THE CARDIOVASCULAR EFFECTS OF AZEOTROPIC HALOTHANE-ETHER[1]

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THE AZEOTROPIC MIXTURE of halothane-ether was first described by Hudon, Jacques, and Boivin in 1958 (1–4). On the basis of their preliminary reports the mixture seemed to have sufficient advantages to merit extensive clinical and experimental investigation.

When this present study was undertaken, some clinical experience with the azeotropic mixture as an adjunct to nitrous oxide anaesthesia had been gained already in our institution (5). We had found the mixture more easily controllable than halothane and less depressing to cardiorespiratory function. Further clinical experience with azeotropic halothane-ether as a supplement to nitrous oxide has permitted us to discard calibrated vaporizers and to administer the mixture from the ether or trichlorethylene bottle of any standard anaesthesia machine. In long cases, we have found the azeotrope superior to trichlorethylene in that awakening is more rapid and cardiac irregularities have rarely occurred. Because of these apparent advantages a controlled study seemed indicated.

METHOD

Experiments carried out on seven healthy unpremedicated male volunteers were designed in a manner similar to that described in a previous communication (6). Cardiac output as well as peripheral and pulmonary artery pressures was measured and recorded, total peripheral and pulmonary resistances were calculated, vein-to-artery circulation time was determined, and the electrocardiogram and electroencephalogram were monitored and recorded.

At least two control cardiac output determinations were done and all control values were recorded. Control cardiac output measurements by the dye method were compared with simultaneous Fick determinations. Anaesthesia was induced with small doses of 2.5 per cent sodium thiopental until smooth maintenance of anaesthesia with the azeotropic mixture alone became possible. The mixture was administered from a Fluotec vaporizer in a semi-closed system using a 10 L./min. flow of oxygen. The concentration of the mixture was gradually increased until 3 per cent was reached. Thereafter, the concentration of the mixture was progressively increased still further by administering it from the copper kettle of a Foregger machine. If no significant changes occurred, the flow of oxygen was

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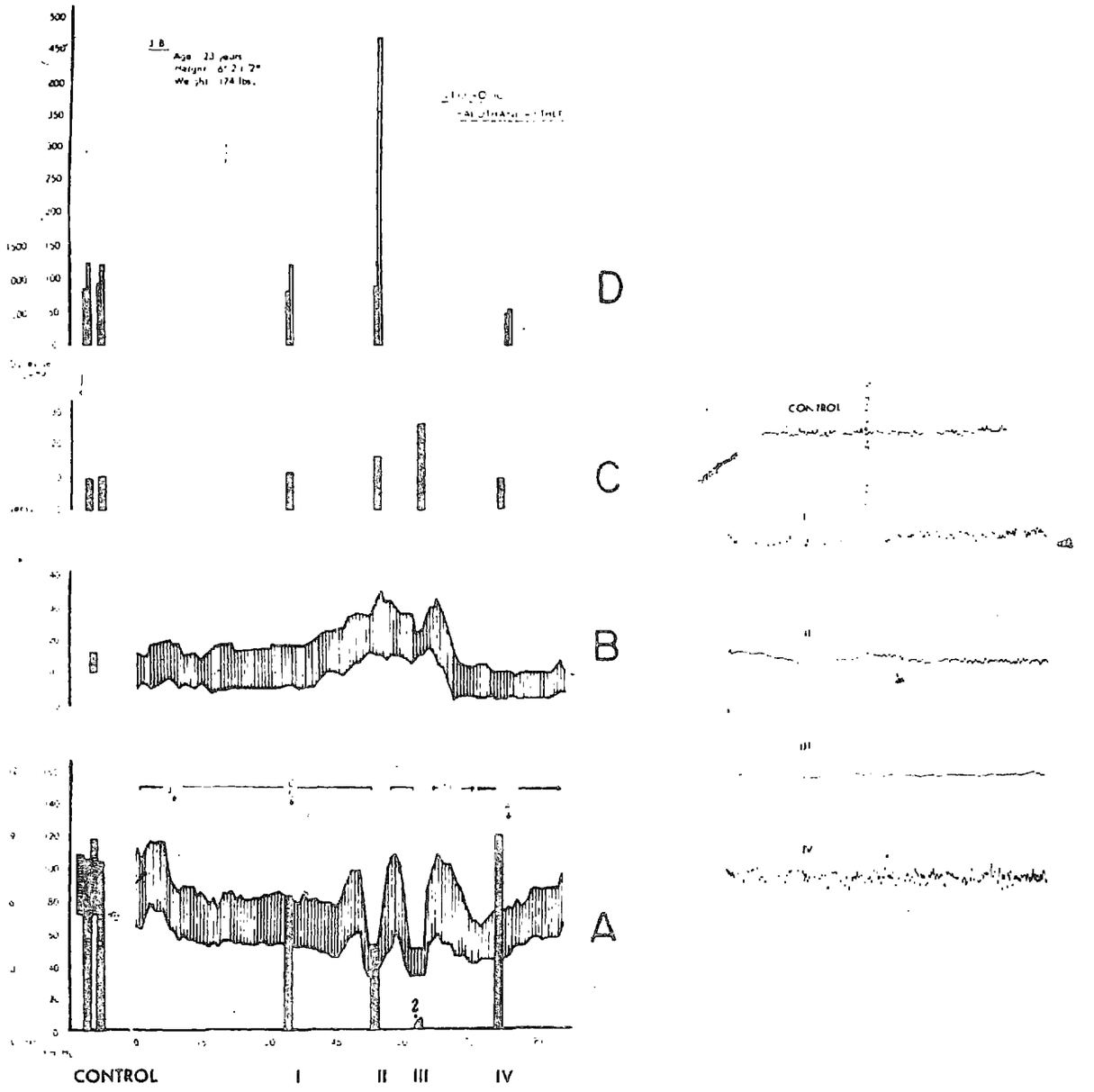

