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Role of Anticoagulant Therapy in Acute Ischemic Stroke in Intensive Care Unit

Essay Submitted in Partial Fulfillment for Master Degree in Intensive Care

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List of abbreviations

AA: Aortic Atheroma

ABC: Airway, Breathing, and Circulation

ACCP: American College of Chest Physicians

ACS: Acute Coronary Syndrome

ADLs: Activities of Daily Living

ANA: Antinuclear Antibody

aPTT: Activated Partial Thromboplastin Time

AT: Antithrombin

BBB: Blood Brain Barrier

CA: Cerebral Autoregulation

CAOD: Coronary Artery Occlusive Disease

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

CGRP: Calcitonin Gene-Related Peptide

CPP: Cerebral Perfusion Pressure

CRP: C-Reactive Protein

CSF: Cerebrospinal Fluid

CT: Computed Tomography

CVR: Cerebrovascular Resistance

DWI: Diffusion-Weighted Imaging

ECG: Electrocardiogram

EU: European Union

FDA: Food and Drug Administration

FFP: Fresh Frozen Plasma

HIT: Heparin-Induced Thrombocytopenia

ICA: Internal Carotid Artery

ICP: Intracranial Pressure

INR: International Normalized Ratio

LACI: Lacunar Cerebral Infarction

LMW: Low Molecular Weight

MAP: Mean Arterial blood Pressure

MI: Myocardial Infarction

MMPs: Matrix Metalloproteases

MRA: Magnetic Resonance Angiography

NIHSS: National Institutes of Health Stroke Scale

NO: Nitrous Oxide

NOS: Nitric Oxide Synthase

OT: Occupational Therapy

PACI: Partial Anterior Circulation Infarction

PAOD: Peripheral Artery Occlusive Disease

PCC: Prothrombin Complex Concentrate

PEG: Percutaneous Endoscopic Gastrostomy

PF_4: Platelet Factor 4

PIDs: Peri-Infarct Depolarizations

POCI: Posterior Circulation Infarction

PT: Physical Therapy

PT: Prothrombin Time

PWI: Perfusion-Weighted Imaging

RIND: Reversible Ischaemic Neurological Deficit

ROSIER: Recognition Of Stroke In the Emergency Room

RPR: Rapid Plasma Reagent

rt-PA: Recombinant tissue-type Plasminogen Activator

SAH: Subarachnoid Hemorrhage

SLP: Speech-Language Pathology

SUD: Stroke of Undetermined

TACI: Total Anterior Circulation Infarction

TIAs: Transient Ischaemic Attacks

TNF-∝: Tumor Necrosis Factor-∝

TOAST: Trial of Org 10172 in Acute Stroke Treatment

tPA: Tissue Plasminogen Activator

VKAs: Vitamin K Antagonists

VTE: Venous Thromboembolism

WARCEF: Warfarin and Aspirin in the patients with Reduced Cardiac Ejection Fraction

Anatomy and physiology of cerebral circulation

All arterial blood supply to the brain and brainstem traverses branches of either the internal carotid or vertebral arteries (figure 1). These arteries, in turn, receive blood from major branches of the arch of the aorta: the internal carotid is a major division of the common carotid artery while the vertebral is derived from the subclavian artery ***(Drake et al., 2005)***.

