Neurology and Cardiology: Points of Contact

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INTRODUCTION

Neurologists and cardiologists are frequently involved in coordinating the care of patients with a variety of conditions, the most common being stroke. This article reviews the diagnosis and management of conditions that have both cardiac and...
neurologic manifestations. The review is organized by cardiac disorders that predispose to neurological complications and neurological conditions that can involve the heart.

NEUROLOGICAL COMPLICATIONS OF CARDIAC DISEASE

Cardiac diseases can be complicated by stroke, cognitive impairment, and brain infections. Cardiac conditions including atrial fibrillation (AF), cardiomyopathies, valvular heart disease and interatral septal anomalies account for 20%-30% of all ischemic strokes. The mechanism of cardiogenic stroke is often embolic, but hypoperfusion may also occur, particularly in those with cerebral steno-occlusive disease. Cognitive decline can be associated with congestive heart failure (CHF) and coronary artery bypass graft procedures, whereas meningitis and brain abscesses are possible complications of infective endocarditis (IE).

Atrial Fibrillation

Nonvalvular AF is the most common cause of cardiogenic stroke, accounting for 50% of cardiogenic emboli and 10% of ischemic strokes. It affects about 1% of the general population and is the most common cardiac arrhythmia in the elderly, having a prevalence of nearly 10% in those older than 80 years. AF is associated with a 4- to 5-fold increased risk of stroke across all age groups; those who also had a prior stroke or transient ischemic attack (TIA) have an additional 2.5-fold increase in stroke risk. 1 Overall, AF is the most common cause of cryptogenic strokes in some series. Cardiac monitoring to detect a transient ischemic attack (TIA) have an additional 2.5-fold increase in stroke risk. 1,2 The incidence of stroke among nonvalvular AF ranges between 4.5% and 13% per year. 1 Depending on comorbidities, the incidence of stroke among non-anticoagulated patients with AF ranges between 4.5% and 13% per year. 1 Both persistent and paroxysmal AF increase the risk of first and recurrent stroke. AF explains up to about a quarter of cryptogenic strokes in some series. Cardiac monitoring to detect paroxysmal AF in stroke patients is cost effective across a wide range of factors. 5,9 Heart failure, hypertension, increasing age, diabetes, prior thromboembolism including prior strokes, left ventricular dysfunction, left atrial enlargement, mitral annular calcification, spontaneous echo contrast, and left atrial thrombus increase stroke risks in those with AF. The predictive capacity of stroke risk stratification schemes in patients with nonvalvular AF vary greatly. The CHADS2 score is among the most commonly used schemes; it assigns 1 point for CHF, hypertension, age over 75 years, diabetes mellitus, and 2 points for a history of stroke or TIA. Each point increase in the CHADS2 score increases the stroke risk by a factor of 1.5 (95% confidence interval [CI], 1.3-1.7); the stroke rate per 100 patient-years is 1.9 (95% CI, 1.2-3.0) for a score of 0 and 18.2 (95% CI, 10.5-27.4) for a score of 6. 7 Multiple clinical trials have established the benefit of warfarin in patients with nonvalvular AF. Warfarin was compared to placebo in 5 primary prevention trials. Two of these also compared acetylsalicylic acid to placebo. Pooled data from these 5 trials reflect a 68% risk reduction with warfarin (95% CI, 50% to 79%) and a 36% reduction (95% CI, 4% to 57%) with acetylsalicylic acid. Warfarin treatment results in 3.1% (p<0.001) absolute annual stroke risk reduction: 31 ischemic strokes are prevented for every 1000 patients treated. An international normalized ratio [INR] between 2.0 and 3.0 is recommended for preventing strokes while minimizing the risk of hemorrhage. Warfarin, however, remains underutilized in patients with AF because of its narrow therapeutic index and its numerous food and drug interactions that necessitate frequent INR monitoring. Alternative strategies have included the use of antiplatelet drugs, direct thrombin inhibitors and factor Xa antagonists. Warfarin was superior to acetylsalicylic acid (300 mg) in the secondary prevention of stroke/TIA in the European Atrial Fibrillation Trial (EAFT); hazard ratio (HR) for the combination of vascular death, any stroke, myocardial infarction (MI) and systemic embolism 0.60, (95% CI, 0.41-0.87). Warfarin was also superior to acetylsalicylic acid in elderly patients with nonvalvular AF enrolled in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study. The relative risk (RR) for stroke was 0.49 (95% CI, 0.28-0.80) in favor of warfarin, with no significant difference in the rate of hemorrhage. The American Heart Association (AHA)/American Stroke Association recommends acetylsalicylic acid for those with AF who are unable to take oral anticoagulant. High risk patients who take an anticoagulant and stop it temporarily are at high risk for strokes. Bridging with a low molecular weight heparin administered subcutaneously is deemed to be reasonable in this setting.

