Published in final edited form as:
Perspect Biol Med. 2011 ; 54(2): . doi:10.1353/pbm.2011.0018.

Experimental Arrest of Cerebral Blood Flow in Human Subjects:

the Red Wing studies revisited

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Abstract

Loss of consciousness in pilots during rapid ascent after bombing missions was a major problem in World War II, and experiments were undertaken to study the cause of this phenomenon. Postulating impaired cerebral blood flow as a likely mechanism, the investigators developed a neck device, the KRA Cuff, which when inflated could shut off blood supply to the brain. With cessation of blood flow for up to 100 seconds, the investigators observed a sequence of responses, including unconsciousness, followed by dilated pupils, tonic/clonic movements, loss of bladder and eventually bowel control, and appearance of pathological reflexes. This study, carried out in prisoners and patients with schizophrenia in 1941–42, largely disappeared from public discourse for a number of years. It has received occasional attention subsequently and been considered controversial. Recently discovered records, including extensive written and photographic data from the studies, shed new light on the methods and motives of the research team. We describe here this new information and its implications for the scientific and ethical assessment of the study.

Aircraft with increasingly high performance were important to the war effort in World War II. Changes in technology allowed aircraft to reach faster speeds and to complete missions at higher altitudes. With these changes came new obstacles for pilots who had to tolerate these stresses. Of primary concern to the U.S. War Department was the loss of consciousness that often occurred with high-speed maneuvers and especially during pull-up after dive-bombing missions. In some cases, pilots would experience up to 9G of force during rapid ascent, much more than the 6G threshold that typically leads to loss of consciousness. In 1941, a research team in Red Wing, MN, proposed experiments to elucidate the mechanism underlying these phenomena (Wood 1991).

The Red Wing investigators employed a novel approach to study the effect of reduction in blood supply to the brain (Rossen, Kabat, and Anderson 1943). While they had not worked together before, all had connections through the University of Minnesota, and each brought unique scientific strengths to the study. Herman Kabat, Ph.D., an assistant professor of physiology pursuing his M.D. degree at the time (University of Minnesota 1941; Katrina

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Correspondence and other documents drawn from John P. Anderson's Personal Collection (Anderson Collection), property of the Anderson Family in Red Wing, MN, and LaCrosse, WI.

Roth, personal communication, Aug. 4, 2009), had studied the effect of cerebral circulation occlusion on dogs, and found that the brain could tolerate up to six minutes of cerebral blood flow cessation before clear evidence of permanent damage to the animal ensued (Kabat 1940; Kabat and Dennis 1938; Kabat, Dennis, and Baker 1941). John P. Anderson designed a device to completely but transiently interrupt blood supply to the brain in human subjects, drawing on Kabat's experience shutting off blood flow in dogs. Ralph Rossen, M.D., principal investigator of the study, had been an assistant in medicine at the University of Minnesota Medical School, and at the time of the Red Wing Studies, was superintendent of a psychiatric facility and was interested in the possibility that anoxia might have implications for treating schizophrenia (Rossen 1951; University of Minnesota 1936).

By February 1941, the investigators developed a clinical protocol, initially using themselves as study subjects. They used the device developed by Anderson. To address intellectual property issues, they jointly drafted and signed a memorandum that it would be called the KRA (Kabat-Rossen-Anderson) Cuff. The cuff, shown in Figure 1, was a leather collar with a bladder that connected to a compressed air tank. The cuff was placed around the lower third of the neck. When activated, it inflated to 600 mmHg pressure around the neck in one-eighth of a second. The rapid application of high pressure shut off blood flow almost completely in the interval between two heartbeats. Sudden application of this high pressure shut off both venous and arterial blood flow simultaneously, preventing engorgement of blood in the brain. The deflation of the cuff was also instantaneous, with release of pressure occurring in a fraction of a second. The device was constructed in such a way that both the clinician and the test subject (while conscious) could stop the device and thus terminate the study at any time.

The developers had in mind several possible uses for the apparatus beyond its application in the primary study. In a memorandum sent to the War Department, they suggested it might be used to test the sensitivity of pilots to blackout, in order to classify them into appropriate aviation roles. In addition, they hypothesized that the cuff when inflated at a lower pressure might paradoxically help keep pilots conscious during flight. Nevertheless, its primary purpose was to induce an acute, brief anoxia of the human brain, without affecting respiration.

