

**THE INTRAVENOUS USE OF A THIOPHANIAM
DERIVATIVE (ARFONAD — RO2-2222) (*)**

**For the production of flexible and rapidly reversible
hypotension during surgery (**)**

MORRIS J. NICHOLSON, M. D.

Department of Anesthesiology,
The Lahey Clinic,

and

STANLEY J. SARNOFF,

Associate Professor of Physiology,
Harvard Public Health School,
(Boston, Massachusetts)

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It was observed by Koster (9) in 1928 that patients given spinal anesthesia without sympathomimetic medication appeared to lose less blood during operation than those in whom arterial pressures were well maintained. In recent years a renewal of attempts to diminish blood loss during operation by maintaining a low arterial blood pressure has found expression in the blood-letting-reinfusion technic of Gardner (3) and of Hale (7), the technic of high spinal anesthesia of Gillies (4, 5, 6) and the use of ganglionic blocking agents as suggested by Hale Enderby (1, 2) and Pelmore and by Hughes (8). From the point of view of maintaining the metabolic requirements of the organism, it would seem desirable to lower arterial pressure by diminishing systemic vascular resistance rather than by diminishing the circulating blood volume. From the point of view of feasibility, the use of an agent that could be given

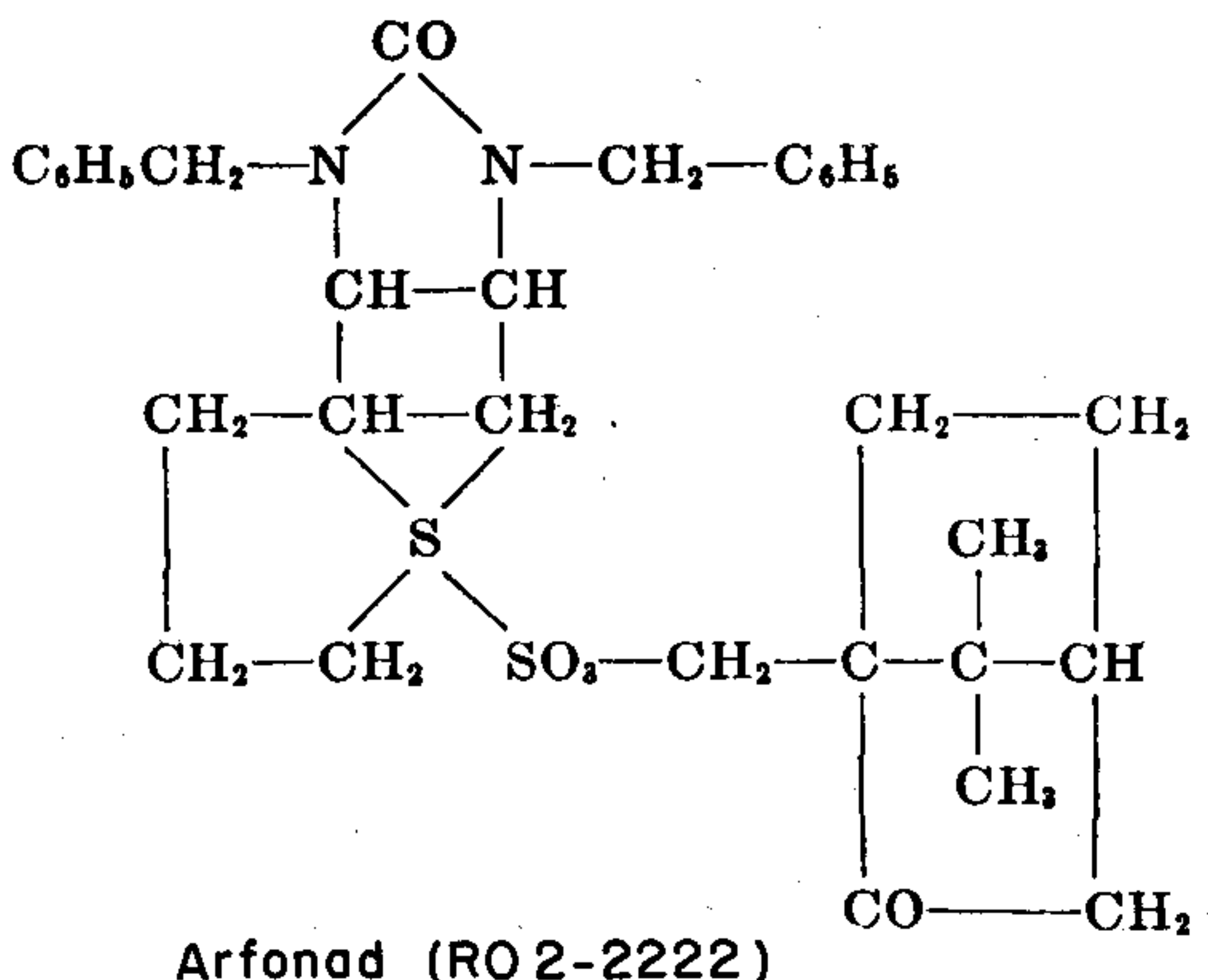
(*) Arfonad is the name that has been assigned to the drug formerly known as RO2-2222. Throughout the paper the term arfonad will be used.

The authors wish to express their thanks to Dr. Elmer L. Sevringhaus, of Hoffmann-La Roche, Inc., Nutley, N. J., for generous supplies of the compound used in this study.

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intravenously seems more desirable and convenient than does the use of spinal anesthesia.

Randall, Peterson and Lehmann (12) have described the experimental pharmacologic and sympatholytic characteristics of a series of thiophanium compounds, among which was *d*-3,4(1',3'-dibenzyl-2'-keto-imidazolido)-1,2 trimethylene thiophanium *d*-camphor sulfonate (arfonad; fig. 1). In the course of a recent series of laboratory and clinical investigations on the mechanisms and therapy of acute hypertensive pulmonary edema, it was found that arfonad was capable of consistently lowering arterial pressure in



d-3,4(1',3'-dibenzyl-2'-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate

Fig. 1

unanesthetized man to levels that varied with the rate of administration of the drug when the latter was given by a continuous intravenous drip (12-18). When the rate of administration was reduced, it was noted that the arterial pressure rose toward control levels and promptly returned to normal levels when the drug was discontinued. Further, arterial pressure could be elevated by sympathomimetic medication (ephedrine sulfate or neosynephrine hydrochloride) even while arfonad was being administered. Although the latter has not thus far been found necessary, it might at times

be desirable to know that the ganglionic blocking effects of this drug and the resultant hypotension can be corrected readily and rapidly with sympathomimetic medication. The hypotension induced by arfonad in the conscious patient was seldom accompanied by a significant increase in pulse rate; frequently, it remained the same or decreased. Neither tachyphylaxis nor the occasional pressor responses that have been noted with tetraethylammonium chloride (10) have been observed with the use of this agent. Finally, stable levels of low arterial pressure could be maintained for periods of time not likely to be exceeded by surgical procedures.