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) study found that warfarin was superior to the combination of clopidogrel plus acetylsalicylic acid for the prevention of vascular events. For patients for whom a vitamin K antagonist was deemed “unsuitable,” ACTIVE W found that the combination of clopidogrel and acetylsalicylic acid was superior to acetylsalicylic acid alone in preventing vascular events (RR = 0.89; 95% CI, 0.81-0.98; p=0.01) but carried a higher risk of major bleeding (RR=1.57; 95% CI. 1.29-1.92). Ximelagatran and dabigatran are direct thrombin inhibitors that were compared to warfarin in patients with AF. Ximelagatran was not inferior to warfarin with a comparable bleeding risk in two randomized controlled trials (SPORTIF III and SPORTIF V), but caused clinically significant hepatotoxicity. Depending on dose, patients randomized to dabigatran had rates of stroke and systemic embolism similar to those taking warfarin, with lower rates of major hemorrhage. Dabigatran was recently approved by the United States Food and Drug Administration as an alternative to warfarin in patients with AF. Dabigatran may interact with other drugs, such as P-glycoprotein inhibitors.

Rivaroxaban (ROCKET AF study) and Apixaban (ARISTOTLE trial) are oral factor Xa inhibitors. Initial reports indicate that this class of drug may be a viable alternative to warfarin in patients with AF. The anticoagulant effects of direct thrombin inhibitors and factor Xa inhibitors are not immediately reversible. Whether patients who receive these drugs can be treated with intravenous thrombolitics if they were to have a stroke is unknown.

Abbreviations

ASA: atrial septal aneurysm
CHF: congestive heart failure
ECG: electrocardiogram
IE: infective endocarditis
MD: muscular dystrophy
MI: myocardial infarction
PFO: patent foramen ovale
TIA: transient ischemic attack

Patent Foramen Ovale/Atrial Septal Aneurysm

A causal relationship between patent foramen ovale (PFO) and cryptogenic stroke remains uncertain. Approximately 25% of the
general population has a PFO. Patients with a PFO may also have an atrial septal aneurysm (ASA), defined as >10 mm septal excursion with a base of 1.5 cm or greater. Potential mechanisms of stroke in patients with PFO with or without an ASA include: a) paradoxical embolization; b) embolization of thrombus from the rim of the ASA; c) paroxysmal AF related to damage to the cardiac conduction system; d) passage of unmeasured vasoactive humoral substances that escape pulmonary degradation; and/or e) causes not related to the defect. A potential source of paradoxical embolization is identified in 10% to 57% of patients with PFO and cryptogenic strokes.

A meta-analysis of case-control studies established a higher prevalence of PFO and ASA in stroke patients overall and in those who had cryptogenic strokes. The combination was more frequent in those with stroke compared to nonstroke control subjects (odds ratio [OR] = 5.25; 95% CI, 2.91-9.45), in those with cryptogenic stroke versus known stroke cause (OR = 20.74; 95% CI, 4.14-103.90), and cryptogenic stroke versus nonstroke controls (OR = 23.9; 95% CI, 3.09-185.42). The association of PFO/ASA abnormalities with stroke was higher in patients who were younger than 55 years. These studies, however, are largely based on hospitalized patients, possibly reflecting a referral bias. Population-based studies do not find such a relationship. For example, PFO was present in 140 of 585 (24.3%) and ASA in 11 (1.9%) randomly sampled subjects older than 45 years from Olmstead County, Minnesota. The combination of PFO and ASA was present in 6 (4.3%) and was not associated with an increased stroke risk over 5 years.

