

^{99m}Tc -HEPIDA hepatic clearance as a diagnostic tool: usefulness of plasma and hepatic clearance for assessment of hepatic parenchyma performance

Izabela Frieske¹, Marian J. Surma¹, Małgorzata Bieńkiewicz¹,
Jolanta Białkowska-Warzecha², Julian Liniecki¹,
Jan Kuydowicz², Jacek Kuśmierek¹

¹Nuclear Medicine Department of the Medical University, Łódź, Poland

²Department of Infectious Diseases of the Medical University, Łódź, Poland

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Abstract

Plasma clearance of ^{99m}Tc -HEPIDA (Cl_{pl}) has been used for two decades for assessment of liver function in patients with diseases of this organ. A specific determination of ^{99m}Tc -HEPIDA liver clearance (Cl_{hp}) has been developed that provides more direct possibility to evaluate performance of liver parenchyma. Both tests have been studied in healthy volunteers of varying age (48 individuals) and in 83 patients with varying degree of liver damage.

The liver damage has been evaluated on the basis of 5 biochemical tests (AspAT, ALAT, GGTP, bilirubin serum concentration, proteinogram) and a score system used for total impairment, which was calculated for each patient.

Normal range of Cl_{pl} and Cl_{hp} was determined from a study on healthy individuals (volunteers). The results seem independent of age, but show sex differences. The following values (mean

\pm SD) of Cl_{hp} were found in males and females of: (181 ± 31) ml/min/1.73 m² and (158 ± 22) ml/min/1.73 m², and of Cl_{pl} were (224 ± 33) ml/min/1.73 m² and (202 ± 25) ml/min/1.73 m² respectively. Accepted lower boundaries of both quantities (mean -2SD) are 115 ml/min/1.73 m² and 150 ml/min/1.73 m² correspondingly.

Negative correlation of individual values of both clearances in all patients with individual score of liver damage were highly significant and correlation coefficients obtained were higher for Cl_{hp} ($r = -0.63$) than those for Cl_{pl} ($r = -0.56$). Factorial analysis was performed with the intention of seeing which of the studied factors had the highest factor loading for parenchyma performance that was assumed as the common factor responsible for correlations. The highest value was obtained for hepatic clearance (Cl_{hp}) of ^{99m}Tc -HEPIDA. In conclusion this quantity seems highly promising as a clinically useful test for assessment of liver performance, both in screening for liver damage and for monitoring of organ conditions during therapy and follow-up of patients.

Key words: ^{99m}Tc -HEPIDA total plasma clearance, ^{99m}Tc -HEPIDA hepatic clearance

Introduction

Chronic diseases affecting liver parenchyma count among the most frequent ailments of the digestive system. Complexity of metabolic functions of the liver requires numerous laboratory tests for diagnostic assessment of the organs' condition and performance. Abnormal results of respective biochemical tests, indicating damage to hepatocytes, permit detection of a disease and its nature but do not allow for clear assessment of organs' performance or degree of the damage incurred. The decisive role is attributed to the histopathological examination of the thick needle punctuate of the liver. However, due to the accompanying relatively high risk of complications there are numerous contraindications

Correspondence to: Marian J. Surma
Department of Nuclear Medicine, Medical University of Łódź
ul. Czechosłowacka 8–10, 92–216 Łódź, Poland
Tel: (+48 42) 678 36 84; fax: (+48 42) 679 17 80
e-mail: mjsurma@csk.am.lodz.pl

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tions to application of the procedure. The risk involved increases, of course, at repeated application of the puncture in the course of monitoring the patient's condition, e.g. for assessment of transience or the acute viral hepatitis into a chronic form of the disease [1, 2]. In such situations there appears to be a need for a non-invasive and relatively simple test, which could provide credible information on the degree of liver damage and its dynamics in time.

In the 1980s, there was a test introduced into the diagnostics of liver diseases based on determination of the plasma clearance (Cl_p) of the ^{99m}Tc complex of dimethylacetanilid diiminoacetic acid (^{99m}Tc -HEPIDA) [3]. After intravenous administration (bolus injection) the compound is taken up by hepatocytes, secreted into the bile and eliminated via the gastrointestinal tract. The test, based on analysis of biological decay of the radiopharmaceutical in the plasma, is safe and can be used both for assessment of the degree of liver parenchyma impairment — with exclusion of mechanical jaundice — and for monitoring the therapy [1–3]. The test is not a substitute for liver puncture but its use can reduce the frequency of the latter.