With these observations at hand, it was suggested that this agent might be adaptable to the production of controlled hypotension to prevent excessive blood loss during certain operations. It was also thought that the prompt rise in arterial pressure associated with the discontinuance of the intravenous administration of this drug might eliminate or at least diminish the need for sympathomimetic medication during the postoperative period as has sometimes been found necessary when the single injection technics utilizing the longer acting ganglionic blocking agents have been employed.

This report is an attempt to answer partially the question of whether the previously noted characteristics of this agent observed in the unanesthetized hypertensive patient are operative in the anesthetized normotensive patient who is undergoing surgical treatment.

Report of Cases

CASE 1. A 47 year old white woman who suffered from markedly increased intracranial pressure was found by preliminary ventriculography and percutaneous left carotid arteriography to have a large tumor of the left temporal lobe. Following ventriculography and arteriography, which was done under pentothal-nitrous oxide-ether anesthesia, the patient was placed in the supine position in a 5 degree head-up position. A light surgical stage of endotracheal ether-oxygen anesthesia was maintained by the carbon dioxide absorption technic for the remainder of the operation.

The intravenous administration of a solution of arfonad containing 1 mg. per cubic centimeter was begun at a rate of 4 mg. per minute. The blood pressure gradually fell from 110 mm. to 60 mm. systolic and from 78 mm. to 40 mm. diastolic in approximately. See insert 1 mg. per minute and a hypotensive state was maintained satisfactorily for the remainder of the operation, which took 140 minutes (fig. 2). A large, vascular, deep-seated meningioma of the left temporal lobe was removed. On discontinuing the administration of the drug the blood pressure promptly rose to 100 mm. systolic and 80 mm. diastolic in ten minutes. The rate of administration was reduced to approximately. By the time the patient had reached her room, the blood pressure was 120 mm. systolic and 80 mm. diastolic. Five hundred cubic centimeters of whole blood was then administered as it was thought that this probably represented the amount of blood lost during the operation. The general condition of the patient was good for forty-eight hours, then she gradually grew less responsive and the presence of a postoperative hematoma was suspected. Re-elevation of the bone flap failed to confirm this suspicion but

did reveal a very edematous brain. Postoperatively, the patient responded favorably to a vigorous regimen of dehydration and ultimately made a normal recovery.

CASE 2. A 59 year old man, who weighed 160 pounds, had moderately advanced arteriosclerotic cardiovascular disease and a right bundle branch block. He had experienced several attacks of unconsciousness and because of this a right, percutaneous carotid arteriogram was made which showed a large, right temporoparietal brain tumor. A light surgical stage of ether anesthesia was induced and the patient was placed supine in a 5 degree head-up position for the operation.

The intravenous administration of a solution of arfonad containing 0.5 mg. per cubic centimeter was started at a rate of approximately 1 mg. per minute. The blood pressure was reduced from 150 mm. to 70 mm. systolic and from

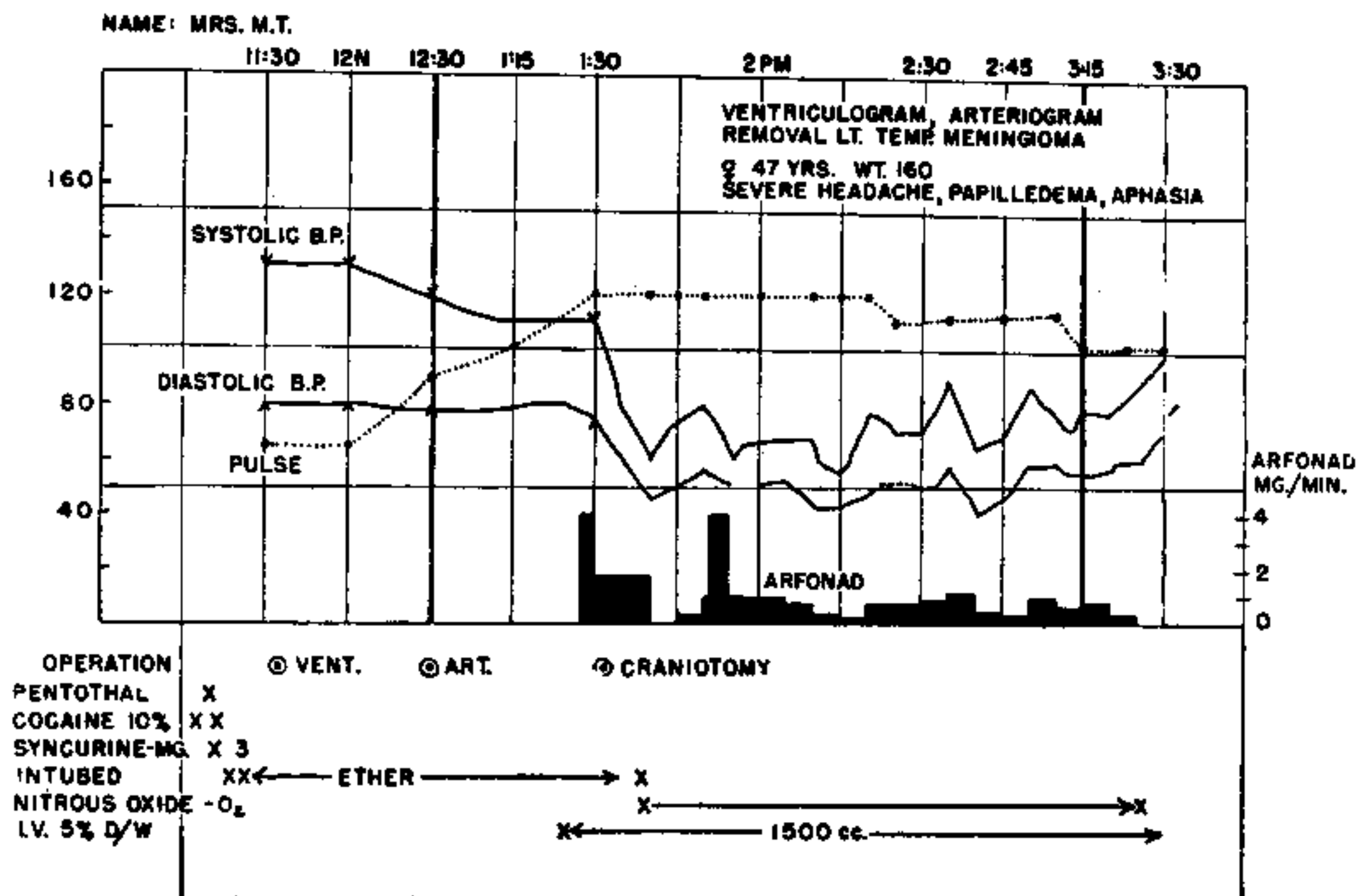


Fig. 2 — Sustained hypotension produced by small amount of arfonad administered by constant intravenous drip.