Despite this uncertainty, clinical trials have been conducted or are in progress evaluating treatments of patients with stroke in the setting of PFO with or without an ASA. The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) was a substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) that randomized patients with otherwise cryptogenic stroke to acetylsalicylic acid as compared to warfarin. There was no difference in the rate of stroke or death between these with a combination of PFO and cryptogenic stroke based on the presence of a PFO and no overall difference in the effect of acetylsalicylic acid versus warfarin on recurrent stroke risk. The results of the prospective Spanish multicenter study (CODOCA) were similar. In contrast, the Patent Foramen Ovale and Atrial Septal Aneurysm Study found that the combination of PFO and ASA was associated with an increased risk of recurrent strokes among patients aged 18 to 55 years with cryptogenic stroke who were receiving acetylsalicylic acid. The differing results may be due to differences in patient populations (younger cryptogenic stroke patients and only those taking acetylsalicylic acid in the Patent Foramen Ovale and Atrial Septal Aneurysm Study). Currently, there are insufficient data to recommend anticoagulation over acetylsalicylic acid for secondary stroke prevention in patients with PFO or PFO/ASA, and either choice may be reasonable.

The role of endovascular PFO closure for secondary stroke prevention is also uncertain. An open-treatment nonrandomized study comparing percutaneous PFO closure to medical therapy (Vitamin K antagonist or antiplatelet therapy) in patients with cryptogenic stroke did not find an overall benefit of PFO closure after 4 years. An initial report of the CLOSURE 1 trial, comparing endovascular PFO closure with medical therapy in patients with stroke or TIA, found no benefit from PFO closure, which was associated with several periprocedural complications (presented at AHA Scientific Sessions, November 2010). Other randomized trials of PFO closure for secondary stroke prevention are in progress.

**Acute Myocardial Infarction and Left Ventricular Thrombus**

There is a short- and long-term increased risk of stroke following MI. Although the exact cause of MI-associated stroke is often unclear, embolization from left ventricular thrombus is a possible mechanism. Left ventricular thrombus complicating acute myocardial infarction (AMI) results from turbulent blood flow and stasis related to an akinetic left ventricular wall segment or aneurysm. The incidence of left ventricular thrombus was 6.2% in a study of 642 patients with anterior wall AMI followed for 6 years, and did not differ between patients treated conservatively, with thrombolysis, or with a primary percutaneous intervention. Predictors of left ventricular thrombus were low ejection fraction and severe mitral regurgitation.

The incidence of stroke in the acute phase following MI is approximately 1%. Risk factors include large MI, anterior wall involvement, prior stroke, and increasing age. The incidence of stroke was 0.7% at 30 days in patients with AMI without persistent ST-segment elevation in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrin Therapy (PURSUIT) trial that enrolled 948 patients; 84% of all strokes were ischemic. Strokes occurring after MI resulted in high morbidity and mortality and were predicted by a higher baseline heart rate. The long-term risk of stroke following MI is about 6%. Strokes are mainly ischemic. Risk factors include advancing age, diabetes mellitus, previous history of stroke, history of hypertension, and smoking.

The risk of post-MI stroke may be highest over the first 3 months. Some data suggest that treatment with warfarin (target INR, 3.0-4.0) or the combination of acetylsalicylic acid and warfarin (INR, 2.0-2.5) may be more efficacious than acetylsalicylic acid alone in preventing recurrent cardiovascular events after MI, including strokes. Warfarin, however, is not generally recommended after MI for stroke prevention unless a stroke or TIA occurs in association with a left ventricular mural thrombus. In this setting, oral anticoagulation with a target INR of 2.5 for at least 3 months is suggested. The American College of Chest Physicians guidelines recommend considering moderate intensity oral anticoagulation (INR, 2.0-3.0) in addition to low-dose acetylsalicylic acid (<100 mg/d) for high-risk post-MI patients, including those with a large anterior MI, significant heart failure, intracardiac thrombus, AF, or a history of a thromboembolic event.