A disadvantage of the original form of the ^{99m}Tc HEPIDA clearance (plasma clearance) is a partial and variable elimination of the compound via the urinary tract [4, 5]. Contribution of the latter to the plasma clearance is unpredictable and therefore can obscure the specific elimination of the complex by the liver (hepatic clearance), which reflects the performance of hepatocytes. Thus, a method has been elaborated that enables determination of the specific hepatic clearance (Cl_{Hp}), which should give a better diagnostic insight into liver parenchyma function than the overall plasma clearance [8, 9]. Preliminary studies have shown that Cl_{Hp} may be useful for evaluation of liver excretory function [10, 11]. There is still a need, however, to compare the diagnostic efficacy of Cl_p and Cl_{Hp} for assessment of the function.

The objective of the present study has been therefore a comparative evaluation of the usefulness of plasma and hepatic clearance of ^{99m}Tc -HEPIDA for assessment of liver excretory function in chronic diseases of various aetiology affecting the organs' performance.

Material and methods

The studied group consisted of:

1. Patients treated for chronic liver diseases in the Hospital Department of Infectious Diseases of the Medical University of Łódź. They were treated for:
 - chronic viral hepatitis, type B and C — 28 individuals (8 females, 20 males);
 - liver cirrhosis — 22 individuals (8 females and 14 males);
 - alcoholic disease — 14 individuals (6 females and 8 males);
 - other diseases — 22 individuals (11 females and 11 males).

There were altogether 88 patients (33 females, 55 males, of age varying between 18 and 68 years [av. 45 years]). From these patients in 5 (3 males, 2 females) a liver disease was excluded upon clinical investigation; these individuals were then included in the group of healthy individuals.

2. Healthy volunteers, altogether 43 individuals: 22 females and 21 males in three age brackets:

- 17 persons (9 females, 8 males) 19.4–24.3 years of age (av. 22.4 years);
- 12 persons (6 females and 6 males) — 31.5–38.8 years (av. 35 years);

- 14 persons (7 females and 7 males) 50.8–55.5 years (av. 52.7 years).

The study on 43 healthy volunteers was approved by the Ethical Committee of the University.

All individuals participating in the study, both patients and healthy volunteers, were clinically examined, their health status assessed and appropriate clinical diagnoses established on the basis of required information.

Laboratory examinations specific for the purposes of the present study

In all subjects studied five basic biochemical tests were performed, used in hepatological diagnostics:

1. Activity of enzymes in blood plasma: asparagine aminotransferase (AsPAT), alanine aminotransferase (ALAT), gamma-glutamyltranspeptidase (GGTP).
2. Concentration of bilirubin in blood serum.
3. Proteinogram of the serum.

^{99m}Tc -HEPIDA clearance determinations: the plasma clearance (Cl_p) and hepatic clearance (Cl_{Hp}) were determined applying a single injection multisample and a simplified single sample method as described in detail elsewhere [7–9]. The values obtained were standardised to the body surface of a given individual, calculated from his (her) body height and mass, according to the DuBois formula.

Assessment of liver condition

Integral evaluation of liver performance, as deduced from biochemical determination (five biochemical indices) was made in two ways: 1) using a standard clinical algorithm as reported by Bialkowska et al. [2, 3] and 2) by applying a specially developed procedure (see below).

The standard clinical algorithm uses 4 intervals of values for each of the biochemical indices. To each of the intervals a number of points (rangs) has been attributed (from zero to 3), as defined in Table 1.