FIGURE 1. A. Systemic blood pressure in mm. Hg (pulse pressure shaded). Cardiac output (black bars) in L./min. Bracket denotes duration of administration of azeotropic halothane-ether. The time when 3% concentration was reached and when the copper kettle was introduced into the system is marked by "3%" and "CC" respectively. B. Pulmonary artery pressure in mm. Hg. C. Vein-to-artery circulation time in seconds. D. Total systemic resistance (black bars; scale on left) and total pulmonary resistance (white bars; scale on right); both in dynes/sec./cm.$^{-5}$. Numbers in the bottom line refer to the identically numbered E.E.G. tracing on the right.

risen to 9 L. with circulation time back to normal. At 465 and 53 dynes/sec./cm.$^{-5}$ respectively, both pulmonary and systemic resistances had fallen below control levels. The electroencephalogram at this time showed a pattern indicative of very light anaesthesia.

Case 2 (Fig. 2)

This was a 25-year-old healthy young man, 69½ in. tall, and weighing 146 lb. In this case, induction was very stormy and prolonged lasting 13 min. and requiring a total of 750 mg. thiopental and a high flow of oxygen through the copper kettle before induction was complete. At that time, the systemic blood pressure was almost identical to the control level, namely 135/82 mm. Hg, the pulmonary artery pressure having