80 mm. to 50 mm. diastolic in approximately ten minutes. The rate of administration was reduced to 0.25 to 0.5 mg. per minute and the desired hypotensive state was maintained for 180 minutes (fig. 3). During this interval a large, vascular meningioma of the right temporoparietal region was removed and 500 cc. of whole blood administered. When the drug was discontinued the blood pressure promptly returned to 100 mm. systolic and soon thereafter reached 120 mm. systolic and 80 mm. diastolic. The patient responded in the operating room and his postoperative course was entirely uneventful.

CASE 3. A 71 year old woman came to the clinic because of a cancer of the right breast. Thirteen years previously a left radical mastectomy had been performed for carcinoma of the breast. At that time the presence of mild diabetes mellitus was discovered which was controlled by diet. The preoperative blood pressure was 140 mm. systolic and 90 mm. diastolic, and the pulse rate 100 per minute. Anesthesia was induced with pentothal-decamethonium

bromide and nitrous oxide-oxygen. After endotracheal intubation was accomplished, a light stage of surgical anesthesia was maintained by the administration of nitrous oxide-ether by the closed carbon dioxide absorption technic.

A solution containing 0.5 mg. per cubic centimeter of arfonad was administered intravenously at a rate of 3 mg. per minute and the blood pressure gradually decreased to 60 mm. systolic and 40 mm. diastolic during the next ten minutes (fig. 4). The rate of administration was reduced to 1 mg. per minute and the desired state of hypotension was maintained for the next seventy-five minutes. During this time a right radical mastectomy was performed; the measured blood loss was 325 cc. When the drug was discontinued, the blood pressure promptly returned to 110 mm. systolic and 60 mm. dias-

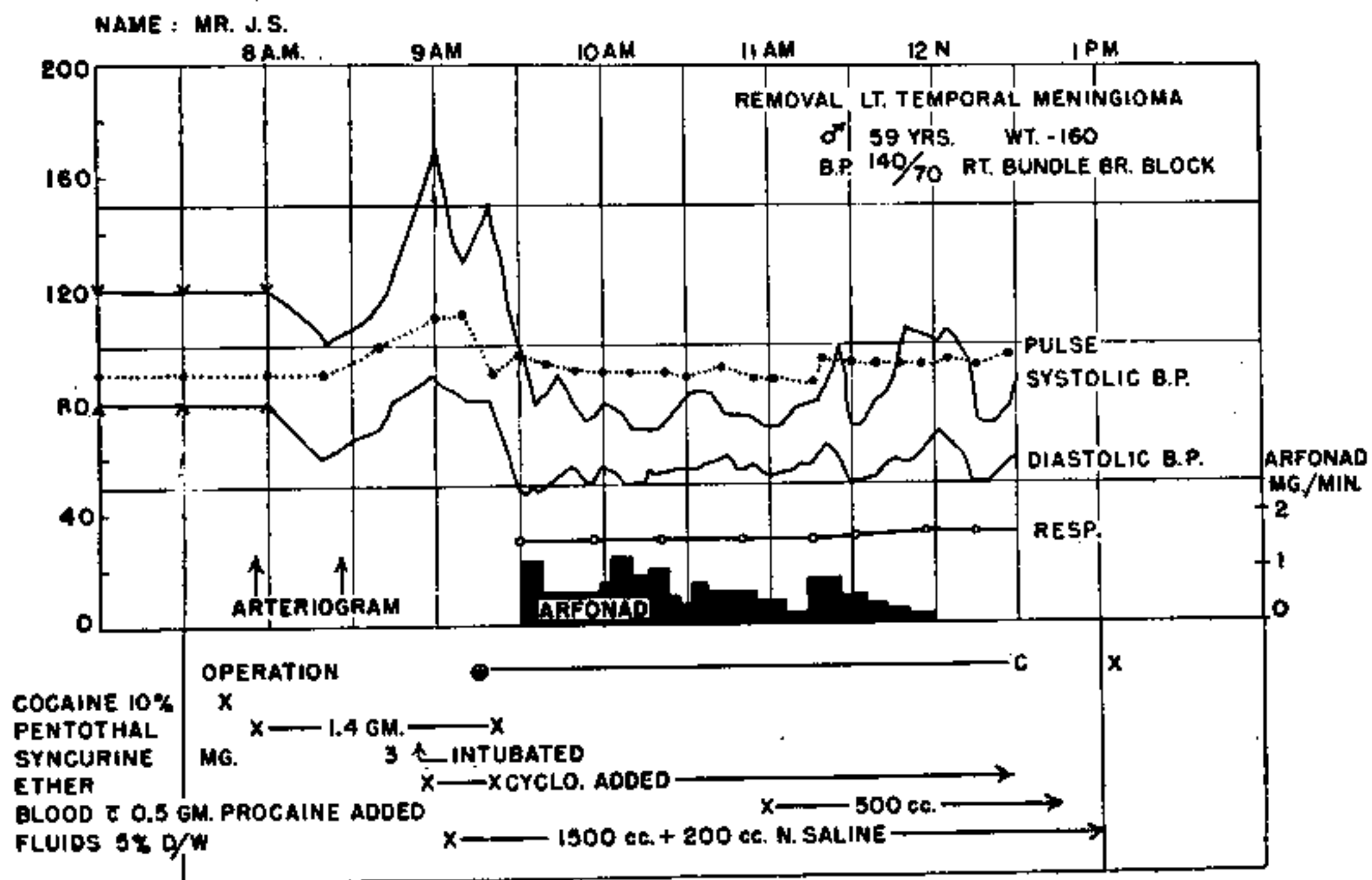


Fig. 3 — Fairly typical response of a moderately hypertensive older patient to arfonad. Note decrease in blood pressure without change in pulse rate.

tolic. A tight dressing was applied to the operative region and by the time the patient reached her room she was awake. The postoperative course was uneventful.

CASE 4. A 72 year old man suffered from intractable pain associated with metastatic malignant disease. Twenty months before admission an abdomino-perineal resection had been performed for adenocarcinoma of the rectosigmoid junction.

Nine days previous to this particular operation a left thoracic chordotomy had been done which gave the patient relief of pain on the right side below the operative site. Because of loss of 25 pounds in weight over the past twenty months and the presence of moderate anemia, this patient was considered to be in poor general health.

