David S. Warner, M.D., Editor

Why Question Established Practice?

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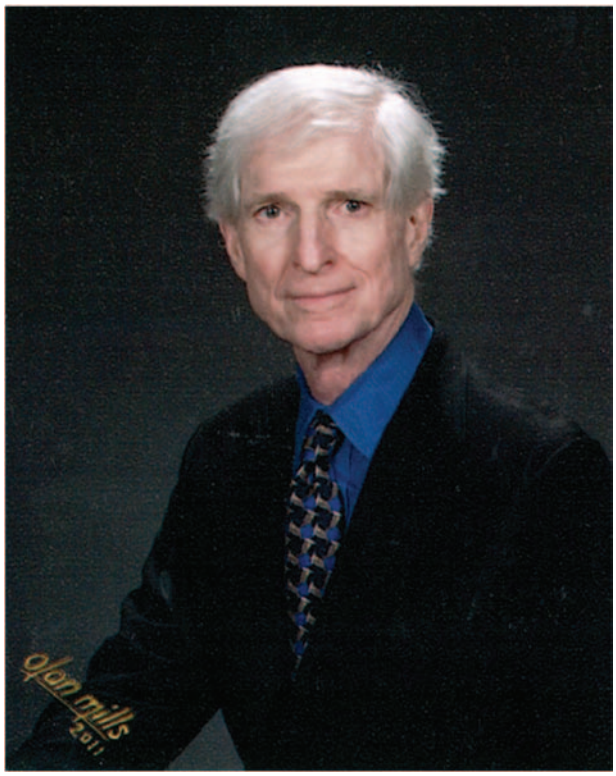
An Evaluation of Vasopressor Therapy for Maternal Hypotension during Spinal Anesthesia. By James FM III, Griess FC, Kemp RA. Anesthesiology 1970; 33:25-34. Abstract reprinted with permission from Wolters Kluwer Health.†

Abstract: During hypotension resulting from conduction anesthesia in gravid ewes, uterine blood flow (UBF) decreased roughly in proportion to the decrease in maternal blood pressure. Ephedrine or mephentermine significantly increased UBF over that accomplished by metaraminol. Presumably, the preferential effects of these agents were the result of increased cardiac output owing to inotropic and chronotropic actions. However, UBF never exceeded 90% of prespinal levels with any vasoactive agent, and, for a given maternal system, the UBF response was variable, generally increasing but frequently remaining constant or decreasing. For these reasons, all other methods of combating hypotension should be used initially. If vasopressors are still required, agents of choice are those whose principal mode of action lies in cardiac stimulation rather than peripheral vasoconstriction.

HYPOTENSION presents significant problems during spinal anesthesia for cesarean section. Mothers experience associated nausea and vomiting, and legitimate concern arises regarding presumed decreases in uterine blood flow (UBF) and potential fetal compromise. In addressing this issue, Frank C. Greiss, Jr. M.D., Richard A. Kemp, M.D., and I explored the efficacy of several vasopressors and found those with significant β-agonist properties more effectively improved UBF.[1] How did I become involved in this influential study, and what lessons does it offer today?

A month-long rotation on the obstetric service as an intern at Philadelphia General Hospital and 2 yr spent delivering babies as a general medical officer in the United States Air Force ignited my initial interest in obstetric anesthesia. That interest grew during a residency and 1 yr on the faculty



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of the Department of Anesthesia at the Hospital of the University of Pennsylvania. Knowing that Frank Greiss, an obstetrician, was on the faculty at the Bowman Gray School of Medicine (BGSM) influenced my decision to accept the 1968 invitation from Thomas H. Irving, M.D., to join him in the Section of Anesthesia in Winston-Salem. At the 78th Annual Meeting of the American Gynecological Society in May 1955, Frank R. Lock, Sr., M.D., chair of Obstetrics and Gynecology at BGSM, presented a lecture on maternal deaths related to anesthesia (personal communication, Frank C. Greiss, M.D., February 2012). Lock and Greiss published the lecture in the American Journal of Obstetrics and Gynecology and noted that spinal shock caused 25.4% of maternal deaths because of anesthesia, whereas the aspiration of gastric contents produced 24.5%.[2] Stimulated by Lock's work, Greiss became interested in the problems associated with anesthesia,[3] and began to investigate uterine blood flow during spinal anesthesia. He employed a pregnant sheep model in his studies. In 1965, Greiss and D. LeRoy Crandell, M.D., head of the Section of Anesthesia, reported that spinal anesthesia decreased UBF and rapidly infusing intravenous fluid improved UBF more effectively than vasopressor therapy with norepinephrine, phenylephrine, or angiotensin amide.[4] Upon my arrival at BGSM, now the Wake Forest School of Medicine, Tom Irving granted me 1 day a week to work in Greiss's laboratory. The first study on which Greiss and I collaborated helped to cement ephedrine as the vasopressor of choice to restore maternal blood pressure and UBF when hypotension occurred during spinal anesthesia.[1]