**Congestive Heart Failure**

Congestive heart failure can lead to cerebral embolism and hypoperfusion-related ischemia, causing both stroke and cognitive impairments. The risks and mechanisms of cognitive decline with CHF are less well understood than the risk for stroke. Severe CHF can be associated with impaired alertness, behavioral change and cognitive impairment similar to metabolic encephalopathy. There is not a consistent improvement in neuropsychological functioning in patients with CHF-associated cognitive impairments after cardiac transplantation.

Accounting for 9% of strokes, CHF is second after AF as a cause of cardiogenic stroke and CHF and AF coexist in about 2% of stroke patients. In community studies, CHF is associated with more than a 2-fold increased stroke risk, but much less in clinical trials. Some studies suggest that the risk may increase with decreasing ejection fraction.

The optimal strategy for decreasing stroke risk in the CHF setting is uncertain. Two large prospective, randomized, controlled studies assessed whether warfarin is superior to acetylsalicylic acid
A multicenter prospective incidence cohort study of 1437 patients with left-sided IE reported a stroke incident rate of 4.82/1000 patient-days over the first week of therapy that fell to 1.71/1000 patient-days in the second week, with a further decline with continued antimicrobial therapy. Stroke risk factors included infection with Staphylococcus aureus, mitral valve vegetations, and myocardial abscess. Other risk factors include mobile vegetations or vegetations >10 mm in diameter occurring on the anterior mitral leaflet.70,72,73

Surgery to prevent further embolic complications remains controversial because stroke risk falls dramatically with effective antimicrobial therapy.70 Moreover, the safety of cardiopulmonary bypass following stroke is uncertain due to concerns for intracranial hemorrhage related to anticoagulation during the procedure and potential hemodynamic worsening of the ischemic infarction. Despite these concerns, surgery may still be considered if performed early (ie, within 72 h) when embolic rates are highest and when there are other predictors of poor outcome (eg, recurrent embolization, CHF, prosthetic valve IE).74,75 Furthermore, the outcome of stroke patients following cardio-pulmonary bypass may be better than previously thought, with the exception of those with ICH.70,71,76 Large prospective studies quantifying the risk of cardiac surgery after IE-related ICH are lacking, but delaying for 4 weeks before cardiac surgery is often recommended.77 The AHA recommends stopping anticoagulation for at least the first 2 weeks of antibiotic therapy in the case of recent embolic stroke in the setting of Staphylococcus aureus prosthetic valve IE.74

Neurologic Complications of Cardiac Interventions

Stroke can complicate many cardiac procedures, including percutaneous coronary intervention (PCI), coronary artery bypass operations, valvuloplasty, and catheter ablation for AF. Stroke infrequently complicates PCI (about 0.3%), with the risk increasing with age, advanced renal failure, diabetes mellitus, hypertension, previous stroke, and emergency use of an intra-aortic balloon pump.78,79 Stroke complicating PCI portends high in-hospital and 1-year-mortality.78,79

There are no established guidelines for stroke prevention in the setting of cardiac interventions. Furthermore, the management of stroke in these settings is not straightforward. For example, in the case of stroke complicating cardiac catheterization, intravenous tissue plasminogen activator (IV-tPA) has been contraindicated in patients with MI within the 3 months prior to stroke, previously excluding many of these patients from treatment; recent MI is, however, no longer an absolute contraindication for IV-tPA.80 Other concerns include tPA-related bleeding due to the invasive procedure, concurrent use of antithrombotics, and conjectures about the composition of clots that may be less amenable to lysis.81 There is, however, some evidence that thrombolysis, whether intra-arterial or intravenous, might improve early outcomes after post-catheterization strokes.81

Coronary artery surgery, especially conventional on-pump coronary artery bypass graft, carries a higher rate of stroke and cerebral dysfunction than PCI.82 Because of the bleeding risk, IV-tPA is contraindicated for perioperative strokes. Case series suggest reasonable safety and efficacy for intra-arterial thrombolytic therapy; however, adequate controlled studies with appropriate follow-up are lacking.83,84