Anesthesia was induced with thiopental sodium-syncurine-nitrous oxide, intubation was performed and the patient was placed in the prone position with the upper thoracic region elevated so that the feet were in approximately a 10 degree dependent position. It was obvious that the blood volume was already reduced, so intravenous administration of a solution of arfonad, con-

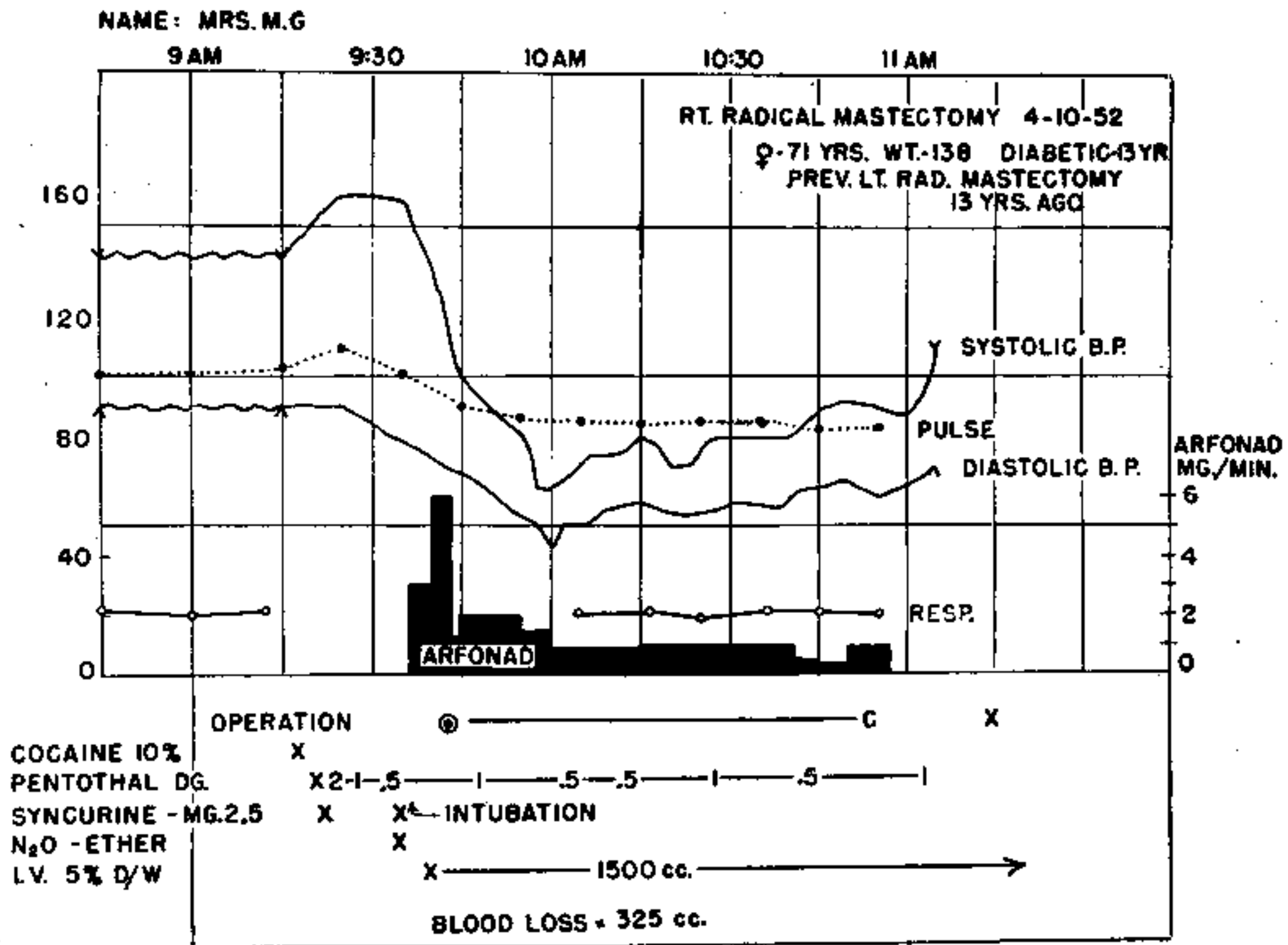


Fig. 4 — Satisfactorily controlled hypotensive state in an elderly diabetic patient undergoing radical mastectomy. Bleeding in operative field was markedly reduced.

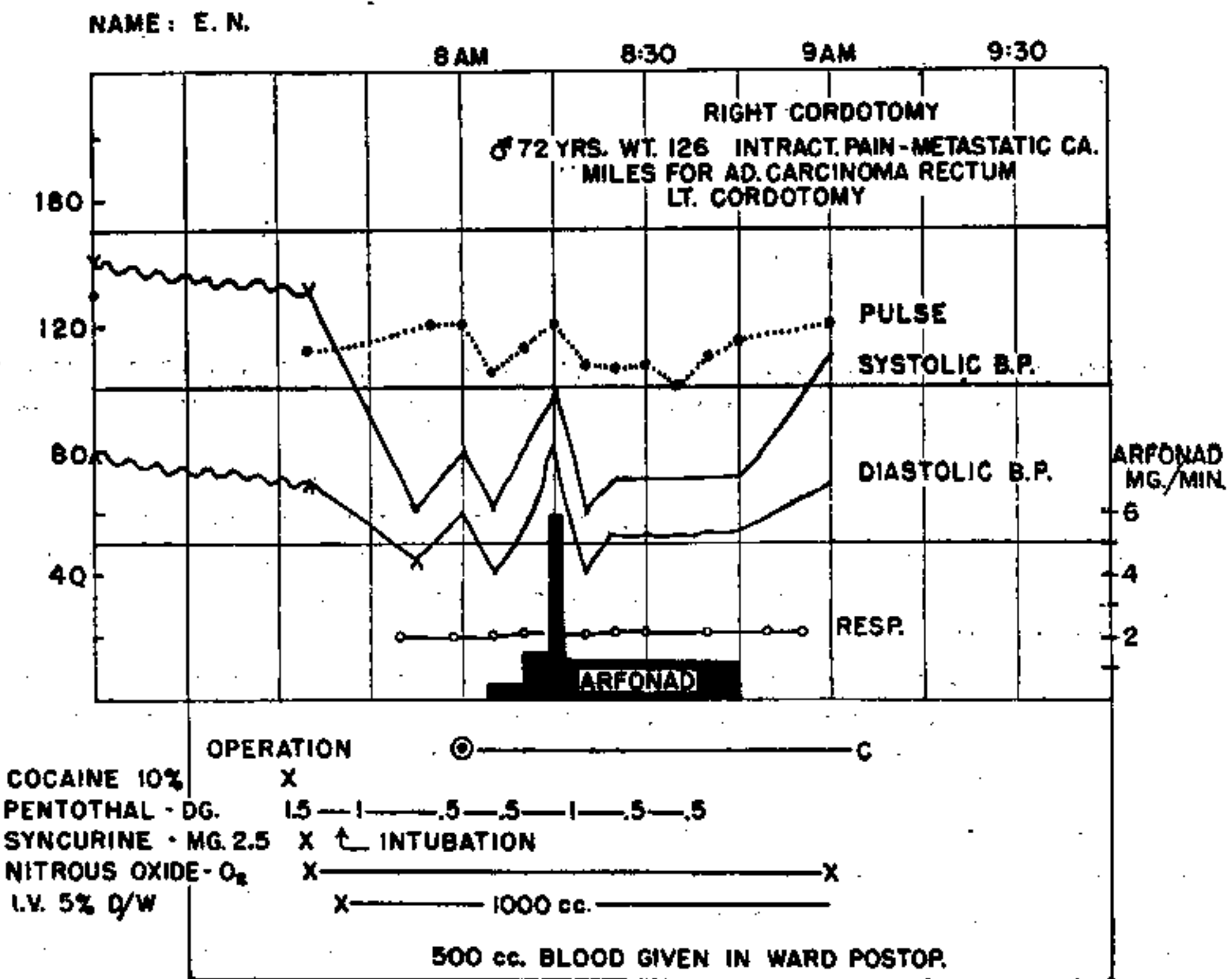


Fig. 5 — Extremely debilitated patient who responded satisfactorily to intravenous administration of arfonad. Very little blood lost during operation. Excellent postoperative recovery.