The investigators initially tested the device on themselves and noticed no adverse effects. Even so, the necessity for great caution with the KRA cuff was driven home to Anderson in early experimentation. On one occasion he had activated the device when the other investigators were temporarily out of the laboratory. After the cuff inflated and he began to feel the escalating symptoms of oncoming unconsciousness, he wanted to release the valve to deactivate the cuff, but he very nearly lost consciousness before somehow managing to physically release the valve. In later years he professed that he considered himself fortunate to have survived that experience. Thereafter, multiple investigators were present when the device was used.

They soon began to perform their studies on other human subjects. These included a small group of schizophrenic patients, a larger group of inmates at the Minnesota State Prison at Stillwater, and youthful (as young as 17 years old) offenders housed at the St. Cloud Reformatory in St. Cloud, MN.

Once initiated, this project moved forward rapidly because of its perceived importance to the war effort. The investigators showed that the brain is highly dependent on a steady supply of oxygenated blood to maintain consciousness. In the subjects tested, interruption of blood supply for as little as 4 seconds, or at most 10 seconds, led to a loss of consciousness (see

Figure 2). The response to restoration of blood flow was also rapid, ranging from 3 to 11.5 seconds. The subjects showed a remarkably consistent pattern of effects.

Subjects were asked to follow a pendulum or the examiner's finger after the pressure was applied. At one-half to 1 second before losing consciousness, the subject's eyes would become fixed in mid-position. When asked afterwards, subjects stated they still could see, but could not move their eyes. In the seconds prior to losing consciousness, many subjects experienced symptoms that included blurred vision, rapid narrowing of the field of vision, streaks, spots or twinkling lights. Lacrimation and nystagmus were noted in several subjects.

After losing consciousness, several subjects experienced tonic/clonic convulsive movements, which the investigators called "seizures."These lasted for 6 to 8 seconds, usually after the release of the KRA Cuff. If the blood supply was restored when the subject's eyes became fixed, no convulsions occurred. If the restoration began several seconds after eye fixation began, the seizure activity was more severe and prolonged.

Subjects lost consciousness at about one second after fixation of their eyes. Some subjects reported an awareness of some events with an inability to move prior to complete loss of consciousness. Approximately half of the subjects described a variety of symptoms, including numbness, tingling, and shooting pain. In one instance, a subject described pain that felt like electric shock that caused him to release the trigger and stop the device. These pains were felt throughout the body but were most frequently reported in the hands, arms, head, and face. Subjects reported these symptoms several seconds prior to losing consciousness. Some of these were likely elicited by the powerful and sudden force of the KRA Cuff on the cervical spine.

Several other consistent findings emerged from these studies. For periods of arrest of cerebral circulation up to 30 seconds, the heart rate did not change markedly, but after 30 seconds, a slowing was often noted that could be prevented by atropine. After restoration of circulation, a temporary increase in heart rate was often observed. In 20 tests blood pressure was recorded; up to a 15% rise or fall in systolic blood pressure was observed, with no apparent change in diastolic pressure.

The corneal reflex was usually lost between 5 and 15 seconds after blood flow occlusion, but could persist for as long as 30 seconds. The corneal reflex returned within 5 to 10 seconds after cuff release, depending on the duration of the blood flow occlusion. This reflex was tested in 150 trials and the loss of this reflex was quite constant for each individual; for example, one patient showed loss of this reflex on three successive days at 11, 12, and 11 seconds, another patient at 5, 6, 5, and 6 seconds for four trials.

Abdominal reflexes diminished or disappeared soon after loss of the corneal reflexes and returned very soon after recovery of consciousness. The Babinski and Hoffman signs often appeared on one or both sides after 30 or 40 seconds of cuff inflation, and they always disappeared within a few seconds of restoration of cerebral circulation. The appearance of these signs occurred after disappearance of the corneal and abdominal reflexes. Appearance of pathological reflexes was not a constant phenomenon.

Ophthalmoscopic observations were made in a number of studies. No change was noted in the optic nerve head or in the retinal arteries, but there was a slight to moderate dilation of the retinal veins, which disappeared immediately on deflation of the cuff. The pupils usually dilated during cerebral anoxia, although exact diameter was not measured.

