EFFECTS OF ALTHESIN, ETOMIDATE AND FENTANYL ON HAEMODYNAMICS AND MYOCARDIAL OXYGEN CONSUMPTION IN MAN

D. Patschke, J.B. Brückner, H.J. Eberlein, W. Hess, J. Tarnow, and A. Weymar*

Cardiovascular depression on induction of anaesthesia is a common complication, especially in patients with impaired myocardial function. This disturbance of circulation is the result of one or more of reduced venous return following peripheral vasodilatation, negative inotropic effects, and an unbalanced ratio between myocardial oxygen demand and oxygen supply. The simultaneous effect of various intravenous induction agents upon haemodynamics, the inotropic state of the heart, coronary blood flow, and myocardial oxygen consumption in healthy individuals were studied by Sonntag and coworkers.[21,22,35,36] For their measurements, anaesthetic and haemodynamic steady state conditions were required. Such conditions were established by continuous infusion of the anaesthetics studied, or were taken for granted after the sharp exponential decline of the anaesthetic blood level following intravenous administration of the drug. However, since a steady state does not occur at induction, the purpose of this study was to explore the acute effects of some induction agents upon the cardiovascular system in man. Clinical dosages of the following drugs were scheduled for investigation.

The short-acting, non-barbiturate hypnotic etomidate,[19,23] the new steroid anaesthetic agent althesin,[6–8,31] and the short-acting narcotic fentanyl, which is frequently utilized as a sole anaesthetic in patients requiring open-heart surgery.

Methods

The investigations were performed in 15 patients undergoing general anaesthesia for urological surgery. Pre-operatively all patients were informed of the nature of the anaesthetic procedure and the haemodynamic measurements during anaesthesia. The age of the patients studied ranged from 38 to 74 years (average 61 years). All were ASA physical status I and II. None had a history or objective evidence of any cardiopulmonary or metabolic disease.

Premedication, consisting of meperidine 50–100 mg, promethazine 50 mg, and atropine 0.5 mg, was given intramuscularly one hour before induction.

Anaesthesia was induced with thiopentone 3.0 mg/kg (etomidate- and althesin group) and etomidate 0.5 mg/kg (fentanyl group) respectively. Tracheal intubation was facilitated with succinylcholine 1.0 mg/kg. Anaesthesia was maintained with 0.3 volumes per cent of halothane (etomidate- and althesin group) and 0.3 volumes per cent of isoflurane (fentanyl group) respectively in nitrous oxide and

*Department of Anaesthesiology, Free University of Berlin, Spandauer Damm 130, 1 Berlin 19, Federal Republic of Germany.

oxygen (ratio 2:1). Ventilation was controlled by an Engström respirator using a circle system with a soda-lime absorber. Normoxic and normocapnic conditions and acid-base equilibrium were controlled by repeated blood gas analyses.

An 18-standard wire gauge cannula was inserted percutaneously into the radial artery for monitoring arterial blood pressure and for blood sampling. An F7 SWAN-GANZ flow directed catheter was placed into the right antecubital vein by cutdown and advanced into the pulmonary artery, for measurement of pulmonary arterial and central venous pressure (CVP), and for the determination of cardiac output (CO) utilizing the thermodilution technique.[32] Using a modified Seldinger technique a catheter-tip-manometer (Milar PC 350) was inserted into the left ventricle through the femoral artery and connected to a Statham SP 1400 amplifier. The position of all catheters was confirmed by evaluation of the pulse pressure contour. The first derivative of the left ventricular pressure pulse (LV dp/dt) was obtained with a differentiating circuit. The lead II electrocardiogram (ECG) was monitored throughout the procedure. All pressures, dp/dt and ECG were continously recorded on a multichannel recorder (Hellige EK 21).

Derived variables were calculated as follows:

Total peripheral resistance (TPR) as dyn × sec × cm^{-5}.

$$TPR = \frac{(MAP - CVP) \times 80}{CO}$$

where MAP is mean arterial pressure, cardiac index (CI) by dividing CO by body surface area and stroke volume (SV) by dividing CO by heart rate (HR). HR was derived from the ECG-tracing. Since the product of HR and arterial systolic pressure[24,28] or the product of the square root of HR and the systolic pressure[2] allows only the evaluation of relative changes in myocardial oxygen consumption (LV $\dot{V}_{O_2}$), the new complex haemodynamic parameter developed by Bretschneider, *et al.*[3] was used for the quantification of LV $\dot{V}_{O_2}$. This haemodynamic parameter consists of five additive determinants (Table), each of which quantitatively represents the energy costs of defined activities of the working heart. This new concept takes into consideration that the myocardial energy demand is determined mainly by cardiac rate, ejection time, systolic blood pressure and velocity of contraction achieved by the left ventricle[1,4,33,34] and therefore requires the measurement of systolic pressure, left ventricular max dp/dt, heart rate, ejection time and systolic duration. The end-systolic volume per 100 g ventricle (ESV) was calculated using the formula for approximation[5]:

