Chapter 6
Cardiovascular Risk and Instability: Evaluation, Management, and Triage

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Overview

The cardiovascular system interacts with the neurologic system on many levels. This has implications for disease states in both systems. Therefore, when treating patients with neurosurgical disease, the provider must consider and be prepared to address pathological changes and consequences of treatment in the cardiovascular system. In the USA alone, approximately one of five persons has been diagnosed with some form of cardiovascular disease; and 40% of these patients are 65 years of age or more. With the progressive increase in life expectancy in the 21st century, the percentage of patients with significant cardiovascular disease and a comorbid neurological condition is also expected to increase.

Implications for the Neurosurgical Patient

Signs of Myocardial Damage

Cardiac disease in the neurosurgical population increases the overall morbidity and mortality. In patients who have suffered a cerebrovascular accident (stroke), cardiac manifestations may include EKG changes, cardiac arrhythmias, myocardial injury, and dysfunction, as well as neurogenic pulmonary edema.

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EKG changes are very common in stroke patients and occur in 49–100% of cases, with higher incidence in patients suffering from intracerebral or subarachnoid hemorrhage and lower incidence in patients with ischemic stroke. These changes consist of large inverted T waves, prolonged QT intervals, and large U waves, all observed primarily in the septal leads. This pattern has been considered distinctive of cerebrovascular accidents. Arrhythmias ranging from bradycardia to fatal ventricular fibrillation are also seen in the acute period following onset of stroke symptoms.

Elevation of troponins and echocardiographic changes consistent with myocardial ischemia may also exist in this group. These typically reversible (but significant) changes seen on echocardiography span the whole clinical spectrum from hypokinesis with normal cardiac index to low output cardiac failure. However, in a cohort of patients who sustained subarachnoid aneurysmal hemorrhage, no differences in mortality were found in patients demonstrating cardiac abnormalities vs. patients in the control group. This finding may be due to the lack of coronary artery disease in many of the patients who present with signs and symptoms of cardiac injury in connection with their neurological insult. Nonetheless, any serious cardiac manifestation is a potential risk factor for mortality and additional morbidity and should be treated to prevent further decline of cardiac function.

Hypothalamic stress following subarachnoid hemorrhage (increased intracranial pressure) leads to a massive release of catecholamines. This causes hypertension and increased cardiac work, which result in the cardiac sequelae. Despite these "sequelae", there is usually no permanent cardiac injury, and, therefore, no consistent association with EKG abnormalities, histological cardiac lesions, or serum markers of cardiac injury.

Neurosurgical Patients and Anticoagulation

Pharmacological and Physiological Risks for Bleeding. Patients with neurosurgical disorders are often older and, therefore, can have disease processes that require anticoagulation for management. These typically originate from the cardiovascular system and include atrial fibrillation, thromboembolism, or atherosclerotic manifestations like carotid artery disease.

Anticoagulant therapy can cause spontaneous bleeding. Listed below are several classes of pharmacological agents with representative drugs that can cause bleeding.

- Antiplatelet agents: Acetylsalicylic acid (ASA), clopidogrel (Plavix), and abciximab (Rheopro)
- Heparins: Unfractionated (no trade name, usually from pork intestine); low-molecular-weight heparins (LMWHs) – enoxiparin (Lovenox), dalteparin (Fragmin)
- Inhibitors of Vitamin K-dependent coagulation factors: Warfarin (Coumadin) with a half-life of 36–42 h

- Direct thrombin inhibitors: Lepirudin, bivalirudin, agatroban (all parenteral drugs)
- Fibrinolytic agents: Tissue-type plasminogen activator (tPA).

In addition to these pharmacological risks, patients may present with congenital clotting defects (e.g., Von Willebrand's disease, hemophilia). Further, patients with unrelated diseases may be prescribed pharmaceuticals with anticoagulant properties and/or have interactions with other drugs that act to change the patient's coagulation status (i.e., drug–drug, drug–food, and drug–genomic interactions). In addition, patients with severe liver disease may manifest increased bleeding tendency due to decreased synthetic function of the liver with reduced production of coagulation factors. Patients who have a malignancy may have antibodies to clotting factors and/or to platelets or have a consumptive coagulopathy and present with excessive bleeding (in addition to their neurologic disease).