The square wave electromagnetic flowmeter (EMF) manufactured by the Carolina Medical Electronic Company in Winston-Salem enabled UBF to be monitored. This device evolved from the interest of Merrill Spencer, M.D., a member of the Department of Physiology at BGSM, in renal blood flow in humans and in how the giraffe maintained cerebral blood flow upon rapidly raising its head to an erect position after drinking, a distance of 10 m. Spencer and John Kiger, a technician at the Western Electric Company in Winston-Salem, both sang in the choir of their church and the idea of the EMF evolved from their choir loft conversations. They enlisted the help of Adam B. Denison, M.D., in the Department of Physiology, and with encouragement from the Department Chair, Harold D. Green, M.D., the EMF became a reality.[5] Kiger and another Western Electric technician began building the flowmeters in the basement of one of their homes and subsequently formed a company, Kiger-Dennard Associates of Winston-Salem, which made the first commercial model. As business grew, the company was renamed Carolina Medical Electronics, which more accurately reflected the organization's product. The flowmeter was applied to the external wall of the vessel to be studied and worked by emitting a magnetic field. Blood flowing through the vessel produced magnetic-generated voltage that was detected by electrodes on the surface of the vessel and converted into a waveform. The EMF was the first practical instrument to measure blood flow without cannulating blood vessels. The first human use of the flowmeter occurred at the North Carolina Baptist Hospital to measure renal blood flow in the mid-1950s.[6] Subsequently, Charles A. Barefoot, a research technician at BGSM, developed a small flowmeter that provided the first noncannulating recording of a surgically exposed coronary artery.[7] Barefoot became Director of Production at Carolina Medical Electronics. Subsequently, the EMF benefitted patients and their surgeons in measuring blood flow through venous coronary artery bypass grafts, carotid arteries before and after endarterectomy, and renal artery surgery. Ultimately, sophisticated noninvasive Doppler techniques replaced the EMF.

Greiss and I worked together in the clinical setting and in the research laboratory. These activities fostered a positive relationship that helped us to promote the formation of a consolidated obstetric service in Forsyth County, North Carolina, at the Forsyth Memorial Hospital. Private practitioners, academic obstetricians and anesthesiologists, and resident physicians staff this unit that serves as a model for town/gown cooperation and houses more than 6,000 deliveries per year. Both Frank and I eventually became the chair of our respective departments, with both departments benefitting from our positive relationship.

Until the last few decades of the 20th century, general anesthesia was often the method of choice for cesarean section. In the 1960s, approximately 2,500 women in the United States were dying of causes related to childbirth, with 10% of these women dying from obstetrical anesthesia.[8] Anesthesia ranked as the sixth leading cause in a series of 2,065 maternal deaths reviewed by Kaunitz in 1985.[9] Failed tracheal intubation, the aspiration of gastric contents, maternal awareness, and respiratory depression of the newborn during surgery all represented problems associated with general anesthesia. Maternal hypotension frequently accompanied spinal and epidural anesthesia. Intravenous fluid administration, left uterine displacement, and vasopressor therapy all served to prevent and treat hypotension during regional anesthesia. The question was which type of vasopressor most effectively combated maternal hypotension and the accompanying decrease in UBF. Both maternal and fetal outcome had to be considered. Our animal study of ephedrine, mephentermine, and metaraminol indicated that ephedrine and mephentermine provided better restoration of UBF (fig. 1),[1] whereas Shnider *et al.* reported that ephedrine decreased acidosis and corrected fetal bradycardia after restoration of blood pressure in gravid ewes.[10] Additional laboratory studies supported the efficacy of ephedrine with its mixed α and β effects over pure α-acting agents such as phenylephrine.[11,12] For decades ephedrine remained the vasopressor of choice to counter maternal hypotension during spinal and epidural anesthesia. Ephedrine proved successful in combating maternal hypotension, and newborn outcome was favorable. However, debate and research continued to

