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Balanced Alpha/Beta Blockade of Adrenoceptors

A rational therapeutic concept in the treatment
of hypertension and coronary heart disease

Balancierte Blockade von Alpha- und Beta-Adrenozeptoren

Ein rationales Konzept zur Behandlung der
Hypertonie und der koronaren Herzerkrankungen

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Clinical Pharmacology of Labetalol in Elderly Hypertensives

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Introduction

Most estimates suggest that approximately one half of all drugs prescribed are intended for those over 60 years of age. Furthermore, this group bears the brunt of adverse reactions, perhaps due in part to the disproportionately large volume of prescribing. In addition, however, there are many differences both in pharmacokinetics and pharmacodynamics of drugs in the elderly, and while the pharmacokinetics alterations with ageing have been reasonably well described changes in pharmacodynamics are poorly understood. Sensitivity to drugs is thought to be increased in some cases e.g. those acting on the central nervous system and anticoagulants but responsiveness is decreased with other drugs such as beta adrenoceptor blocking drugs and agonists.

In the present work we have examined the pharmacokinetics of labetalol in the elderly and in addition have examined the blood pressure lowering and renal haemodynamic effects of this drug in elderly hypertensives. In order to carry out this work we initially had to devise an assay for the drug and we describe this also.

Assay of Labetalol

Most published studies in which measurement of plasma labetalol concentrations have been employed have used a spectrofluorometric technique [1]. More recently a high performance liquid chromatographic assay for labetalol has been described [2]. Since labetalol competitively antagonizes both alpha and beta adrenoceptors and since its metabolites in man are inactive [3], a radioreceptor assay might provide a sensitive and specific method for its estimation in biological materials. We have developed such an assay, based on the ability of labetalol, extracted from plasma, to inhibit the binding of ³H dihydroalprenolol (DHA) to beta adrenoceptors.

A cardiac membrane preparation served as the source of beta adrenoceptors. A fresh sheep's heart was sliced and homogenized in 4 volumes of Hanks Balanced Salt Solution (HBSS). The homogenate was centrifuged at 2,000 g for 5 min and the supernatant filtered through two layers of muslin. The filtrate was centrifuged at 30,000 g for 30 min. The resulting pellet was washed and resuspended in HBSS. This was then divided and placed in glass screw-capped bottles. All the above steps were carried out at 4 °C. The stock preparations were stored at -80 °C and remained usable for at least 6 months.

Samples of plasma (0.5 ml or 1 ml) were made alkaline by adding an equal volume of normal ammonia solution and labetalol extracted by shaking with 5 ml diethyl ether for 10 min. The specimens were centrifuged to separate the phases, 4 ml of the organic layer removed and evaporated to dryness in glass conical bottomed tubes. Dried extracts were reconstituted with 300 μ l of HBSS and used directly in the binding assay. To each tube were added 100 μ l of HBSS containing 0.6 pmole of DHA (102 Ci/mmole) and 100 μ l of HBSS containing 10 mg cardiac membranes. These amounts were chosen to result in binding of 10–20 % of added radioactivity, producing of the order of 4,000 counts/min in the zero calibration standard. Tubes were vortex-mixed and incubated at

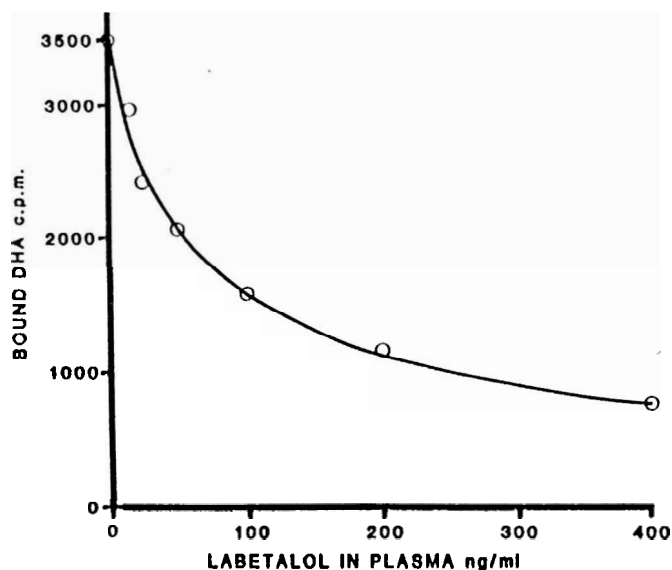


Fig. 1
Binding of ^3H DHA to cardiac membranes versus concentration of labetalol in plasma (Ref. [30]).

room temperature for 30 min. The incubation was ended by adding 2 ml ice-cold buffer with immediate filtration through Whatman GFC filters. After washing, the radioactivity in the filters was determined by liquid scintillation counting in a Triton X100/toluence-based cocktail. Calibration standards containing labetalol in the concentration range 0–400 ng/ml were carried through the same procedure on each day and a typical calibration curve is illustrated (Fig. 1). All samples were assayed in duplicate. The useful range of the assay was 5–400 ng/ml using 0.5 ml plasma specimens.

