Sorbitol clearance during exercise as a measure of hepatic and renal blood flow

Busse M[1], Nordhusen D,Tegtbur U[2], Machold H[3], Panning B[4]

[1]Institute of Sports Medicine, University of Leipzig
[3]Ilmtalklinik, Pfaffenhofen
[2]Center of Sports Medicine, Hannover Medical School
[4]Department of Anesthesiology I, Hannover Medical School

Abstract

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Background: To measure total and hepatic sorbitol clearance during moderate and intense constant load exercise.

Methods: Plasma sorbitol concentration was measured during a constant rate sorbitol infusion (40%, 8ml/min) at rest and during 40% and 60% of the individual maximum work load (W_{max}). From the respective sorbitol clearance and the hepatic extraction rate for sorbitol, hepatic and renal sorbitol clearance were calculated.

Results: Mean values for hepatic and renal sorbitol clearance at rest were 1.01 $\pm$ 0.22 l/min and 0.13 $\pm$ 0.07 l/min. The respective exercise values were: 40% VO2-max: 0.59 $\pm$ 0.13 l/min and 0.08 $\pm$ 0.05 l/min; 60% VO2-max: 0.35 $\pm$ 0.07 l/min and 0.05 $\pm$ 0.03 l/min. No steady state sorbitol clearance was obtained during the 44 ($\pm$ 15) min of the 60% VO2-max level, and thus the estimated functional hepatic blood flow may still overestimate the real values. Hepatic sorbitol clearance (CL_{hep}) was calculated from exercise heart rate (HR): $CL_{hep} = 0.0048 \cdot HR + 1.2$. From total sorbitol clearance (CL_{tot}), hepatic sorbitol clearance (CL_{hep}), estimated hepatic blood flow (EHBF) and estimated hepatic plasma flow (EHPF) can be calculated as follows: $CL_{hep} = 0.87 \cdot Cl_{tot}$; $EHBF = 1.58 \cdot Cl_{tot}$; $EHPF = 0.91 \cdot Cl_{tot}$.

Conclusions: The results correspond well with former measurements of hepatic and renal blood flow, using indocyanine green, PAH or sorbitol, respectively. Moderate exercise reduces liver blood flow to a minor extent, whereas intense constant load exercise slightly below the anaerob threshold reduces liver blood flow markedly without an apparent steady-state end-point. Drawback of the method is a long equilibration time and the necessity of frequent urine sampling, when high precision is desired.

Key words: exercise, sorbitol, liver blood flow, liver plasma flow

Introduction

Changes in hepatic and renal blood flow are of interest during physical exercise to judge the respective impairment of organ perfusion and the hepatic uptake of drugs or hormons with a high hepatic extraction ration. It has been stated that the measurement of hepatic blood flow using a constant flow sorbitol infusion, may be superior to the use of indocyanine green (ICG) (12,13). This is mainly due to the fact that the extraction ration of sorbitol is near 1, if no marked impairment of the liver function such as cirrhosis, is present (12,13,19). The present study was designed to compare the constant rate sorbitol infusion method, as proposed by Zeh et al. (19), with measurements of liver and kidney blood flow, using indocyanine green, sorbitol and PAH, at rest and during moderate and intense constant load exercise.

Methods

Two series, series 1 during resting conditions, series 2 at rest and during moderate and strenous exercise, were performed. The study protocol was approved by the local Ethics Commitee of the Hannover Medical School. All subjects gave written informed consent. Before the sorbitol infusion a dietary history was taken from the volunteers to exclude fructose intolerance. Infusion protocol: An i.v. infusion of 40% sorbitol with an infusion rate of 8 $ml \cdot h^{-1}$ was given throughout the test period (19). The precise amount of sorbitol for the respective adjustment of the infusion pump was determined after the test session using a high precision scales (Sartorius, Göttingen, West Germany). Arterialized blood samples were withdrawn in li-heparinized syringes from a forearm vein using an indwelling teflon catheter (5). Plasma pH, PCO_2, hemoglobin concentration (OSM 3, Radiometer, Copenhagen, Denmark), plasma potassium concentration ($[K^+]_p$; KNA 1, Radiometer, Copenhagen, Denmark) and the hematocrit (Hct) were measured immediately after blood sampling. The syringes were stored in ice cold water for the measurement of plasma protein and blood lactate concentration ($[Lac^+]_p$) (Merck, Darmstadt, Germany) and blood glucose concentration (Böhriger Mannheim, Germany) immediately after the tests. Syringes for $[K^+]_p$

measurement were stored at room temperature and measured almost immediately after blood sampling. Sorbitol concentration in plasma was measured by the sorbitol dehydrogenase method described by Bergmeyer et al (2). Plasma sorbitol concentrations ($[Sorbitol]_p$) were corrected for plasma volume changes using the changes in plasma protein concentration.