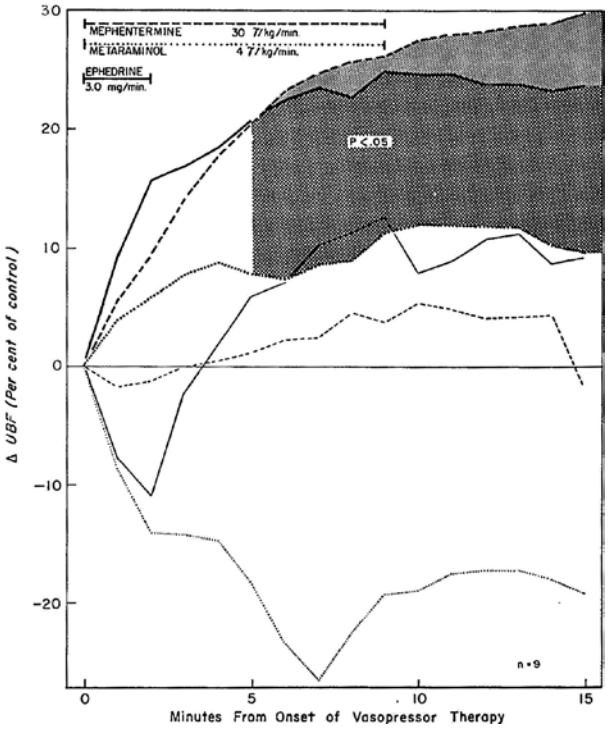

Fig. 1. Comparison of variations of uterine blood flow (UBF) responses. *Light lines* describe curves of two standard deviations around the mean response, or *heavy lines*. With ephedrine and mephentermine, UBF rarely decreased below spinal hypotensive levels. With metaraminol, UBF frequently decreased further during therapy. Reprinted with permission from James FM III, Griess FC, Kemp RA: An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. ANESTHESIOLOGY 1970; 33:25–34.

develop regional anesthesia for cesarean section. α and β agonists were investigated using a variety of dose ranges and bolus *versus* continuous infusion methods to prevent and to treat maternal hypotension.

During the last 15 yr, multiple studies in humans have demonstrated that both ephedrine and phenylephrine are effective, but the latter seems to more reliably prevent maternal nausea and vomiting while producing measurably better newborn status. In 2009, Ngan Kee *et al.* studied 102 women and found that ephedrine crossed the placenta more readily than phenylephrine and was associated with both lower fetal pH and base excess values. Ephedrine resulted in higher uterine artery and uterine vein lactate levels and greater uterine artery PcO_2.[13] These and other results led the authors to hypothesize that ephedrine caused more fetal acidosis than phenylephrine by increasing fetal metabolic processes. In 2012, Habib published an extensive literature review of the use of phenylephrine and concluded that although both ephedrine and phenylephrine effectively correct maternal hypotension, the latter may be associated with less maternal nausea and vomiting and better uterine artery pH and base excess levels, though the difference in pH is small and not likely to be clinically significant in low-risk Cesarean sections.[14] Current practice clearly favors phenylephrine administered by infusion or intermittent boluses during cesarean sections, but less so in the labor room because of its shorter duration of action compared with ephedrine.

Investigators typically perform initial investigations of the efficacy of a drug in animals. One species may respond differently than another, whereas further variation may occur in humans. The saga of the transition from ephedrine to phenylephrine as the vasopressor of choice in regional anesthesia for cesarean section exemplifies the need to continue to question accepted therapeutic beliefs through additional animal studies and human investigation. Advances in monitoring and laboratory methods make more sophisticated studies possible. For example, Doppler techniques enable both investigators and clinicians to measure blood flow noninvasively in numerous kinds of blood vessels, making the EMF obsolete. The ability to noninvasively measure blood flow at various locations in the human fetus promises to advance our knowledge even further in the future. The welfare of two patients, the mother and the fetus, adds additional concerns to studies in pregnant women. Hopefully, the increasing restrictions research practice committees are placing on clinical protocols will not markedly inhibit human studies. As medicine has advanced over the years and the practice of anesthesia has become much safer, some have questioned the need for additional research. The life and welfare of every mother and child justify continuing research to improve maternal and fetal outcome at the time of birth.

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