$$ESV = \frac{P_{syst}}{\sqrt{dp/dt\ max}} \times 11.$$

In animal experiments[20] a good correlation between the calculated LV $\dot{V}o_2$ using the complex haemodynamic parameter and the LV $\dot{V}_{O_2}$ conventionally measured (coronary blood flow × myocardial av-difference) could be proved in a wide range of circumstances. However, it should be mentioned that no attempt has been made to prove such a correlation in man so far.

Control measurements for the haemodynamic variables were made before surgical stimulation when the patients were in a circulatory steady state. Then a

TABLE I

$E_T = E_0 + E_1 + E_2 + E_3 + E_4$ (ml O_2/min × 100 g)

E_T = total left ventricular energy demand

$E_0 = c_0$ ($c_0 = 0.7$)
O_2-consumption of the resting heart in normothermia

$E_1 = t_{syst} \times n \times c_1$ ($c_1 = 0.3 \times 10^{-1}$)
O_2-consumption of the electrophysiological activity

$E_2 = P_{syst} \times \sqrt{ESV/100\ g} \times t_{eject} \times n \times c_2$ ($c_2 = 2.0 \times 10^{-4}$)
O_2-consumption for maintaining tension during the ejection phase

$E_3 = \max dp/dt \times n \times c_3$ ($c_3 = 1.2 \times 10^{-6}$)
O_2-consumption for generating tension during the isovolumetric phase

$E_4 = \max d^2p/dt^2 \times n \times c_4$ ($c_4 = 0.1 \times 10^{-7}$)
O_2-consumption for the inactivation of the contractile system

The complex haemodynamic parameter quantifying the myocardial oxygen consumption.
n = heart rate, t_{syst} = systolic duration, P_{syst} = systolic pressure, ESV = end-systolic volume/100 g left ventricle, t_{eject} = ejection time, max dp/dt = maximal rate of rise of left ventricular pressure, d^2p/dt^2 = second derivative of left ventricular pressure, $c_0 - c_4$ = experimental constants.

group of nine patients received etomidate 0.3 mg/kg and 20 min later althesin 0.075 ml/kg (=0.9 mg/kg of the stock solution) intravenously within 25 seconds. Etomidate can be presumed to be totally degraded into inactive metabolites after this interval.[19] In a second group of six patients fentanyl 0.01 mg/kg was administered. The circulatory response was followed for 10 minutes.

Specific comparisons were made using the Student's t-test for paired data. Values were considered significant at $P < 0.05$. The control values are presented as means ± SEM.

Results

Blood Pressure (Figure 1)

Figure 1 demonstrates in terms of percentage change from control the immediate effect of althesin, etomidate and fentanyl on the mean systemic pressure during a 10-minute interval after drug administration. While there was a sharp but short fall in blood pressure with althesin (control: 91.5 ± 5.0 mm Hg) by 24 per cent, fentanyl caused a delayed and more prolonged hypotension of the same order (control: 93.3 ± 5.7 mm Hg). The decrease in blood pressure after etomidate (control: 94.5 ± 4.8 mm Hg) was not of clinical significance.

Heart Rate (Figure 2)

Heart rate increased by 11 per cent after althesin, as compared to controls (64 ± 3 l/min), remained unchanged with etomidate (control: 67 ± 4 l/min) and decreased after fentanyl (control: 72 ± 5 l/min) by 18 per cent.

Cardiac Index (Figure 3)

A significant decrease in cardiac index was seen only after althesin (15 per cent) and fentanyl (13 per cent) as a result of diminished stroke volume and bradycardia respectively.