Calculation of sorbitol clearance and hepatic and renal blood flow: Total sorbitol clearance (Cl_{tot}) was calculated as the infusion rate, divided by the respective plasma concentration (C_s). For clearance and organ plasma or blood flow values steady-state values were used. When no steady-state was reached during exercise, the last sorbit concentration value of the respective exercise period was used. The renal clearance (Cl_{re}) was calculated as the fraction of the total sorbitol clearance, corresponding to the fraction of sorbitol excreted in the urine. Renal sorbitol clearance for all time points before the second urine sample was calculated by linear intrapolation. In series 2 (see below), it was thereby assumed that a decrease in renal sorbitol clearance would have occured with the beginning of the 40% exercise level (3). The extrarenal (hepatic) sorbitol clearance (Cl_{hep}) was calculated as the difference between Cl_{tot} and Cl_{re}. Estimated hepatic (parenchymal) plasma flow (EHPF) was calculated as Cl_{hep} divided by the hepatic extraction ratio for sorbitol of 0.96 (12,19). Estimated hepatic blood flow (EHBF) was calculated as EHPF/ (1-Hct*0.91); the factor 0.91 describes the relation between the hematocrit in the large vessels and the whole boldy hematocrit (8). The estimated renal plasma flow and blood flow (ERPF and ERBF) were calculated under the assumption that the renal sorbitol clearance approximately equals the glomerular filtration rate (GFR; 16) and that the ration of the GFR to the renal plasma flow is about 0.16 – 0.2.

Series 1. In 3 male subjects (mean age 24 $\pm$ 2.7 years, mean weight 68.3 $\pm$ 3.5 kg) sorbitol clearance was measured over about 2 hours. After the initial distribution phase, samples were taken in 5 to 15 min intervalls (Figure 1). The subjects participated in each in two studies, one with the usual 8 ml $\cdot$ h^{-1} infusion, another with an additional sorbitol bolus (40%) of 5ml or 10ml or 20 ml (Fig. 1). To avoid phlebitis, the bolus was given with a simultaneous isotonic NaCl-bolus (5ml sorbitol + 15ml NaCl; 10ml sorbitol + 30ml NaCl; 20ml sorbitol + 40ml NaCl).

Series 2. 7 subjects (6 male, 1 female, mean age 23 $\pm$ 4.3 years, mean weight 70.7 $\pm$ 10.2 kg) participated in this series. Exercise protocol: a resting period of 2 hours (W_0) was followed by a 1 hour constant load exercise period of 40% of maximum workload (W_{40}) and the a constant load intensity of 60% of maximum workload (W_{60}). The subjects were asked to empty the bladder immediately before the infusion and immediately after exercise. Intermediate urine sampling was possible only in 1 case before the 40% load and in another case before the 60% load. Arterialized blood samples (5) were taken before $W_{(0)}$, during $W_{(0)}$ in 15 min intervals, during $W_{(40)}$ after 3,5,10,15, 30, 45 and 60 min with minor individual variations as displayed in the figures; the same protocol was used for the W_{60} level until exhaustion (the mean endurance time of the 60% level was 44 $\pm$ 14.8 min).

Statistics: Data are presented as single values and as means $\pm$ standard deviation. Equations were calculated by linear or nonlinear regression analysis. Significance of differences was calculated by Friedman nonparametric repeated measures anova.

Results

Series 1: Fig. 1 shows the sorbitol concentration/time plots of 3 subjects at rest in Series 1. No relevant effects of an additional sorbitol bolus independently of the bolus volume are seen in these single cases.

