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Controlled hypotension: a review of the literature on Arfonad

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CONTROLLED HYPOTENSION

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INTRODUCTION

The practice of maintaining low arterial pressure during surgery in order to diminish blood loss has recently been revived by the discovery of a thiophanium compound with a potent vasodilator property. This drug is known as Arfonad. It is said that Arfonad has provided the anesthetist with a thoroughly controllable and rapidly reversible method for the induction of hypotension during anesthesia. The purpose of this paper is to review the literature on Arfonad in an attempt to determine the role of this drug in the procedures of controlled hypotension.

PHYSIOLOGY OF HYPOTENSION

Arterial blood pressure is maintained through a number of factors, the chief ones of which are: (1) cardiac output; (2) peripheral resistance; (3) circulating blood volume; (4) blood viscosity; (5) elasticity of the arterial walls. Of these the first four factors contribute in regulating systolic blood pressure, while the last factor is chiefly instrumental in the maintenance of diastolic pressure. Any change in any of these factors, sufficiently great or sustained to overcome the compensatory powers of the organism, will effect a rise or fall of blood pressure.

In circumstances that produce shock, such as hemorrhage, the immediate reaction is a constriction of the arterioles, or more precisely of the metarteriolar sphincter mechanism. This represents an attempt at compensation which tends to maintain the blood pressure at its previous level. Trying to maintain the circulating volume at an adequate level, fluid is next shifted from the interstitial spaces into the blood stream, thus increasing the total plasma volume. When this takes place, "compensated" or "incipient" shock follows. If hemorrhage continues without adequate replacement or if anoxic or stagnant hypoxia is superimposed, then arteriolar and capillary

dilatation and stasis will develop. The consequence of this is a reduction of venous return and a fall of cardiac output with subsequent failure of compensation, hypotension, and the development of "frank" shock. If shock is not promptly corrected, the hypoxia increases until finally the integrity of the capillary wall is lost with such irreparable hypoxic damage as to make the shock "irreversible". The phenomenon of capillary stasis is demonstrated clinically by the increase of capillary refill time. The mechanism of hypotension as described pertains to cases of so-called "oligemic shock".

Another mechanism by which hypotension may be produced is one in which primary dilatation of the arteriolar bed occurs. Thus, by augmenting grossly the vascular bed and by decreasing peripheral resistance, a fall in arterial blood pressure ensues. In this kind of hypotension, capillary circulation should remain adequate, as can be demonstrated by very prompt refill time. Hence, venous return remains satisfactory and cardiac output is only moderately reduced. This is the mechanism acting in "neurogenic shock", and is encountered clinically, for example, during spinal anesthesia.

It is, therefore, the adequacy or inadequacy of capillary circulation that determines whether or not the blood pressure fall is or is not a true shock state.

From the foregoing it is seen that hypotension of the first type associated with tissue hypoxia and leading to tissue changes cannot be tolerated for very long, and must be corrected by all the means at our disposal. Hypotension of the second type, on the other hand, has few deleterious e fects, provided capillary circulation remains adequate and sufficient oxygenation of the blood is maintained. These are the two physiological requirements for controlled hypotension. If these two prerequisites are followed, no damage will result to such vital organs as the brain, heart, kidney, liver, and adrenals.

EFFECTS OF CONTROLLED HYPOTENSION ON VITAL FUNCTIONS

Metabolism. A systolic blood pressure of 60mm, Hg, if blood is well oxygenated, is considered adequate for cellular respiration and metabolism in the normal human (1). Hale (2) states that if pressure drops below 30 mm. Hg capillary flow ceases. Significant arteriovenous oxygen differences are seen only in moderate to severe hypotension (3,4). Greene, et al (4) found, in man, no significant change in blood concentrations of cellular metabolites or acid-base balance resulting from the hypotensive state.

Kidney. Filtration of urine probably ceases if the systolic pressure in the renal arteries falls below 75 mm. Hg (5). However, the nephron remains undamaged with pressures probably as low as 45-50 mm. Hg and may be even less, so tha formation of urine is resumed when the filtration pressure is again reached (5). Selkurt (6) demonstrated on dogs that renal blood flow remains at about 75 per cent of normal when arterial pressure drops to 50-60 mm. Hg. He also demonstrated that renal flow persists when arterial pressures dip to 15 mm. Hg. Thus indicating renal damage should not commonly follow hypotension. Greene, et al (4) and Lynn, et al (7), found in man, no significant changes in renal function tests resulting from hypotension.

