0270-9139/88/0805-1079$02.00/0
HEPATOLOGY

Vol. 8, No. 5, pp. 1079–1083, 1988
Printed in U.S.A.

Galactose Elimination Capacity and Liver Volume in Aging Man

GIULIO MARCHESINI, VINCENZO BUA, ALESSANDRA BRUNORI, GIAMPAOLO BIANCHI, PAOLO PISI, ANDREA FABBRI, MARCO ZOLI AND EMILIO PISI

Istituto di Clinica Medica Generale e Terapia and Istituto di Radiologia, University of Bologna, Policlinico S. Orsola, I-40138 Bologna, Italy

The galactose elimination capacity, a measure of the functional liver cell mass, and liver volume were measured in 50 normal subjects of five different age groups (<50, 51 to 60, 61 to 70, 71 to 80 and >81 years). The volume of the liver was evaluated by ultrasonography. All subjects had normal routine liver function tests and no history of liver disease. Galactose elimination progressively decreased from 3.05 ± 0.58 (S.D.) mmoles per min in younger subjects to 1.83 ± 0.24 mmoles per min in subjects over 81 ($p < 0.00003$), without any change in the apparent volume of distribution of the sugar. Similarly, the estimated volume of the liver decreased from 110 ± 14 units to 75 ± 13 units with increasing age ($p < 0.0002$). Both galactose elimination capacity and the estimated liver volume inversely correlated with age ($r = -0.728$ and $r = -0.579$, respectively) whereas a positive correlation was observed between galactose elimination and the estimated liver volume ($r = 0.520$). Part correlation analysis confirmed that age, when entered in a multiple regression already containing body weight and estimated liver volume as independent variables, had a significant effect on liver function, whereas no significant independent effect of liver volume was present. Both age and body weight had a significant independent effect on the estimated liver volume.

The maximum functional capacity of the liver, measured by galactose elimination, is reduced in the elderly. Although several factors may play a role, our data suggest that aging is associated with a slight decline in the intrinsic metabolic activity of the hepatic parenchyma.

In recent years, the progressive increase in the life span has led to a growing social and scientific interest in the medical problems of the elderly. Most of the patients admitted to Italian medical departments, as well as to hospitals in most developed countries, are of geriatric age. In these subjects, aging itself may cause alterations in the laboratory data, in the absence of any well-defined disease.

Received March 11, 1987; accepted February 26, 1988.
Supported by Research Contract 84.02466.56 from the Consiglio Nazionale delle Ricerche, Rome, Italy: Target Project "Preventive Medicine and Rehabilitation"; Subproject SP2 "Mechanism of aging."
Address reprint requests to: G. Marchesini, M.D., Istituto di Clinica Medica Generale, Policlinico S. Orsola, Via Massarenti 9, I-40138 Bologna, Italy.

Although renal function has long been extensively investigated (1), little is known about hepatic function, for which tests for quantitative determination are still under debate and limited to research departments (2). Scanty and conflicting data (3–6) are available on bromosulfophthalein retention in the elderly, while microsomal activity, measured by the kinetics of several drugs, is variably altered (7). Recently, reduced microsomal activity and impaired galactose elimination capacity were reported in subjects over 70 years (8), in comparison to normal values previously obtained in younger subjects.

Decreased hepatic function might result from either impaired hepatocellular activity or decreased liver volume. In the elderly the volume of the liver, measured by ultrasound, is reduced and correlates positively with total body weight, lean body mass and surface area (9).

We prospectively measured the volume of the liver and the galactose elimination capacity in a large series of normal subjects of different age groups to study the relationship between liver function and liver volume in the course of aging.

MATERIALS AND METHODS

Subjects. Fifty subjects were studied. They were divided into five age groups (<51, 51 to 60, 61 to 70, 71 to 80 and >81 years) of 10 subjects each. The age range of the under 51 group was 26 to 46 years (median = 40 years). All but five had been admitted to hospital because of gastrointestinal diseases (six cases), renal stones (three cases), mild cardiovascular symptoms (six cases), pneumonia or chronic bronchitis (seven cases), psychiatric illness (eight cases), cerebrovascular diseases (10 cases), or osteoarthritis (five cases). Five subjects in the youngest age group were members of the medical staff and were examined as outpatients. Hospitalized subjects were studied after recovery from the acute illness which had caused hospital admission. At the time of the study, no subject was taking medications known to affect liver function or glucose metabolism. Their body weight and height are reported in Table 1. Body weight was within ±10% of ideal body weight (Metropolitan Life Insurance Tables). Body mass index (weight/height^2) was 24.1 ± 1.9 in subjects under 50 years and 22.9 ± 3.0, 24.0 ± 2.7, 22.8 ± 3.4 and 21.0 ± 3.2 in the different age groups (not significantly different).