Although coronary artery bypass graft has been associated with an increased risk of cognitive impairments, studies comparing the cognitive status of patients after coronary artery bypass graft with an appropriate control group of otherwise similar patients with
cardiac disease not undergoing coronary artery bypass graft do not find greater decline after the operation.\textsuperscript{85-87} Furthermore, it does not seem to be a sustainable difference in cognitive function in patients who had on-pump versus off-pump coronary artery bypass graft.\textsuperscript{88}

**CARDIAC COMPLICATIONS OF NEUROLOGICAL DISEASE**

**Cerebrovascular Disease**

Just as stroke may complicate a variety of cardiac disorders, cerebrovascular disease can affect the heart. Electrocardiographic (ECG) changes suggesting MI occur in patients with intracerebral hemorrhage, subarachnoid hemorrhage, and 15% to 40% of those with ischemic stroke.\textsuperscript{89} Stroke can cause large inverted T-waves in anterior ECG leads and a variety of cardiac arrhythmias. Severe strokes can cause myocardial cytolyis. Monitoring for cardiac arrhythmias and tests for myocardial injury are part of the standard evaluation of stroke patients.\textsuperscript{83}

**Neuromuscular Disorders**

Cardiac disorders accompany a wide variety of neuromuscular diseases (Table 1).\textsuperscript{90-92} For example, left ventricular hypertrophy (LVHT), a cardiac disorder characterized by prominent trabeculations and intertrabecular recesses within the left ventricle, is associated with neuromuscular disorders in up to 80% of cases.\textsuperscript{93} Cardiac involvement is frequent in mitochondrial disorders and can be the primary determinant of prognosis. Cardiomyopathy may also be the presenting and main feature of Becker muscular dystrophy (BMD) and Emery-Dreifuss muscular dystrophy (EDMD).\textsuperscript{94} Depending on the underlying neuromuscular disorder, management of cardiac involvement should be aimed at determining the degree and type of abnormalities, preventing complications and alleviating symptoms.\textsuperscript{95}

**Mitochondrial Disorders**

Mitochondrial disorders result either from mutations affecting mitochondrial DNA encoding protein subunits of the respiratory chain complexes or from mitochondrial defects originating from nuclear DNA.\textsuperscript{95,96} Cardiac involvement usually manifests in childhood or early adulthood, can precede the diagnosis of mitochondrial disease, and is associated with increased mortality.\textsuperscript{95} Cardiac involvement varies between different mitochondrial disorders and can present as hypertrophic myopathy, dilated cardiomyopathy, and conduction abnormalities. Symptoms include CHF, syncope, and sudden death.\textsuperscript{96}

For example, Kearns-Sayre syndrome is characterized by ativoventricular conduction abnormalities that can progress rapidly to complete ativoventricular block, often warranting prophylactic pacemaker implantation.\textsuperscript{96,97} In contrast, myoclonus epilepsy and ragged red fibers (MERRF) and mitochondrial disease, and is associated with increased mortality.\textsuperscript{95} Cardiac involvement usually manifests in childhood or early adulthood, can precede the diagnosis of mitochondrial disease, and is associated with increased mortality.\textsuperscript{95} Cardiac involvement varies between different mitochondrial disorders and can present as hypertrophic myopathy, dilated cardiomyopathy, and conduction abnormalities. Symptoms include CHF, syncope, and sudden death.\textsuperscript{96}

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The diagnosis can often be made by mitochondrial enzymatic analysis in skeletal or cardiac muscles biopsies.\textsuperscript{96} Regardless of cardiac symptoms, cardiac evaluation is recommended for patients with suspected mitochondrial disorders because of the strong association with cardiac disorders and risk for sudden death.