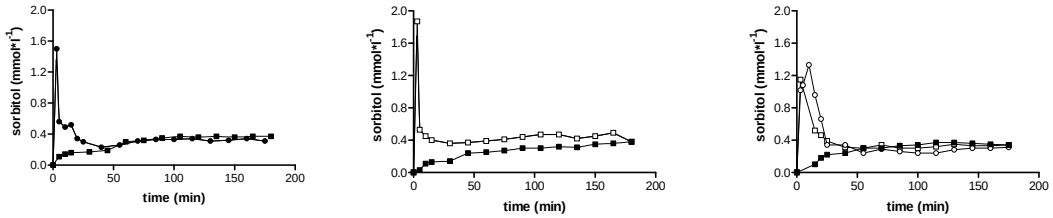

Figure 1
Sorbitol concentrations during an 8 ml $\cdot$ h^{-1} infusion (sorbitol 40%; closed squares), with additional 10 ml bolus (10 ml sorbitol 40% with 30 ml NaCl 0.9% within 5 min; closed circles) or with additional 5 ml bolus (5 ml sorbitol 40% with 15 ml NaCl 0.9% within 5 min; open circles) or with additional 20 ml bolus (sorbitol 40% with 30 ml NaCl 0.9% within 5 min; open squares

Series 2: Fig. 2 shows the sorbitol concentration/time plots of 6 subjects at rest and during the 40% and 60% exercise periods. In Table 1 the respective sorbitol clearance values, as calculated from steady state sorbitol concentrations at

the end of the pre-exercise and 40% exercise period and from the sorbitol concentrations at the end of the 60% period, are displayed. In Table 2 the EHPF, EHBF, ERPF and ERBF with the corresponding oxygen uptake (VO_2), heart rate (HR), ventilation (VE), plasma potassium ($[K^+]_p$) and ($[Lac^-]_b$ are given.

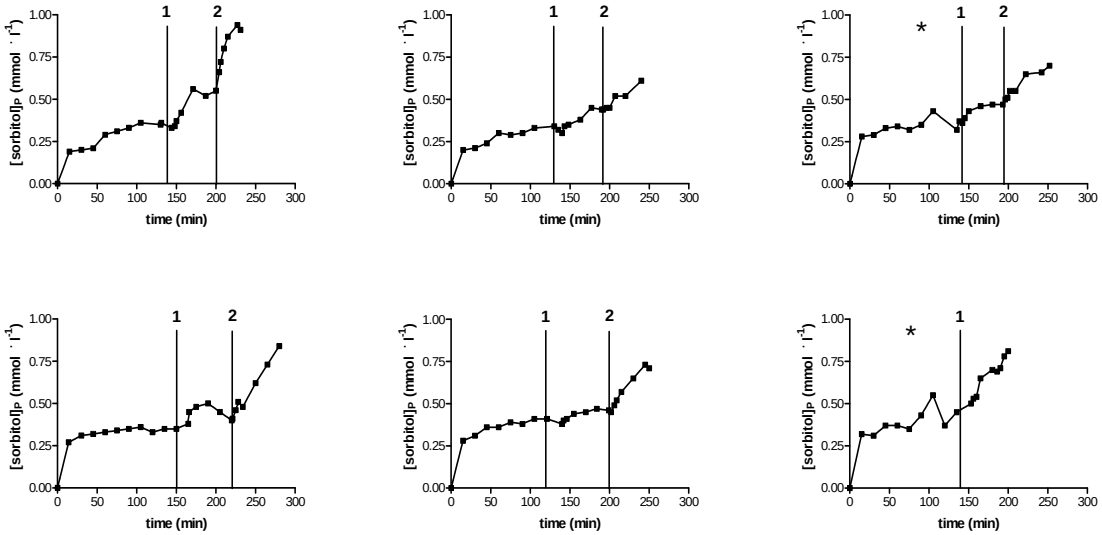

Figure 2
Plasma time vs. concentration plots of 6 subjects at rest and at the end of the 40% W_{max} and 60% W_{max} exercise period (subject 1, who stayed the 40% W_{max} level only is left out).

From Fig. 3 the relation between the estimated hepatic blood flow vs. the corresponding values of VO_2, Ve, $([K^+]_p$ and $[Lac^-]_b$ values can be read.