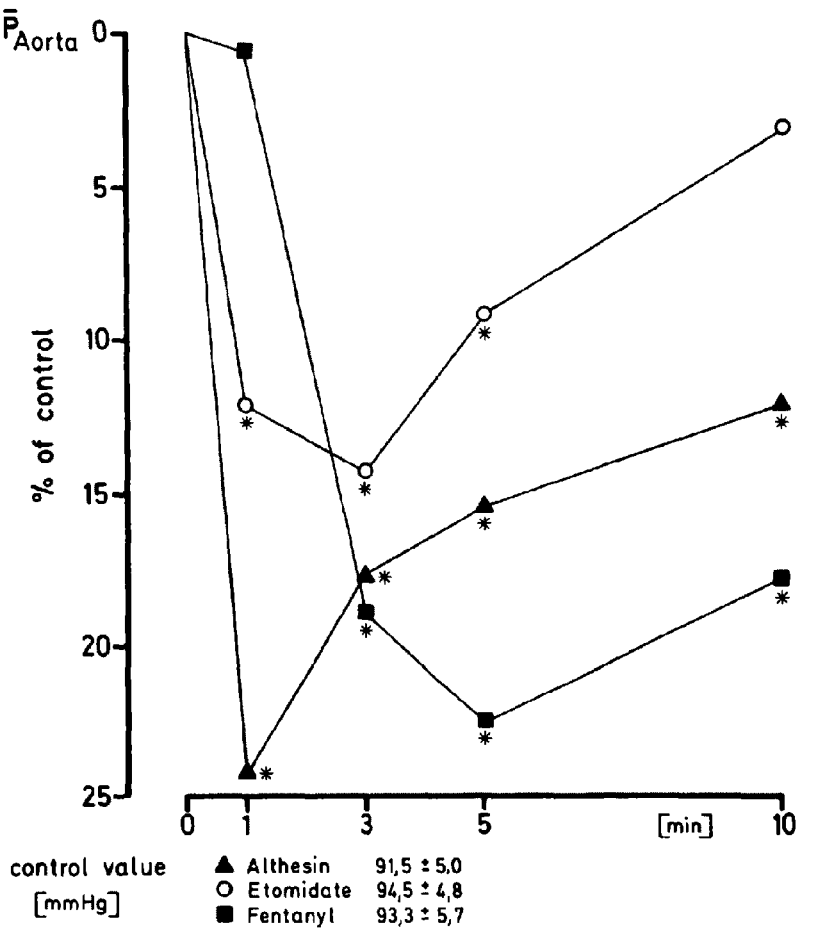

FIGURE 1. Change of mean arterial pressure ($\bar{P}_{Aorta}$) following injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

Total Peripheral Resistance (Figure 4)

While etomidate and fentanyl tended only to reduce the total peripheral resistance, althesin, by contrast, caused a marked vasodilatation of 32 per cent (control: 1686 ± 163 dyn × sec × cm^{-5}).

Left Ventricular max dp/dt (Figure 5)

The inotropic parameter LV max *dp/dt* decreased with all anaesthetics studied. While althesin (control 914 ± 55 mm Hg/sec) and fentanyl (control 1067 ± 76 mm Hg/sec) led to a fall in max dp/dt of approximately 20 per cent, the reduction in rate of rise of LV pressure was less than 10 per cent after etomidate (control 940 ± 85 mm Hg/sec).