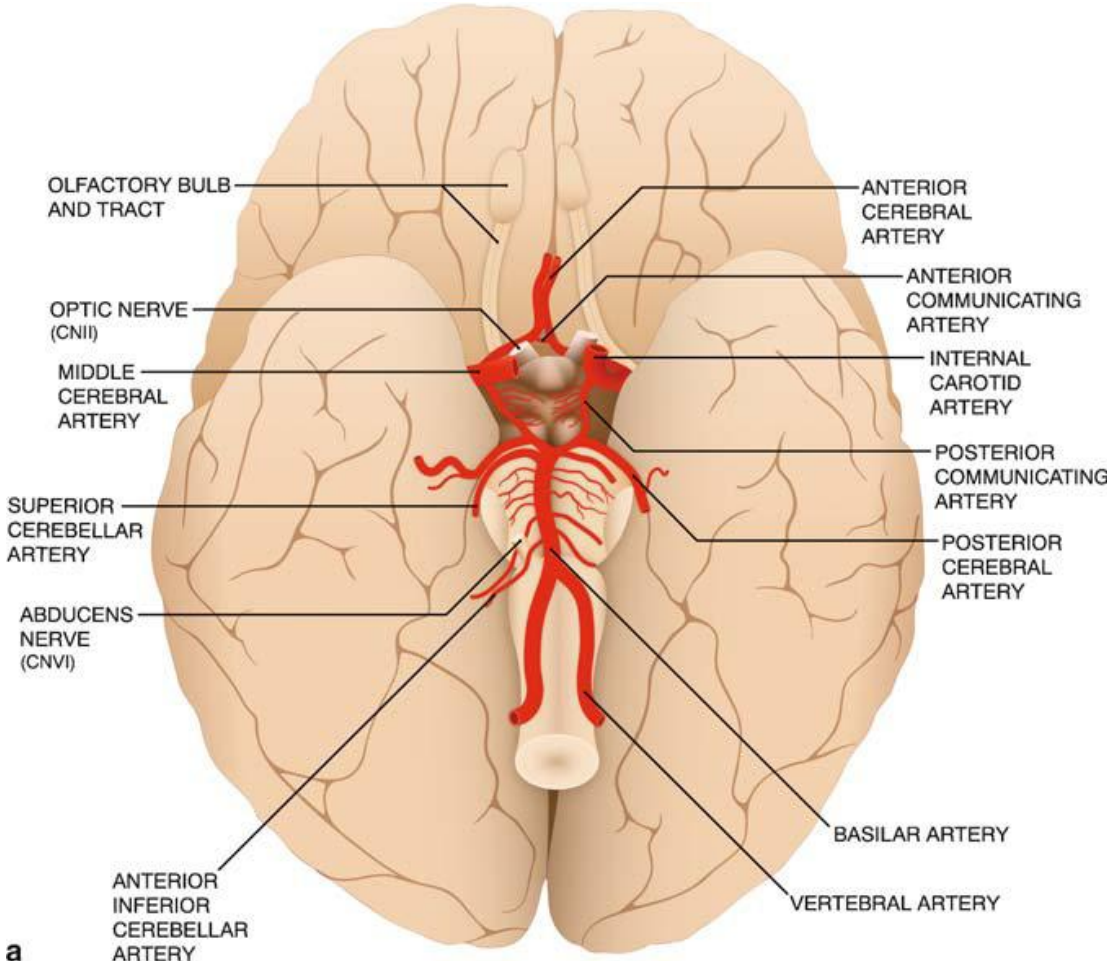

Figure (1)*:** Vessels that contribute to the arterial circle of Willis at the base of the brain ***(Drake et al., 2005)

The blood supply to the brainstem, cerebellum, occipital lobe and the inferior aspect of the temporal lobe is derived from branches of the vertebral system. The frontal, parietal, upper 75% of the temporal lobes and the insular cortex receive their blood supply from the middle and anterior arteries, both of which are branches of the internal carotid system ***(Desesso, 2009)***.