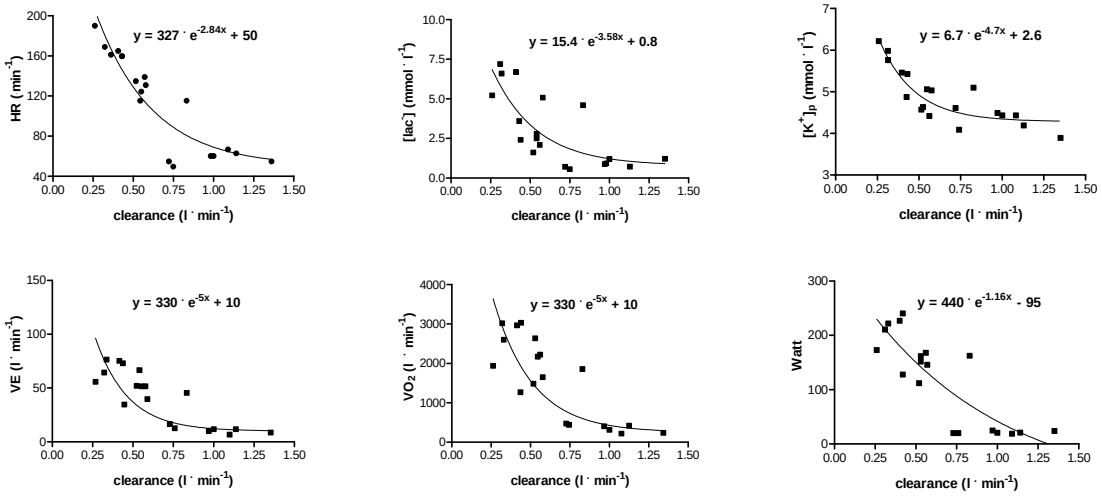

Figure 3
Relation between hepatic clearance and exercise parameters (HR, $[Lac^-]_P$, $[K^+]_P$, VE, VO_2, workload).

Discussion

D-Sorbitol is safe, is easy to measure and has anexceptionally high extraction ration in the normal liver of 0.93 (13). These are also advantages compared to interest when metabolic pathways of metabolites like lactate or of administerd substances are discussed. Liver volume (7) and perfusion (e.g. 3, 6, 9, 11, 14, 15, 17, 19) during exercise in humans has been examined, but no studies

comparing sorbitol clearance or extrarenal sorbitol clearance in moderate and intense constant load exercise have come to our nowledge.
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Time to reach a steady-state level in [Sorbitol]$_p$.
A drawback of the method is the equilibration time. The results in series 1 and 2 show that within 2 hours a steady-state [Sorbitol]$_p$ occurs. This is in line with results of Molino et al (12). Burggraff et al (4) have shown that even in 45 min steady-state conditions may be reached. In our present results, after 45 min a short intermediate steady-state of [Sorbitol]$_p$ appears to be reached, but the concentration then again increases (Fig. 1,2). Mean values after 45, 60 and 135 min in series 2 are 0.31, 0.33 and 0.37, respectively (differences not significant). It remains unclear, whether a further [Sorbitol]$_p$ increase after 45 to 60 min is an effect of persistent equilibration or a decrease of hepatic sorbitol clearance due to the resting position (e.g. a decrease in cardiac output).
No relevant decrease in equilibration time was reached when using a sorbitol bolus in addition to the sorbitol infusion independently of the bolus volume (Fig.1).

Possible misrepresentations of renal sorbitol clearance
Apparently the precise estimation of the renal sorbitol clearance during exercise may become problematic, if the workload would be changed during a test and no catheterization of the bladder would be possible. Nevertheless, renal sorbitol clearance at rest is in the range of about 12% (19) (own present results in Series 1: 12% to 17%) of total sorbitol clearance. Thus even an error of 50% would change total sorbitol clearance values by not more than about 6%-8%. Further the estimation of changes in total sorbitol clearance would remain nearly unaffected.

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No relevant decrease in equilibration time was reached when using a sorbitol bolus in addition to the sorbitol infusion independently of the bolus volume (Fig.1).