The alternative algorithm, developed for the purpose of the present study, utilises distribution statistics of biochemical indices in healthy subjects. The values of indices (except albumin concentration in serum) displayed nonsymmetrical, right hand side skewed distributions. If logarithms of these observed, individual values were assembled, they could be satisfactorily fitted to the

Table 1. Rangs attributed to individual biochemical indicators based upon results of the determinations

AspAt [U/l]	Alat [U/l]	GGTP [U/l]	Serum conc. of bilirubin [mg/dl]	Proteinogram	Rang
Norm	Norm	Norm	Norm	Norm	0
< 100	< 100	< 100	< 2	Slight hyper- gammaglobuli- naemia	1
100–300	100–300	100–200	2–3	Hypoalbumi- naemia and hyper- globulinaemia	2
> 300	> 300	> 200	> 3	Hypoprotei- naemia	3

Table 2. Lower and upper ranges of biochemical indicators as found in 131 individuals studied

Results	AspAT [U/l]	Alat [U/l]	GGTP [U/l]	Bilirubin serum conc. [mg/dl]	Albumin [mg/dl]	Gammaglob. [mg/dl]
Min	10	11	8	20	18	55
Max	295	308	1629	664	517	298

Gaussian distribution. On the basis of the distribution analysis four intervals were selected as defined in Table 2, and ranges (0 to 3) were attributed to each interval, as shown in the same table.

The values of albumin plasma concentrations were treated in the same way; however, respective intervals were based on standard deviations of the direct normal distribution in healthy individuals.

For each patient and each algorithm the ranges for each index were added obtaining the final sum of ranges (SR).

Selection of a factor most adequately characterising functional condition of the liver

On the basis of all the data acquired from the patients and healthy individuals, a factorial analysis has been performed aiming at identification of a factor that most adequately characterises the functional status of the liver. The quantities considered were: sum of the ranges (two variants), hepatic and plasma clearance of ^{99m}Tc -HEPIDA, and discrete values of all the individual biochemical indices determined. The analysis performed utilised a STATISTICA program.

Investigation of correlation between discrete values of the clearances and sums of ranges (biochemical classification)

Variance analysis of individual SR and clearance values was performed. The analysis utilised Spearman's correlation theory for non-continuous variables.

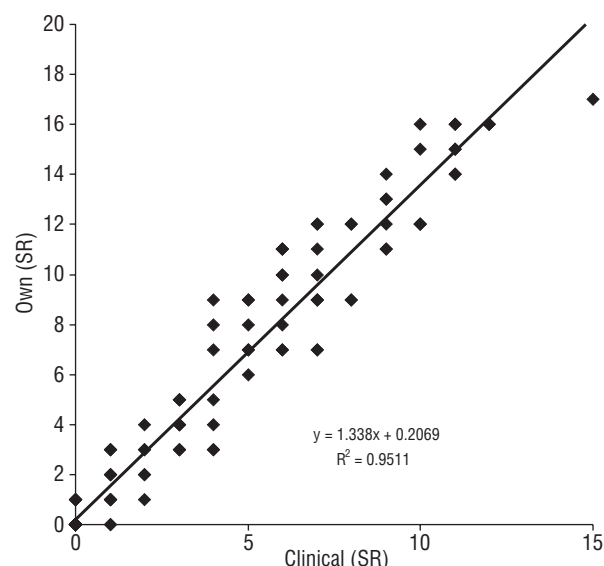
Results

Biochemical indices

The ranges of values obtained in all studied individuals varied considerably. Classification of patients and healthy individuals according to the two algorithms (the standard, and that developed for this paper) is presented in Table 3. In Figure 1 a regression between results (SR) of two classifications is shown for all patients. The correlation obtained is very tight ($r = 0.9752$), and the slope of the regression line indicates that the new classification yields on average somewhat higher sums of ranges.

Table 3. Numbers of individuals with different sums of ranges acc. to the two algorithms

Range of SR	Number of individuals	
	Clinical algorithm	Own algorithm
0	48	45
1–5	40	34
6–10	28	20
> 10	15	32
Total	131	131

**Figure 1.** Regression between values of SR as obtained from classification of patients acc. to two alternative algorithms (see text).

^{99m}Tc -HEPIDA clearance values in healthy individuals

The values obtained for Cl_{Pl} and Cl_{Hp} in all healthy individuals of both sexes (means, standard deviations) are presented in Table 4.

Statistical analysis (t-Student's test) reveals that mean values of the standardised clearances (Cl_{Pl} , Cl_{Hp}) in females are significantly lower than those observed in males ($p = 0.013$ and 0.0057 for Cl_{Pl} and Cl_{Hp} , respectively).