The research team also completed studies assessing the impact of "pre-engorgement" of the brain, elicited by providing a small amount of pressure so arterial blood continued to enter

the brain but venous blood flow from the brain was occluded. Seven subjects were exposed to 80 to 85 mmHg for 15 to 18 seconds. After this pre-engorgement phase, the subject had one second of normal blood flow before being exposed to the full 600 mmHg occlusion pressure of the KRA Cuff. The rationale behind the one-second intermission was to allow venous return from the brain. The results for these subjects showed that while the time to loss of consciousness was not changed, time to recovery was significantly reduced. Subject recovery time improved by 2 to 3 seconds.

Engorgement, trapping of excess blood in the cerebral circulation causing gradual reddening of the eyes and face, occurred in 35 out of the 73 subjects, and in 60 out of 184 trials in the Minnesota State Prison group of subjects with an older version of the KRA Cuff that was not secured to the lower part of the neck. In some subjects, engorgement appeared in some tests and not in others. A number of subjects showed marked tendency to engorgement, which was quite consistent in repeated tests. This phenomenon appeared to be the result of some continued blood flow to the brain, with venous occlusion preventing out-flow and therefore resulting in relatively incomplete cerebral anoxia. In subjects experiencing engorgement, there was blanching of the sclera on release of pressure with complete blanching in about two minutes. To help address engorgement, a new cuff (shown in Figure 1 and depicted schematically in Figure 3) was designed, with adjustments that allowed the cuff to be secured to the lower third of the neck. The adaptation ensured that pressure would be applied on the first part of the vertebral artery, where it is surrounded by muscle. As a result, engorgement became very infrequent in later trials.

On return of consciousness, symptoms were usually brief. In the context of our current understanding of the role of cerebral hypoxia in the phenomenon of choking games, some comments in the records might be interpreted as suggesting that for some participants at least, the overall experience was pleasurable, but this issue was not directly addressed:

> A variety of mental symptoms were observed on the subjects returning to consciousness … the subject was dazed and appeared confused, usually having a foolish smile on his face. Some appeared temporarily excited and euphoric. Some insisted that they did not lose consciousness. Others appeared frightened and tense for a few seconds and then suddenly relaxed, smiled and appeared normal. (Anderson Collection)

The KRA Cuff was also used for testing the effects of various agents that might alter either the resistance of the human brain to acute anoxia, or on recovery time from a blackout. Although study sample sizes were small, there was a suggestion that B complex vitamins, including nicotinamide, thiamine, and riboflavin, might speed recovery time slightly, but the investigators concluded that further study would be needed before any conclusions could be drawn. To our knowledge, such studies were never done.

Other agents studied included intravenous glucose and manganese chloride, and oral dextro-benzedrine. None showed clear benefit or deleterious effects.

Implications and Ethical Considerations

The results obtained in this study were subsequently considered in the development of the G-Suit (antigravity garment), as well as in investigations of the physiology and function of the brain and the importance constant blood flow plays in consciousness. In addition, the information emerging from this study bolstered interest in the human centrifuge, which is used in studies of acceleration stress today.

Nevertheless, there has been a great deal of controversy regarding this study, both before and after it was undertaken. Some distinguished and internationally recognized physicians

and scientists, like Ancel Keys at the University of Minnesota (developer of the eponymic "K-rations" provided to American troops in World War II, and later internationally honored as the pivotal advocate for reduction of dietary cholesterol to prevent heart disease), and Earl Wood at the Mayo Clinic, whose career focused on health aspects of aerospace medicine, were supportive of the experiments. In a telegram to Lt. Loyd E. Griffis on July 14, 1942, Keys wrote: "Dr Ralph Rossen requests I wire you my opinion on cerebral anoxia investigations. I believe these offer much promise for study and application to military problems of both altitude anoxia and dive bombing. Suggest importance warrants your personal investigation" (Anderson Collection).

However, some were unconvinced of the ultimate value of this line of investigation. The investigators hoped that once the KRA Cuff results described above were public, the value of this experimental model would be widely appreciated. However, convincing key governmental and military officials to support further work proved to be problematic. A follow-up study had been submitted to the National Research Council, in the hope that a positive review would overcome questions about the technique, but apparently it failed to elicit a sufficiently strong endorsement. Rossen lamented to a friend: "It is rather difficult to convince the National Research Council that the KRA apparatus can be used to study acute anoxia … our group would not feel quite so bad if we had asked the Council for $50,000; but our request was only for one dollar per year" (Anderson Collection). Unfortunately, the actual records of this review have not yet been found.