Subject	Cl_{tot}	CL_{hep}	CL_{re}	EHPF	EHBF	ERPF	ERBF
1	1.25	1.00	0.06	1.05	1.84	0.32	0.57
2	1.19	1.09	0.09	1.14	1.92	0.52	0.88
3	1.36	1.1.3	0.23	1.18	1.97	1.27	2.15
4	0.89	0.75	0.14	0.78	1.3	0.77	1.31
5	1.17	0.98	0.19	1.02	1.79	1.07	1.81
6	0.89	0.73	0.16	0.76	1.34	0.9	1.53
7	1.4	1.35	0.04	1.41	2.49	0.24	0.4
$\bar{x}$	1.16	1.01	0.13	1.06	1.81	0.73	1.24
SD	0.20	0.22	0.07	0.23	0.40	0.39	0.65

Table 1a. Steady state sorbitol clearance and estimated hepatic and renal plasma and blood flow at rest
Note: Total clearance (Cl_{tot}), hepatic clearance (Cl_{hep}), renal clearance (Cl_{re}), estimated hepatic and renal plasma (EHPF, ERPF) and blood flow (EHBF, ERBF) are given in $l \cdot min^{-1}$

Subject	Cl_{tot}	CL_{hep}	CL_{re}	EHPF	EHBF	ERPF	ERPF
1	0.87	0.83	0.03	0.87	1.55	0.18	0.33
2	0.48	0.44	0.04	0.46	0.84	0.21	0.39
3	0.68	0.57	0.12	0.59	1.03	0.64	1.11
4	0.64	0.54	0.10	0.56	0.96	0.55	0.94
5	0.70	0.58	0.12	0.61	1.07	0.64	1.09
6	0.67	0.55	0.12	0.57	1.01	0.68	1.15
7	0.54	0.52	0.52	0.54	0.82	0.01	0.14
$\bar{x}$	0.65	0.58	0.08	0.60	1.04	0.43	0.74
SD	0.13	0.12	0.05	0.13	0.24	0.26	0.43

Table 1b. Steady state sorbitol clearance and estimated hepatic and renal plasma and blood flow at 40%Wmax
Note: Total clearance (Cl_{tot}), hepatic clearance (Cl_{hep}), renal clearance (Cl_{re}), estimated hepatic and renal plasma (EHPF, ERPF) and blood flow (EHBF, ERBF) are given in $l \cdot min^{-1}$

Subject	Cl_{tot}	CL_{hep}	CL_{re}	EHPF	EHBF	ERPF	ERPF
1							
2	0.29	0.26	0.02	0.28	0.51	0.13	0.24
3	0.52	0.44	0.09	0.45	0.77	0.49	0.83
4	0.43	0.41	0.02	0.43	0.72	0.13	0.23
5	0.38	0.32	0.06	0.33	0.56	0.35	0.59
6	0.4	0.33	0.07	0.34	0.58	0.41	0.69
7							
$\bar{x}$	0.41	0.35	0.05	0.37	0.63	0.30	0.51
SD	0.09	0.07	0.03	0.07	0.11	0.16	0.27

Table 1c. Steady state sorbitol clearance and estimated hepatic and renal plasma and blood flow at 60%Wmax
Note: Total clearance (Cl_{tot}), hepatic clearance (Cl_{hep}), renal clearance (Cl_{re}), estimated hepatic and renal plasma (EHPF, ERPF) and blood flow (EHBF, ERBF) are given in $l \cdot min^{-1}$

Subject	VO_2	HR	$[K+]_p$	$[Lac^-]_B$
Rest	369	58	4.19	0.86
SD	99	6	0.27	0.28
40% Wmax	1920	132	4.81	3.05
SD	470	15	0.37	1.23
60% Wmax	2730	168	5.60	5.87
SD	460	12	0.54	1.44

Table 2. Oxygen consumption, heart rate, plasma potassium and blood lactate values (means ± SD) at rest, 40% and 60% Wmax, corresponding to the respective clearance values in Table 2, 3 and 4.

Possible misrepresentations of renal sorbitol clearance:
Apparently the precise estimation of the renal sorbitol clearance during exercise may become problematic, if the workload would be changed during a test and no catheterization of the bladder would be possible. Nevertheless, renal sorbitol clearance at rest is in the range of about 12% (19) (own present results in Series 1: 12% to 17%) of total sorbitol clearance. Thus even an error of 50% would change total sorbitol clearance values by not more than about 6%-8%. Further the estimation of changes in total sorbitol clearance would remain nearly unaffected.