^{99m}Tc -HEPIDA clearance and age

Dependence of the plasma and hepatic clearance upon age has been presented for healthy individuals in Figure 2 and 3 (for males and females, respectively). Low values of slopes and substantial scatter of the data around the regression lines indicate that both the plasma and hepatic clearance do not show a clear relationship with age. There are, however, as was already stated above, significant differences between standardised clearance values in males and females. The lower boundary of normal values for the plasma clearance (mean -2SD) can be set at

Table 4. Mean values and standard deviations of the standardised clearances of ^{99m}Tc -HEPIDA in 46 healthy volunteers (multisample method)

Clearance	Males ($n_m = 24$)	Females ($n_k = 24$)
Cl_{Pl} [ml (min 1.73m^2) $^{-1}$]	224 ± 33	202 ± 25
Cl_{Hp} [ml (min 1.73m^2) $^{-1}$]	181 ± 31	158 ± 22

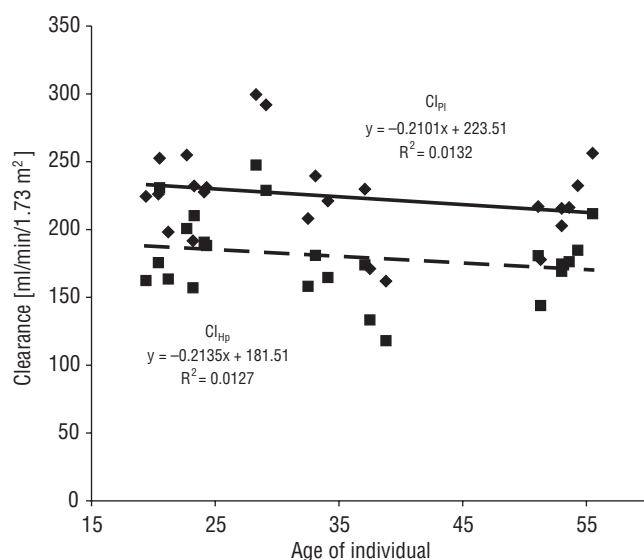


Figure 2. Relation of two clearances, Cl_{PI} (◆) and Cl_{HP} (■) with age; males (healthy volunteers).

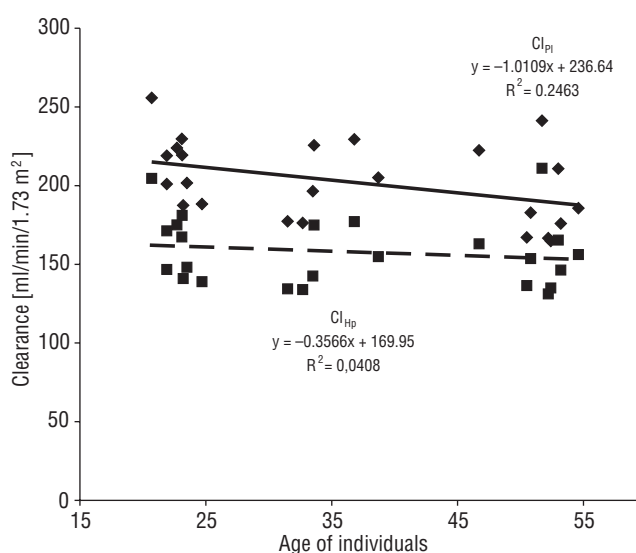


Figure 3. Relation of two clearances, Cl_{PI} (◆) and Cl_{HP} (■) with age; females (healthy volunteers).