taining 0.5 mg. per cubic centimeter, was started very slowly, at a rate of 0.5 to 1.5 mg. per minute. The blood pressure was quickly reduced to 70 mm. systolic and 50 mm. diastolic and the operative field was practically bloodless (fig. 5). This hypotensive state was maintained for thirty-five minutes. Ten minutes after the drug was discontinued, the blood pressure returned to 100 mm. systolic and 70 mm. diastolic. Five hundred cubic centimeters of whole blood was administered to the patient in his room to restore the blood volume to normal. The postoperative course was uneventful from the standpoint of the operation and the anesthesia.

CASE 5. A 40 year old normotensive man whose chief complaint was nocturnal convulsions and a transient hemiplegia was found by arteriography to have a large right frontoparietal-occipital angiomatous lesion. A light surgical stage of ether anesthesia was induced and the patient placed supine in a 5 degree head-up position for the craniotomy.

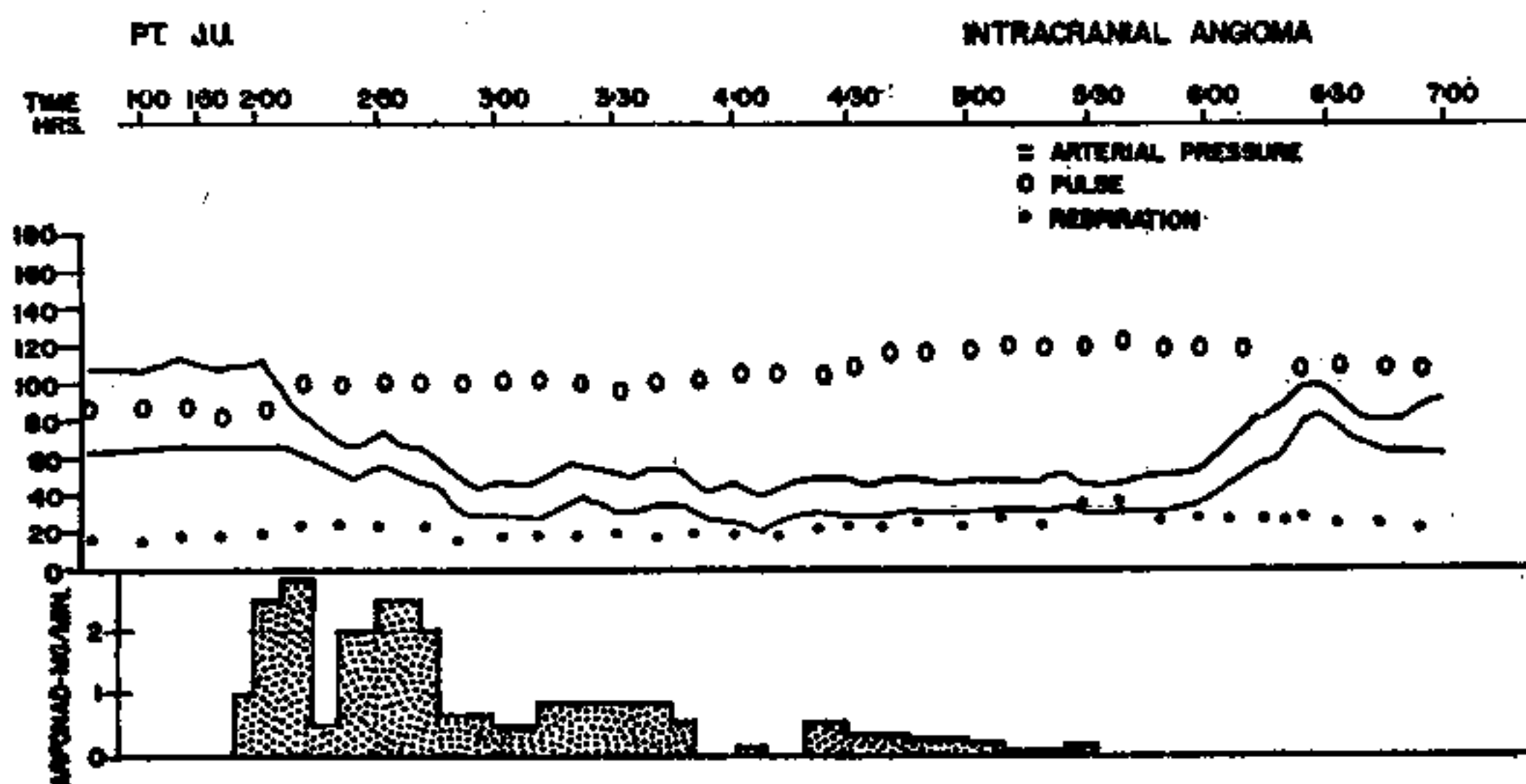


Fig. 6 — In spite of this well controlled hypotensive state, 3500 cc. of blood was lost during the removal of a large intracranial angioma.

The intravenous administration of a solution of arfonad containing 0.25 mg. per cubic centimeter was started at an approximate rate of 3 mg. per minute. The blood pressure gradually fell from 115 mm. to 70 mm. systolic and from 60 mm. to 40 mm. diastolic. The rate of administration of the arfonad was reduced to from 0.75 to 0.5 mg. per minute and the hypotensive state maintained for the next three and one-half hours (fig. 6). During this period the pulse rate gradually rose from 80 beats to 110-120 beats per minute. In spite of this apparently ideal hypotensive state, the patient bled profusely from the large angiomatous vessels and 2500 cc. of whole blood was administered during the procedure. Nevertheless, the hemoglobin, which was 16.4 gm. preoperatively, had fallen to 8.8 gm. postoperatively, and an additional 1000 cc. of blood was administered during his convalescence.

CASE 6. This patient, a 46 year old normotensive man weighing 140 pounds, had signs of increased intracranial pressure. Anesthesia was induced with sodium surital and syncurine intravenously and maintained in a light surgical stage with endotracheal ether while ventriculography and craniotomy were performed.