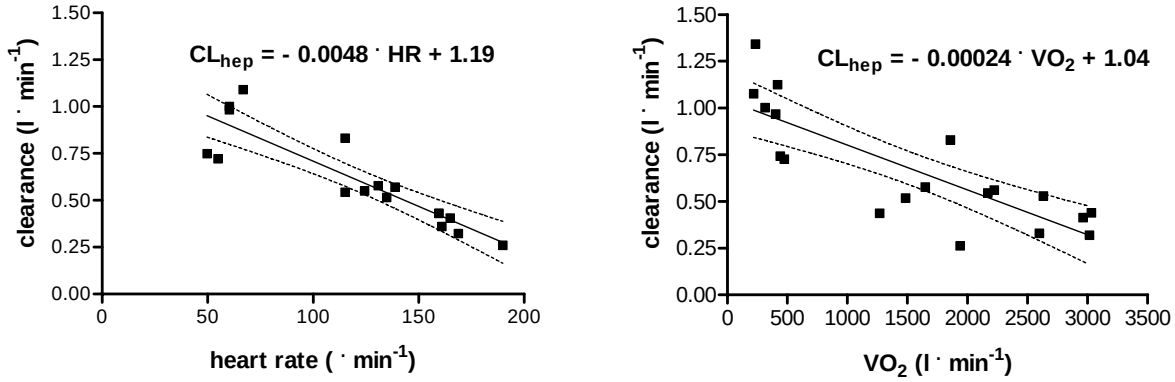

Figure 4. Linearized relation between heart rate or oxygen uptake and hepatic clearance.

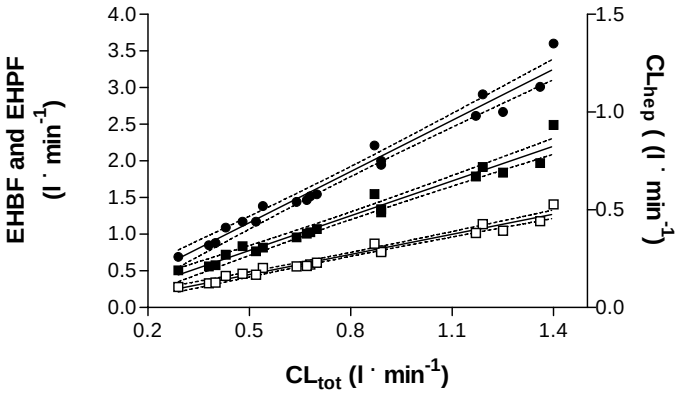

Figure 5.
Relation between total sorbitol clearance (CL_{tot}) and hepatic sorbitol clearance (CL_{hep}; closed circles), estimated hepatic blood flow (EHBF; closed squares) and estimated hepatic plasma flow (EHPF; open squares).

The regression lines between total sorbitol clearance and EHBF or EHPF are:

CL_{hep}	$= 0.87 \cdot CL_{tot}$	(r = 0.99);
EHBF	$= 1.58 \cdot CL_{tot}$	(r = 0.98);
EHPF	$= 0.91 \cdot CL_{tot}$	(r = 0.99)

Comparison of the present data with other results on hepatic blood flow using sorbitol:

a. In 3 untrained subjects, pedalling at 100 W, Zeh et al (19) found a decrease in hepatic and renal sorbitol clearance to 55 ± 8% and 64 ± 20%, respecitvely. Unfortunately, the maximum workload of these subjects has not been mentioned. Assuming an average maximum workload of about 250W for these subjects (age 25-30 years, weight 63-88 kg) 100 W may have been in the range of 40% of their W_{max}, and may thus well be compared to the values of our 40% exercise level. The corresponding portions of resting hepatic and renal sorbitol clearance were 59 ± 16% and 63 ± 17%, respectively.

b. Kemme et al (11) used exercise as a model of reduced liver perfusion (11). Sorbitol was infused during initially increasing and later on constant load exercise (about 70% VO_{2max}). During constant load exercise no steady state plasma sorbitol concentration was reached. Estimated liver blood flow decreased from 1.4 l*min^{-1} to 0.4 l*min^{-1}, where heart rate was about 150 l*min^{-1}. According to Figure x, this rate would amount to a mean hepatic clearance of 0.48 l*min^{-1}.