Labetalol Pharmacokinetics in the Elderly

Labetalol is subject to presystemic metabolism by the liver [4]. Its oral bioavailability accordingly varies widely with resulting large variations in blood concentrations after oral administration [5, 6]. We have examined the effects of age on the bioavailability and elimination of labetalol.

Observations were made in ten, drug-free mild-to-moderate hypertensive patients. The study had previously been approved by the Hospital Ethics Committee and each patient gave informed consent. Labetalol was administered to each person on two occasions,

once orally and once intravenously. The doses were administered in random order, separated by at least one week. The oral dose was 200 mg except in the two oldest and one young subject, when 100 mg was given. Three subjects received an intravenous dose of 1 mg/kg and 0.5 mg/kg was given to the remaining seven. Blood samples for estimation of plasma labetalol concentrations were taken over a period of 11 hours following administration of the drug. The plasma specimens were stored at -20°C prior to assay by the radioreceptor method described above. From the results for each patient were calculated the elimination half life of labetalol by linear least squares regression analysis of the terminal part of the log concentration-time graph and the area under the plasma concentration-time curve by the trapezoidal rule. Plasma clearance was calculated by dividing the intravenous dose by the area under the plasma concentration-time curve extrapolated to infinity ($\text{Cl} = \text{DOSE}/\text{AUC}_{\infty}$). The apparent volume of distribution was calculated as $\text{Vd} = \text{Cl} \times t_{1/2}/0.693$. Bioavailability was calculated from the ratio of the areas under the oral and intravenous plasma concentration-time curves, extrapolated to infinity and corrected for dose differences.

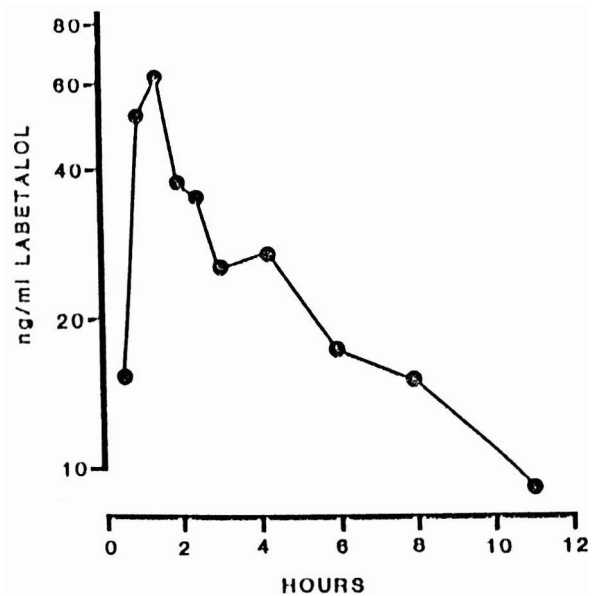


Fig. 2
Plasma concentrations of labetalol after oral administration of 200 mg. Typical results from one subject (Ref. [30]).

A typical graph of plasma concentrations of labetalol at the various times after administration of 200 mg orally to one subject is shown (Fig. 2). Typically, peak concentrations were observed at between 0.5 and 2.5 hours after oral administration of labetalol and this did not change with age. In the seven patients who received labetalol 200 mg, peak plasma concentrations varied from 63 ng/ml to 354 ng/ml and peak concentrations increased with age ($r = 0.87, p < 0.05$). Labetalol bioavailability varied from 8.9 % to 68.4 % and was also significantly related to age (see Fig. 3; % bioavailability = $0.78 + 0.81 \text{ age}$, $r = 0.7, p < 0.05$).