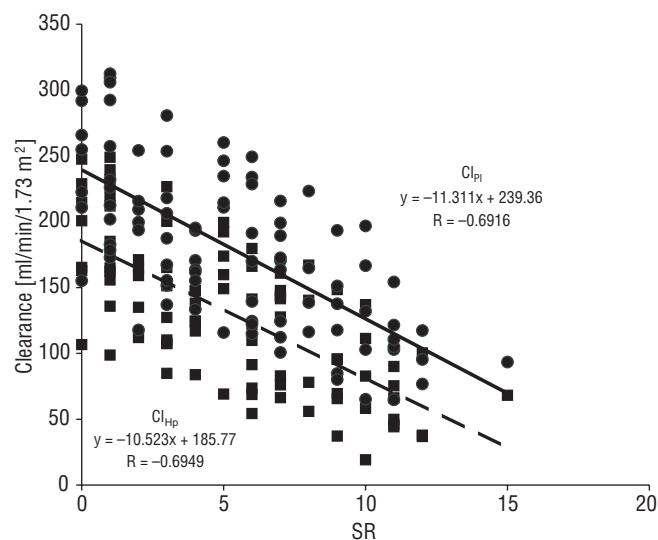


Figure 4. Correlation and regression lines describing the relationship of the sum of ranges (SR) as obtained from the standard clinical algorithm for assessment of liver damage, with the plasma (Cl_{PI}) (●) and hepatic (Cl_{HP}) (■) clearance of ^{99m}Tc -HEPIDA. (multisample method)

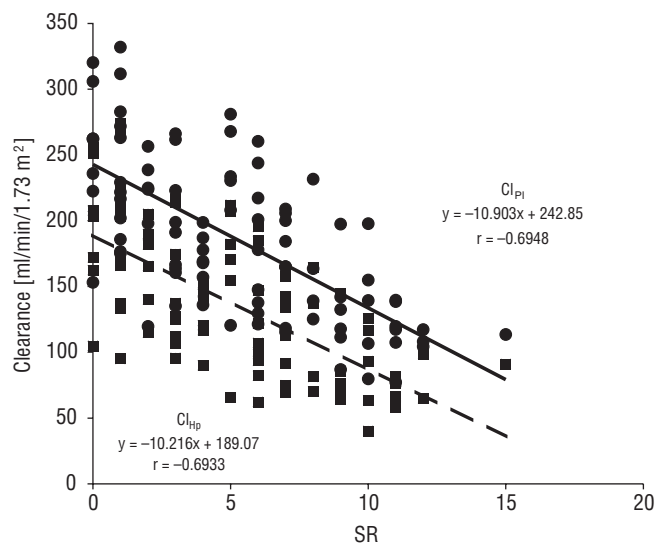


Figure 5. Correlation and regression lines describing the relationship of the sum of ranges (SR) as obtained from the standard clinical algorithm for assessment of liver damage, with the plasma (Cl_{PI}) (●) and hepatic (Cl_{HP}) (■) clearance of ^{99m}Tc -HEPIDA (single sample method).

160 ml/min/1.73 m² and 150 ml/min/1.73 m² in males and females, respectively. For hepatic clearance analogous values would be 120 and 115 ml/min/1.73 m².

Correlation between clinical and biochemical classifications and ^{99m}Tc -HEPIDA clearances

Figures 4 and 5 illustrate correlations between sums of ranges, obtained from the standard clinical classification of individual patients and the determined Cl_{PI} and Cl_{HP} , by means of multi- and single-sample methods, respectively. Analogous correlations between results of our own biochemical classification and corresponding values of the clearances are shown in Figures 6 and 7. All correlations are significant, the correlation coefficients for Cl_{HP}

tend to be higher than those for ^{99m}Tc -HEPIDA overall plasma clearance.

Search for a common factor determining trends in values of all quantities measured in the patients (factorial analysis)

From the knowledge of physiological mechanisms underlying biochemical tests for liver performance and those responsible for ^{99m}Tc -HEPIDA uptake and excretion to the bile, one can postulate that, if there were a common factor codetermining behaviour of these measurements, it should be the functional capacity of liver parenchyma.

Factorial analysis resulted in values of "factor loading" for all measured quantities. From Table 5 it follows that most of the