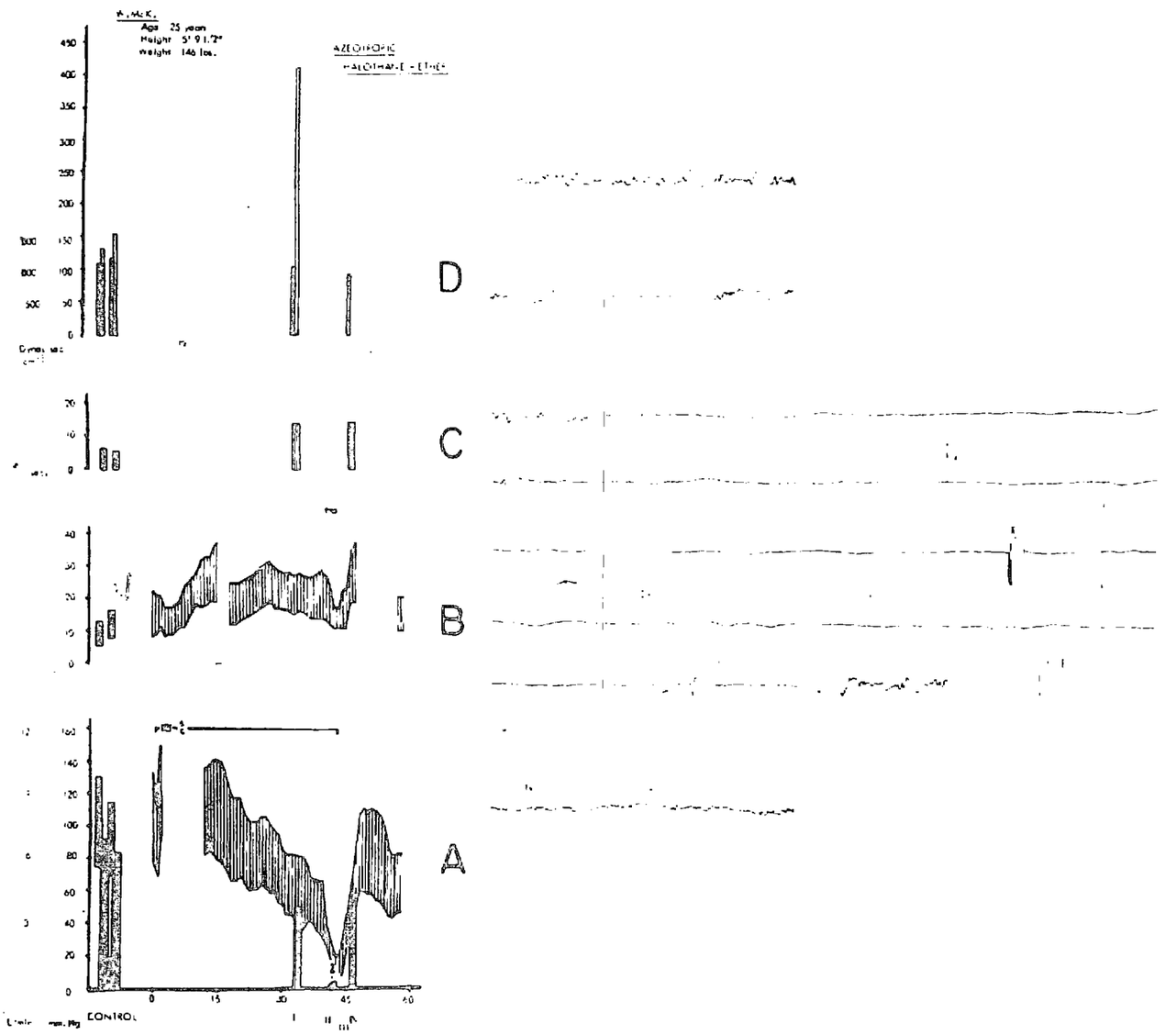

FIGURE 2. Same as Figure 1.