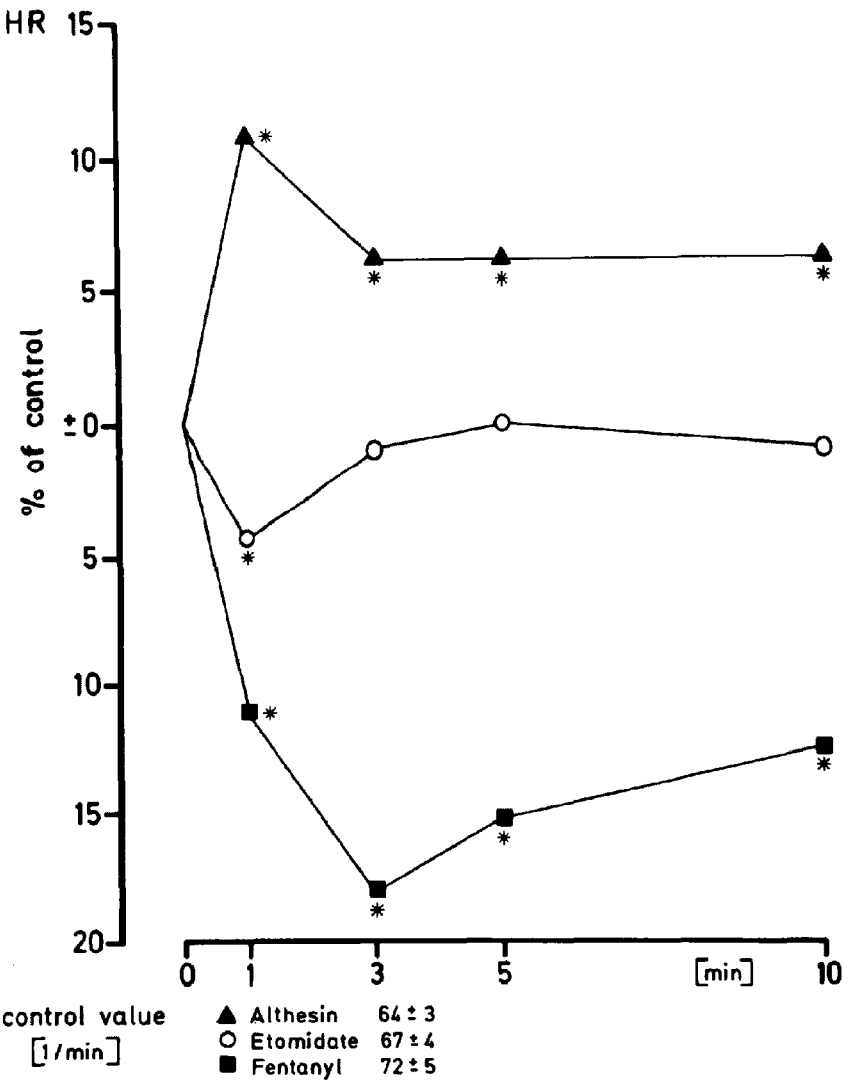

FIGURE 2. Change in heart rate from control following the injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

Myocardial Oxygen Consumption (Figure 6)

The calculated oxygen consumption of the left ventricle decreased with althesin (control 5.56 ± 0.70 ml O_2/min × 100 g) and etomidate (control 6.01 ± 0.89 ml O_2/min × 100 g) by approximately 14 per cent and tended to return to pre-injection level within the interval of observation. Fentanyl, however, reduced the energy demand of the heart (control 6.44 ± 0.77 ml O_2/min × 100 g) by more than 30 per cent during the same period.

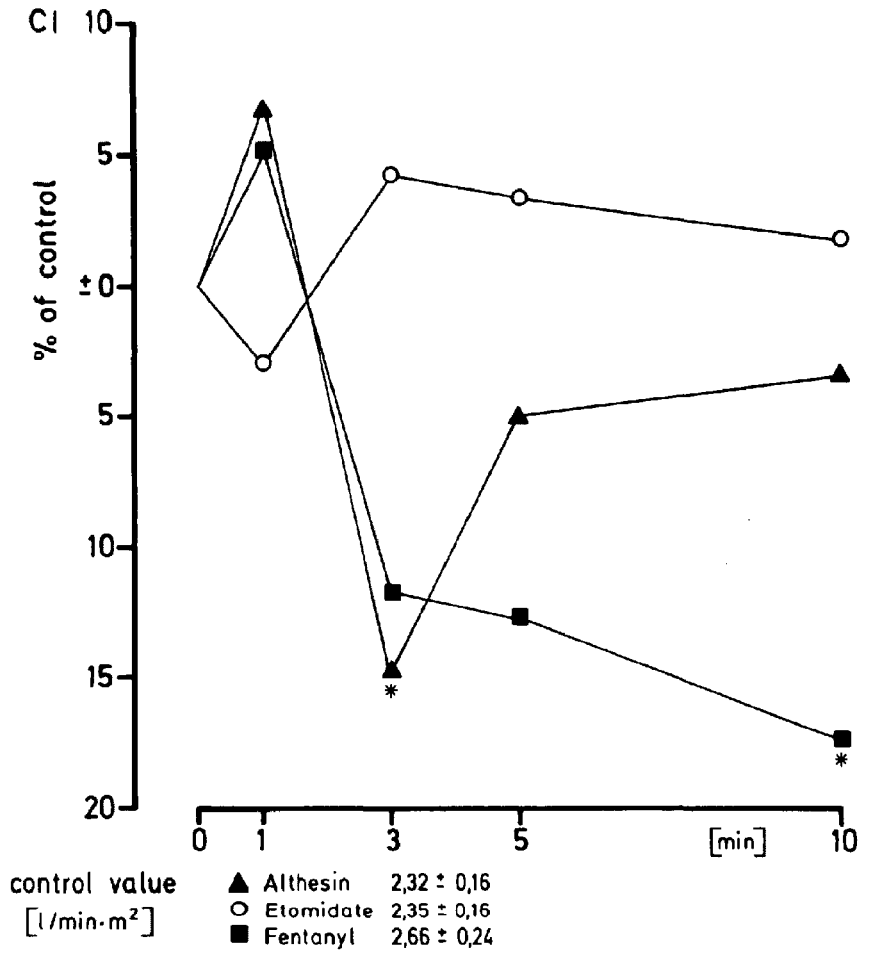

FIGURE 3. Change in cardiac index (CI) from control after injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

DISCUSSION

A quantitative comparison of the cardiovascular effects of the induction agents studied would have required standardized conditions. Although all our investigations were performed on basically healthy aged patients with isolated urologic disease, identical premedication, and normoventilation, thus avoiding any interference related to respiratory depression, the results can only be evaluated qualitatively for two reasons:

1) Halothane-nitrous oxide basic anaesthesia was used in the etomidate and althesin groups, whereas fentanyl had to be investigated under isoflurane base, becaues of a preceding circulatory study of isoflurane[39] and because such extensive monitoring of haemodynamic variables for research purposes could only be arranged occasionally in anaesthesia.