The mean volume of distribution of labetalol was $7.7 \pm 1.1 \text{ l/kg s.e.m.}$ (range 3.2–13.7 l/kg) and was not related to age. The mean clearance overall was $22.4 \pm 3.5 \text{ ml/min/kg}$ (range 8.8–41.8 ml/min/kg). Clearance tended to be lower in elderly people. The mean

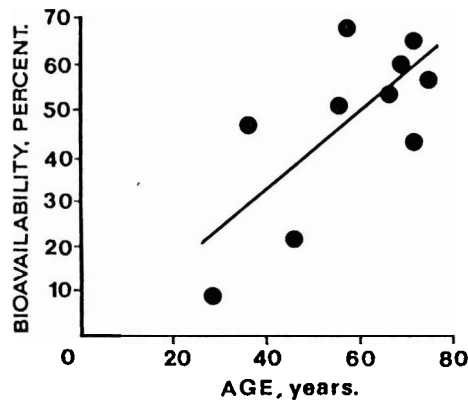


Fig. 3
Bioavailability of labetalol at various ages, showing the line of best fit (Ref. [30]).

clearance in younger subjects (aged less than 60 years) was 28.3 ± 5.5 ml/min/kg and in older subjects (aged greater than 60 years) was 16.4 ± 2.7 ml/min/kg. Elimination half life varied from 3.5 hours to 4.9 hours and increased with age (half-life = $2.62 + 0.026$ age; $r = 0.73$, $p < 0.02$).

Labetalol is a high 'first pass effect' drug demonstrating large variability in peak plasma concentrations and bioavailability after oral administration. Advancing age is associated with increases in peak plasma concentrations and bioavailability and a decrease in the rate of elimination of the drug.

For most metabolised drugs, age-related changes in elimination rates show no consistency. There are clear age associated effects for some but not for others [7]. Drugs subject to a high first pass effect, however, tend to show a fairly consistent age-related pattern. For these substances, the ability of the liver to extract the drug from blood is so high that the kinetics are determined by how quickly the drug is delivered to the liver [8]. Age related decreases in portal blood flow [9] together with possible decreases in rates of hepatic metabolism may contribute to a decreased first pass efficiency in the elderly. This is commonly seen as an increased bioavailability, previously reported for chlormethiazole [10], propranolol [11] and lignocaine. Labetalol then is no exception in that we have shown a pronounced age-related increase in its bioavailability. This is accompanied by decreased elimination of the drug. Changes of the magnitude found by us could result in greatly altered plasma concentrations of labetalol in the elderly. It would seem prudent then to administer labetalol in smaller doses to older people.

Hypertension in the Elderly

There are few data on which to base therapeutic decisions in hypertension in the elderly. Thiazide diuretics are effective in lowering blood pressure in the older hypertensive patient but long term use may be associated with a significant decrease in glucose tolerance, a rise in serum uric acid levels and serum creatinine, and a fall in serum potassium [13]. The blood pressure lowering effect of beta adrenoceptor blocking drugs in the elderly has not been well studied, and the possibility that they might have an adverse effect on the renal circulation is of concern. In young adult hypertensives a reduction in renal blood flow and/or glomerular filtration rate has been described following non-selective beta-

adrenoceptor blocking drugs such as propranolol [14] and pindolol [15], when given intravenously, and following oral propranolol [16, 17]. Wilkinson et al. [18] have demonstrated a reduction in creatinine clearance with propranolol while they observed no change in patients taking the cardioselective agent atenolol. The situation is further complicated by the findings of Hollenberg and colleagues [19] who showed an increase in renal blood flow after intravenous administration of nadolol – a non-selective beta-adrenoceptor blocking drug. Recently Textor and colleagues found that in chronic use nadolol did not change renal blood flow [20].

In order to assess the possible role of beta-adrenoceptor blocking drugs in the management of hypertension in the elderly we undertook to study the effects of labetalol – a non-selective beta-adrenoceptor blocking agent with alpha-blocking activity – both for its blood pressure lowering effect and for any action it might have on renal circulation in elderly hypertensives.

Patients and Methods

Nine elderly and nine young outpatients with untreated essential hypertension were studied. Hypertension was defined as a diastolic blood pressure greater than 95 mmHg (phase 5) on each of three successive outpatient visits. Elderly was defined as 65 years of age or older and the young were 55 years of age or less. The age of the elderly group ranged from 65 to 85 years (mean 78); the younger patients ranged from 22 to 55 years (mean 40). Patients were excluded if they had the usual contraindications to beta-adrenoceptor blocking drugs, a recent myocardial infarction or liver disease. Those with raised blood urea nitrogen or serum creatinine were also excluded. Baseline blood urea nitrogen, serum creatinine and serum electrolytes were carried out in each patient prior to entry into the study and at the end of each treatment phase. Blood pressure was measured using a standard sphygmomanometer and heart rate was measured from the pulse rate for 30 seconds. Mean arterial blood pressure was calculated as one third of pulse pressure plus diastolic pressure.