Comparison of the present date with results on hepatic blood flow using ICG:

a. Rowell et al (15): resting EHBF was 1.6 l*min^{-1} (present own results: 1.6 l*min^{-1}). After about 10 min of treadmill exercise (3 mph, increasing incline) the authors found a decrease in EHBF to about 82% ± 10% for the 40% VO_{2max} level (n=6); respective own results after 10 min; 76.9 ± 15.5%, after 1 h: 58.3 ± 18.4%. For the 60% VO_{2max} Rowell et al (15) described a decrease in EHBF to about 57 ± 7% after about 10 min of exercise (n=10). In the 60% level of the present series we found a decrease to 53.9 ± 14.4 after 10 min and to 38.7 ± 11.7% when the workload could no longer be sustained after a mean of 44 min.

b. Swartz et al (17): during moderate exercise (total 3 hours, 3 mph for 20 min of every 30 min) a decrease in ICG plasma clearance to 64% of resting values was reported.

c. Chandler et al (6): The authors present a formula to calculate exercise splanchnic blood flow (SBF) using

exercise heart rate and resting SBF. The underlying data are based on indocyanine clearance studies (3). Compared to our results (relation between heart rate and hepatic sorbitol clearance) the respective regression lines appear quite similar (Fig. 5).

d. Perko et al (14): A constant load exercise of about 75% VO_{2max} reduced mesenteric, coeliac and splanchnic blood flows by 0.18, 0.42 and 0.6 $l*min^{-1}$, corresponding to a respective increase in vascular resistance by 76, 165 and 126%, respectively.

Comparison ot the present date with results on renal blood flow using PAH:

Grimby (10) found a decrease in ERBF to about 75% for the 45% VO_2max-level after 45 min of cycle ergometer exercise (respective present results for 40% VO2max: 57.6 $\pm$ 15%).

Ylitalo (18): A constant load exercise of about 40 and 60% VO_{2max} reduced renal blood flow (RBF) to about 81% and 60% of resting values (respective present own results for 40% and 60% VO_{2max}: 58% and 41% of resting RBF with a high range of variation; Table 1 b,c)

In spite of a somewhate rough approach of the urinary sorbitol clearance, the results are quite near to the above mentioned studies. This is not surprising, mainly for two reasons: a. It has been calculated, that even high misrepresentations of the urinary sorbitol clearance or hepatic sorbitol clearance (see calculations above; 12,19). The comparison with renal sorbitol clearance, given by Zeeh et al. (19) and the ERPF calculated from the PAH clearance (10) further indicates, that the intrapolation method, used in this series, revealed comparable quantitative changes during exercise. Thus uretral catheterization would not be justified by a possible (minor) improvement of HBF and RBF estimation. b. the extraction ratio (*E*) of sorbitol is >0,96 (12,19). This value has been shown to be constant during varying physiological conditions in subjects without liver disease, though no measurements during exercise have come to our knowledge. Anyway, for highly extracted drugs (*E*>0.96) it has been calculated that even a 50% decrease of the intrinsic metabolic activity of the liver cells would produce a relative error in EHBF not exceeding 10% (12).

Possible applications of the results:

1. The constant rate sorbitol method appears to be a quantitative method of hepatic and renal blood flow measurement during constant load exercise of longer duration. During short intense exercise, changes in kidney and liver blood flow are at least qualitatively indicated (non steady state conditions may then be an effect of incomplete sorbitol equilibration and/or changing functional liver or kidney blood flow).
2. The liver blood flow is an important determinant of many metabolic processes and the main determinant for the disappearance of highly excreted substances. From present data heart rate related sorbitol clearance values and respective values of hepatic plasma flow can be derived.

