HAEMODYNAMIC EFFECTS OF LABETALOL-INDUCED HYPOTENSION IN THE ANAESTHETIZED DOG

C. GUSTAFSON, I. AHLGREN, K.-F. ARONSEN AND B. ROSBERG

SUMMARY

Central haemodynamic changes and regional blood flow were studied using the microsphere technique, during labetalol-induced hypotension in dogs anaesthetized with pentobarbitone and fentanyl. Labetalol 15 mg kg⁻¹ decreased mean arterial pressure from an average of 88 mm Hg to 47 mm Hg. Mean pulmonary arterial pressure was unchanged. Cardiac output was reduced by decrease in stroke volume, while heart rate remained unchanged. Myocardial blood flow decreased approximately in parallel with left ventricular work. Perfusion of the brain and kidneys was unchanged.

Drugs used to induce hypotension and which act by effecting sympathetic ganglion blockade (such as trimetaphan camsylate and pentolinum) or by producing direct relaxation of vascular smooth muscle (such as sodium nitroprusside) may cause tachycardia.

Labetalol (Glaxo Laboratories) possesses both alpha- and beta-adrenergic blocking properties (Farmer et al., 1972). Its use in hypotensive anaesthesia has been reported by Scott and others (1978) and Cope and Crawford (1979) who obtained a satisfactory decrease in arterial pressure unaccompanied by tachycardia in patients anaesthetized with halothane. Changes in regional blood flow during deliberate hypotension with labetalol have not been reported. This study reports central haemodynamic changes and regional blood flow during labetalol-induced hypotensive anaesthesia in dogs.

METHODS

Nine healthy dogs (weight 12.5–17 kg; mean 14.5) were studied. Four animals were used only for labetalol dose–response studies. The dogs were deprived of food, but not water, for 12 h before the investigation.

The dose–response study was undertaken in dogs anaesthetized with pentobarbitone receiving mechanical ventilation of the lungs with 66% nitrous oxide in oxygen. Anaesthesia was maintained with a continuous infusion of fentanyl 0.015–0.02 mg kg⁻¹ h⁻¹. A catheter was placed in the aorta, via the femoral artery, for continuous monitoring of the arterial pressure. Labetalol was injected i.v. in repeated doses of 3 mg kg⁻¹ to produce a mean arterial pressure (m.a.p.) of 50 mm Hg.

Haemodynamic changes and regional blood flow. Seven to eight days before the study, a polyethylene catheter was implanted in the left atrium via a thoracotomy under pentobarbitone anaesthesia. The catheter was filled with heparinized saline, and its distal end closed and buried subcutaneously.

On the day of the study, the dogs were anaesthetized with pentobarbitone 25 mg kg⁻¹ and an infusion of fentanyl 0.015–0.02 mg kg⁻¹ h⁻¹. Each dog was placed supine and the lungs ventilated at a rate of 20 b.p.m. with 66% nitrous oxide in oxygen. The tidal volume was adjusted to produce $P_{A_{CO_2}}$, 5 kPa. The subcutaneous end of the left atrial catheter was retrieved and rinsed with saline. Catheters were placed in the aorta, inferior vena cava and pulmonary artery and the positions checked by fluoroscopy. Baseline measurements were taken approximately 1 h after inducing anaesthesia when a steady state was achieved. Measurements were made of (a) mean aortic and mean pulmonary arterial pressure; (b) cardiac output; and (c) regional flow measurements by injection of the first dose of $^{85}$Sr-labelled microspheres through the left atrial catheter.

Hypotension was then induced by injecting labetalol 15 mg kg⁻¹. Twenty minutes later, measurements (a) and (b) were repeated and a second dose of microspheres labelled with...
scandium-46 was injected. Samples for
determination of labetalol concentration in blood
were collected 1, 5, 15, 45 and 60 min after
injecting the drug. One hour after inducing
hypotension, the animals were sacrificed by
intracardiac injection of potassium chloride and
the organs were removed for radioactivity
measurements. Cardiac output (CO) was
determined by a thermodilution technique
(Fegler, 1954) using a Swan–Ganz catheter with a
thermistor at its tip (Forrester et al., 1972) and a
cardiac output computer. There were three
determinations during each period of
measurement, two before and one after the
injection of microspheres, and their mean value
was calculated.

Blood gases were analysed using a Radiometer
ABL-1 apparatus.

Left ventricular work (LVW) was calculated
from the product CO x m.a.p. (Shabot,
Shoemaker and State, 1977).