Heart. The workload of the heart is diminished in the controlled hypotensive state. The decrease in peripheral resistance more than balances the reduced venous return to the heart. Meaning, even though the stroke volume is less, that the minute volume remains essentially the same with the heart expending less energy (5,7,8). The cardiac output decreases only in those patients in whom the diastolic pressure drops markedly (9).

Hypotension has been found to increase blood flow through the coronary arteries (7). Even in individuals with coronary insufficiency, attacks of angina pectoris do not occur if arterial hypotension is induced by arteriolar dilatation, and if arteriosclerotic changes have not reduced the elasticity of the coronary vessels (10,11).

Blood Volume. In controlled hypotension the reduction of bleeding is achieved by producing a moderate fall of systolic pressure without producing a corresponding fall of the diastolic pressure. The result is a diminished pulse pressure. Under these circumstances, capillary oozing is decreased markedly, but larger vessels continue to bleed. These can be controlled with ease (8, 12). Magill (13) believes in addition to the advantage of reduction of hemorrhage that controlled hypotension gives protection from traumatic shock. For his evidence he sites Wyman's current clinical observations (14).

Morris, et al (15) found an increase in blood volume accompanied controlled hypotension. They found this to be mostly plasma. They credited this to lower capillary diffusion with greater tissue fluid uptake and perhaps the opening of vascular reservoirs.

Body Temperature. The controlled hypotensive state is associated with an increase in skin temperature because of peripheral vasodilatation and a state of hypothermia is to be expected at the conclusion of the procedure (9).

Brain. No agreement has been reached about the minimum pressure necessary to maintain adequate nourishment of the brain which is a sensitive and highly specialized organ of high metabolic requirements. According to Finnerty, et al (16) in normotensive subjects anoxic symptoms occurred when mean arterial pressures fell to 55 mg. Hg. This may not be true in anesthetized subjects, as Himwich, et al (17) and Wechsler, et al (18) observed a decrease in the cerebral oxygen utilization during thiopental narcosis. Hale (2) states the belief that a blood pressure of 40 mm. Hg is adequate to transport oxygenated blood to the brain. Woodhall has concluded from his three studies (19,20,21) that an arterial pressure of 50 mm. Hg is the critical level. Morris, et al (15) however, found that when the mean pressure was reduced by 60 per cent there was a significant reduction in cerebral flow.

Schallek and Walz (22) found that depression of the electroencephalogram was correlated with the rate of blood pressure fall. They advised that the blood pressure should be lowered at a rate of not more than 10 mm. Hg per minute. Dripps and Vandam (23) believe that damage to the brain, heart, liver, and kidneys is associated with abrupt changes in blood pressure resulting in inadequate flow, thrombosis, and spasm.

Davison (12) believes that reduction of blood pressure per se, if caused by diminished peripheral resistance, presumably does not reduce bleeding but rather the hydrostatic effect of osture is the factor of great importance. He states that with a systolic blood pressure of 200 mm. Hg, a foot down tilt of 15° will alter the normal ratio of blood flow to the head, which is 1/3, to a ratio of 7/24, an alteration of no appreciable significance. But with a pressure of only 30 mm. Hg, the change will be from the normal of 1/3 to a striking 1/7 ratio. Thus he believes that this maneuver is by no means free of danger in the controlled hypotensive state.

Respiration. Greene, et al (4) found no significant change in pulmonary ventilation during or after hypotension.

Liver. Greene, et al (4) and Lynn, et al (7) found no significant change in liver function test resulting from hypotension.

METHODS OF CONTROLLED HYPOTENSION

Hypotension may be induced by a variety of means, but some, such as large doses of barbiturates and deep general anesthesia, are obviously undesirable. Three principal methods have evolved in recent years. They are:

1. Controlled arteriotomy and arterial re-transfusion.
2. Preganglionic block by spinal anesthesia.
3. Ganglionic and postganglionic block by means of pharmacological blocking agents.

1. Controlled Hypotension by Arteriotomy and Re-Transfusion. This procedure consists essentially of withdrawing blood from an artery until a suitable degree of hypotension is reached, and maintaining this hypotensive level by judicious re-infusion and re-bleeding from time to time (24, 25,26,27). The blood withdrawn is prevented from clotting by the usual methods and is returned to the patient at the conclusion of the operation. Additional blood may then also be given if needed. The blood pressure is maintained at a level insuring a relatively bloodless field, but is never allowed to fall below 80 mm. Hg in a normotensive individual. Correspondingly higher levels must be maintained in hypertensive and arteriosclerotic individuals. The average duration of hypotension possible with this method is reported to be 3 hours with a maximum of 6 hours.

