboli. Indwelling urinary catheters and

excessive numbers of intravenous lines should be avoided, as they can promote infections. Aspiration pneumonia should be avoided by delaying oral feedings until swallowing can well be performed. Early mobilization and rehabilitation should be attempted.

Standard therapies in ICD patients directed at treating the neurologic deficit and to try and prevent worsening include: antithrombotic agents and medications which may affect cerebral edema. Anticoagulants have been employed for many years in ICD but definitive proof for their efficacy remains lacking. Acute anticoagulation with heparin may be considered in patients with cardioembolic stroke to prevent recurrence, patients with stroke-in-evolution to prevent progression and multiple T1A patients to inhibit stroke development. Cardioembolic stroke patients have an approximately ten percent risk for recurrence within two weeks of their initial event. Heparin therapy may reduce this risk and should be considered within twenty-four to forty-eight hours of the initial stroke **1.** Patients with large infarcts should probably not receive heparin, because these patients have a higher risk for bleeding into the area of infarction **7.** Stroke-in-evolution can be difficult to define and quantitate, but if diagnosed heparin therapy should be considered[12]. Definitive proof that heparin impedes progression is not presently available. Heparin therapy is also employed in patients with incomplete or partial deficits, who are not actively progressing, to prevent worsening. One recent double blind, randomized trial of heparin versus placebo in this setting demonstrated no benefit for heparin **10.** A large trial with heparinoid is present in progress and may finally answer these vexing problem. Patients with multiple TIAs would appear to be at higher risk for stroke development tran single TIA patients **20.** Therefore, heparin therapy is used in these patients despite lack of proof that it is effective. Heparin is not recommended by many authorities for single TIAs patients. When heparin is used for any of the previously described conditions, it should be initiated as a constant infusion trying to maintain the partial thromboplastin time at 1.5-2.0 times control. Large boluses should be avoided. Aspirin has been shown to significantly reduce the risk of stroke after TIA in some studies but not all and aspirin is widely employed for this indication **28.** Ticlopidine, a new antiplatelet medication, has also been observed to reduce the risk for recurrent stroke **27.** The rate and severity of side effects with ticlopidine appears to be greater than with aspirin and until this medication receives FDA approval, aspirin prophylaxis should be considered in patients with ICD because it may prevent recurrence and is relatively safe. Dipyridamole has not been shown to be effective in either TIA or completed stroke patients for reducing stroke risk.

The development of *cerebral edema in ICD patients* is typically maximal in 48-72 hours after onset. Cerebral edema in ICD is predominantly related to cytotoxic mechanisms as compared to vasogenic mechanisms for edema associated with brain tumors. This difference in mechanism for cerebral edema may explain why randomized trials of corticosteroids have demonstrated conflicting results in ICD **23.** Hyperglycemia associated with corticosteroids may actually be detrimental, although the effects of elevated serum glucose levels on outcome remains unclear in acute ICD **29.** Osmotic diuretics such as mannitol are of uncertain value for cerebral edema associated with ICD. We do consider using pulse doses (one gm/kg, then 0.25 gm/kg every six hours) if massive edema begins to develop. Intracranial pressure monitoring to guide therapy should also be considered in this setting. Intravenous glycerol therapy may also be considered, if preparations with fructose to reduce hemolysis are available.

Carotid endarterectomy should not be considered for patients with completed stroke. Its role in TIA patients is controversial, although it is widely performed in patients with carotid territory TIAs and carotid artery narrowing **5.** An ongoing randomized trial of carotid endarterectomy versus medical therapy for TIA patients will hopefully help to define which therapy should be used in particular patient subgroups. Anedoctal reports have described marked improvement for progressing stroke patients who undergo carotid endarterectomy. Surgical mortality and morbidity is probably higher in such patients and the efficacy of endarterectomy, as compared to medical therapy, is uncertain. Many surgeons are reluctant to operate in this situation.

At this time there is no therapy available which has been definetly proven to improve neurologic outcome or reduce mortality in ICD patients. Many potential therapies have been studied in animal stroke models and human clinical trials. The more promising and important newer therapeutic agents will be discussed. Approaches to acute ICD treatment are aimed in two major directions, therapies which

attempt to correct or modify the cellular consequences of ischemia and therapies which attempt to restore impaired blood flow, primarily by dissolving the insighting thrombus.

Intracellular calcium influx is an important cellular consequence of ischemia, which can lead to irreversible neuronal injury. A voltage sensitive calcium channel blocker, nimodipine, has been employed in clinical trials of acute ICD. A Dutch study demonstrated that 30 mg of nimodipine orally every six hours reduced acute mortality and improved functional outcome A large multi-center trial in the United States revealed no overall effect on mortality or outcome. However, subgroup analysis demonstrated that patients started on 40 mg of nimodipine orally three times a day within twelve hours of stroke onset may have benefited. These studies provide preliminary evidence that nimodipine may improve outcome of ICD, but further evaluation of patients treated within six to twelve hours of stroke onset are needed before definitive recommendations can be made. Receptor mediated calcium channel inhibitors have also been studied in experimental stroke models with favorable results. There is much interest in studying these agents in humans, but no clinical data are presently available.

Free radicals are generated in areas of ischemic brain which are partially perfused or during reperfusion after clot dissolution. These toxic oxygen metabolites have a variety of deleterious effects, which can lead to enhanced tissue injury. Therapy with superoxide dismutase and catalase, naturally occurring free radical defense mechanisms, has been shown to reduce tissue injury and reduce cerebral edema in animal models. Lipid peroxidation can be inhibited by the novel corticosteroid derivatives, 21-aminosteroids, and these agents without purported glucocorticoid or mineralocorticoid side effects have been shown to improve outcome and reduce neuronal damage in an animal stroke model is. Clinical trials of these drugs are being organized.

Hemodilution therapy has been tried in acute ICD because lowering of whole blood viscosity improves cerebral blood flow and tissue oxygenation. Two European trials of isovolemic hemodiluton demonstrated no benefit even in patients treated within 24 hours of stroke onset A small trial with hypervolemic hemodilution reported a greater than fifty percent improvement (not significant) in treated patients versus controls. Unfortunately, there were four deaths in the treated group secondary to cerebral edema and only one in the controls, leading to early termination of this study. Enthusiasm for hemodilution therapy for ICD has waned. Another mechanism for improving blood flow is to remove the offending thrombus. Fibrinolytic therapy with exogenous agents, urokinase and streptokinase, was attempted in the past, but not continued because of excessive hemorrhagic complications. The availability of relative fibrin specific fibrinolytic molecules such as tissue plasminogen activator (t-PA) has revived enthusiasm. In animal models, t-PA has been shown to effectively and safely dissolve intracranial cerebral thrombi and to improve neurologic outcome[3]. Currently, human trials are being performed to assess the safety of t-PA and efficacy trials are being organized. Hopefully, fibrinolytic therapy can be safely and effectively employed in acute ICD as it has been in acute myocardial infarction, but many questions remain concerning time of treatment, appropriate dose, and the use of concomitant medications.

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