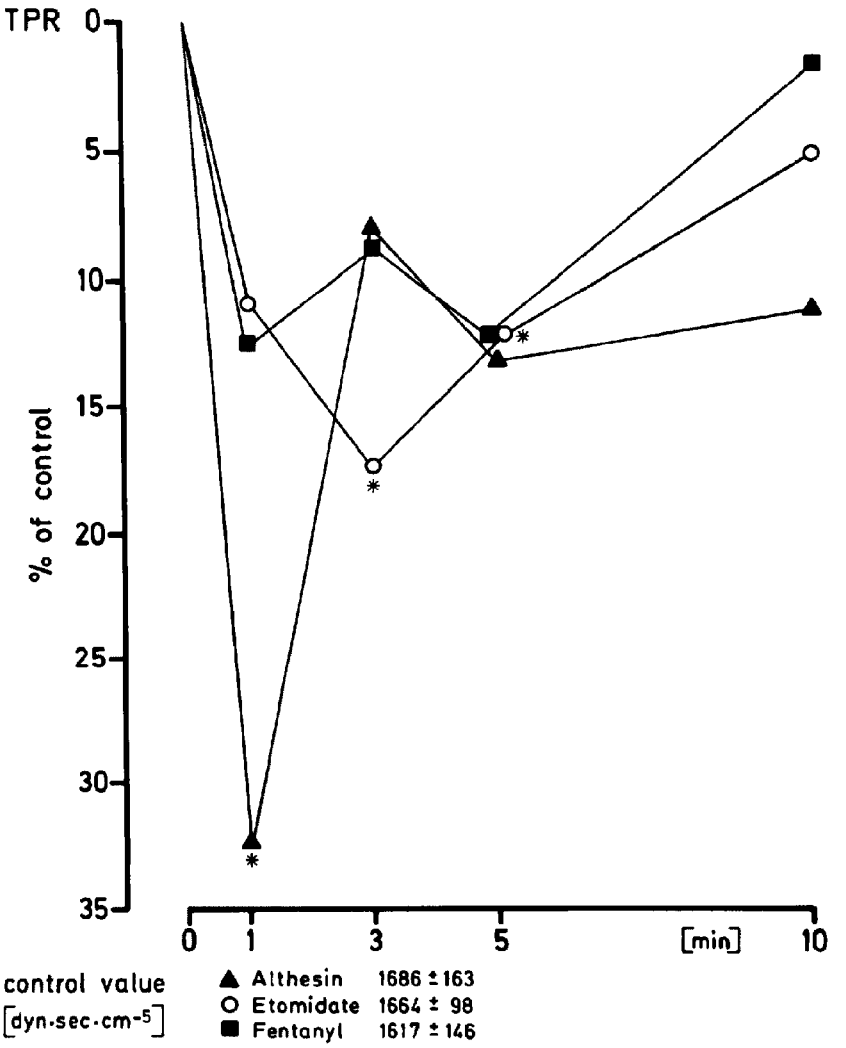

FIGURE 4. Change in total peripheral resistance (TPR) from control after injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

2) A comparative study implies equipotent dosages. While potency of inhalational anaesthetics is fairly well determined by the MAC values,[11] no convincing method of defining the potency of induction agents has been developed so far.[7] In our study therefore, we used clinical dosages of the anaesthestics investigated. Furthermore, the short-acting narcotic fentanyl is not generally accepted as an induction agent. However, since this drug is frequently used for induction and maintenance of anaesthesia, especially in patients with impaired myocardial performance, it was included in our study.

