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Contributions of Anesthesiology to the Surgical Treatment of Cerebrovascular Disease

The Role of Arthur S. Keats, M.D.

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Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. By B. A. Wells, A. S. Keats, and D. A. Cooley. Surgery 1963; 54:216–23.

Local anesthesia with little or no preoperative sedation is currently recommended as the anesthetic of choice for temporary carotid occlusion during carotid endarterectomy. Purported advantages include minimal circulatory and respiratory changes from the local anesthetic, and constant verbal contact can be maintained with the patient so that neurologic changes are promptly recognized. However, local anesthesia may not be satisfactory in uncooperative or semiconscious patients. We therefore undertook a trial of general anesthesia in 56 consecutive patients undergoing carotid endarterectomy. Patients were induced in standardized fashion using intravenous thiopental (100–400 mg), atropine (0.2 mg), and succinylcholine (40–80 mg). Cyclopropane, along with deliberate hypercapnia and hypertension, was used for anesthesia maintenance. All patients tolerated carotid occlusion for periods of up to 30 min during general anesthesia without shunt, bypass, or hypothermia. Except for one patient, electroencephalogram evidence of cerebral ischemia was not apparent during occlusion, and no patient suffered postoperative neurologic sequela. Twenty percent of patients who had their carotid arteries occluded preoperatively for 30–60 s without general anesthesia suffered convulsions. These data suggest that general anesthesia increased the tolerance to cerebral ischemia. Potential mechanisms involved might include: 1) decreased cerebral metabolic rate for oxygen; 2) increased cerebral blood flow from hypercapnia; 3) increased arterial oxygen tension; and 4) recruitment of new routes of collateral circulation.

ALTHOUGH the history of cerebrovascular disease spans many centuries, many of the seminal observations that influence current practice were described within the past 55 yr. We review the early contributions our discipline made to the surgical treatment of cerebrovascular disease, with special emphasis on the role of Arthur S. Keats, M.D. (Professor and Chief, Division of Cardiovascular Anesthesiology, Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Texas; 1923–2007)‖ in the evolution of cerebral protection during carotid endarterectomy (CEA).[1]

In 1905, Hans von Chiari, M.D. (1851–1916), first suggested a link between carotid artery disease and stroke after finding thrombus superimposed on the carotid artery atherosclerotic plaques of four patients at autopsy who had suffered a cerebral embolism.[2] However, it was not until 1914 that James Ramsay Hunt, M.D. (1872–1937), described the clinical syndrome of stroke due to cervical carotid disease.[3] In 1927, Antonio Egas Moniz, M.D., of Portugal (1874–1955) reported the first case of cerebral angiography at the Societe de Neurologie in Paris.[4] However, at this time, most angiograms were performed to look at the intracranial portion of the carotids in patients with tumors to look for abnormal displacement of arterial branches, with little interest in vascular disease *per se*.[5] Indeed, it was not until 1951 that Charles M. Fischer, M.D., would describe the clinical implications of transient ischemic attacks and their

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‖ I have been fortunate in my relatively brief medical career to personally know and befriend two of the great grandfathers of American anesthesiology: Leroy D. Vandam, M.D., who passed away in 2004; and Arthur S. Keats, M.D., who died during the writing of this article. Dr. Keats told me that everything he knew about being a journal editor he learned from Dr. Vandam. I dedicate this article to the memory of these two fine physicians who so significantly impacted my academic career.

relation to carotid disease and stroke. In this same article, he wrote, "it is even conceivable that some day vascular surgery will find a way to by-pass the occluded portion of the artery during the period of ominous fleeting symptoms." Just 2 yr later, Michael E. DeBakey, M.D., would perform the first successful CEA in 1953,[6] while H. H. G. (Felix) Eastcott, M.S., F.R.C.S., F.A.S.C. (Hon.), would perform the first CEA with carotid artery cross clamping in 1954,[7] and Denton Cooley, M.D. (1920–), would be the first to use an intravascular shunt.[8]

At the beginning of the 1960s, local anesthesia with little or no preoperative sedation was widely recommended as the anesthetic of choice for temporary carotid occlusion during CEA.[1] At that time, it was thought that local anesthesia minimized circulatory/respiratory changes and allowed the patient to maintain constant verbal contact so that changes in neurologic status would be promptly recognized. In 1963, Buford Wells, M.D., Arthur Keats M.D., and Denton Cooley, M.D., observed in a consecutive series of 56 patients with carotid disease that 20% of the patients developed unconsciousness or convulsions in response to preoperative manual compression for 30–60 s without anesthesia, but that these same patients could tolerate temporary occlusion of the carotid artery in the absence of a carotid shunt or systemic hypothermia for up to 30 min during general anesthesia with a high inspired oxygen tension (F_{IO_2}) and deliberate hypercapnia without electroencephalographic evidence of cerebral ischemia or postoperative neurologic sequelae.[1] Therefore, Wells, Keats, and Cooley postulated that general anesthesia increased the tolerance to cerebral ischemia after carotid occlusion by one or more of four potential mechanisms: (1) a decreased cerebral metabolic rate for oxygen ($CMRO_2$), (2) an increased cerebral flow from hypercapnia, (3) an increased arterial oxygen tension, and (4) recruitment of new routes of collateral circulation.