Assessing Coagulation Status. Coagulation status is most commonly determined by measuring the International Normalized Ratio (INR) of the prothrombin time (PT) test, which indicates function of vitamin K-dependent coagulation factors and the synthetic function of the liver. Fibrinogen levels can also be useful in assessing the coagulation status of the perioperative neurosurgical patient since fibrinogen is the main "building block" of clot. The activated partial thromboplastin time (APTT) test helps to assess the effectiveness of unfractionated heparin; and measuring Factor Xa levels helps to assess the effectiveness of LMWHs, although this test is not commonly used.

Unfortunately, it is somewhat difficult to get a quick evaluation of platelet function in patients on antiplatelet agents. A normal platelet count does not ensure normal platelet function. Lancet-induced bleeding time is also not a good predictor of platelet function. There are specialized tests to evaluate platelet function, but these are generally not readily available. Examples are flow cytometry, thromboelastography (TEG), and Sonoclot evaluations.

D-Dimer is a test that helps to assess the presence of a hypercoagulation state, which may be present in some stroke patients. There are two main types of stroke: ischemic (85% of all strokes) and hemorrhagic (15%). Ischemic stroke occurs when an obstruction in the arterial system causes ischemia in the brain. Hemorrhagic stroke occurs when a vessel ruptures and bleeds into the brain or into the subarachnoid space (when a large vessel ruptures). In hemorrhagic stroke patients, coagulation increases when fibrinogen is converted to fibrin to form a clot. This process yields fibrin degradation products, and a positive D-dimer test signals a high level of these products in the plasma. (It should be noted that D-dimer is a nonspecific test and may also be elevated following surgery, liver disease, heart disease, and cancer.)

Many more specialized tests are available and may be ordered by a hematologist when caring for a complicated patient. For a patient who requires reversal of anticoagulation, the general approach is to first elucidate the level of anticoagulation and define the mechanism of anticoagulation. Normally, all common coagulation tests (INR, APTT, CBC including platelet count, fibrinogen, and D-dimer) are performed

simultaneously to expedite the diagnosis. In the acute patient, more advanced coagulation investigations may not be available in a timely manner, since more sophisticated blood tests require longer processing times.

Treating coagulation disorders. Treatment for coagulation defects in neurologically impaired patients targets specific deficiencies that persist after stopping anticoagulation therapy. For bleeding patients with platelet dysfunction, platelets should be transfused. This is also recommended for patients with a normal platelet count when platelet dysfunction is suspected. The target value for platelet count is 50,000 for patients scheduled for surgery or for patients with hemorrhage that could be life-threatening. The usual recommended dose is 1 U of platelets per 10 kg body weight. One unit of platelets will increase the platelet count by $5–10 \times 10^9$ per liter. (One unit of platelets is 5×10^{10} platelets in 50–70 mL plasma; typically, 5–10 U [random donor platelets] are pooled in one component bag for ease of administration. Apheresis platelets [from a single donor] may also be used and contain $3–5 \times 10^{11}$ platelets in 200–400 mL plasma, equivalent to 4–6 U of platelets. Platelet transfusion is also the treatment of choice for reversal of antiplatelet agents such as clopidogrel.

DDAVP at a dose of 0.3 μg/kg can also be tried to improve coagulation in patients on antiplatelet agents. DDAVP releases factor VIII and Von Willebrand factor and is a manufactured analog of vasopressin without its vasoconstrictive effects. However, like AVP, DDAVP causes antidiuresis and could be associated with congestive heart failure in patients with poor cardiac function. Therefore, smaller doses of DDAVP (e.g., 0.15 μg/kg) should be considered for elderly patients and patients with cardiovascular diseases.

Unfractionated heparin has an antidote in protamine. The usual dose is 1 mg protamine (IV) for each 100 U of heparin given. This dose is reduced by 50% (i.e., 0.5 mg protamine for each 100 U of heparin) at 60–120 min after heparin has been discontinued. The recommended rate of administration is 5 mg protamine per minute. Intravenous protamine can cause hypotension via histamine release as well as more severe reactions such as anaphylaxis and, very rarely, catastrophic pulmonary vasoconstriction (resulting in pulmonary hypertension and vascular collapse). In patients with significant neurologic disease, treatment of these protamine reactions should be primarily supportive, with standard approaches ranging from small boluses of intravenous fluid and intravenous ephedrine (or phenylephrine) to treat hypotension up to full treatment of anaphylaxis with intravenous fluids, epinephrine, anti-histamines, and possibly steroids and intubation, if indicated.