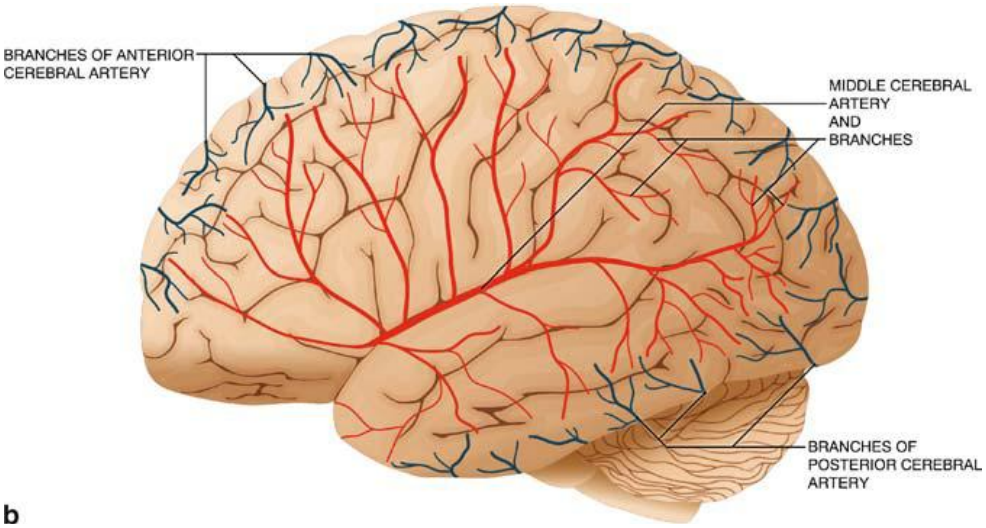

Figure (2): Distribution of blood supply to the lateral surface of the cerebrum ***(Desesso, 2009)***

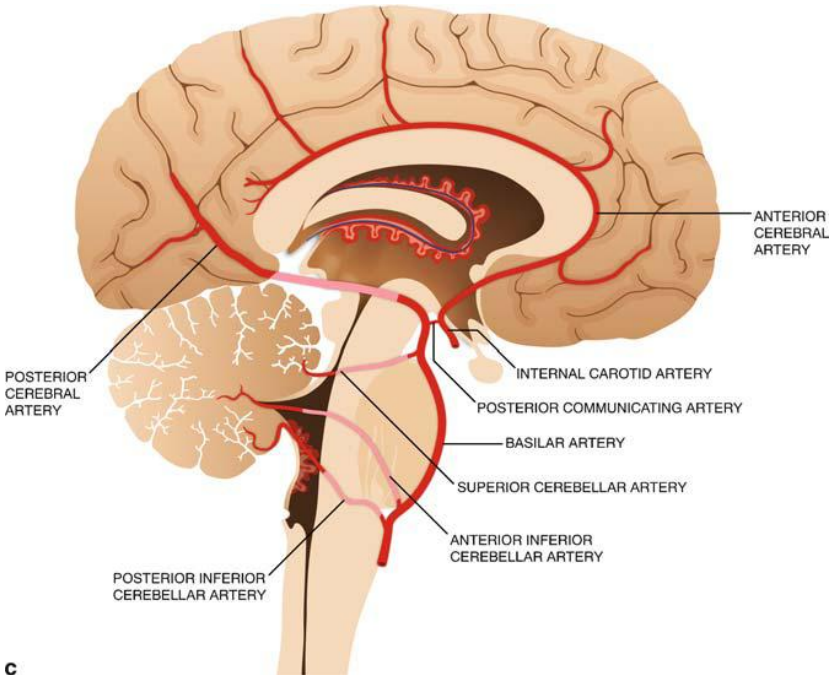

Figure (3): Sagittal section that depicts the distribution of blood flow to the cerebrum ***(Drake et al., 2005)***

Although the vertebral and carotid systems supply distinct areas of the brain and brainstem, the two systems are structurally joined by means of a multi-sided system of interconnected vessels (the circle of Willis) located at the base of the brain where they surround the stalk of the pituitary gland, the optic chiasm and optic tracts, and the hypothalamus.

The basilar artery (derived from the fused vertebral arteries) terminates as the posterior cerebral arteries. The internal carotid arteries contribute the anterior and middle cerebral arteries and the posterior communicating arteries. The anastomosis is completed by the short anterior communicating artery between the two anterior cerebrals and the paired posterior communicating arteries between the posterior cerebral arteries and the middle cerebral artery. The latter arteries connect the vertebral and carotid blood supplies. Interestingly, the diameters of the arteries vary considerably, especially in the case of the posterior communicating arteries, which frequently may be extremely small on one side or even absent ***(Drake et al., 2005)***.

Consequently, the anastomosis is often only a potential channel and tracer studies in adults have shown that the two blood streams (vertebral and internal carotid) do not mix.