Over time, publication of the KRA Cuff research got the attention of both supporters and critics, leading to heated debate. But not all reports were alarming. An early review of the study appeared in the *New York Times* on April 9, 1944, in a section of the newspaper titled "Notes on Science":

> In a publication of the American Medical Association Lieut. Ralph Rossen, Dr. Herman Kabat and John P. Anderson tell how they completely stopped the flow of blood to the human brain by means of an inflatable head-cuff applied to the lower third of the neck. Flow of blood to the brain is thus stopped in one-eighth of a second. The pressure can be released at once either by the subject or the physician. Consciousness is lost in six to seven seconds. Recovery is rapid. The procedure is free from danger in competent hands. Effect of stoppage of blood for as long as 100 seconds was studied on schizophrenics. No improvement was observed. (New York Times 1944).

More recently, the Red Wing studies were cited as one of the "ten worst publications in the history of psychiatry," along with publications concerning lobotomies and satanic abuse (Laurance 2001; Simon Wessely, personal communication, July 7, 2009).

Our recent discovery of detailed original records of the experiments, including well-preserved films of a number of subjects undergoing occlusion of cerebral blood flow, provides a broader context for assessing these clinical experiments. The Red Wing Studies are remarkable for the dramatic nature of the experiments undertaken, and the unusual degree of detail, both scientific and historical, which the investigators revealed about the context and conduct of their experiments. One key aspect of the study was the fact that all involved were part of an intense national push in support of the war effort.

The intended purpose of this study was to learn more about why pilots were blacking out and what potential methods might be devised to minimize in-flight loss of consciousness. Doubtless, informed consent, as we know it today, was not obtained. However, participation in these studies seems to have been viewed by at least some prisoners as a way they could participate in activities of use to the war effort.

In the detailed information available on each of the 44 study subjects from the St. Cloud Reformatory, the study subjects seem to have been average to the extent we can determine. IQ testing was carried out and averaged 106.2, with a range from 74 to 160, which follows a normal distribution. Their ages ranged from 17 to 32. Over half were described as having an "athletic" build, and most others were described as "asthenic."

The newly discovered records include handwritten letters from some prisoners who were subjects of these tests. Rossen's follow-up letters inquiring whether the prisoner participants suffered any late problems elicited responses from the prisoners themselves. The following excerpt is typical of the tone of inmate letters to Rossen:

> May I extend my sincere thanks for your kind letter of September 3rd. If my services were of any use whatsoever, I shall consider myself well repaid. Should you, or anyone else, at any time in the future, desire my services for any type of test which may aid our United States in attaining complete victory, do not hesitate to call on me. (Anderson Collection)

While records available to us cannot definitively rule out complications in study subjects, we were unable to identify any complication, either transient or permanent, that resulted from the participation of the 129 subjects in these experiments, other than the study results described above. A letter to the prison warden from Ray G. Johnson, the prison physician, on September 9, 1942, concludes:

> as far as I can determine there were no bad after-effects of any kind. In conversation with several of the men tested, they state they experienced no untowards [sic] effects. They seemed very enthusiastic about the whole thing, because they thought they contributed their bit towards the War effort. They were practically unanimous in their assertion that they would submit to further test[s] if called upon to do so. (Anderson Collection)

The opportunity to spend a day in a non-penal environment may have been a benefit as well. Several of the inmates volunteered as many as nine times. In the patriotic fervor of this time, genuine informed consent would probably have been challenging to obtain in a study of this kind, even if it had been sought.

The race of study subjects in early 20th-century human experiments in the United States has often been of concern. The Red Wing studies do not specifically address this issue, nor were the individual subjects identified by race in any of the materials found. The surnames of most subjects suggest an ethnic origin in Scandinavia or Central or Eastern Europe, probably reflecting the demographics of Minnesota in the mid-20th century. All subjects filmed during the experimental loss of consciousness with the KRA Cuff were Caucasian.

Although the results of experiments performed on the psychiatric patients doubtless contributed to the understanding of the impact of anoxia on pilots, those trials were undertaken, at least in part, to learn more about treating these patients. During this time period, many methods were tested in efforts to treat or cure mental health diseases. In the early 20th century, electroshock therapy (ECT) and insulin-induced comas were among such efforts to treat mental illness. Given the favorable reports about "electric shock to the brain" benefiting depression in patients, Rossen may have hoped that the "shock" of anoxia might have equal or greater benefit. It was not uncommon for clinicians in this era to undertake experiments on such patients in pursuit of treatment and cure.