Subcutaneous heparin for prophylaxis of deep vein thrombosis (DVT) is usually not reversed. LMWHs, unfortunately, cannot be fully reversed by protamine. However, some authors recommend 1 mg of protamine (IV) for each milligram of enoxaparin administered over the previous 4–8 h. Anticoagulation by inhibitors of vitamin K-dependent pathways can be reversed by administering vitamin K, either intravenously (risk of anaphylaxis and hypotension) or subcutaneously. In non-life-threatening situations, the recommended dose of vitamin K is 1–2 mg. For life-threatening situations, the recommended dose is 10 mg vitamin K, which accelerates the onset of effect and also presents a higher risk of complication. The higher dose

is also associated with some difficulty in subsequent titration of anticoagulation; however, in the case of brain hemorrhage, this becomes a secondary concern. Vitamin K should not be used as sole treatment to reverse anticoagulation because it takes hours to normalize INR. For immediate effect, fresh frozen plasma (FFP) should be infused at 15–20 mL/kg. However, administration of FFP increases the risk for anaphylaxis, blood-borne diseases (e.g., HIV, hepatitis), and fluid overload, with subsequent heart failure, because of the large amount of FFP that may be required to achieve the desired level of improved coagulation.

When clinicians have significant concern about the negative consequences of the large volume of fluid required when using FFP to improve coagulation, an alternate treatment option is to infuse prothrombin complex concentrates at doses based on weight and actual INR and INR goal. Typical doses are 15–50 U/kg. Factor IX concentrates can also be administered.

Recombinant-activated Factor VII is currently being investigated as a treatment for coagulopathy. The FDA indication for clinical administration of recombinant-activated Factor VII is bleeding associated with hemophilia and antibodies to Factors VIII or IX. A wide range of doses has been tested, but the typical dose is approximately 90 μg/kg. Off-label recombinant-activated Factor VII has been used in a variety of clinical bleeding scenarios, including neurosurgical bleeding, with varied results.

Fibrinolytic agents such as tPA can be reversed by 6–8U of platelets or cryoprecipitate (6–8 doses) that contains Factor VIII. No antidotes are known for bleeding due to the administration of direct thrombin inhibitors. Congenital clotting defects and bleeding are best managed with help from an experienced hematologist.

Hypertension and Neurosurgical Disease

Many neurosurgical disease states such as intracerebral hemorrhage, ischemic neurological injury, and carotid artery disease are affected by the blood pressure. Finding an optimal level of blood pressure depends on many factors including severity of chronic hypertension, patient age, and impairment of intracranial compliance (e.g., patients with elevated ICP). Blood pressure control may be particularly critical in patients with (or at risk for) hemorrhage in areas that place neurologic tissue at risk for further injury (e.g., brain or spinal cord).

For individual patients with neurologic injury, the optimal blood pressure range is often difficult to establish. Ideally, the blood pressure range would allow for optimal cerebral perfusion without placing the patient at risk for cerebral hemorrhage or edema. This can be difficult to demonstrate since CT and MRI – the usual scanning methods – are static exams and are impractical for providing information over time. More advanced studies such as PET scanning can give more insight but are not readily available. One study in stroke patients shows a U-shaped blood pressure curve with increased mortality for patients presenting with blood pressures greater than 220/111 or less than 100/61. Hypotension is rare in patients in the acute setting of stroke. When hypotension is observed in this population, potential etiologies include aortic dissection, dehydration, blood loss, sepsis, and decreased cardiac output.

If hypotension is noted, immediate steps should be taken to correct the hypotension and to identify and treat the underlying cause.

Hypertension is more commonly seen in the acute setting following stroke, and the possible etiologies include acute stress, pain, hypoxia, and increased ICP. For patients with intracerebral hemorrhage, the 2007 AHA/ASA guidelines suggest (class IIb evidence) only reducing blood pressure to approximately 160/90 (mean blood pressure 110 mmHg). First-line antihypertensives should be agents that are unlikely to inadvertantly raise ICP (e.g., labetalol, nicardipine, esmolol, and enalapril). Significantly increased ICP can manifest as severe impairment following acute stroke, severe hypertension, bradycardia, decreased level of consciousness, and abnormal respirations (i.e., Cushing's reflex). Since these findings are often premorbid, it is critical that the clinician define the nature of the intracranial pathology and treat appropriately. Great caution must be used in administering direct vasodilators to control blood pressure (e.g., nipride and nitroglycerin) as these drugs may cause reduced cerebral perfusion and increased ICP with worsening of neurologic injury.