With regard to tissue blood supply, the organization of the brain and brainstem differs from that of the rest of the body in that there are no anastomoses within the nervous tissue. Each arterial branch is a functional end artery; if it were to be occluded, the territory of the

brain that it supplied would become hypoxic and ischemic. Because the blood supply to the brain and brainstem is critical for normal cognitive function, a more complete description of the arterial supply follows.

The vertebral arteries branch from the subclavian arteries in the root of the neck and ascend within the foramina of the transverse processes of six of the cervical vertebrae (C_6-C_1). Upon exiting the transverse foramina of C_1, the vertebral arteries enter the skull through foramen magnum and approach each other in the midline where they fuse to form the basilar artery at approximately the level of the pontomedullary junction. The basilar artery travels rostrally in a groove on the base of the pons until it terminates as the superior cerebellar and posterior cerebral arteries ***(Desesso, 2009)***.

The basilar artery distributes blood via numerous small vessels that enter the pons to supply the pontine nuclei, corticospinal tract, and the pontine portion of the reticular formation. At its termination, the basilar artery gives off the superior cerebellar and posterior cerebral arteries each of which (plus the posterior communicating arteries) gives off numerous small arteries that penetrate the posterior perforated substance to supply the midbrain. Thus, geographically distinct regions of the midbrain receive blood supply from the posterior cerebral, posterior communicating, and superior cerebellar arteries. Each of these arteries gives off numerous small branches throughout their extents; these branches penetrate the nervous tissue to supply the various regions of the brainstem. The bulk of the lateral midbrain reticular formation is supplied by the

superior cerebellar artery; whereas the colliculi, periaqueductal gray matter, and raphe nuclei receive blood from the posterior cerebral artery; and the majority of the cerebral peduncles are vascularized by branches from the posterior communicating arteries ***(DeSesso, 2009)***.

Physiology of cerebral circulation:

In the brain, Cerebral Blood Flow (CBF) varies directly with cerebral perfusion pressure (CPP which is defined as the difference between mean arterial pressure and intracranial pressure) and inversely with cerebrovascular resistance (which is the sum of the resistance to flow generated by the vasculature, particularly at the level of the small pial arteries and penetrating pre-capillary arterioles). In general, the contribution of any given cerebral vessel to overall CBF is defined by factors such as its radius and length, and the viscosity and pressure of blood flowing through it ***(Werner, 1998)***.

The average rate of blood flow in the brain is approximately 50-55 ml/100 gm/minute. In pathological states, this global flow rate may decrease. The link between flow rate and electrophysiological and clinical findings underlies the concept of "flow thresholds". Remarkably, clinical evidence for a neurological deficit may not appear until average flow has fallen to 50% or below of normal levels (i.e. to approximately 25-30 ml/100 gm/minute). At this threshold, global neurological impairment is noted and, below this, the margin between reversible and irreversible ischemic damage

becomes narrow. Brain "electrical failure" begins at rates of about 16-18 ml/100 gm/minute, while cytotoxic edema from failure of ionic pumps, particularly Na^+/K^+ATPases, develops at 10-12 ml/100 g/min. Finally, metabolic failure with gross disturbance of cellular energy homeostasis occur at rates of less than 10 ml/100 gm/minute ***(Friedman et al., 2005)***.

The incompressibility of the cranial vault mandated a relatively constant intracranial blood volume at all times. Any variation in the volume of one of the three principal intracranial contents, namely brain parenchyma (1200-1600 ml), blood (100-150 ml) and cerebrospinal fluid (CSF, 100-150 ml), was accompanied by a compensatory change in the volume of the other two. In fact, this latter notion forms the basis of the relationship between intracranial pressure and Cerebral Blood Volume (CBV). This pressure-volume relationship implies that in order to maintain a constant intracranial pressure in the face of rising CSF volume, blood volume must fall and when this can no longer occur, the brain will herniate caudally. Importantly, as intracranial pressure rises there is a fall in CBF in association with reduced CBV, most likely from structural compression of the vasculature ***(Friedman et al., 2005)***.