risen markedly to 33/18 mm. Hg presumably because of the very stormy induction. At the time induction was complete the patient had been on the copper kettle for 5 min. and within another 7 min. a gradual decline in systemic blood pressure took place, until 33 min. after the start of the experiment it had reached 82/46 mm. Hg. Pulmonary artery pressure was then 28/16 mm. Hg, a marked elevation over the control value of 17/9 mm. Hg. Cardiac output had fallen markedly to 3.7 L., the vein-to-artery circulation time was prolonged to 13 sec., but total peripheral resistance was not greatly changed. Total pulmonary resistance however, had reached 410 dynes/sec./cm.$^{-5}$. At this stage, every second breath was assisted and the electroencephalogram showed a pattern of moderate depth. After the output determination had been completed, respiration was controlled and quite soon there was a precipitous fall in systemic blood pressure to 42/27 mm. Hg and beyond, with a subsequent fall in pulmonary artery pressure to 17/11 mm. Hg 2 min. later. Cardiac output at that time could not be recorded because of the flat curve and the electroencephalogram showed a pattern of very deep anaesthesia with 8 sec. burst suppression. An electroencephalogram carried out immediately after the cardiac output determination had been completed showed complete burst suppression for 2 min., 25 sec., and the administration of the azeotropic mixture was discontinued and oxygen was administered. This was followed by a sharp rise in systemic and pulmonary artery pressures, a cardiac output of 4 L. being recorded with circulation time and peripheral resistance comparable to those previously established for