Viewed from the perspective of contemporary clinical and translational research, the events of 70 years ago in Red Wing seem very distant and quite frightening. From our current knowledge of how the brain functions in health and disease, we recognize how easily some

of the Red Wing studies could have gone seriously awry, and how fortunate the subjects were that none did. Perhaps Kabat's experience with the apparent safety of much longer periods of anoxia in animals gave the investigators a false sense of security as they embarked on the human studies. The ethical framework now seems unacceptable, but ethical norms for research were not well defined at that time (Koski 2009). Indeed, during the same time period that the Red Wing Studies were being carried out, radiation experiments were being performed elsewhere in the United States to better understand the effects that radiation had in humans. These experiments, which included injecting radioactive iodine into pregnant women and newborns, were performed under government secrecy, to keep the findings on American soil. In some of these cases, the subjects of these experiments were unaware of what was being done to them (Advisory Committee 1996; Emanuel 2008). The ethical propriety of the Red Wing studies is perhaps best evaluated in the context of the time period in which they were performed, as well as by how the results were acquired.

Acknowledgments

This research has been supported by P01 HL056693, R01 HL071784, U54 NS065736, and UL1 RR024975 from the NIH, and by the National Dysautonomia Research Foundation (NDRF). The authors thank the Anderson family in Red Wing, MN, and La Crosse, WI, for much valuable help in data acquisition.

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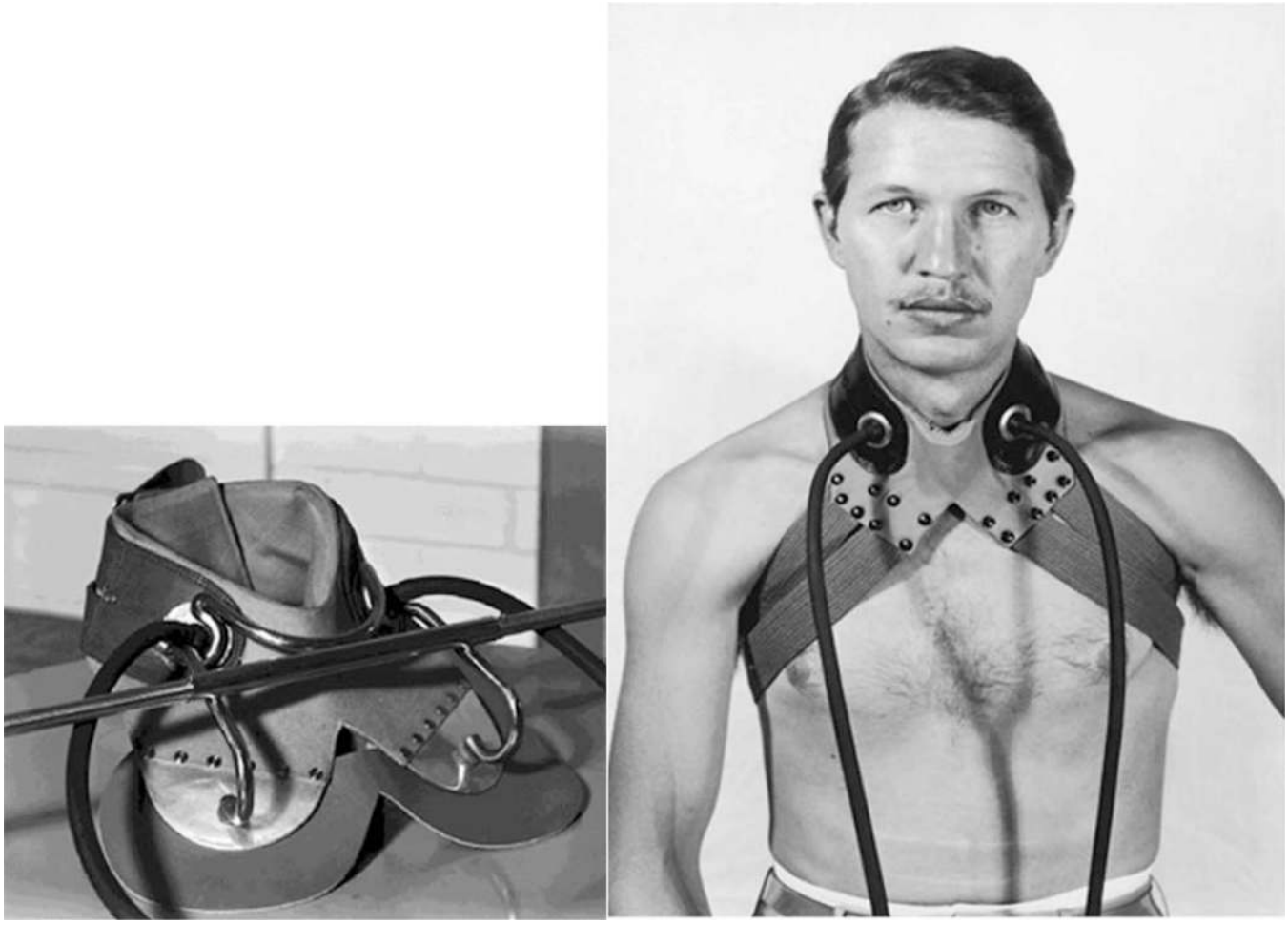