All patients were started on labetalol 50 mg orally twice daily. The dose was doubled at weekly intervals until the diastolic pressure was lowered to or less than 90 mmHg or was reduced by 15 mmHg, or until a maximum daily dose of 1 g labetalol was reached. In all cases the appropriate blood pressure response was observed at doses below the maximum dose. Following this dose finding phase patients were entered into a randomised double-blind placebo-controlled trial, each phase lasting for 12 weeks.

Patients received the pre-determined dose of labetalol or appropriate placebo tablets. At the end of each 12 week period glomerular filtration rate and effective renal plasma flow were estimated using plasma clearance of intravenously injected ^{51}Cr EDTA and ^{125}I hippuran respectively. A single injection technique was employed, using 30 μCi of each isotope in 8 ml of normal saline. Venous blood samples were taken at intervals after the injection (5, 10, 15, 20, 30, 40, 50, 60, 80, 100, 120, 140, 160 and 180 minutes). Clearance values were calculated using an open two-compartment model [21]. The values obtained for GFR and effective renal blood flow were then corrected to 1.73 m² body surface area. Effective renal plasma flow was corrected for a simultaneous haematocrit to give effective renal blood flow. Data are presented as mean \pm the standard error of the mean. Statistical comparison is by Student t-test, paired or unpaired as appropriate.

Results

Data for both supine and standing blood pressure are given in Table 1. Baseline data in the two age groups were different; in the elderly group supine mean arterial pressure was higher, the mean systolic pressure being 31.5 higher and diastolic 6.4 mmHg higher in the elderly.

Labetalol lowered supine blood pressure in all patients. In the elderly group supine mean arterial pressure fell by 17.1 ± 2.1 mmHg ($P < 0.001$), the systolic pressure falling by 21.8 ± 7.4 mmHg ($P < 0.001$), and the diastolic pressure by 14.8 ± 2.1 mmHg ($P < 0.001$). In the young group supine mean arterial pressure was reduced 13.7 ± 2.5 mmHg ($P < 0.001$), the systolic pressure falling by 17.4 ± 3.9 mmHg ($P < 0.001$) and the diastolic pressure by 12.0 ± 2.1 mmHg ($P < 0.001$). There was considerable variability in daily dose of labetalol required to get the desired blood pressure effect, but there was no significant difference in the daily mean dose for the elderly group (388.8 ± 58.8 mg) and the young group (266.7 ± 33.3 mg).

Heart rates for each age group were significantly lowered. The elderly group heart rate on placebo was 75.0 ± 4.3 compared to 70.7 ± 4.0 per minute on labetalol ($P < 0.02$). In the young heart rate fell from 74.1 ± 2.2 to 68.5 ± 2.5 beats per minute ($P < 0.01$).

Average glomerular filtration rate (Table 2) on placebo was 87.9 ± 8.2 in the young and 62.6 ± 6.3 ml/min/1.73 m² in the elderly ($P < 0.001$). The average effective renal blood flow on placebo was 652.9 ± 68.0 in the young group and 469.0 ± 53.3 ml/min/1.73 m² in the elderly ($P < 0.001$).

There was no significant change in either effective renal blood flow or glomerular filtration rate with labetalol. Following the 12 week course of labetalol mean glomerular filtration rate was 97.6 ± 7.1 in the young group and 60.2 ± 4.2 ml/min/1.73 m² in the

Table 1: Blood Pressure, Supine and Standing, on Placebo and Labetalol

		Supine	
<i>Blood Pressure mmHg</i>		<i>Young</i>	<i>Elderly</i>
Mean arterial	Placebo	113.4 ± 3.1	128.2 ± 4.0
	Labetalol	99.7 ± 2.5	111.1 ± 3.7
Systolic	Placebo	149.2 ± 5.6	180.7 ± 9.0
	Labetalol	131.8 ± 5.0	158.9 ± 8.9
Diastolic	Placebo	95.6 ± 2.1	102.0 ± 2.4
	Labetalol	83.6 ± 1.5	87.2 ± 1.8
		Standing	
Mean arterial	Placebo	113.7 ± 3.2	126.6 ± 8.1
	Labetalol	100.2 ± 2.1	108.0 ± 12.3
Systolic	Placebo	146.9 ± 5.5	176.4 ± 7.9
	Labetalol	132.6 ± 4.6	152.3 ± 8.0
Diastolic	Placebo	97.2 ± 2.4	101.7 ± 2.4
	Labetalol	83.7 ± 1.7	85.9 ± 3.1