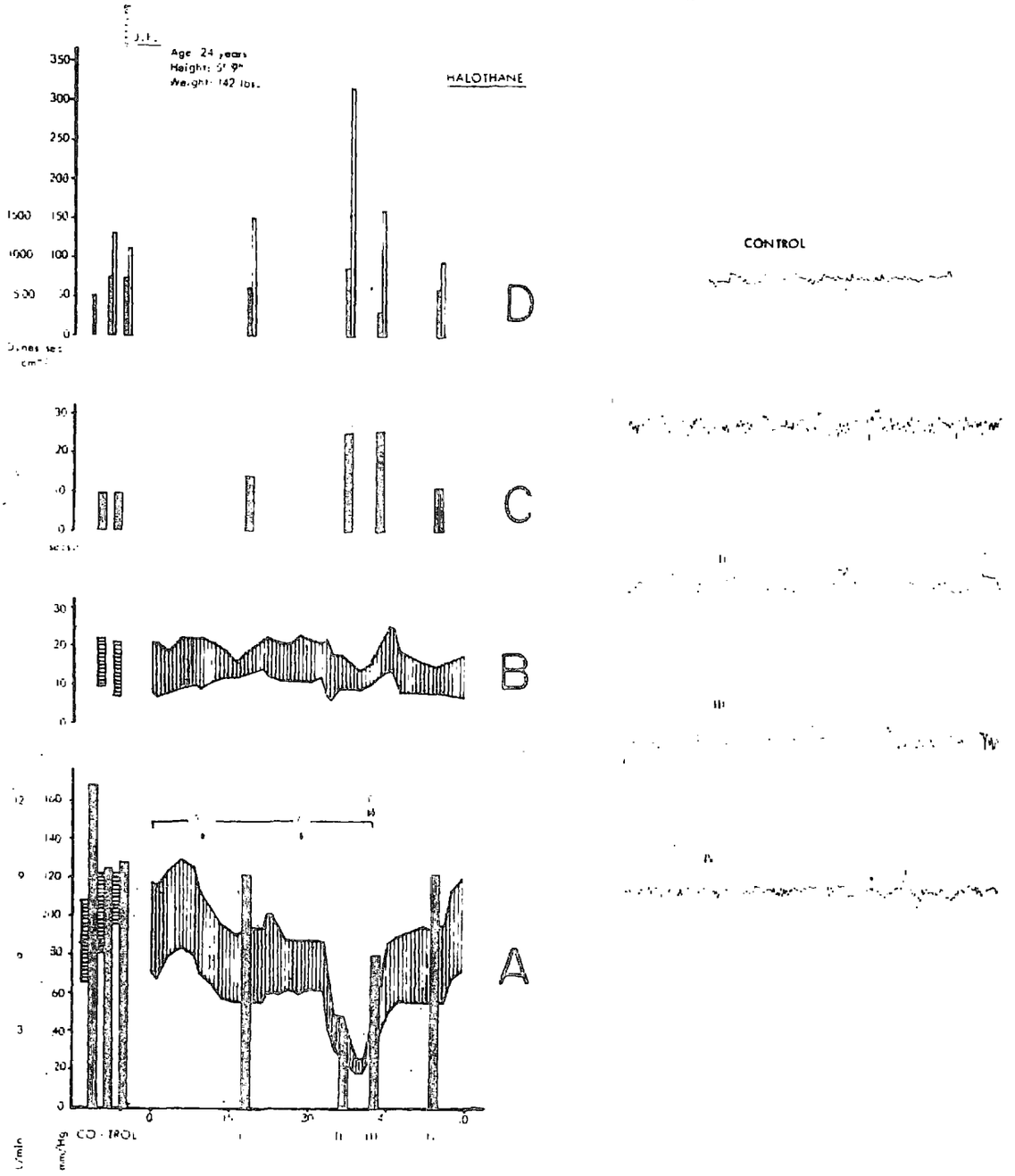

FIGURE 3. Same as Figure 1, but for azeotropic halothane-ether read "halothane." C: system closed; P: phenylephrine given.

a comparable systemic blood pressure. Systemic artery pressure continued to rise to 112/58 mm. Hg and then gradually declined to 83/45 mm. Hg towards the end of the experiment.

COMPARISON WITH HALOTHANE (6) AND DISCUSSION

In order to obtain profound hypotension with the azeotropic mixture, it had to be administered through a more potent vaporizer than the Fluotec. Indeed, the copper kettle was required in the "full-on" position and respiration had to be controlled before deep hypotension could be achieved. With halothane on the other hand, all that was required was a short period of controlled respiration in a closed system with the Fluotec vaporizer at 3 per cent to produce precipitous