Figure 1.
The KRA Cuff. When inflated to 600 mmHg, the cuff shuts off blood flow to the brain. The photograph shows it being worn in 1942 (in its uninflated state) by John P. Anderson, who designed it. In the inset (left), a slightly different earlier version of the device is shown.

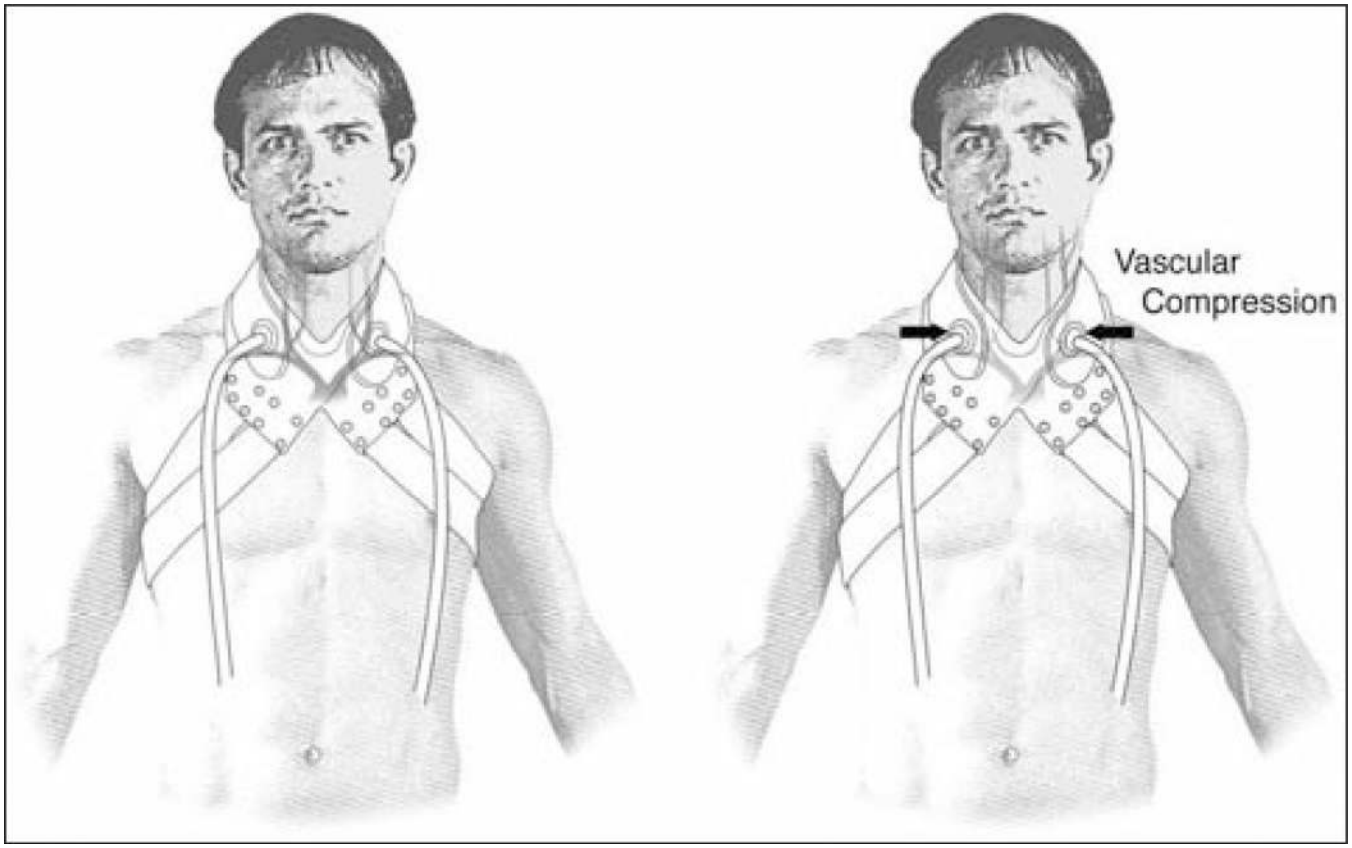

Figure 2.