Values are mean ± SEM

Table 2: Renal Haemodynamics on Placebo and Labetalol

		<i>Young</i>	<i>Elderly</i>	
GFR ml/min/1.73 m ²	Placebo	87.9 ± 8.2	62.6 ± 6.3	P < 0.001
	Labetalol	97.6 ± 7.1	60.2 ± 4.2	—
ERBF ml/min/1.73 m ²	Placebo	652.9 ± 68.0	469.0 ± 53.3	P < 0.001
	Labetalol	656.1 ± 35.9	385.4 ± 42.6	—

Values are mean ± SEM

elderly group, while effective renal blood flow was 656.1 ± 35.9 in the young group and 385.4 ± 42.6 ml/min/1.73 m² in the elderly group.

Neither serum creatinine or blood urea nitrogen were significantly altered in either group during labetalol therapy. Mean creatinine values on placebo were 88.9 ± 7.1 µmol/litre in the elderly and 78.6 ± 6.7 in the young. Corresponding values on labetalol were 90.2 ± 6.2 and 74.1 ± 5.8. Mean blood urea nitrogen was 6.3 ± 0.6 mmol/l in the elderly group while on placebo compared to 6.6 ± 0.5 during labetalol therapy. Corresponding values in the young group were 5.6 ± 0.3 and 5.5 ± 0.2 respectively.

A postural fall in blood pressure was seen in one elderly patient who was on a daily dose of 400 mg. His supine blood pressure on placebo was 170/105 mmHg and standing 150/100 mmHg. After three months on labetalol the corresponding figure were 130/80 and 105/68 mmHg.

Discussion

Doubts have been expressed about the efficacy of beta-adrenoceptor blocking drugs in the management of hypertension in the elderly [22]. The present results show that labetalol decreased blood pressure in the supine and erect positions in young and elderly hypertensives. The differences in baseline blood pressure values in the two groups make a comparison of blood pressure responsiveness in the two groups difficult. However, in both groups the fall in blood pressure was similar; 17.4/12.0 mmHg in the young, compared to 21.8/14.8 mmHg in the elderly hypertensives.

Most [2, 23, 24] but not all [25] reports indicate that in young hypertensives labetalol does not dramatically alter renal circulation or function. The lack of an effect of labetalol on effective renal blood flow or glomerular filtration rate may be due to two factors – the tendency of non-selective beta-adrenoceptor-blocking drugs to decrease effective renal blood flow [15, 18] on the one hand and the effect of vasodilators to increase it on the other [26]. Our findings of unaltered serum creatinine and blood urea nitrogen are in agreement with the flow data. Significantly, the elderly had a similar fall in blood pressure to the young hypertensives and in common with them demonstrated no adverse renal effects.

It is perhaps surprising that the pharmacodynamics of labetalol were similar in our old and young patients. Older people have been shown to be resistant to a number of effects of beta-adrenoceptor agonists and blocking drugs [27, 29]. On the other hand, and as described in this paper labetalol bioavailability increases with age [30]. It is likely there-

fore that the similarity of blood pressure and heart rate response in the young and elderly represent the balance between opposing pharmacokinetics and pharmacodynamic changes that occur with ageing, the former tending to increase effect with the latter decreasing responsiveness in the elderly.

Renal blood flow decreases with age [31], and as would be expected we found that baseline effective renal blood flow and glomerular filtration rate were reduced in elderly compared with younger hypertensive patients. It is important in such patients that anti-hypertensive therapy does not compromise renal function further. Therefore, the absence of a deleterious effect of labetalol on effective renal blood flow and glomerular filtration rate in such patients is particularly pertinent. While we cannot make general recommendations on the basis of these results in a small number of patients, it would seem that larger studies on efficacy and unwanted effects of beta adrenoceptor blocking drugs in elderly patients are worthwhile.

Conclusion

Like other beta adrenoceptor blocking drugs, it is possible to assay labetalol using a radio receptor technique. There is a marked increase in bioavailability of labetalol in the elderly. Labetalol is an effective blood pressure lowering drug in the elderly.

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Discussion

Borchard

You measured your pharmacokinetics after acute application. As we know from drugs with high bioavailability, after chronic administration the data could be different. Have you measured this?

O'Malley

What you say is absolutely true. There are very significant differences but we didn't get that information, I'm afraid.