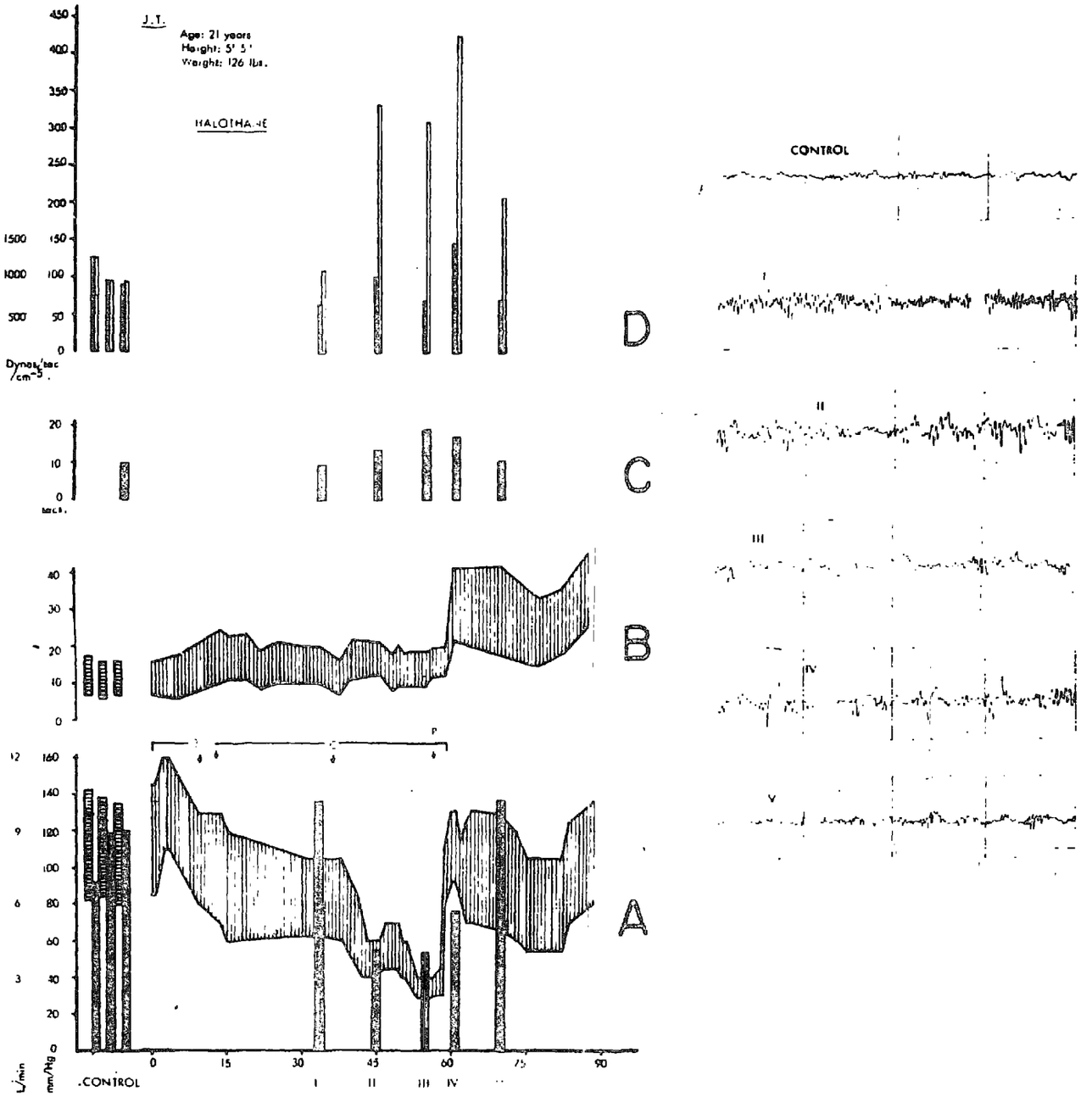

FIGURE 4. Same as Figure 3. S: succinylcholine 10 mg. given.

hypotension. In order to allow for comparison, two previously published tracings of the halothane experiment are reproduced with electroencephalograms added (Figs. 3, 4). From these tracings it is obvious that hypotension with halothane-ether occurs only when very deep anaesthesia is reached, and in that respect the mixture is comparable to ether. With halothane on the other hand, the electro-encephalogram shows relatively light anaesthesia at a time when equally profound hypotension is evident.

The changes in *cardiac output* under the azeotropic mixture are consistent with the degree of blood pressure fall obtained and thus parallel depth of anaesthesia (Fig. 5). Only during emergence from anaesthesia is this relationship not consistently maintained. In four instances high cardiac output is associated with persistent reduction of mean systemic blood pressure which indicates residual peripheral dilatation.