The control values revealed that the light basic anaesthesia caused no major

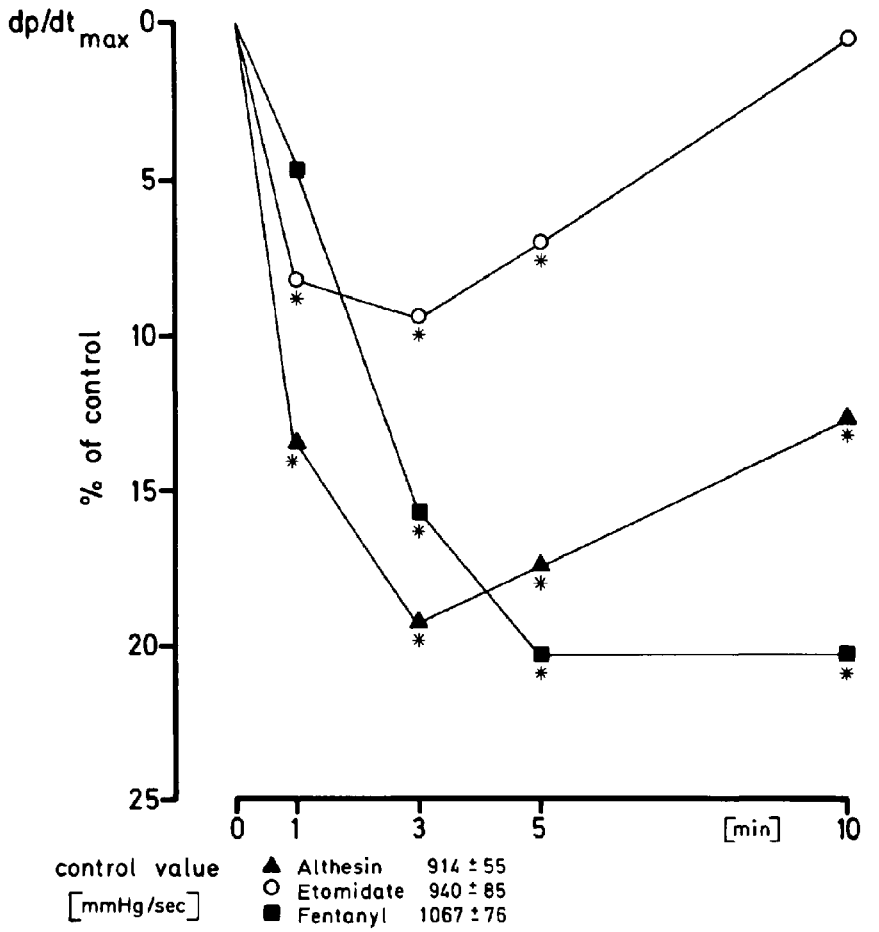

FIGURE 5. Change in left ventricular maximum dp/dt from control after injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

cardiovascular depression. Heart rate, cardiac index, maximum dp/dt of the left ventricle and myocardial oxygen consumption are believed to be in the low normal range for patients in this age group. However, we cannot entirely rule out a contribution of the basic anaesthesia to the observations reported.

Our study demonstrated an arterial hypotension with all induction agents under investigation. The fall in blood pressure after althesin was produced by a sharp reduction in total peripheral resistance due to vasodilatation resulting from diminished sympathetic tone,[29] from release of histamine[10] or from a direct effect on smooth muscle.[6] Despite a reflex tachycardia, probably mediated through baroreceptors,[6,29] there was no increase in cardiac output to compensate for peripheral vasodilatation and thus to stabilize arterial pressure. Our observations confirm the findings reported by Campbell, *et al.*,[6] Clark, *et al.*,[8] and Savege, *et al.*[30,31] and differ only in regard to the cardiac output from those made by Sonntag *et al.*[35] Similar but much less extensive changes were seen with etomidate,