This method of selective hypotension has been used mainly in the past for cranial surgery, and the advantage claimed for it is better visualization of the operative field as it is not obscured by blood, the visualization is further aided by the reduction of the volume of the brain itself. Various apparatuses have been constructed for the withdrawal and re-transfusion of blood, and are described in the literature (24,25,26,28). A number of fatalities have occurred with the technique and this is understandable as the mechanism of producing this type of hypotension is by arteriolar constriction and carries with it all the potential inherent dangers of shock. Frank shock is avoided by maintaining the blood pressure at about 80 mm. Hg, but the margin of safety is relatively small. Another danger is possible damage to the artery and even loss of the artery. Failure of the apparatus may occur and the possibility of air embolism is real. It must be remembered that the power of compensation may be extremely poor in dehydrated and hypovolemic patients. High oxygen concentration must of course be maintained throughout the operation and extra blood must be available to maintain the existing state of incipient shock. At the time this technique was developed, nothing better was available. Probably because of its inherent dangers and its dependence upon all compensatory powers

of the body, this method has only a few proponents and is now being superseded by other less hazardous techniques.

2. Controlled Hypotension by So-Called Total Spinal Anesthesia. This method was first described by Griffiths and Gillies in 1948 (29, 30, 31). The hypotension is produced by arteriolar dilatation resulting from a preganglionic sympathetic block which paralyzes the vasoconstrictor innervation. It has been shown that the severity of the fall in blood pressure depends upon the number of spinal segments blocked, and that the fall is relatively greater the more cephalad the segments have been blocked. Hence for maximum effect a block as high as the first thoracic segment is necessary. Blocks at higher levels are undesirable and cause no further fall of blood pressure as no sympathetic vasomotor fibers arise above T1 (31). It has also been shown that with blocks higher than T1, death may result from respiratory paralysis caused by paralysis of the phrenic nerves. Cardiovascular failure is a secondary phenomenon (32) that can be prevented by adequate oxygenation. With artificial respiration, the blood pressure can be maintained at 40-60 mm. Hg (33).

Greene has applied the term "hypotensive spinal anesthesia" to this technique (34). General anesthesia must be used throughout the operation. The patient is kept in the Trendelenburg position, and as long as

capillary circulation remains sufficient and tissue oxygenation adequate, the method is safe. The level of hypotension can be controlled by intramuscular injections of vasopressor drugs. If the fall in pressure is abrupt and severe small repeated doses of vasopressor drugs must be introduced intravenously until the pressure is restored to within normal limits. In Miller and Lorhan's series (35) seven and one-half hours at a pressure of 80 mm. Hg or less was the longest period of hypotension by spinal anesthesia.

While this method has proven satisfactory and apparently safe in the hands of Gillies and others, it too has not achieved widespread acceptance because of its complexity and because it combines the inherent danger of a spinal anesthetic and the dangers of general anesthesia.

3. Controlled Hypotension by Means of Blocking Agents. In 1950 Enderby (36) suggested methonium compounds may have value in producing controlled hypotension and thus serve as a more practical substitute for Gillies' method of total spinal anesthesia. Enderby pointed out that the methonium drugs act by blocking autonomic ganglia, producing an increase in blood flow by arteriolar dilatation and thus a subsequent fall of arterial pressure.

Enderby's technique (36,37) to obtain a relatively

bloodless surgical field is divided into two distinct procedures. The first consists of lowering the blood pressure to 55-65 mm. Hg which he considers the optimum, the other of elevating the side of operation, to effect what he called "postural ischemia".

Hexamethonium in man lowers the blood pressure in 1-4 minutes following intravenous administration (38,39). Hypertensive subjects are more sensitive than normotensive ones, and 20 per cent of subjects (chiefly robust, young adults) are not affected by the drug (39). In Shackelton's series (40) two and one-half hours at a pressure of 60 mm. was the longest period of hypotension by hexamethonium bromide. A big disadvantage of the methonium compounds is the degree of uncertainty of the response of the patients to these drugs. Blood pressure falls may result from as little as 12.5 mg. of hexamethonium in some cases and in others doses of 200-300 mg. may have little or no effect (8). Hypotension induced with the methonium compounds can be reversed promptly by the use of vasopressors, preferably those acting peripherally, such as norepinephrine and phenylephrine (40).