All subjects had normal routine liver and kidney function tests (albumin, prothrombin activity, bilirubin, AST, ALT, alkaline phosphatases, creatinine and BUN) and normal serum potassium. All subjects gave their informed consent to take

part in the study. The protocol was approved by the steering committee of the Consiglio Nazionale delle Ricerche, Rome, Italy.

Methods. Galactose elimination capacity was measured in fasting subjects, starting between 8:30 and 9:00 a.m. Galactose concentrations were determined every 5 min in capillary blood 20 to 45 min after the i.v. injection of 0.5 gm per kg of body weight of galactose in a 30% solution (w/v). The galactose elimination capacity was calculated according to Tygstrup's procedure (10), assuming a urinary loss of galactose equal to 10% of the injected dose.

Galactose was determined enzymatically (test-combination galactose; Boehringer Mannheim, Federal Republic of Germany). Routine liver function tests (albumin, prothrombin activity, cholesterol, bilirubin) were measured 1 to 3 days before the galactose test by means of standard laboratory techniques.

The size of the liver was evaluated by ultrasonography 2 to 4 days before the galactose elimination test, using a real-time instrument (Aloka SSD-280; Aloka Co., Ltd., Japan), equipped with a 3.5 MHz linear array-type probe. The hepatic volumetric index (HVI) (11), modified for real-time instruments and linear array probe (12), was calculated on the basis of the 3 maximum diameters of the liver [anteroposterior (A-P), craniocaudal (C-C) and transverse (L-L)] with the following formula:

$$HVI = (A\text{-}P \times L\text{-}L \times C\text{-}C)/27$$

Liver volume was also measured by computed tomography (CT) (13), in nine subjects, ages 46 to 82 years, in order to validate the ultrasound assessment. Transverse scans across the liver were obtained at 1-cm intervals on a Thomson-CGR Model CE 12000 (Thomson-CGR, Paris Cedex, France), with a cycle time of 6.8 sec. The outline of each section area was traced using a track ball device, and the area was electronically calculated by the computer. The volume of the entire liver was then obtained by summing up the volumes of the individual slices.

In this small series a positive correlation was observed between HVI (mean = 95 ± 32 units) and CT liver volume (1,196 ± 396 ml) (r = 0.975). The equation of the curve, which predicts liver volume at any given HVI value, is:

$$y = 36.8 + 12.1 \times HVI$$

where y is liver volume in cm^3 and HVI is in units. The line passes in proximity to the origin of the coordinates. The S.E. of liver volume estimated on the basis of HVI is 93 cm^3.

Statistical Analysis. All data were submitted to the Kolmogorov-Smirnov goodness-of-fit test, which did not reject the hypothesis of a normal distribution. Differences between the mean values of the different parameters in the various age groups were tested for significance by means of one-way analysis of variance (ANOVA). p values lower than 0.05 were considered statistically significant. The data in the test and in the tables are given as means ± S.D. The coefficients of correlation (r) between individual variables were assessed by linear correlation analysis. Since several parameters (age, weight, liver volume and galactose elimination) were significantly correlated to each other, a multiple regression analysis considering either liver volume or galactose elimination as the dependent variable was also carried out. The method estimates the total amount of variance of the dependent variable which is explained by the interaction of the three independent variables. In addition, it calculates the coefficients of part determination (R^2). This coefficient represents the percentage amount of variance of the dependent variable which is explained by adding each single independent variable to the equation already containing the other two independent variables (14, 15).

RESULTS

Body weight progressively declined in the course of aging, although no clear-cut differences were observed among groups. A negative correlation was observed between age and body weight (r = −0.435).