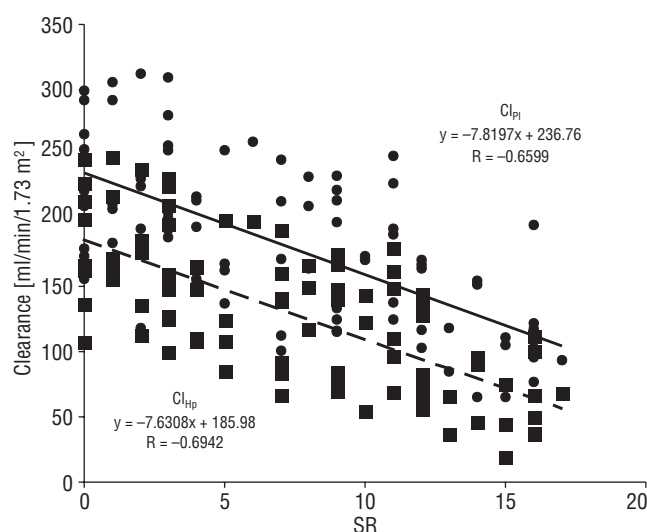


Figure 6. Correlation and regression lines describing the relationship of the sum of ranges (SR) as obtained from own algorithm for assessment of liver damage, with the plasma (Cl_{Pi}) (●) and hepatic (Cl_{Hp}) (■) clearance of ^{99m}Tc -HEPIDA (multisample method).

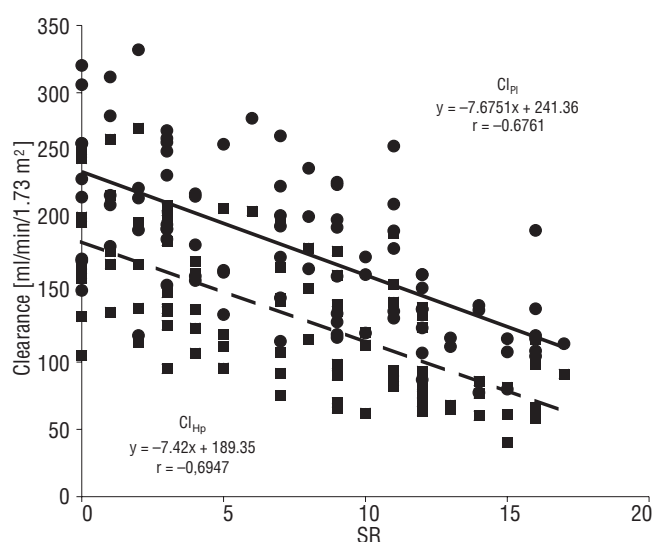


Figure 7. Correlation and regression lines describing the relationship of the sum of ranges (SR) as obtained from own algorithm for assessment of liver damage, with the plasma (Cl_{Pi}) (●) and hepatic (Cl_{Hp}) (■) clearance of ^{99m}Tc -HEPIDA (single sample method).

measured values contain substantial loading of the common factor. The “plus” sign indicates that a given quantity correlates positively with the “factor”, a minus sign indicates a negative correlation. The hypothetical factor (here the functional capacity of liver parenchyma) is most strongly reflected by the hepatic ^{99m}Tc -HEPIDA clearance; a weak correlation can be seen only for GGTP.

Discussion

One category of liver functions is elimination of metabolic and toxic wastes. It can be postulated that this capacity, related to blood plasma, is exemplified by clearance of ^{99m}Tc -HEPIDA. Some of the substances leave the system also via the urinary system and this applies to the iminodiacetic derivative mentioned above too. In clinical practice plasma clearance of ^{99m}Tc -HEPIDA has already been used as an indicator of liver function impairment [1–3].

However, the variability of urinary elimination obscures interpretation of this test. Determination of a more specific hepatic clearance of ^{99m}Tc -HEPIDA (by subtracting the urinary clearance from plasma clearance [7–11]) should be a more appropriate indicator of liver excretory function, particularly when assessment of the latter is made for a given patient.

The range of values of all indices of liver parenchyma condition, as measured in the patients in this study, had been very wide (Fig. 1). There appeared, therefore, a chance to quantitatively compare in the studied patients the strength of correlation between the sum of ranges of biochemical indicators of liver damage and corresponding values of Cl_{Hp} and Cl_{Pi} .

The results of these correlation studies indicate that the correlations for Cl_{Hp} tended to be stronger than those for Cl_{Pi} even if the differences in the coefficients were small. This happened in spite of the fact that precision of Cl_{Hp} determination should be inferior to that of Cl_{Pi} (Cl_{Hp} is a difference of two clearances: Cl_{Pi} and Cl_{Ur} and variance of the former should equal the sum of Cl_{Pi} and Cl_{Ur} variances). These results confirm our logical a priori expectation that for the purpose of liver damage assessment a more specific test (Cl_{Hp}) should be superior to the overall plasma clearance of ^{99m}Tc -HEPIDA.