Cerebral Vasospasm

Following subarachnoid hemorrhage or severe head injury, many patients develop acute cerebral vasospasm causing cerebral ischemia. The current treatment principle is to keep the cerebral perfusion pressure (CPP) above 60–70 mmHg by managing the patient with fluids and vasopressors to ensure adequate perfusion. Following aneurysmal subarachnoid hemorrhage, many centers employ a strategy of pharmacologically induced hypertension and hypervolemia in hopes of facilitating improved cerebral perfusion. This treatment approach places the patient at risk for myocardial dysfunction (an imbalance between myocardial oxygen consumption and supply) and congestive heart failure.

Concerns and Risks

The EKG changes reflect myocardial processes caused by sympathetic stimulation associated with neurosurgical bleeding, even in patients with no organic ischemic cardiac disease. To ensure optimal oxygen delivery to the brain, support of circulation must be initiated when cardiac dysfunction leads to decreased cerebral oxygenation and perfusion. With appropriate hemodynamic monitoring (e.g., invasive arterial pressure, central venous pressure, and possibly pulmonary artery pressure) to guide therapy, standard treatment with inotropes may be necessary for low cardiac output states that have been confirmed by clinical exam and supporting investigations such as echocardiography. Anti-arrhythmics are indicated for hemodynamically significant arrhythmias. These treatments are started in all patients when indicated. A cardiac workup can then be performed to separate the patients with true

underlying cardiac disease from patients with only temporary cardiovascular manifestations resulting from their acute neurological condition.

Anticoagulation therapies can worsen the outcome of the neurosurgical process and must often be discontinued after carefully weighing the risk/benefit ratio of continued anticoagulation vs. discontinuation. Patients are placed on anticoagulation treatment for a variety of reasons, and some indications may be weaker than others. For example, some biological cardiac valve prostheses may not need more aggressive anticoagulation than aspirin; on the other hand, cardiac stents require more intensive anticoagulation therapy, and discontinuation would place the patient at risk for catastrophic stent thrombosis – in BMS (bare metal stents) especially the first month and in DES (drug-eluding stents) especially the first year. These treatment decisions are best made in consultation with a cardiologist.

In acute ischemic strokes, acute lowering of the blood pressure may decrease the risk for hemorrhagic transformation (cerebral hemorrhage after an ischemic stroke) and cerebral edema; however, actively lowering the blood pressure can worsen neurological injury by increasing the ischemia in the penumbra (the zone of reversible ischemia surrounding the infarct) because of inadequate driving pressure through a stenosis. In contrast, a blood pressure that is too high can cause increased edema and increased bleeding, especially in patients with ruptured aneurysms or arteriovenous malformations who are at risk for rebleeding.

Consideration should be given to maintaining an adequate CPP, i.e., greater than 70 mmHg. CPP is the difference between mean arterial pressure and the downstream pressure, either the jugular venous pressure or the intracranial pressure, whichever is higher. For stable patients, noninvasive blood pressure monitoring is adequate; but in unstable patients who require continuous intravenous antihypertensives, and in deteriorating patients, an invasive arterial catheter should be considered to provide beat-to-beat monitoring and an easy way to measure metabolic status. Unfortunately, this metabolic information will only reflect the global status and not the focal values that would better guide therapy. For patients with cardiac disease, control of blood pressure is indicated to tip the myocardial oxygen balance in favor of reduced work and, therefore, lower the risk for ischemia.

Key Points

- Signs of myocardial damage without underlying cardiac disease can be present in patients with neurosurgical disease, and these manifestations must be evaluated and treated.
- Rapid and aggressive reversal of anticoagulation may be indicated in patients with critical bleeding in the central nervous system.
- Control of blood pressure is often necessary to mitigate the effects of hypertension on intracerebral hemorrhage. It reduces the risk for rebleeding in patients with hemorrhagic strokes and reduces the risks for cerebral edema and hemorrhagic transformation in patients with ischemic strokes.

Suggested Reading

Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, MacDonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. American Heart Association Stroke Council and Council on Cardiovascular Nursing. Stroke. 2010;41(9): 2108–29.

Khaja AM. Acute ischemic stroke management: administration of thrombolytics, neuroprotectants, and general principles of medical management. Neurol Clin. 2008;26(4):943–61.

Kopelnik A, Zaroff JG. Neurocardiogenic injury in neurovascular disorders. Crit Care Clin. 2006;22(4):733–52.

Macmillan CS, Grant IS, Andrews PJ. Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management? Intensive Care Med. 2002;28(8):1012–23.

Powner DJ, Hartwell EA, Hoots WK. Counteracting the effects of anticoagulants and antiplatelet agents during neurosurgical emergencies. Neurosurgery 2005;57(5):823–31, discussion 823–31.