Effect of activation of cuff occlusion device on blood flow. The improved KRA device is shown in its inactivated (left) and activated (right) state. With activation, blood flow beneath the cuff is shut off (arrows).

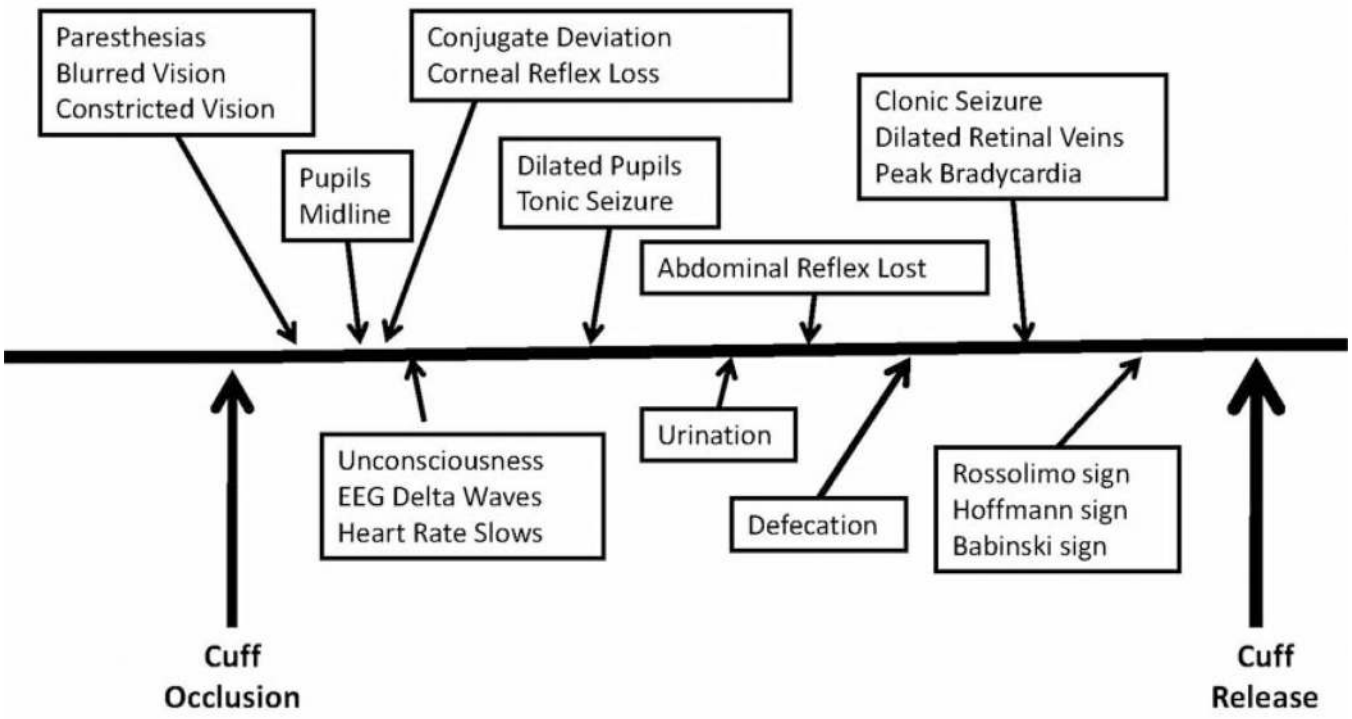

Figure 3.
Response to arrest of cerebral blood flow. The time course of physiological effects as blood flow to the brain is shut down.