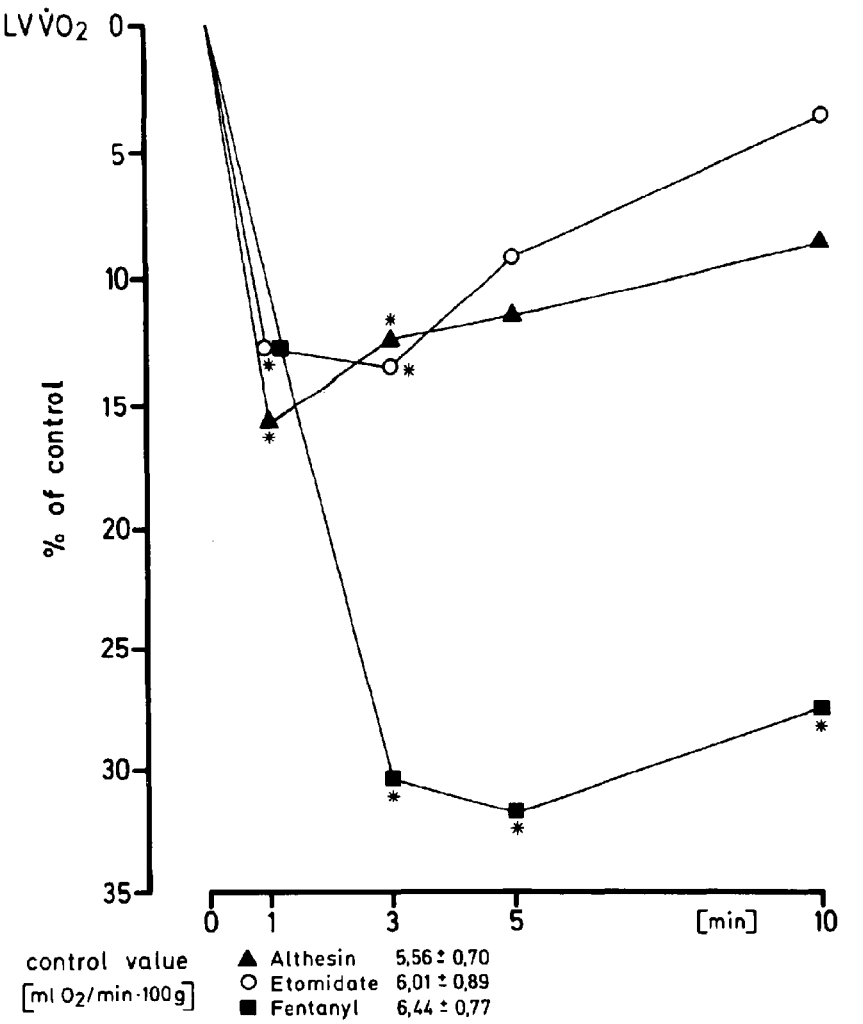

FIGURE 6. Change in oxygen consumption of the left ventricle (LV $\dot{V}_{O_2}$) from control after injection of althesin, etomidate, and fentanyl.
*Significant ($P < 0.05$).

corroborating the clinical and experimental work of Doenicke,[9] Hempelmann,[18] Kettler,[21] Morgan,[23] Weymar[40] and their co-workers. Hypotension after fentanyl was the result of decrease in cardiac output due to a slowing of heart rate, while the peripheral vascular resistance was only slightly affected. Bradycardia, a common observation after the administration of narcotics, is probably caused by central stimulation of the vagal cardio-inhibitory centre, leading to increased release of acetylcholine at cholinergic endings in the heart.[13] A direct negative chronotropic effect cannot be excluded, however. These findings suggest the use of atropine to prevent a heart-rate-dependent arterial hypotension with fentanyl.

When analysing the site of action of induction agents on systemic blood pressure,

myocardial depression must be kept in mind as a possible factor in hypotension, apart from the effect on peripheral vasculature. With regard to althesin, animal experiments suggest some negative inotropic effects.[13,15,17,27] However, conflicting data were reported from studies performed on man,[18,35,36] probably the result of different methods and of the difference in the physical status of the patients investigated. In the cases of etomidate[21,40] and fentanyl[14,25,36,37] there is unanimous evidence that these drugs do not or only slightly depress myocardial contractility. In our study we interpreted changes in the maximum rate of rise of the left ventricular pressure (max dp/dt) as changes in inotropism. However, max dp/dt is a reliable index for the characterization of myocardial contractility only if the loading conditions and the heart rate are taken into consideration simultaneously.[39] Since the increase in heart rate and the decrease in afterload (diastolic pressure) after althesin affected max dp/dt inversely and a change in preload (left ventricular end-diastolic pressure) was not seen from the left ventricular pressure tracing, the decrease in max dp/dt with althesin has to be understood as a moderate myocardial depression. On the other hand a negative inotropic effect of fentanyl could not be proved, as the bradycardia and the fall in afterload probably resulted in the observed decrease in max dp/dt. For the same reasons there is not sufficient evidence of myocardial depression after etomidate. Heart rate, systolic pressure, ejection time and the velocity of myocardial contraction are the main determinants of the metabolic demands of the heart.[1,4,33,34] The immediate decrease in arterial pressure, max dp/dt and with respect to fentanyl also in cardiac rate therefore diminished the oxygen consumption of the left ventricle after etomidate, althesin and fentanyl by 14 per cent, 16 per cent, and 32 per cent respectively. Considering that the Kettler and Sonntag team[21,22,35,36] did not study the acute effects, their results largely agree with our findings. These investigators found no change in the energy demand of the heart with etomidate and a slight decrease in neuroleptanalgesia (droperidol plus fentanyl) as compared with control values of the awake unpremedicated subject. However, animal studies[26] and the investigations in healthy man carried out by Sonntag, *et al.*[35] demonstrated an increase in myocardial oxygen consumption with althesin. The discrepancy with our results may be explained by species differences and by the fact that our patients were geriatric individuals and were basally anaesthetized, which might have modified the haemodynamic response to althesin. Thus the rise in heart rate, a major determinant of myocardial energy demand, was much more pronounced in the studies, mentioned above than in ours.