To test these hypotheses, Goldstein, Wells, and Keats conducted a follow-up study in 1965 using a dog model of cerebral ischemia.[9] Specifically, they wanted to investigate whether it was oxygen, carbon dioxide, or the anesthetic agent that was the primary factor in their previous clinical observation that general anesthesia with a high F_{IO_2} and deliberate hypercapnia increased tolerance to cerebral ischemia after carotid occlusion. In this experiment, dogs received either local (procaine) or general (morphine or pentobarbital) anesthesia with or without an increased F_{IO_2} or hypercapnia. Local anesthesia, an increased F_{IO_2}, or induced hypercapnia did not significantly attenuate neurologic damage (measured using a behavioral scale) after a period of circulatory arrest ranging from 8 to 15 min. Only pentobarbital was shown to significantly attenuate neurologic damage after circulatory arrest ($P < 0.001$).[9] This led the authors to postulate that a decreased $CMRO_2$ secondary to pentobarbital administration increases the brain's tolerance of prolonged periods of cerebral ischemia (The authors also recognized at this time that morphine decreased $CMRO_2$ but attributed its lack of brain protection in the experiment to the fact that it also increased cerebral blood flow and theoretically caused post–circulatory arrest brain edema.)

To place these early clinical observations in their proper historical context, one must recognize that the mechanistic role of barbiturates and other anesthetics in cerebral protection was not systematically studied until 5–10 yr later in the 1970s.[10–18] One of the first individuals to systematically investigate the role of anesthetics in cerebral protection was John D. Michenfelder, M.D., who has since been called the "father of neuroanesthesia."[19] However, irrefutable data supporting the efficacy of barbiturates and other anesthetics for cerebral protection have proved elusive.[20]

Several factors might have confounded these early studies of anesthetic-mediated cerebral protection. First, experimental subjects were often poorly controlled, and there was a failure to recognize that factors such as blood glucose, brain temperature, and perfusion pressure were also important determinants of ischemic outcome, and that anesthetics independently modulated these factors.[20] Second, many early studies compared one anesthetic against another, with the assumption that the "control" anesthetic was not protective. However, subsequent studies often found considerable protection from the "control" anesthetic when compared with an awake state.[20] Therefore, the field remained confused for more than a decade, and insufficient data were generated to warrant human trials.[20]

This fact was not lost on Dr. Arthur Keats, who in his 1983 Rovenstine Lecture to the American Society of Anesthesiologists specifically used CEA as a perfect example of what he termed "circus movement."[21] A circus movement describes what happens when after trying all variations on a theme and finding that none of them work, you end up just where you started. For example, CEA first began with local anesthesia on awake patients with trial carotid artery occlusion to determine the need for a shunt. This was replaced by general anesthesia for all patients, general anesthesia with hypercapnia with no shunt, then a shunt only if internal jugular oxygen saturation was low, then only if the stump pressure was low, then only if the electroencephalogram changed, and then only if regional flow was low.[21] No method successfully prevented all strokes, and at the time of his 1983 lecture, some surgeons were returning to local anesthesia on awake patients with trial carotid artery occlusion!

To quote Dr. Keats,[21]

> Circus movements strongly suggest to me the original premise was wrong and the wrong question was asked. I believe these problems will be solved only when a new hypothesis is proposed and the right question asked. Moreover, normality is not tanta-

> mount to virtue. Low body temperature is at times better than normal, very large doses of thiopental may be better than small doses, low hemoglobin may be better then normal hemoglobin, and under some circumstances, abnormally high systemic vascular resistance may be life saving. Being anesthetized is not normal, nor is being operated on, nor being perfused extracorporeally, nor having the blood supply to organs temporarily cut off. Keeping everything normal may keep us blameless, but it might not be the best patient care. We must at least entertain the possibility that normality may not be best, that abnormal values of something may be better during anesthesia, and most important, whether it makes any difference either way on the outcome of the surgical treatment.

When human trials using thiopental for cerebral protection were eventually conducted (with Dr. Keats' involvement) in patients undergoing coronary artery bypass graft and valve replacement surgery in 1986 and 1991, not surprisingly, they yielded conflicting results.[22,23] Possible reasons for these differing outcomes included differences in procedures performed, patient populations, thiopental administration, cardiopulmonary bypass management, intraoperative temperature, and flow rates. Moreover, preclinical experimental models strongly suggest that anesthetic-mediated cerebral protection is maximized in situations of focal, and not global, ischemia, and only if the anesthetic is present during the ischemic injury.[20] Although there are multiple technical reasons one can list as to why both experimental and human trials have yielded conflicting results with regard to anesthetic-mediated cerebral protection, perhaps Dr. Keats is right and we are still not asking the correct questions 55 yr later.

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