No differences in the plasma levels of albumin, total bilirubin and prothrombin activity were observed in the various groups (Table 1). Cholesterol levels were significantly reduced in the older age groups. The kinetics of galactose (Table 2) showed a reduced elimination capacity in the elderly, in the absence of any significant difference in the volume of distribution of the sugar, estimated by the intercept on the *y* axis of the regression of galactose concentration on time. The concentration of galactose 45 min after i.v. injection was significantly higher in the elderly. When measured in relation to body weight, the galactose elimination capacity was 41.6 ± 3.2 μmoles per kg × min in younger subjects and 38.1 ± 3.3, 37.1 ± 4.1, 34.1 ± 3.0 and 32.6 ± 5.4 μmoles per kg × min with increasing age (p = 0.0002).

A negative correlation (Figure 1) was observed between increasing age and decreasing galactose elimination (r = −0.728; p < 0.001).

The volume of the liver was also reduced in the older age groups, by approximately 30% in subjects over 81 years in comparison to normal subjects below 50 years. When related to body weight, liver volume decreased in older age groups, but the difference was not statistically significant (<50 years: 1.56 ± 0.27 units per kg body weight, and 1.45 ± 0.38, 1.36 ± 0.20, 1.39 ± 0.29 and 1.36 ± 0.38 with increasing age; p = 0.567).

A negative correlation was observed between increasing age and the estimated liver volume (r = −0.579; p < 0.001) (Figure 2). Liver volume, estimated by the HVI, directly correlated with galactose elimination (r = 0.520; p < 0.001) (Figure 3) and with body weight (r = 0.334; p < 0.05). The amount of galactose removed per unit of volume was not statistically different in the various age groups. However, it slightly decreased in the elderly and negatively correlated with increasing age (r = −0.283; p < 0.05).

In a multiple regression analysis, we calculated the relative contribution of age, weight and liver volume to decreased galactose elimination, as well as the effect of age and body weight on liver volume (Table 3). When age was added to the regression already containing body weight and liver volume as independent variables, it still explained more than 10% of the total variance of galactose elimination. Similarly, body weight had a significant independent effect, while the estimated liver volume failed to contribute significantly to the regression. As for liver volume, both age and body weight had a small but significant independent effect.

DISCUSSION

The present study confirms a previous finding of reduced galactose elimination capacity in the elderly (8).

In the analysis of the data, we assumed a urinary loss of galactose equal to 10% of the injected dose. In very old people, the glomerular filtration rate is also reduced in the presence of normal creatinine levels. This might

TABLE 1. Anthropometric measurements and routine liver function tests in the different age groups (mean ± S.D.)

Age (years)	Body weight (kg)	Body height (cm)	Albumin level (gm/dl)	Cholesterol level (mmoles/liter)	Prothrombin activity (%)	Total bilirubin (μmoles/liter)
<51	72 ± 10	172 ± 10	3.99 ± 0.26	5.21 ± 1.06	97 ± 4	12.2 ± 2.1
51–60	65 ± 11	168 ± 5	3.84 ± 0.29	6.14 ± 1.02	98 ± 4	11.6 ± 1.6
61–70	65 ± 9	165 ± 7	4.08 ± 0.22	6.01 ± 0.95	96 ± 6	12.4 ± 1.5
71–80	64 ± 12	167 ± 6	4.18 ± 0.33	4.84 ± 0.88	93 ± 7	10.9 ± 2.6
>81	57 ± 10	165 ± 6	4.01 ± 0.28	4.25 ± 0.72	93 ± 8	12.0 ± 1.1
ANOVA: p =	0.071	0.124	0.141	0.0003	0.262	0.446

TABLE 2. Liver volume and kinetic parameters of galactose elimination in the different age groups (mean ± S.D.)

Age (years)	Volume of the liver (units)	Galactose elimination test				
		Elimination capacity (mmoles/min)	Volume of distribution (liters)	Concentration (mmoles/liter)		Galactose elimination/unit of volume (μmoles/min × unit)
				0 min[a]	45 min[b]	
<51	110 ± 14	3.05 ± 0.58	25.6 ± 4.8	7.89 ± 0.78	1.16 ± 0.49	28.0 ± 6.5
51–60	97 ± 22	2.57 ± 0.55	22.8 ± 7.9	8.50 ± 2.27	2.09 ± 0.86	27.3 ± 6.5
61–70	88 ± 13	2.40 ± 0.25	23.7 ± 8.7	8.28 ± 2.11	2.16 ± 0.63	27.6 ± 4.1
71–80	86 ± 12	2.19 ± 0.48	22.3 ± 7.3	8.44 ± 1.42	2.75 ± 0.75	25.7 ± 7.1
>81	75 ± 13	1.83 ± 0.24	18.5 ± 5.6	9.05 ± 2.05	3.22 ± 1.09	25.3 ± 6.0
ANOVA: p =	0.0002	0.00003	0.271	0.668	0.00006	0.672

[a] Intercept on the y axis of the regression of galactose concentration on time.
[b] Measured concentration at time 45 min.