Two algorithms of patients' classification (degree of liver damage)

The heretofore used clinical algorithm for liver damage [1, 2, 6, 10, 11], has been based upon attribution of scores (ranges) to results of a series of biochemical tests. This convention has been based, however, on a rather arbitrary definition of the independent variable, i.e. the numerical ranges of test results to which

Table 5. Loads of individual factors used for assessment of liver condition (factorial analysis)

Measured quant	Factor load	Measured quant	Factor load
Rang sum (clinical algorithm)	−0.7303	Bilirubin serum conc.	−0.5792
Rang sum (own algorithm)	−7234	ASPAT act. conc.	−0.6136
Cl_{Hp} (mult. sampl. method)	0.9769	ALAT act conc.	−0.5077
Cl_{Pi} (mult. sampl. method)	0.9703	GGTP act conc.	−0.1328
Cl_{Hp} (simple method)	0.9712	Albumin conc.	0.665
Cl_{Pi} (simple method)	0.9676	Gamma glob.	−0.4975

a given score was attributed. The algorithm developed for the purposes of this study avoided to some extent the arbitrariness by selecting the ranges and therefore basing the scores upon the probability of their occurrence in healthy individuals (deviation from a normal range of mean \pm 2SD by one, two etc. standard deviations). The advantage of this procedure rests with the clear rule of range delimitation.

The two algorithms, as can be seen from Figure 1, classify somewhat differently the same patients, even if the internal correlation of two classes of results is very strong ($r = 0.98$). The own developed algorithm tends on the average to give higher scores to the patients than the clinical algorithm used so far. There is, however, no obvious indication that either of the algorithms is more or less correct than the other. From the standpoint of the question posed, i.e. whether the liver assessment damage by means of Cl_{Hp} or Cl_{Pi} substantially differ with either classification of patients, the answer is negative. In both cases, however, the hepatic clearance seems to demonstrate a somewhat stricter correlation than the plasma clearance.

Factorial analysis

From the factorial analysis it follows that the higher "factor loading" obtains for the hepatic clearance, even if the difference from that for the plasma clearance is small. This is probably due to the reasons specified above for the differences in correlation studies of total score for liver damage and clearance values (Cl_{Hp} , Cl_{Pi}).

Normal values of Cl_{Hp} and Cl_{Pi} and their relation to sex and age

As can be seen from Table 4, mean values of Cl_{Hp} and Cl_{Pi} in healthy males are higher than their counterparts in females. This result is similar to that seen for kidney clearances (GFR, ERPEF) [12–14].

The effect of age on hepatic and total plasma clearance of ^{99m}Tc -HEPIDA is different from that observed for kidney clearances. The latter change with age, their highest values are observed in the age bracket 20–30 years and they decline with advancing age [12–14]. As can be seen in Figure 2 and 3 for both Cl_{Hp} and Cl_{Pi} there seems to exist a slight trend (statistically, however, insignificant) for decline with age, more readily apparent for Cl_{Pi} , than for Cl_{Hp} . In general one can assume, particularly for Cl_{Hp} , that age has no important effect on this clearance. Perhaps a slight trend seen for Cl_{Pi} may result from decline with age of its urinary component.

Lower boundaries of normal values for Cl_{Hp} and Cl_{Pi}

In clinical practice an important question is that of the lower boundaries of the test, which can help to differentiate health from disease. At present it seems that this boundary can be taken as a mean for males or females minus two standard deviations. The respective values for Cl_{Pi} are 160 and 150 ml/min/1.73 m² for male and females, respectively. For Cl_{Hp} they would correspondingly be 120 and 115 ml/min/1.73 m². For this latter clearance the difference is very small and probably of little, if any, clinical significance. Therefore it seems acceptable to recommend lower normal boundaries for Cl_{Hp} and Cl_{Pi} of 115 and 150 ml/min/1.73 m², respectively.

For an assessment of the clinical usefulness of Cl_{Hp} for monitoring of patients' condition a further study on standard errors of clearance determination and its relation to absolute magnitude of the clearance seems indispensable. Respective studies are under way.

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