Sadove, et al (8) said "this method of controlled hypotension is not a simple one. It requires skill in administration and, above all, sound judgment for its use. It should not be used in arteriosclerotic individuals,

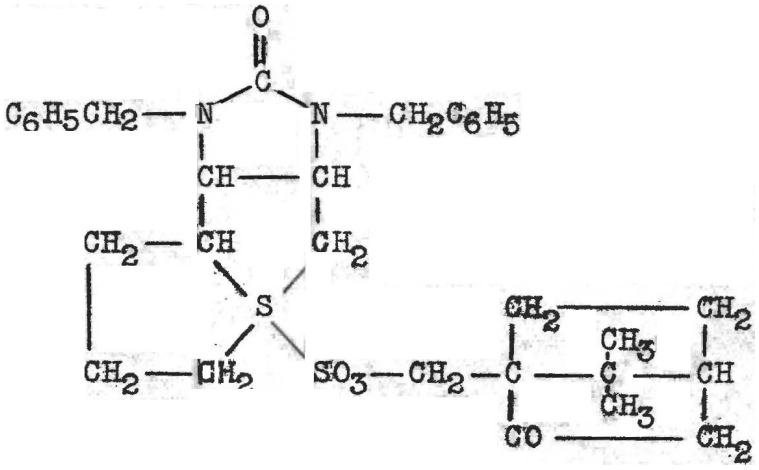
nor should it be entrusted to the novice. Slight indiscretions in the conduct of hypotensive anesthesia may mean the difference of life or death to the patient. Above all, it must be indicated definitely by the problems at hand, rather than to save a bottle of blood for transfusion. It must never be employed after severe bleeding has been encountered and the patient is consequently in a state of incipient shock."

A new drug has been introduced which shows promise in producing a controllable hypotensive state. This drug is a thiophanium derivative called Arfonad. One of the advantages claimed for this drug over methonium compounds is the short duration of its action so that a solution of it may be given by continuous drip, the blood pressure rising or falling with increasing or decreasing rate of administration.

PHARMACOLOGY OF ARFONAD

Chemistry

Chemically, this drug is d-3,4(1',3'-dibenzyl-2'-keto-imidazolido -1,2-trimethylene triophanium d-camphor sulfonate. It is generally referred to by the code number, RO 2-2222 or the trade name Arfonad Camphorsulfonate. It has the following structure:



This drug is available as a solution in 10 cc. ampuls, containing 50 mg. Arfonad Camphorsulfonate per cc.

The manufacturers claim Arfonad Camphorsulfonate solutions are not compatible with Pentothal (thiopental), Surital (thiomytal), Flaxedil, strongly alkaline solutions, iodides, or bromides, and recommends Arfonad Camphorsulfonate should not be employed as a vehicle for simultaneous administration of any other drug (41).

Pharmacodynamics in Animals

Action. Randall, Peterson, and Lehmann (42) have demonstrated that this thiophanium derivative has vasodepressor and ganglionic blocking properties in dogs, cats, monkeys, mice, rats, and rabbits. Their report has shown that it is 30 times as potent as TEAC (tetraethylammonium chloride) and lasts two times the duration of TEAC in the dog, cat, and monkey.

The experimental data of McCubbin and Page (43) revealed that Arfonad was a potent but brief hypotensive drug when given intravenously in dogs. Doses of 0.05 or 0.1 mg. produced a sharp drop in blood pressure ranging from 20 to 50 mm. or more. The duration of maximum hypotension was brief and in 2-8 minutes the blood pressure returned to normal or near normal. In larger doses variation in hypotension from animal to animal was greater. Refractoriness often developed when repeated small doses were given, but unlike tachyphylaxis increased doses of the drug would elicite a large response. A sustained hypotension could be produced by continuous infusion. Its hypotensive action was more marked in neurogenic hypertensive dogs than in normal ones, but this enhancement was not as striking as with TEAC.

With a moderate fall in blood pressure, sympathomimetic drugs, such as ephedrine, elevated the arterial

pressure, even while Arfonad was being administered (42,43). Large amounts of neostigmine counteracted the hypotensive effects (42). Occasionally Priscoline reduced or reversed the depressor response of Arfonad (43). The administration of Arfonad, in contrast to TEAC, did not enhance responsiveness to sympathomimetic drugs (43).