Calculation of distribution of blood flow.
Microspheres (15 ± 5 (SD) μm) were labelled with
the radionuclide strontium–85 or scandium–46 (3-
M Company, St Paul, Minnesota, U.S.A.) and
suspended in dextran. Aggregation was prevented
by one drop of Tween 20. Depending on the
activity of the microspheres, $4 \times 10^5$ to
$1 \times 10^6$ spheres were used for each injection.
The technique for measuring organ blood flow was
the same as that used in earlier investigations from this
laboratory (Ericsson, 1971; Ohlsson, 1971;
Ahlgren, 1976; Rosberg and Wulff, 1979) with the
following modifications:
(1) The infused activity was calculated from the
difference in activity of syringe before and after
the injection. The syringe was measured in a special
plastic holder 38 cm from the centre in a lead-
shielded scintillation detector with a 10 x 7.6 cm
thallium-activated sodium crystal.
(2) "Organ phantoms", made from polyacryla
m gel, containing known amounts of the radio-
uclides, were used to correct geometric errors.
The output of the detector was connected to a
gamma-spectrometer (Canberra scaler, model
818), with window-settings 420–580 keV
(strontium–85 and 750–1250 keV (scandium-
46).

The fractional distribution of each radionuclide
was calculated by dividing the activity in each
organ by the total activity of each radionuclide
injected. Individual organ blood flow was
calculated by multiplying the fractional value by
the cardiac output determined at each
measurement. The difference between the sum of
activities measured and the activity of the isotope
injected, was taken as carcass activity.

Labetalol concentration in plasma was
determined by the fluorimetric method according
to Martin, Hopkins and Bland (1976).

Statistical methods. Calculations were made of
the mean (M) and standard error of the mean
(SEM). Comparisons were made using Student's $t$
-test for paired observations. Degrees of signifi-
cance are marked as follows: *$0.05 > P > 0.01$,
**$0.01 > P < 0.001$; ***$P < 0.001$.

RESULTS
In the dose–response study, labetalol 15 mg kg$^{-1}$
reduced mean m.a.p. from 88 mm Hg to 50
mm Hg.

Haemodynamic data from the study of regional
blood flow are presented in table I. The injection

<table>
<thead>
<tr>
<th></th>
<th>Before injection</th>
<th>After injection</th>
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<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>88 ± 6</td>
<td>47 ± 2**</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial</td>
<td>16 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beat min$^{-1}$)</td>
<td>80 ± 14</td>
<td>85 ± 5</td>
</tr>
<tr>
<td>Cardiac output (litre min$^{-1}$ x 10$^{-3}$)</td>
<td>2020 ± 512</td>
<td>1190 ± 99*</td>
</tr>
<tr>
<td>Stroke volume (litre x 10$^{-3}$)</td>
<td>25.9 ± 3.9</td>
<td>14.0 ± 1.0**</td>
</tr>
<tr>
<td>LVW (J h$^{-1}$)</td>
<td>1472 ± 372</td>
<td>452 ± 54*</td>
</tr>
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of labetalol decreased mean m.a.p. from 88 mm Hg
to 47 mm Hg. Systemic arterial hypotension was
achieved almost immediately following i.v.
injection of labetalol. Thereafter, m.a.p. increased
continuously and reached 80% of the prehypoten-
sive value after 1 h. Mean pulmonary arterial
pressure and heart rate remained unchanged.

During hypotension, cardiac output (CO)
decreased ($0.05 > P > 0.01$) because of diminished
stroke volume. Left ventricular work was reduced
($0.05 > P > 0.01$). CO returned to the
prehypotensive value within 1 h.

The relationship between m.a.p. and labetalol
concentration during the study is shown in figure
1. The fractional distribution of CO and the
individual organ blood flow before and after injection of labetalol are shown in table II. There were no changes in the fractions delivered to heart and to kidneys. During hypotension, significant increases were found in the fractions delivered to brain, intestine, total liver and preportal area. The registered fraction of microspheres delivered to the lungs was significantly less during hypotension.

Myocardial blood flow decreased during hypotension. Individual blood flow to the other measured organs showed no significant changes.

**DISCUSSION**

The dogs in our study tolerated thoracotomy well and recovered rapidly. There were no signs of pleural bleeding at the time of necropsy.