The following conclusions may be drawn from the present study: in patients without cardiovascular disorder the anaesthetics investigated seem to be useful drugs for induction of anaesthesia. However, patients suffering from diseases such as mitral stenosis or constrictive pericarditis, which restrict the cardiac output, are intolerant to sudden vasodilatation. Fatal arterial hypotension might occur if althesin was administered to such a patient. Although there was only moderate myocardial depression with althesin, the results seem to favour the use of etomidate or fentanyl in patients with myocardial insufficiency. Special attention should be focused on the ratio between myocardial oxygen demand and supply during induction. In patients with undisturbed coronary function the oxygen demand of

the heart is adequately balanced by the coronary blood flow autoregulated by means of intrinsic mechanisms.[16] In patients with restricted coronary reserve due to coronary atherosclerosis, however, the coronary blood flow depends mainly on a linear pressure-flow relationship. To discuss the clinical implications of our results for these patients, the myocardial oxygen consumption has to be correlated to the coronary perfusion pressure. After althesin the energy demand of the heart decreased by 16 per cent acutely, while the fall in diastolic blood pressure was more pronounced (24 per cent). On induction with althesin there is danger of an insufficient oxygen supply to the heart muscle and consequently anaerobic glycolysis may occur. A myocardial oxygen debt is believed not to occur with tomidate, since the decrease in myocardial oxygen consumption was paralleled with an identical fall in coronary perfusion pressure. In this regard fentanyl seems to be the safest of the anaesthetics studied, as the myocardial energy demand decreased by 32 per cent whereas the blood pressure fell only 23 per cent.

Summary

The acute effects of althesin, etomidate and fentanyl upon haemodynamics, myocardial contractility and oxygen consumption of the heart were studied in healthy premedicated patients (n = 15) lightly anaesthetized with N_2O–O_2 (ratio 2:1), 0.3 volumes per cent of halothane and isoflurane respectively. All individuals were ventilated at a normal level. The patients (n = 9) in the halothane group received etomidate 0.3 mg/kg and 20 minutes later althesin 0.075 ml/kg intravenously. In a second group of 6 patients on isoflurane fentanyl 0.01 mg/kg was given. Etomidate did not affect the cardiovascular system significantly.

While the decrease in blood pressure after althesin (24 per cent) was the result of a reduction in total peripheral resistance (32 per cent), hypotension associated with fentanyl (23 per cent) was caused by diminished cardiac output due to bradycardia (18 per cent). Load data, heart rate, and maximum dp/dt indicated moderate negative inotropic properties only of althesin. Using the complex haemodynamic parameter developed by Bretschneider the myocardial oxygen consumption was calculated. The energy demand of the heart decreased with etomidate, althesin and fentanyl by 14 per cent, 16 per cent and 32 per cent respectively.

It is concluded that the risk of cardiovascular depression at induction in patients with impaired myocardial performance and coronary insufficiency can be minimized with etomidate and/or fentanyl.

Résumé

Les effets aigus de l'althésine, de l'étomidate et du fentanyl sur l'hémodynamique, la contractilité myocardique et la consommation d'oxygène du cœur ont été étudiés chez 15 patients en bon état général, anesthésiés légèrement avec N_2O–O_2 (2:1) et 0.3 pour cent d'halothane, ou N_2O–O_2 (2:1) et 0.3 pour cent d'isoflurane. Tous ont été normoventilés. Les neuf patients anesthésiés à l'halothane ont reçu 0.3 mg/kg d'étomidate et 20 minutes plus tard 0.075 mg/kg d'althésine par voie

intra-veineuse, tandis que l'autre groupe de six patients anesthésiés à l'isoflurane a reçu 0.01 mg/kg de fentanyl.

L'étomidate n'a pas semblé affecter le système cardio-vasculaire de façon significative.

La diminution (24 pour cent) de la pression artérielle après l'athésine résultait d'une diminution (32 pour cent dans la résistance totale périphérique; l'hypotension observée après le fentanyl (23 pour cent) était attribuable à une diminution du débit cardiaque (technique de thermodilution) par bradycardie (18 pour cent). Les données de pré et post-charge, la fréquence cardiaque, le rapport dp/dt max, ont montré des propriétés inotropiques négatives modérées avec l'althésine seulement. Grâce au paramètre hémodynamique complexe développé par Bretschneider, on a pu quantifier la consommation du myocarde en O_2 : la demande énergétique du cœur a diminué avec l'étomidate, l'althésine et le fentanyl, soit dans l'ordre de 14 pour cent, de 16 pour cent et de 32 pour cent.

Nous concluons que le risque de dépression cardio-vasculaire à l'induction chez des patients à fonction myocardique comprise et porteurs d'insuffisance coronarienne peut être diminué avec l'emploi de l'étomidate et/ou du fentanyl.

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