With the patient supine in a 5 degree head-up position, a solution of arfonad containing 1 mg. per cubic centimeter was started at a rapid rate

and the blood pressure slowly fell from 130 mm. to 90 mm. systolic and from 80 mm. to 70 mm. diastolic. In spite of a continued rapid rate of administration, the blood pressure failed to drop any lower but the pulse rate rose from 120 beats to 150 beats per minute. After a total of 400 mg. of arfonad had been administered, it was discontinued and an attempt was made to drop the blood pressure to a lower level by the administration of 100 mg. of hexamethonium chloride intravenously during the next ten minutes, but it remained stationary (fig. 7). Although the anesthesiologist thought this degree of hypotension was unsatisfactory, the neurosurgeon was pleased with the diminished amount of bleeding in the operative field.

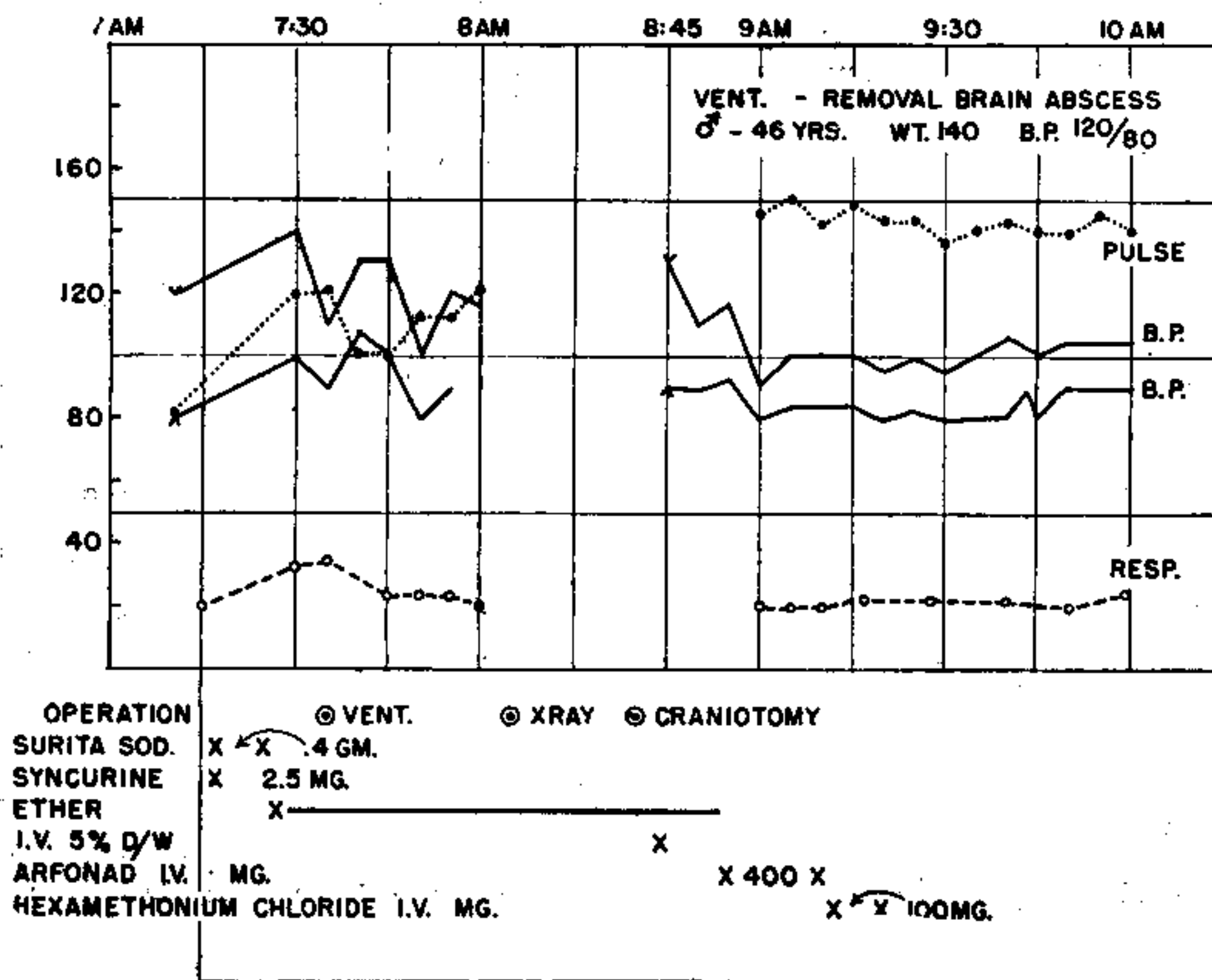


Fig. 7 — Response of a normotensive patient to arfonad and hexamethonium chloride. Note elevation of pulse rate in spite of only a moderate decrease in blood pressure. Although the anesthesiologist considered this degree of hypotension unsatisfactory, the surgeon noted a marked reduction in bleeding.

Discussion

The results reported contribute nothing toward the decision as to whether the maintenance of hypotension during an operative procedure is sound physiologic surgical practice, except the observation that the postoperative course of patients so managed did not appear to differ materially from that of other patients. The indications for transfusion during or after operation are not hard and fast. Therefore, the fact that this group of patients managed by the reported hypotensive technic during operation required administration of less blood during and after operation than might

otherwise have been expected cannot be interpreted precisely, although it would seem to be helpful and suggestive information.

On an *a priori* basis it should probably be assumed that severely depressed perfusion pressures may inflict some hardship on a kidney, brain or heart, whose vascular bed may be compromised by organic vascular disease. Unpublished data indicate that, although renal function is moderately depressed during the initial stages of hypotension induced with arfonad, it rises toward normal during the continued administration of the drug (18). As with any clinical procedure, definite indications and contraindications develop only with prolonged experience. It is anticipated that such will prove to be the case with this practice of inducing hypotension.

On the positive side, four observations were of significance. 1) Arfonad did not exhibit any apparent incompatibilities with the anesthetic agents used (ether, cyclopropane, nitrous oxide, thiopental sodium or syncurine [decamethonium bromide]). 2) The same flexible, graded and readily reversible lowering of the arterial pressure was obtained in anesthetized patients who were undergoing operations as was previously obtained in unanesthetized patients. 3) It was the impression of the operating surgeons that the tendency to bleed and the actual loss of blood during the procedures were less than would have been anticipated had the arterial pressure not been lowered. 4) Postoperative hemorrhage, such as might be expected from smaller vessels that had been severed but had not been observed because of the hypotension, was not encountered.

The effect of arfonad on the dog appears to differ somewhat from that on man, and these differences are worthy of mention. First, a single injection of 0.04 mg. per kilogram in the dog produced a more prolonged hypotensive state. Mitchell (11) and co-workers have demonstrated that in this species blood levels of histamine are elevated after the drug is given. Repeated observations have not revealed the clinical signs of histaminemia in man; that is, the flush, pounding and headache that follow the injection of histamine have not been observed with those rates of administration that are capable of producing marked lowering of arterial pressure. Second, after administration of very large doses of arfonad the clotting time of the blood was prolonged in dogs. This observation has not been noted in man to date, nor did the postoperative course of the patients studied indicate that there was any interference with the clotting mechanism. However, a careful study of this important aspect is indicated.