Site of Action. Randall, Peterson, and Lehmann (42) have described Arfonad as a ganglionic blocking agent which reduces arterial pressure in anesthetized dogs and cats. They reported that it blocks transmission through the superior cervical ganglion, that it blocks vagus action on the heart and the carotid sinus pressor reflex. Thus they concluded that Arfonad has the characteristic ganglionic blocking and hypotensive effects of tetraethylammonium bromide.

Mitchell, et al (44) in dogs, demonstrated histamine release when Arfonad was administered. They thought histamine could play a part in lowering the blood pressure.

McCubbin and Page (43), in experimental work on dogs, showed that the hypotensive action of Arfonad was not diminished by section of the spinal cord at C6, removal of the paravertebral sympathetic chain or ganglionic blockage with TEAC or hexamethonium bromide. They also showed that it had a strong vasodilator effect in the perfused denervated dog's leg when TEAC was entirely

pressor. They concluded that Arfonad lowers arterial pressure primarily by metarteriolar vasodilatation. Another point they report is that Benadryl did not appreciably modify responses to Arfonad when histamine responses were largely abolished. They believe blocking of sympathetic ganglia and release of histamine play a minor role in the hypotensive responses to small doses.

Action on Special Systems and Organs. The effects of hypotension on vital functions have already been described and will not be considered here. Only those side effects attributed to Arfonad per se are mentioned.

1. Blood: Large doses of Arfonad elicite hemorrhagic lesions in dogs. This is considered to be dependent on the liberation of heparin and histamone (42). This was not observed inthe mouse, rat, rabbit, guinea pig, cat or monkey.

2. Gastrointestinal tract: Arfonad in therapeutic doses has only a slight depressor effect on intestinal tone in rabbits but in large doses is capable of inhibiting gastric motility in dogs (42).

3. Respiratory tract: Arfonad in large doses apparently has no effect on respiration in dogs (43).

Absorption, Metabolism, Fate. By the oral route Arfonad has no effect. Subcutaneous and intramuscular injections

will precipitate a sustained fall in blood pressure (43).

The metabolism and elimination of Arfonad are unknown. The speed of disappearance of its effects leads one to surmise that it is rapidly inactivated in the body.

Toxicity. The acute toxicity varies greatly with route of administration and the species of animal employed.

Arfonad in comparison with TEAC was found to be about 2-4 times more toxic by intravenous route in mice, rats, and rabbits. In dogs it was about 75 times as toxic (42).

The hemorrhagic lesions and lethal amounts of histamine, in dogs, have already been mentioned.

Pharmacodynamics in Man

Action. It has been shown that Arfonad, in single intravenous doses of 0.1 or 0.2 mg. per kilogram of body weight, will produce a prompt but evanescent depressor response of the arterial pressure lasting about 3 minutes. It is thus possible to employ the drug by continuous intravenous infusion technique (11). Observations carried out on human volunteers by Sadove, et al (45) showed that in the conscious patients with a normal blood pressure the degree of vasodepression was self-limited to a final systolic pressure of approximately 90 mm. Hg, even with doses up to five times those usually used in clinical practice. After administration of the drug conscious individuals lost their normal vasomotor position, but they again showed the same tendency of leveling off. Sadove thought this fact indicated that the autonomic blockade was not complete and the compensatory mechanism remained active. The hypertensive individuals were found to be more susceptible (46). In contrast to TEAC, a pressor response did not occur in any of the 14 hypertensive patients to whom Arfonad was administered by Sarnoff and co-workers (11).

All investigators (45,46,47,48) found that doses of Arfonad can be markedly reduced, proportional to the depth of anesthesia. Any degree of hypotension could be

produced; it could be made either gradual or abrupt, depending upon the rate of administration of the drug. There was marked difference in the total dose required by different patients for satisfactory hypotension. Those patients with hypertension required less while younger patients required larger initial doses than older patients (47). With clinical doses the blood pressure fell slowly over a matter of minutes. The blood pressure reversed itself when the administration of Arfonad was slowed or discontinued.

The arterial pressure could be elevated by epinephrine, ephedrine sulfate, neosynephrine hydrochloride and similar vasodepressors even while Arfonad was being administered (46,50). Arfonad did not exhibit any apparent incompatibili ies with ether, cyclopropane, nitrous oxide, thiopentothal sodium or syncurine in the report by Nicholson, et al (46). They found that once the state of hypotension had been induced very little additional anesthetic agent was required. Morphine and Demoral were found to facilitate the vasodepressor action of Arfonad, while procaine hydrochloride or procaine amide potentiated Arfonad as they do methonium compounds. It was pointed out that this latter property could be used in the cases that showed some degree of refractoriness (49).