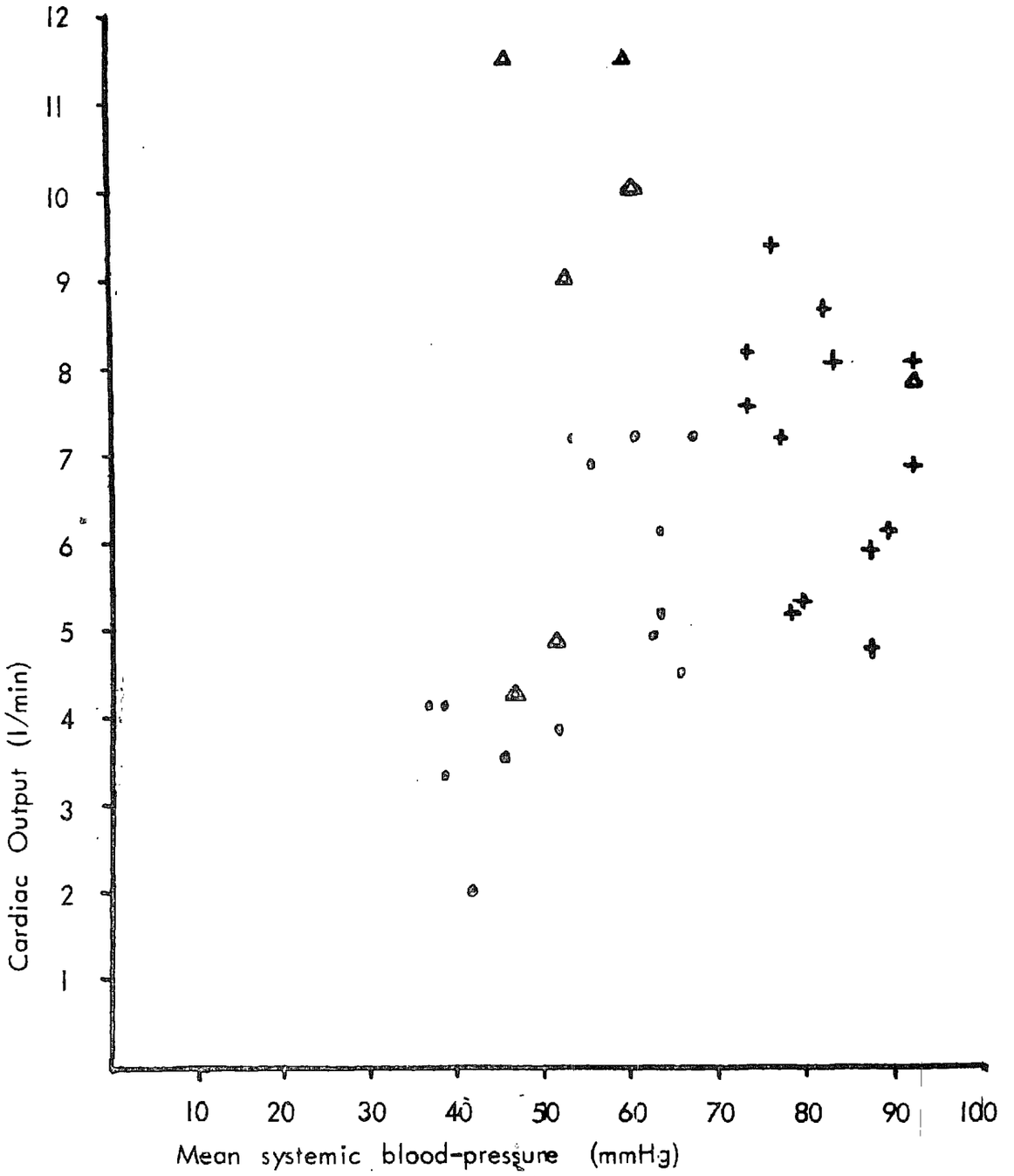

FIGURE 5. Scattergram relating mean systemic blood pressure to cardiac output under anaesthesia with azeotropic halothane-ether. +—control values; •—during maintenance; Δ—during emergence.

The prolongation of *vein-to-artery circulation* time is proportional to the cardiac output, although this prolongation is not quite as pronounced as with halothane anaesthesia. A rise of *pulmonary artery pressure* under halothane-ether is a consistent finding whereas this was not so under halothane alone. Under halothane anaesthesia there was a definite diminution of *peripheral resistance*, indicating peripheral vasodilatation as the plateau of mild hypotension was reached, but this is not evident with the mixture. However, the marked rise in *total pulmonary resistance* was found with both agents. The significance of this is not yet clear and further studies are now in progress in an attempt to elucidate this phenomenon.

The electrocardiogram revealed a split P wave once at the time when the blood pressure had reached its lowest level. Bigeminal rhythm developed twice and was corrected by the administration of procaine amide. Both times the incidence occurred in the presence of a normal blood pressure; in one case the highest concentration of the azeotrope from the copper kettle had just been attained. The experiment was discontinued and this case is not included in this series. The other case occurred on emergence with oxygen and on controlled respiration some 5 min. after discontinuance of the anaesthesia. Both subjects were being or had been exposed to greatly excessive concentrations of the anaesthetic.

Summary and Conclusions

Azeotropic halothane-ether has a less profound effect on the cardiovascular system than halothane alone. Consequently, less rigid control of vapour concentration is needed.