**Duchenne and Becker muscular dystrophies.** Duchenne muscular dystrophy (DMD) and BMD result from X-linked mutations in the dystrophin gene on chromosome Xp21. They initially present with proximal weakness that gradually progresses to involve other muscles, including respiratory muscles.\textsuperscript{94} The dystrophin protein is located on the inner surface of the sarcolemma. It is completely absent or dysfunctional in DMD, but only reduced in BMD.\textsuperscript{94} Children with DMD typically present with muscle weakness and difficulty reaching motor milestones by the age of 5, whereas patients with BMD may present later and have less muscle weakness. Respiratory and cardiac failures are the leading causes of death in DMD, which usually occurs between the second and third decade.\textsuperscript{94} In contrast, patients with BMD have a slower progression of weakness and typically survive into adulthood, but heart failure remains an important cause of death and can be the presenting symptom that brings the patient to medical attention.\textsuperscript{98} Both DMD and BMD female carriers may develop dilated cardiomyopathy without apparent weakness.\textsuperscript{98} Cardiomyopathy in DMD and BMD is thought to be due to absent or diminished dystrophin in cardiomyocytes.\textsuperscript{99} Dystrophin deficiency may further increase the susceptibility to myocarditis that may play an additional role in the progression to heart failure.\textsuperscript{100} In DMD, focal areas of myocardial injury may appear as areas of regional wall abnormalities on cardiac imaging.\textsuperscript{50} Symptoms of cardiac involvement can be masked by reduced physical activity due to skeletal muscle weakness.\textsuperscript{99} Left ventricular dysfunction with predilection for wall motion defects in the posterobasal and posterolateral segments can be diagnosed with echocardiography and cardiac magnetic resonance imaging.\textsuperscript{99,101} Mitral regurgitation can also develop as a result of papillary muscle dysfunction.\textsuperscript{99} Arrhythmias, including sinus node dysfunction, atrioventricular node dysfunction, AF, and ventricular tachycardia/fibrillation may develop later in the course of the disease.\textsuperscript{99} Echocardiography and ECG is recommended starting at age 10 years in children with DMD\textsuperscript{99,102} Treatment of cardiomyopathy includes β blockers, angiotensin-converting enzyme inhibitors, and management of cardiac arrhythmias.\textsuperscript{99} The angiotensin-converting enzyme inhibitor perindopril preserves systolic function in patients with DMD and decreases mortality.\textsuperscript{103,104}

**Emery Dreifuss muscular dystrophy.** EDMD can be X-linked or autosomal. The X-linked form is caused by mutations of the STA gene at chromosome Xq28 encoding emerin, a nuclear membrane protein. The autosomal type is caused by a mutation of the LMNA gene at chromosome 1q21 encoding the nuclear lamina proteins, lamin A and C.\textsuperscript{94} The LMNA mutations cause other pathologies such as dilated cardiomyopathy and conduction system disease, limb-girdle muscular dystrophy with ativoventricular conduction disturbances, an autosomal form of axonal neuropathy, and a rare form of familial partial lipodystrophy.\textsuperscript{105} Early elbow, ankle and cervical spine contractures characterize EDMD.\textsuperscript{105} Proximal upper limb and distal lower limb weakness is usually slowly progressive, with later involvement of the proximal limb-girdle muscles.\textsuperscript{94} Cardiac disease characterized by conduction defects is usually evident by age 30 years and may present without muscle weakness.\textsuperscript{105,106} X-linked EDMD is characterized by AF/flutter, bradycardia, requiring pacemakers, prolongation of PR interval, complete heart block and atrial standstill. Absent P waves due to atrial paralysis is a typical ECG finding.\textsuperscript{94} Embolic strokes can result from cardiac arrhythmias.\textsuperscript{105,107} Heart failure occurs mainly in the autosomal forms of EDMD, with symptoms appearing in the
third or fourth decades of life. Holter monitoring may help early detection of arrhythmias in this population and an ECG should be obtained annually. A pacemaker is recommended after sinus node or atrioventricular conduction is apparent. Sudden death may still occur after pacemaker placement, possibly due to ventricular tachycardia or fibrillation. An intracardiac defibrillator may be warranted in those with documented symptomatic ventricular arrhythmias. Good outcomes following heart trans-
plantation for severe cardiomyopathy in patients with EDMD have been reported.105,107

CONCLUSIONS

Cardiac and neurologic diseases frequently overlap. Randomized trials are ongoing to elucidate the best management strategies in many of these disorders, and have been successful in providing certain management guidelines such as for stroke prevention in AF. Similar studies are more difficult for the less common neuromuscular disorders, although not impossible.103,104

CONFLICTS OF INTEREST

None declared.

REFERENCES