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1. Andrews JR, Wilk KE (1994) The athlet´s shoulder. Churchill Livingstone, New York - Edinburgh - London - Madrid - Melbourne – Tokyo:221-225
2. Belle RM, Hawkins RJ (1991) Dynamic electromygraphic analysis of the shoulder muscles during rotational and scapular strengthening exercises. In: Post M, Morrey BF, Hawkins RJ (eds) Surgery of the shoulder. CV Mosby, St Louis:345-356
3. Brewster C, Moynes-Schwab DR (1993) Rehabilitation of the shoulder following rotator cuff injury or surgery. J Orthop Sports Phys Ther 18: 422-426

References

1. Astrand PO, Hultman E, Juhlin-Dannfeld A (1986) Disposal of lactate during and after strenous exercise in humans. J Appl Physiol 61: 338-343
2. Bergmeyer HU, Gruber W, Gutman I (1975). D-Sorbitol. In: Bergmeyer HU (ed.) Methods of enzymatic analysis. Weinheim: Verlag Chemie: 1323-1330
3. de Boer A, Kluft C, Kroon JM, Kasper FD, Schoemaker HC, J. Pruis, Breimer DD, Soons PA, Emeis JJ, Cohen AF (1992). Liver blood flow as a major determinant of the clearance of recombinant human tissue-type plasminogen activator. Thromb Haemost 67: 83-87
4. Burggraaf J, Schoemaker RC, Lentjes EGWM, Cohen AF (2000) Sorbitol as a marker for drug-induced decreases of variable duration in liver blood flow in healthy volunteers. Eur J Pharm Sci 12: 133-139
5. Busse MW, Maassen N (1989) Effect of consecutive exercise bouts on plasma potassium concentration on during exercise and recovery. Med Sci Sports Exerc 21: 489-493
6. Chandler WL, Levy WC, Veith RC, Stratton JR (1993) A kinetic model of the circulatory regulation of tissue plasminogen activator during exercise, epinephrine infusion and indurance training. Blood 15: 3293-3302
7. Flamm SD, Taki J, Moore R, Lewis SF, Keech F, Maltais F, Ahmad M, Callahan R, Dragotakes S, Alpert N, Strauss HW (1990) Redistribution of regional and organ blood volume and effect on cardiac function in

relation to upright exercise intensity in healthy human subjects. Circulation 81: 1550-1559
8. Gregersen MI, Rawson RA (1959) Blood volume. Physiol Rev 39: 307-342
9. van Griensven JM, Burggraaf KJ, Gerloff J, Gunzler WA, Beier H, Kroon R, Huisman LG, Scheomaker RC, Kluft K, Cohen AF (1995) Effects of changing liver blood flow by exercise and food on kinetics and dynamics of saruplase. Clin Pharmacol Ther 57: 381-389.
10. Grimby R (1965) Renal clearances during prolonged supine exercise at different work loads. J Appl Physiol 20: 1294-1298
11. Kemme MJ, Burggraaf J, Schoemaker RC, Paulson S, Karim A, Lentjes EG, Childs A, Braeckman RA, Cohen AF (2000) The influence of reduced liver blood flow on the pharmacokinetics and pharmacodynamics of recombinant tissue factor pathway inhibitor. Clin Pharmacol Ther 67: 504-511
12. Molino G, Cavanna A, Avagnina P (1987) Hepatic clearance of d-sorbitol. Dig Dis Sci 32: 753-758
13. Molino G, Avagnina P, Belforte G, Bircher J (1998) Assessment of the hepatic circulation in humans: New concepts based on evidence derived from a d-sorbitol clearance method. J Lab Clin Med 131: 393-405
14. Perko MJ, Nielsen HB, Skak C, Clemmesen JO, Schroeder TV, Secher NH (1998) Mesenteric, coeliac and splanchnic blood flow in humans during exercise. J Physiol 513: 907-913
15. Rowell LB, Blackmon JR, Bruce RA (1964) Indocyanine clearance and estimated hepatic blood flow during mild to maximal exercise in upright man. J Clin Invest 43: 1677-1690
16. Smith WW, Finkelstein N, Smith HW (1946) Renal excretion of hexitols and their derivates and of endogenous creatinine like chromogen in dog an man. J Biol Chem 1135: 231-250
17. Swartz RD, Sidell FR, Cucinell SA (1974) Effects of physical stress on the disposition of drugs eliminated by the liver in man. J Pharmacol Exp Ther 188: 1-7
18. Ylitalo P (1991) Effect of exercise on pharmacokinetics. Ann Med 23: 289-294
19. Zeeh J, Lange H, Bosch J, Loesgen H, Eggers R, Navasa M, Chesta J, Bircher J (1989) Steady-state extrarenal sorbitol clearance as a measure of hepatic plasma flow. Gastroenterology 95: 749-759