N. N.

Könnten Sie bitte noch etwas zur Erklärung sagen, ob die Bioverfügbarkeit bei den älteren Patienten so stark zugenommen hatte? Der zweite Punkt ist, wie ist die Eliminationshalbwertszeit der Substanz?

O'Malley

There must be a decrease in the extraction of the drug as it goes to the liver, perhaps due to the shunting of blood; I don't know the answer. The half-lives in our study were about 3 hours to 4.5 hours. There was a positive correlation with age, but I don't think that it has any clinical significance.

Haim

Your renal function studies showed, at least a tendency to a decrease in effective renal plasma flow with an unchanged glomerular filtration rate. This would indicate or would be consistent with an increase in the filtration fraction. Did any of your elderly patients gain weight?

O'Malley

No, they didn't. We see this pattern also with atenolol, and I really cannot explain why that happens. There must be re-distribution.

Rietbrock, N.

Die Leberdurchblutung bei älteren Patienten kann sich doch nicht so total verändern, daß die Bioverfügbarkeit um etwa das Doppelte ansteigt. Haben Sie die über 4 Halbwertszeiten gemessen? Resultieren daraus Unterschiede?

O'Malley

It's possible. We measured for about 3 half-lives, about 12 hours. The question of liver blood flow, I think, would probably explain differences in clearance, as systemic clearance does fall as a function of age. This wasn't very dramatic in the case of labetalol. When one refers to the first pass metabolism we are really concerned with portal blood flow and extraction by the liver. I think, there is some strange thing happening with extraction in aging. It may have to do with the distribution of the portal blood flow in the liver.

Heusinger

How is labetalol metabolised and which enzymes must be affected for the first-pass effect to be reduced?

O'Malley

I'm not sure. Hydroxylation and glucuronidation. Hydroxylation as such tends not to change with age, or doesn't change much with age, whereas glucuronidation tends not to change with the age. I feel that blood flow effects rather than enzyme activity are more important with age. For those drugs with a very long half-life and whose rate of elimination does not depend on liver blood flow, it is difficult to show much change in systemic clearance. The really dramatic changes occur in those drugs whose elimination depends on liver blood flow. That seems to be a flow phenomenon rather than a drug metabolising phenomenon.

Rietbrock, I.

Haben Sie die Verfügbarkeit von Sauerstoff gemessen? Wir haben gesehen, daß, wenn die Verfügbarkeit von Sauerstoff nicht hoch genug ist, die Extraktion abnimmt. Und damit könnte die Bioverfügbarkeit ansteigen.

O'Malley

No, we did not measure oxygen. Could you explain this study to me?

Rietbrock, I.

Wir haben einen Katheter in eine Lebervene geschoben und haben die Sauerstoffextraktion zwischen arteriellem und venösem Blut gemessen, und wir haben diese in Beziehung gesetzt zu der Extraktion. Wir haben nicht Labetalol, sondern andere Substanzen genommen. Es besteht eine enge Beziehung zwischen der Extraktion und der Verfügbarkeit von Sauerstoff. Ist nicht genügend Sauerstoff vorhanden, so sinkt die Metabolisierung bei älteren Patienten ab.

O'Malley

Could both of these problems be linked by shunting, i.e., if the liver blood flow was shunted, so that oxygen was not available for extraction, the drug is also not available for extraction? That may not explain everything, but it may contribute.

Koch

I propose a very simple explanation. Was there a high proportion of heavy drinkers in your material? Alcohol in geriatrics is the most common reason for raising the bioavailability.

O'Malley

I think that is unlikely in the older people. Alcohol is usually consumed before they become old. I would expect that would be a potential problem perhaps in the younger patients but not in the old patients. These are relatively healthy old patients with normal liver function tests.

Koch

We did a similar renal study in younger people and we saw a reduction of both glomerular filtration rate and renal blood flow by about 8 to 10%.

O'Malley

Was that chronic treatment?

Koch

No, that was acute. Single doses.

O'Malley

I think one has to be very careful about extrapolation from single dose to chronic dose.

Heinicke

Are we discussing a problem which really does not exist? You only had three young persons, and you concluded that all young persons have a low bioavailability.

O'Malley

There were in fact five young people, but I take your point, the group was very small. We do the cut-off below 55. I'm not depending only on this study. It has been well demonstrated that propranolol, chlormethiazol, lignocaine, and many other drugs with high first-pass-metabolism are affected in this way. I'm leaning as much on that evidence as on these small numbers.