Several investigators (11,45,46) stated that

tachyphylaxis did not become apparent in their studies. Little, et al (48) claim they had 4 patients who, after the initial induction of hypotension, required increasingly more rapid infusion rates and hence higher total dosage of Arfonad to obtain the optimal blood pressure level necessary to control bleeding. They considered this to be tachyphylaxis. Little, et al (48) are the only investigators to record a case of resistance. A total dosage of 500 mg. was given one patient without any significant drop in blood pressure. They also recorded one instance in which the patient's extreme susceptibility rendered control difficult and produced wide and presumably dangerous swings in blood pressure.

The data from the study on pregnant subjects by Assali, et al (51) showed that the normotensive pregnant subjects and essen ial hypertensive pregnant subjects had a greater fall in blood pressure than the normotensive non-pregnant subjects and the subjects with toxemia of pregnancy. Another interesting finding in this study is that the diastolic pressure dropped more than the systolic pressure inthe normotensive and essential hypertensive pregnant group, while the reverse was shown in the normotensive non-pregnant and toxemic group.

Nicholson, et al (46) stated that they found that hexamethonium chloride superimposed on Arfonad made no

difference in lowering blood pressure.

Action on Special Systems and Organs. All reports of instances where Arfonad was used declared that the tendency to bleed and the actual loss of blood were less than would have been anticipated had the arterial pressure remained normal. This observation applied more to the blood loss from capillaries than to loss from larger vessels.

There have been no indications of prolonged clotting time in man to date (11,46). Even postoperative hemorrhage, such as might be expected from smaller vessels that had been severed but had not been observed because of hypotension, was not encountered (46). The preference is a slow return of normal blood pressure believing that this permits the clots which are forming at the ends of cut blood vessels to become firm so as to afford effective hemostasis (2). Sadove, et al (50) believe that it is important that hemostasis with a normal arterial tension be assured before the wound is closed.

In the unanesthetized human beings Sadove, et al (45) demonstrated several points. The volunteers responded to oxygen deficiency wit tachycardia and to an excess of carbon dioxide with hyperpnea and tendency for the blood pressure to rise again. The venous pressures

remained within normal limits. Plethysmorgraphic recording demonstrated an increase in peripheral pulse pressure, as would be expected from arteriolar dilatation that the drug produces. This would account for the sensation of warmth experienced by some individuals (51). The electrocardiographic and electroencephalographic tracings were essentially unchanged. Cardiac output studies by ballistography indicated a diminished stroke output by 5 to 10 cm. but the minute volume is not markedly altered because of compensatory changes in cardiac rate. Nicholson, et al (46) reported one instance where pulse rate of 160 beats per minute developed, but otherwise found no significant increase in pulse rate; frequently it remained the same or decreased. Sarnoff, et al (11) stated that the largest increase in pulse rate in his series was 15 beats per minute but all returned to control levels during continuous admini tration of Arfonad.

Sarnoff, et al (11) had two patients who experienced nausea and vomiting at the highest dose level, although both of these patients had already been chronically nauseated and vomited intermitently because of uremia, they thought there seemed to be little doubt but that Arfonad did accentuate this symptom. Assali, et al (51) discovered that when severe hypotension occurred nausea, vomiting, pallor, dizziness and other signs of circulatory

collapse were present. These symptoms subsided rapidly when the blood pressure was elevated to control levels by raising the lower extremities to an angle of 90 degrees or by injection of 25 mg. of ephedrine intravenously. Most of Sarnoff's patients experienced the desire to yawn with effective intravenous rates, as did Assali's subjects (51).

Nicholson, et al (46) found rectal temperatures in their patients as low as 97° F after hypotensive procedures with Arfonad. Assali, et al (51) reported that the skin temperatures of the lower extremities rose more markedly than that of the upper extremities. He thought this phenomenon indicated that in the lower extremities there was increased vasomotor tone which makes this part of the vascular bed more responsive to the effects of ganglionic blocking agents.

Sarnoff, et al (11) found that the cold pressor test, which yielded a substan ial rise in both systolic and diastolic pressures during control periods, did not produce a pressor response during the administration of Arfonad. He also had one patient that exhibited clouding of sensorium and restlessness following abrupt lowering of arterial pressure.

The characteristic flush and headache of histamine that accompany the presence of higher than normal blood

levels in man have not been observed in man (11,45,46).