Metabolism:

During resting conditions, approximately 15% of the cardiac output is directed to the brain to match cerebral oxygen consumption which is about 20% of the total body oxygen consumption. Due to the low energy storing capacity of the CNS, regulatory mechanisms are necessary to provide continuous substrate supply. There is a wide

range of metabolic rates within the CNS tissues as resting CBF and metabolism are higher in cortical compared to subcortical tissues. The energetic requirements of the brain during activation are instantaneously met by increases in substrate delivery to the activated functional subunits (i.e. increases in CBF) ***(Werner, 1998)***.

Neurons within the active subunits release vasodilating substances which directly diffuse to the smooth muscle cells of the vascular wall or indirectly change vascular tone via endothelial mediators. Adenosine, nitric oxide, hydrogen and potassium ions appear to be the most important mediators of flow-metabolism coupling. However, the temporal response of any of these mechanisms is too slow to explain the explosive increases in CBF following functional activation***.(Werner,1998).***

Cerebral vessels have sympathetic and parasympathetic innervation. Sympathetic fibres contain norepinephrine, ATP, and neuropeptide Y. The effects of cathecholamines on the cerebral circulation are diverse. Cathecholamines may increase or decrease both Cerebrovascular Resistance (CVR) and CBF. The individual response of the cerebral vasculature is related to the origin of the neurotransmitter ***(Werner, 1998)***.

Autoregulation:

The term Cerebral Autoregulation (CA), coined by Lassen in 1959, describes the tendency of CBF to remain approximately constant when Mean Arterial blood Pressure (MAP) changes over a wide range, typically from 60 to 150 mmHg. ***(Panerai et al., 2004).***

From a functional perspective, the term cerebral autoregulation refers to the ability of cerebral arteries to maintain CBF (and therefore brain perfusion) at a relatively constant level despite fluctuations in CPP. From a physical perspective, autoregulation involves relatively rapid changes in the caliber of cerebral resistance vessels, principally the precapillary arterioles, in response to changes in transmural pressure as CPP varies. As a result of this phenomenon, CBF is relatively independent of CPP between the physiological limits of autoregulation, typically taken to be perfusion pressures of 50-60 mmHg for the lower limit and 150-160 mmHg for the upper. In normal subjects, CPP varies directly with MAP (due to constant ICP), varying directly with systolic blood pressure. Across the autoregulatory range of approximately 100 mmHg, in order to maintain a relatively constant CBF, cerebral arteries constrict as CPP rises and dilate as CPP falls. As a result, CPP and CBV are inversely related through this phenomenon ***(Panerai et al., 2004)***.

The mechanism includes intrinsic changes in vascular smooth muscle tone (***myogenic hypothesis***) modulated by the release of a variety of vasoactive substances from the endothelium (***endothelial hypothesis***) and periadventitial nerves (***neurogenic hypothesis***) in response to changes in transmural pressure. A “metabolic” or

"humoral" hypothesis has also been proposed to aid in the explanation of cerebral autoregulation. The description of metabolic regulation of cerebral vasomotor function rather than cerebral autoregulation is a pressure-dependent response, as follows:

- First, As measured by microdialysis, the extracellular and perivascular concentrations of H^+ and K^+ (key mediators in metabolic vasoregulation) normally do not change in response to CPP alterations in the autoregulatory range.
- Second, As reported in studies measuring changes in cerebroarterial diameter or tone in response to variations in perfusion or transmural pressure, autoregulation begins within a few seconds of the pressure change, and is typically complete within 15-30 seconds. Although not precluding their involvement in this process, this relatively rapid time course suggests that metabolic factors are less likely to be involved.
- Third, it has been reported that the brain's interstitial concentration of adenosine (another key mediator in metabolic hypothesis) may be increased at the lower limit of autoregulation. ***(Friedman et al., 2005)***

Despite the possibility of adenosine contributing to autoregulation at this extreme, its concentrations are known not to vary across the bulk of the autoregulatory range. Fourth, the autoregulatory response has been observed in isolated, perfused vessels in vitro (i.e. not subject to alterations in neuroglial metabolism), providing further evidence against a metabolic hypothesis. Taken together, metabolic factors, despite being capable of strong regulation of cerebral vasomotor function, are unlikely to play a major role in autoregulation.