The injection of microspheres did not cause cardiac arrhythmia or change in CO, systemic arterial pressure or heart rate. The microsphere technique has been shown to be valid for measuring blood flow distribution in different animals (Rudolph and Heymann, 1967; Neutze, Wyler and Rudolph, 1968; Kaihara et al., 1969), and the method is well established in our

| TABLE II. Fractional distribution of cardiac output and individual organ blood flow (mean ± SEM) before and after injection of labetalol 15 mg kg⁻¹ in anaesthetized dogs. †Including arterio-venous shunted microspheres from the systemic circulation. ‡Total flow (ml min⁻¹). *0.05 > P > 0.01; **0.01 > P > 0.001; ***P < 0.001 |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|
| | Before injection | Flow (ml min⁻¹ per 100 g) | | After injection | Flow (ml min⁻¹ per 100 g) | |
| | Fraction (%) | | | Fraction (%) | | |
| Brain | 1.5 ± 0.1 | 41 ± 5 | 2.2 ± 0.2** | 36 ± 3 |
| Heart | 4.8 ± 0.8 | 56 ± 9 | 4.5 ± 0.6 | 31 ± 4* |
| Lungs† | 32.0 ± 2.7 | | 8.5 ± 0.7*** | |
| Kidneys | 10.2 ± 1.5 | 228 ± 25 | 13.5 ± 1.1 | 176 ± 19 |
| Intestine | 8.4 ± 0.2 | 80 ± 11 | 13.8 ± 1.1*** | 74 ± 8 |
| Temporal muscle | 0.07 ± 0.01 | 3 ± 1 | 0.09 ± 0.04*** | 3 ± 1 |
| Liver (hepatic artery) | 2 ± 0.8 | | 2 ± 0.8 | |
| Derived values | | | | |
| Preportal area | 14.9 ± 1.4 | 234 ± 42‡ | 23.1 ± 0.8*** | 190 ± 29‡ |
| Total liver | 15.9 ± 1.3 | | 24.6 ± 0.6*** | |
| Carcass | 35.5 ± 1.9 | | 46.4 ± 1.3*** | |

The measurements in this study were performed during pentobarbitone and fentanyl anaesthesia. Pentobarbitone reduces CO and splanchnic and cerebral blood flow (Price, 1960). Priano, Traber and Wilson (1969) and Rosberg and Wulff (1979) found that prolonged pentobarbitone anaesthesia caused minimal further haemodynamic changes. Anaesthesia with fentanyl, droperidol and nitrous oxide is considered to maintain a stable cardiovascular function (Dobkin et al., 1970; Stoelting et al., 1975). The injection of droperidol and fentanyl to dogs anaesthetized with thiopentone, however, reduced CO because of a reduced heart rate (Irestedt and Andreen, 1979). In our study, fentanyl was administered as a continuous infusion to maintain a steady state during the measurements. Thus our results can be attributed to the action of labetalol.

Information on the pulmonary vascular response to induced systemic hypotension is conflicting. In anaesthetized dogs made hypotensive with sodium nitroprusside, Pace (1978) found an unchanged pulmonary arterial pressure. Contrary to this, Rowe and Henderson (1974), using similar conditions, demonstrated a decrease in pulmonary arterial pressure. In our study, pulmonary arterial pressure did not change after the administration of labetalol.

Following the injection of labetalol CO was significantly reduced. This agrees with the findings of Scott and others (1978) in patients anaesthetized with halothane. However, in our animals, CO diminished solely because of decreased stroke volume, while in patients, the decrease was entirely caused by decreased heart rate.

The fraction of CO delivered to the brain increased during hypotension, thus maintaining constant perfusion, which suggests that cerebral autoregulation is maintained during labetalol-induced hypotension.

Labetalol-induced hypotension did not change the fraction of CO distributed to the heart. As CO decreased during hypotension, the myocardial blood flow was reduced by 45%. However, LVW decreased simultaneously by 69%. This is in agreement with Allela and colleagues (1955) and Berne (1964), who found coronary blood flow to be regulated primarily by cardiac work and only secondarily by CO.

The microspheres distributed to the lungs represent the sum of the flow through the bronchial arteries and systemic arterio-venous (a–v) shunting. In our study using 15-µm microspheres, the initial value representing steady-state fentanyl anaesthesia was 32% of CO. The fraction of spheres distributed to the lungs differs in various studies. Lopez-Majano, Rhodes and Wagner (1969) investigated a–v shunting in the hind legs of dogs anaesthetized with pentobarbitone. Using human albumin microspheres (20–40 µm diameter), they demonstrated shunt fractions ranging from zero to almost 60%, with higher values for the smaller spheres. Kaihara and others (1968) using 15-µm spheres, showed an increase in the fraction of spheres trapped in the lungs from 2.6% to 17.4% during anaesthesia. Ohlsson (1971) found that, with simultaneous injection of 15-µm and 50-µm spheres to pentobarbitone-anaesthetized dogs, 10.5% of the smaller spheres and only 4% of the larger were trapped in the lungs. Rosberg and Wulff (1979), using 15-µm spheres, found 14.8% of the injected activity in the lungs during pentobarbitone anaesthesia. Ohlsson (1971) concluded that anaesthesia induce mainly peripheral shunting, since the trapping of spheres in the liver did not change.