The only side effects discovered by Sadove, et al (45) in man was an occasional atropine-like reaction such as mydriasis, skin flush, conjunctival injection, and dryness of the mouth. Besides the gastrointestinal symptoms already mentioned, Sarnoff, et al (11) also noted dryness of the mouth in patients with prolonged use of Arfonad.

CLINICAL USE

Technique in the use of Arfonad as the blocking agent in controlled hypotension in surgery: Anesthesia is instituted with endotrachael intubation to assure adequate airway for oxygenation. Following induction the patient is positioned by placing the operative sight superiorly to promote venous drainage by gravity from the wound. At this point some authors disagree on the positioning of the head. Nicholson, et al (46) placed their patients in a 5 degree head-up position for removal of brain tumors, without any apparent cerebral damage. Sadove, et al (49) allows the patient's head to be elevated only for large vascular tumors, and then only 2-4 inches above the horizontal plane. Little, et al (48) stated that this maneuver was dangerous and fool hardy and Davison (12) is of the same opinion.

Most anesthetists use a 0.1 per cent intravenous infusion of Arfonad in a 5 per cent glucose solution to elicit the depression response. Kilduff (47) found that the intravenous infusion method required a total dose three times that of the repeated single dose method. Sadove, et al (50) suggest that the administration of Arfonad be started before the incision is made at an approximate rate of 40 to 60 drops per minute. He claims in this manner it is possible to slowly lower the

pressure over a period of 10 to 15 minutes. Thus the cardiovascular system is able to gradually re-establish an equilibrium between venous return and cardiac output. In normotensive patients a systolic pressure of 70 to 80 mm. Hg is cons dered a safe level from which to start. Thereafter the rate can be adjusted to satisfy conditions for the operation. Blood pressure is at all times kept at the highest level compatible with the surgical requirements of the moment and is changed in either direction as circumstances demand.

Patients should be closely observed for signs of peripheral circulatory ailure. The danger signs are tachycardia, air hunger, perspiration, pallor, venous constriction, and increased capillary refill time. It must be remembered that the hypotensive patient is vulnerable to any considerable blood loss. With the compensatory mechanism impaired, blood loss is greatly exaggerated as compared with normal individuals (50). The requirements for success of this method are normal circulating volume and adequate oxygenation (49).

Case Studies: Kilduff (47) used Arfonad in 50 operations on the head, neck, and chest wall. In this series there were no deaths and no evidence of any ill effects during the period in the hospital. A careful follow-up did not disclose any later ill effects which appeared in any way

referable to the hypotensive technique. Magill (52) used Arfonad in 5 cases with highly satisfactory results and no undesirable side effects or complications. Nicholson, et al 46) used Arfonad in 25 operations on the head, neck, and chest wall with the only complication being one case of tachycardia. Sadove, et al (49) have used Arfonad in 200 operative procedures. They reported one case of post-operative bleeding, one case of post-operative liver failure in a patient with impaired liver function, and one case of cerebrovascular thrombosis within 24 hours after the operation. The complications encountered by Li tle, et al (48) were one case of resistance, one case of extreme susceptibility, and four cases of tachyphylaxis. In the remainder of his cases he obtained satisfactory controlled hypotension. Sarnoff, et al (11) used Arfonad in 17 cases of hypertension with and without acute pulmonary edema. It was successful in all cases except those that had azotemia. He found Arfonad of no value when used in 3 cases of acute bronchial asthma, but used it successfully in 2 cases of rheumatic valvular heart disease with pulmonary edema.

Magill (13) claims "it is in the post-operative period that the striking evidence of the value of the method (Controlled Hypotension) becomes apparent. When blood pressure regains normal levels, patients who have

been subjected to major surgical procedures are phenomenally well." He claims that at Westminister Hospital in London the opinion is unanimous that the condition of these patients excels that of those patients which have any other form of anesthesia. Most investigators (46, 47,48) believe that postoperatively their patients do as well as, if not better than, those patients not having the benefit of Arfonad.

Indications: Magill (13) thinks controlled hypotension should be used in any surgical procedure there is apt to be shock from blood loss.

Sadove, et al (49) advocate the use of Arfonad for the following indications:

"1. Control of bleeding when the operation could not be undertaken or would entail an exceptional hazard if more conventional methods were employed.
2. Diminution of trauma because of improved visualization of the field.
3. Inability to replace blood for technical reasons in amounts that would be required if hypotension was not used. This, for instance, may occur in cases of rare blood-group combinations.
4. Control of dangerous hypertension.
5. Treatment of pulmonary edema secondary to

hypertension in the pulmonary bed.