Summary

Studies on 6 patients who had a variety of surgical procedures suggest that arfonad is a useful agent for the production of graded and readily reversible hypotension under ether, cyclopropane, nitrous oxide and pentothal anesthesia, or mixtures of these agents. The necessity to predict the depressor response of any given patient to a given dose of a drug has been modified by the continuous intravenous use of this agent, as the depressor effect of arfonad is evanescent.

Addendum

To date, a state of hypotension has been maintained in 27 patients during operative procedures under general anesthesia. With the exception of 2 patients who had radical mastectomies and one who had a chordotomy, all patients have been subjected to operations for the removal of brain tumor, and these procedures have been done with the patient placed supine in a 5 degree head-up position. Blood pressures have been recorded in the standard clinical fashion with the cuff on the arm, using the auscultatory method, placing the stethoscope disk over the brachial artery. All patients have been allowed to breathe spontaneously and only when it has seemed indicated has assistance been given during the inspiratory phase. No attempt has been made to measure accurately the blood loss except in the 2 patients who underwent radical mastectomy and the one who had a chordotomy, and in these procedures the measured blood loss was markedly reduced. No deaths have occurred nor have any postoperative complications been attributed to the use of this technic.

The middle aged, moderately hypertensive patient is definitely more susceptible to the vaso depressor action of arfonad than the younger, robust, normotensive patient. As demonstrated in figure 7, superimposing hexamethonium chloride on arfonad made no appreciable difference in lowering the blood pressure that appeared resistant to arfonad. Extreme degrees of posture which might enhance the possible pooling effect of blood in the dependent parts have not been employed.

The hypotensive state is associated with an upset in the heat regulating mechanism of the body because of the prolonged peripheral vasodilatation, and a state of hypothermia is to be expected at the conclusion of each operation; rectal temperatures may go as low as 97° F. Once the state of hypotension has been induced very little additional anesthetic agent is required. It was the impression of the operating surgeons 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 applies more to the blood loss from capillaries. No matter how low the blood pressure falls, blood loss can be significant if large arteries and veins are severed. This is demonstrated by the amount of blood lost during the operation in Case 5 in which an ideal hypotensive state was maintained throughout, but large veins and arteries had to be dealt with. The use of arfonad was discontinued in one instance because of a disturbing tachycardia, rate 160 per minute, that developed soon after the drug was administered. It was impossible to maintain a satisfactory hypotensive state by the intravenous administration of arfonad in 2 young, robust, normotensive adults who were being operated on in a 5 degree, head-up position.