In our study, the effect of fentanyl on peripheral a–v shunting is added to the pentobarbitone effect. Labetalol hypotension significantly reduced the fraction of spheres distributed to the lung. This indicates a decrease in a–v shunting in line with the findings in animals with haemorrhagic hypotension (Rosberg and Wulff, 1979). However, in labetalol-induced hypotension, the fraction of CO delivered to carcass (skin, bone and muscle) was significantly increased, while it was decreased after haemorrhage.

Blood flow to the kidneys before and during hypotension did not undergo any significant change. Wang, Lin and Katz (1977) compared the effects of hypotension induced with sodium nitroprusside (SNP) and trimetaphan camsylate (TMP) on renal haemodynamics in dogs. They found that TMP decreased renal blood flow, while SNP produced no change. Behnia, Siqueria and Brunner (1978) found a transient decrease in creatinine clearance with diuresis during SNP-induced hypotension in patients anaesthetized with halothane. When the hypotension was reversed, the values returned to normal.
The gastrointestinal tract, preportal area and liver received a greater fraction of CO during hypotension, thus maintaining the same perfusion before and after labetalol injection. This agrees with the suggestion of Edwards and Flemming (1975) that vasodilator agents, such as SNP or ganglionic blockers, might diminish the reduction in splanchnic flow usually associated with decreased arterial pressure and concomitant increased sympathetic tone.

One must be cautious in applying the results of our study to man. The doses of labetalol needed to establish arterial hypotension in dogs anaesthetized with pentobarbitone and fentanyl were much larger than those used in earlier studies in man (Scott et al., 1978; Cope and Crawford, 1979). In spite of these high doses, however, haemodynamic changes were minimal and perfusion was well maintained.

ACKNOWLEDGEMENTS
This study was supported in part by Glaxo Läkemedel AB, Gothenburg, Sweden. We are grateful to Dr Roy Hansson, M.D. and Mr Frank Tietz, Department of Clinical Chemistry, Växjö Hospital, for analysing the labetalol concentration in plasma. We are also grateful to Mrs Christina Lindqvist for skilful technical help and to Mrs Karin Månsson for typing the manuscript.

REFERENCES
EFFETS HEMODYNAMIQUES DE L'HYPOTENSION PROVOQUEE PAR LE LABETALOL SUR DES CHIENS ANESTHESIES

RESUME
On a étudié à l'aide de la technique des microsphères les variations hémodynamiques centrales et le débit sanguin régional pendant une hypotension provoquée par le labetalol sur des chiens anesthésiés à l'aide de pentobarbitone et de fentanyl. Le labetalol à raison de 15 mg kg⁻¹ a fait baisser la pression artérielle moyenne de 88 mm Hg à 47 mm Hg. La pression pulmonaire artérielle moyenne est restée sans changement. Le débit cardiaque a été réduit par la diminution du volume systolique, alors que la fréquence cardiaque restait sans changement. Le débit sanguin du myocarde a diminué à peu près parallèlement au travail du ventricule gauche. La perfusion du cerveau et des reins est restée sans changement.

HÄMODYNAMISCHE WIRKUNGEN EINER DURCH LABETALOL HERVORGERUFENEN HYPOTENSION BEIM NARKOTISIERTEN HUND

ZUSAMMENFASSUNG
Zentrale hämodynamische Veränderungen und der regionale Blutfuss wurden während einer durch Labetalol bewirkten Hypotension bei Hunden studiert, die mit Pentobarbiton und Fentanyl narkotisiert waren. Labetalol 15 mg kg⁻¹ senkten den mittleren arteriellen Druck von durchschnittlich 88 mm Hg auf 47 mm Hg. Der mittlere Lungenarteriendruck blieb unverändert. Das Herzminutenvolumen wurde durch Absinken des Schlagvolumens reduziert, während die Herzfrequenz unverändert blieb. Der Myokardblutfuss sank etwa parallel mit der Tätigkeit der linken Kammer. Perfusion von Gehirn und Nieren blieb unverändert.

EFECTOS HEMODINAMICOS DE LA HIPOTENSION INDUCIDA MEDIANTE LABETALOL EN EL PERRO ANESTESiado

SUMARIO
Durante la hipotensión inducida mediante labetalol en perros anestesiados con pentobarbitona y fentanilo se estudiaron los cambios hemodinámicos centrales y el flujo regional de sangre, usando la técnica de la microesfera. 15 mg kg⁻¹ de labetalol disminuyeron la presión media arterial desde un promedio de 88 mm Hg hasta 47 mm Hg. La presión media de las arterias del pulmón no varió. La producción cardíaca se redujo mediante una disminución en el volumen del latido al tiempo que el ritmo cardíaco no varió. El flujo miocardial de sangre disminuyó paralelamente al funcionamiento del ventrículo izquierdo. La perfusión del cerebro y de los riñones no varió.