Following induction of anaesthesia, the blood pressure falls slightly to a plateau, where it tends to remain. Fall in cardiac output is proportional to the degree of hypotension. No significant changes in pulmonary artery pressure, vein-to-artery circulation time, total peripheral and total pulmonary resistance are evident at this stage. Further depression of systemic blood pressure occurs only when very deep anaesthesia is produced by deliberate overdosage. This is in marked contrast to the findings under halothane anaesthesia, where similar hypotension is associated with only moderate depth of anaesthesia. In this respect, the azeotropic mixture more closely resembles ether than halothane. Cardiac output falls to very low values as the systemic blood pressure reaches its nadir. Pulmonary artery pressure gradually rises during deepening of anaesthesia and as respiration requires assistance and later control. Vein-to-artery circulation time increases with increasing hypotension. No significant changes are apparent in the total peripheral resistance, but total pulmonary resistance rises greatly and, at the time of maximum hypotension, may be four times the control value.

During emergence from halothane-ether anaesthesia the relation of blood pressure to cardiac output is less strict than during maintenance. The development of bigeminal rhythm is a definite possibility if concentrations of the agent are grossly excessive. No significant electrocardiographic changes were observed at other times.

Résumé

Pour préciser les effets cardiovasculaires de l'halothane-éther azéotropique, nous avons fait des expériences sur sept volontaires masculins en santé et non prémédiqués.

Nous avons mesuré la pression sanguine pulmonaire et systémique, le débit cardiaque, le temps de circulation veine à artère et la résistance total périphérique ainsi que la résistance pulmonaire de la même façon que nous avons décrite dans une communication antérieure traitant des effets cardiovasculaires de l'halothane. Au cours de chacune des expériences, l'électrocardiogramme et l'électroencéphalogramme étaient en marche. Ces circonstances expérimentales nous permet-

tent de comparer l'anesthésie avec le mélange azéotropique halothane practiqué dans les mêmes conditions et de tirer les conclusions suivantes:

L'anesthésie au mélange azéotropique halothane-éther affecte moins le système cardiovasculaire que l'halothane seul. En conséquence, le mélange exige un contrôle moins rigoureux de la concentration de ses vapeurs. Toutefois, le mélange est moins puissant ce qui rend l'induction de l'anesthésie plus difficile, particulièrement chez les jeunes volontaires en santé et non prémédiqués employés pour cette étude.

Après l'induction de l'anesthésie, la tension artérielle tombe légèrement jusqu'à un plateau où elle a tendance à se maintenir. La diminution du débit cardiaque est proportionnelle au degré d'hypotension. A cette phase d'anesthésie, il n'apparaît pas de modifications importantes de la pression artérielle pulmonaire, du temps de circulation veine à artère, de la résistance périphérique totale ni de la résistance pulmonaire totale. Une chute plus marquée de la tension artérielle n'apparaît seulement lorsque nous produisons une anesthésie très profonde par un surdosage calculé. Cela représente un contraste frappant avec les résultats obtenus au cours de l'anesthésie à l'halothane où nous avons observé une hypotension semblable avec un niveau d'anesthésie plus superficiel. Sous cet angle, le mélange azéotropique ressemble plus à l'éther qu'à l'halothane. Le débit cardiaque tombe à des chiffres très bas lorsque la pression artérielle systémique atteint son nadir. Dans l'artère pulmonaire, la pression s'élève graduellement à mesure que s'approfondit l'anesthésie et que la respiration requiert de l'assistance et plus tard du contrôle. Le temps de circulation veine à artère s'allonge selon que s'aggrave l'hypotension. Il n'y a pas de modifications importantes de la résistance totale périphérique mais la résistance pulmonaire totale s'élève considérablement et, au moment de l'hypotension maxima, cette résistance peut quadrupler celle des témoins.

Durant le réveil de l'anesthésie halothane-éther, le rapport tension artérielle et débit cardiaque est moins rigoureux que durant le maintien de l'anesthésie. A l'électrocardiogramme, on n'observe que peu de changements importants même sous anesthésie profonde, ce qui fait un contraste avec les observations faites durant l'anesthésie à l'halothane. Si, pourtant, excessif grandes doses d'azéotrope sont administrées, c'est vraisemblablement que la rhythme bigeminie surviendrait.

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