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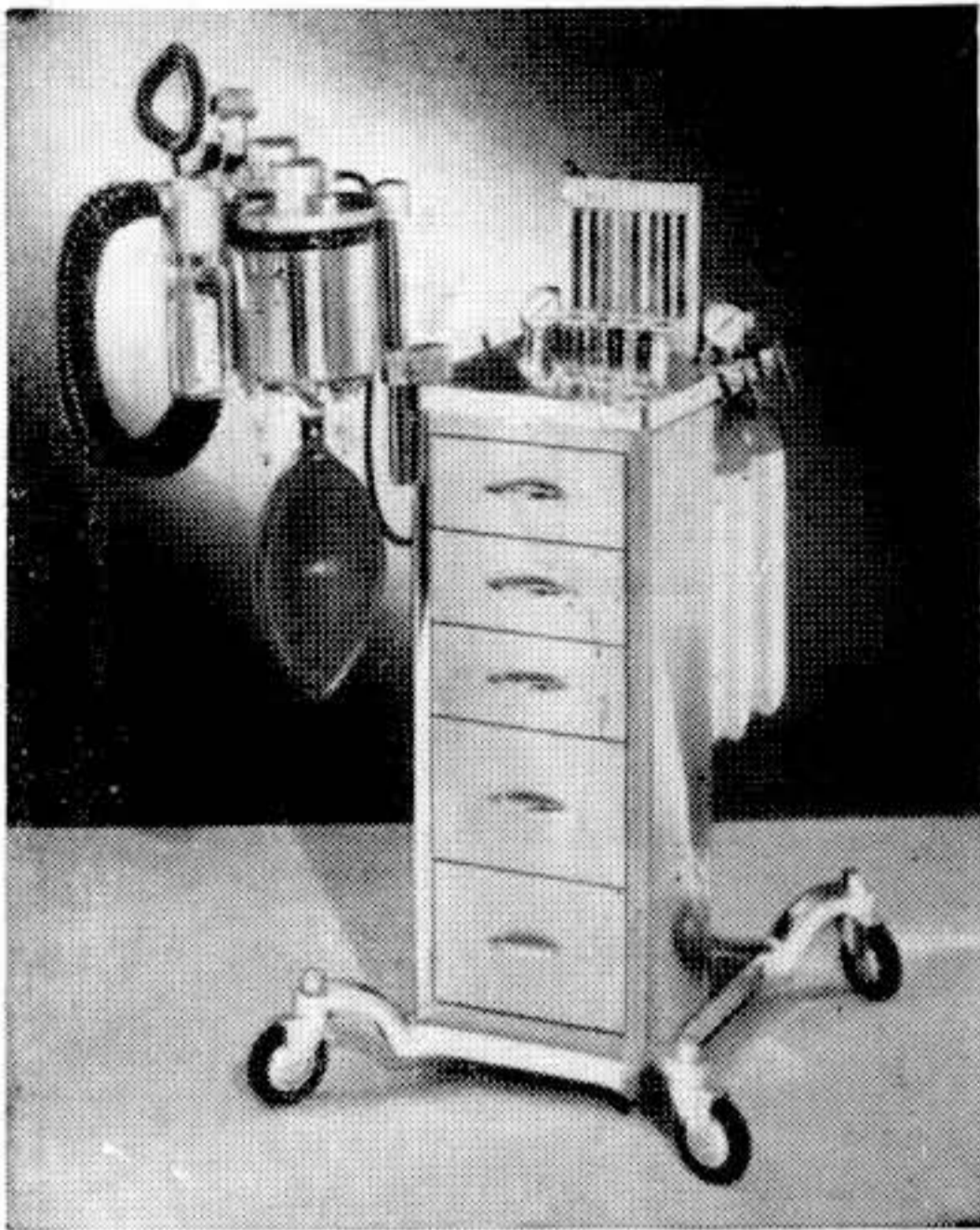
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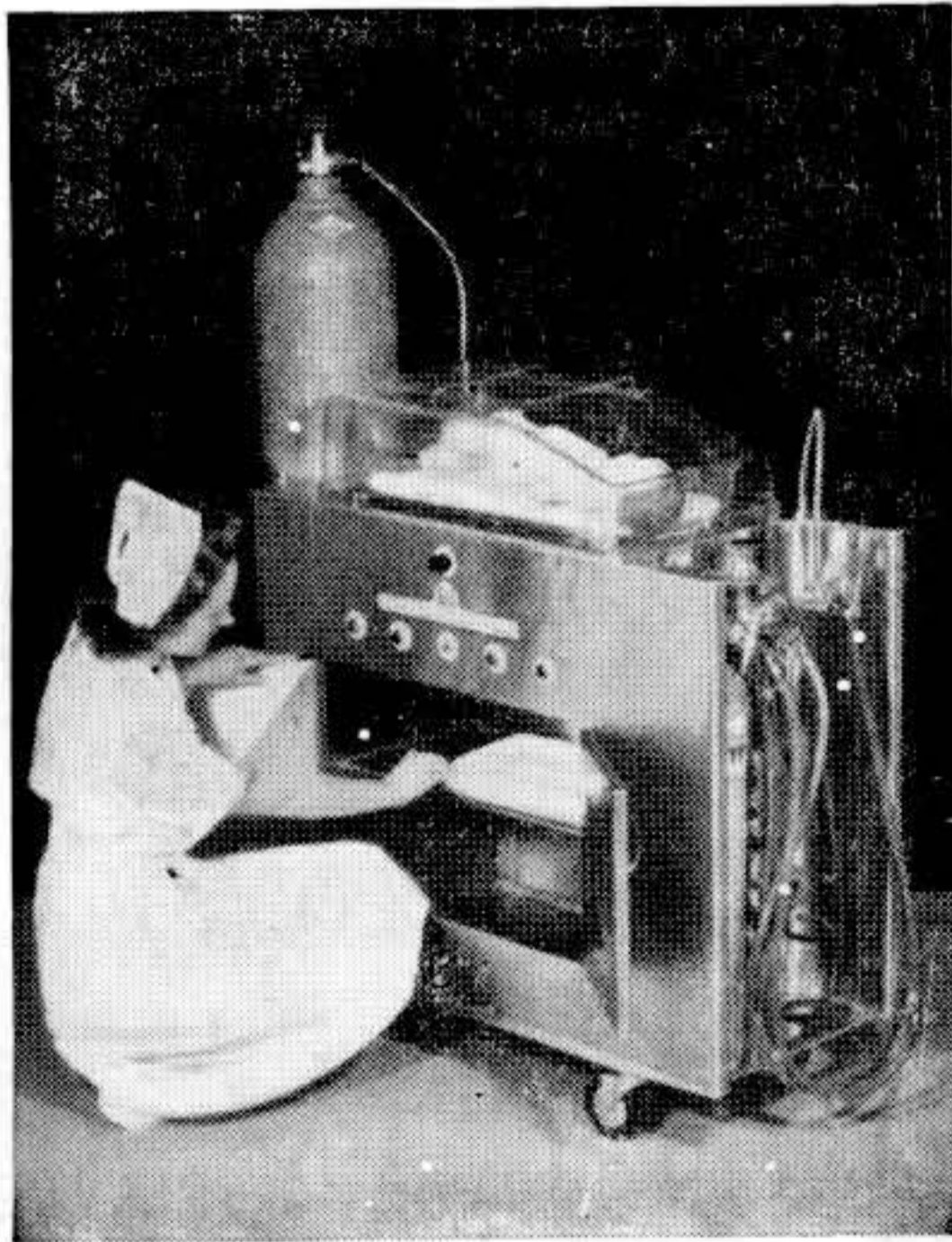
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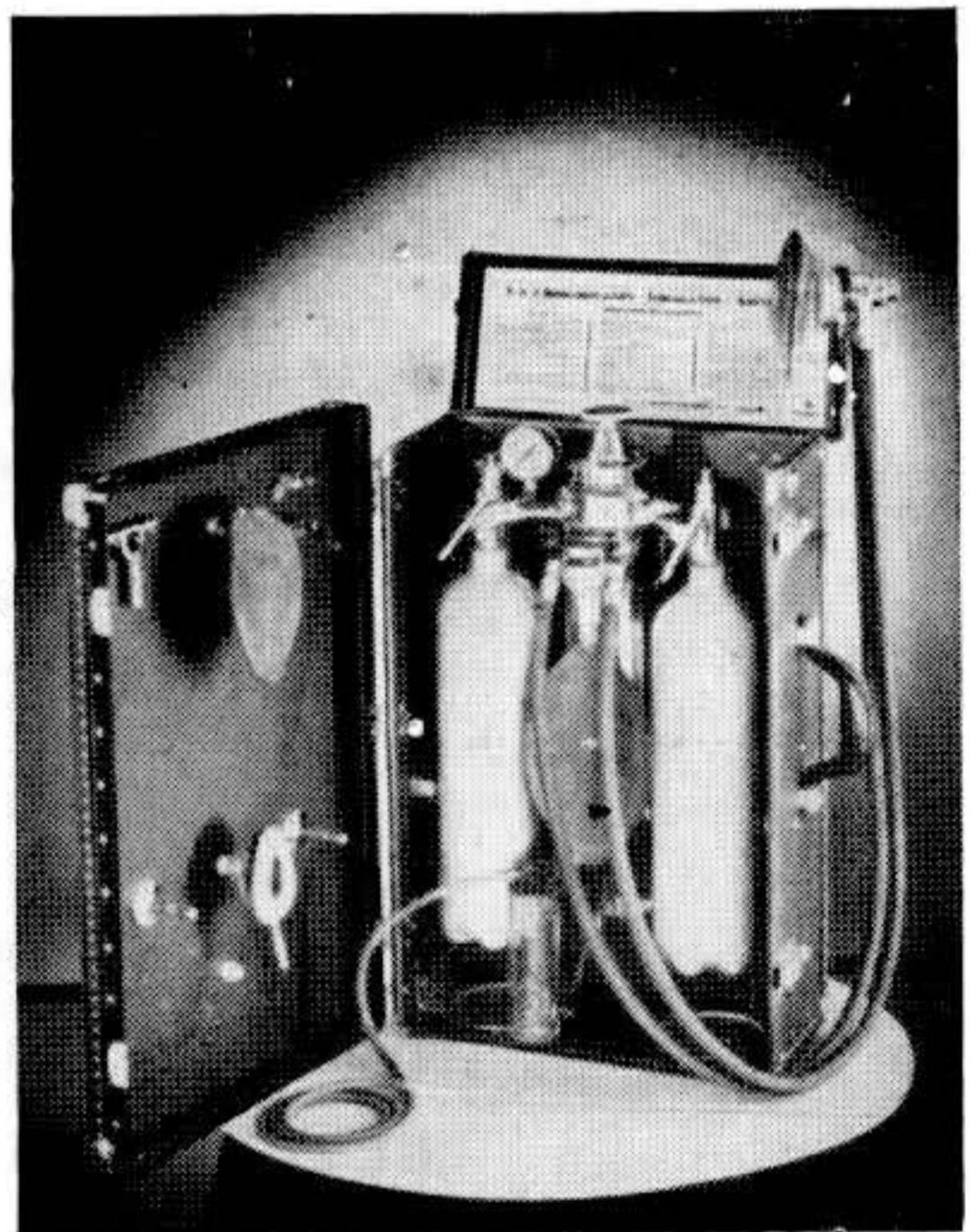
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