6. Facilitation of intracranial exposure because of better visualization and reduction of brain volume.

7. Conservation of time in those cases in which speed is of the essence. The time factor must significantly benefit the patient and must not be an indication if it merely serves the convenience of the surgical team."

The following types of cases are recommended for this technique:

1. Neurosurgery.

Brain tumors; cerebrovascular aneurysms; operations in areas where even slight bleeding markedly interferes with visualization and with the surgeon's work; and cases of difficult exposure, because hypotension causes some shrinking of the brain and renders it more compressible.

2. Peripheral vascular surgery.

Anastomosis of large blood vessels is greatly facilitated by hypotension. The method is useful in aortic grafts and transplants, coarctation operations, and operations for arteriovenous fistula.

3. Removal of highly vascular neoplasms: e.g., hypernephroma.

4. Operations associated with great blood loss: evisceration procedures, pancreatectomy, splenorenal shunts.

5. Patients with unusual blood-group combinations for whom adequate amounts of blood cannot be obtained.

6. Control of dangerous systemic hypertension and treatment of pulmonary edema due to pulmonary hypertension.

Contraindications: Armstrong-Davison (53) and Lynn, et al (7) warn that controlled hypotension should not be used in organic vascular diseases. They fear that these diseases will exaggerate the depressed perfusion pressures causing permanent damage to such organs as the kidneys, heart, or brain.

The following conditions, in the opinion of Sadove, et al (49) constitute contraindications to the use of Arfonad: (1) Shoc , bot incipient and frank; (2) inadequate availability of fluids; (3) inability to replace blood for technical reasons; (4) inadequate skill on the part of the anesthesiologist; (5) severe visceral disease, especially of liver and kidneys; (6) degenerative disease of central nervous system; (7) severe cardiac disease; (8) hypovolemia; (9) uncorrected anemia; and (10) arteriosclerosis.

SUMMARY

The physiology of hypotension indicates that the two prerequisites for control are normal circulating volume and adequate oxygenation. In the presence of the above requirements there is no damage to the vital functions of the body. Thus supression of bleeding by hypotension is a physiological possibility.

Of the three principal methods of controlled hypotension, arteriotomy and re-transfusion seems the least desirable because of its inherent danger of incipient shock. The complexity of the total spinal anesthesia or hypotensive spinal anesthesia has proven to be the cause of its limited use. With the advent of the methonium compounds, a ganglioplegic drug, controlled hypotension has begun to take steps in the direction of real clinical application. The degree of uncertainty of the patients's response to methonium compounds has hindered its acceptance. A new drug, Arfonad, is now being evaluated as a blocking agent.

Arfonad is a thiophanium derivative that produces a prompt and brief depressor response. The drug is administered in a continuous intravenous drip producing a graded reduction of arterial pressure in accord with the rate. Cessation of the infusion is followed by prompt recovery of arterial pressure. In experiments

on dogs the site of action appears to be direct vaso-depressor action on the arteriols with some ganglioplegic effects. Sympathomimetic drugs remain effective. From preliminary reports the undesirable side-effects and complications are apparently minimal.

Nothing is known about the metabolism and elimination of Arfonad. The speed with which it is inactivated leads one to believe it is metabolized quickly. Parenteral and intravenous administration appear to be the only effective routes.

In man, Arfonad has been used in approximately 300 surgical procedures with good results. It has also been used successfully in correcting acute pulmonary edema of cardiac origin and hypertension.

Indications or the use of Arfonad are any surgical procedures where visualization is imperative, speed is of the essence, and impending blood loss is fatal. If preliminary reports are substantiated, neurosurgical procedures, peripheral vascular surgery, excision of highly vascular neoplasms or extensive intra-abdominal surgery will result in decreased morbidity with the use of Arfonad.

Contraindications are shock, any severe cardiac, vascular, hepatic or renal disease, and inexperience.

As Magill (52) said, "If Arfonad continues to live

up to its present reports, Arfonad will take its place on the shelf in the operating room, beside pentothal and succinylcholine."

CONCLUSIONS

1. Controlled hypotension can physiologically be a sound procedure.
2. Controlled hypotension is of value in surgery.
3. Methods for effecting controlled hypotension have been unsatisf ctory todate.
4. Preliminary reports on Arfonad indicate this drug may be the answer to successful controlled hypotension.

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