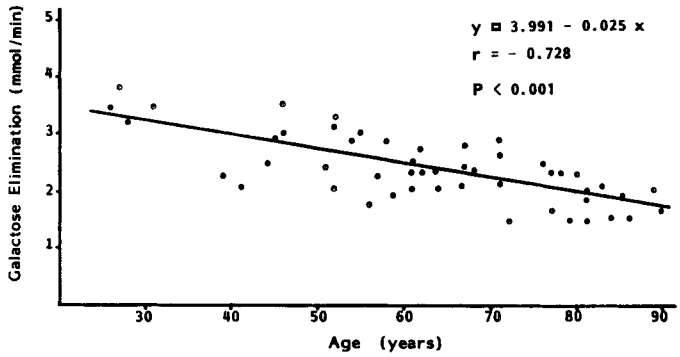

FIG. 1. Correlation between age and galactose elimination capacity in subjects of different age groups.

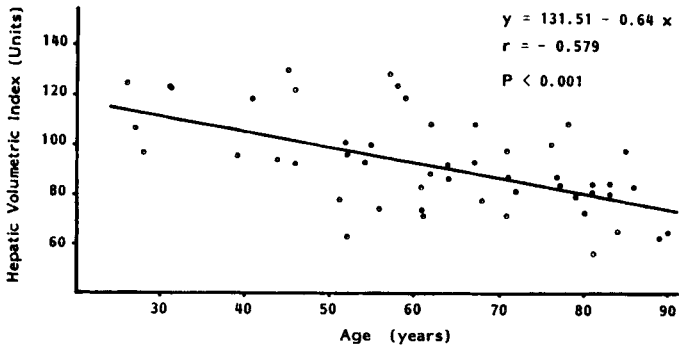

FIG. 2. Correlation between age and liver volume, semiquantitatively measured by calculating the hepatic volumetric index at ultrasound.

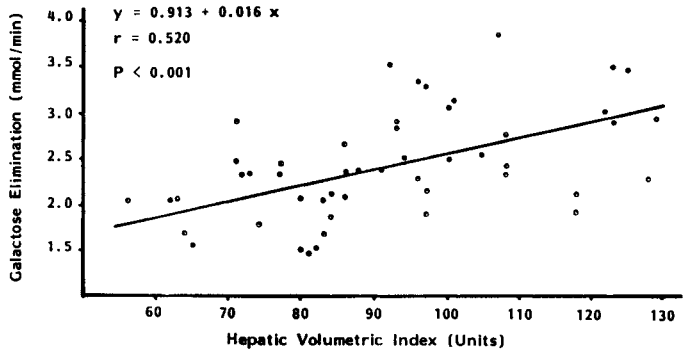

FIG. 3. Correlation between liver volume (hepatic volumetric index) and liver function (galactose elimination capacity) in subjects of different age groups.

lead to reduction of excretion of galactose in urine. However, also assuming that only 5% of the injected dose is excreted in urine in subjects over 70 years old, the galactose elimination capacity would increase to 2.27 ± 0.49 mmoles per min in subjects ages 71 to 80 years and to 1.95 ± 0.24 in subjects over 80. This does not change the results significantly (ANOVA on the whole population, F ratio = 7.70; $p < 0.0002$). Galactose elimination was expressed in mmoles per min and was not related to body weight, as it is frequently reported. Expressing galactose removal per kg body weight implies that liver weight is directly proportional to body weight, and we preferred to include the estimated liver volume, measured by ultrasound, among the independent variables.

The data we present are compatible with a decreased functional hepatic reserve in the elderly, which can be assessed by studying the maximum elimination of a substrate having a low K_m, such as galactose, or measuring the clearance of a substrate having a high K_m, such as antipyrine (2).

The measurement of plasma concentration of endogenous substrates or products of liver metabolism is of no

TABLE 3. Multiple regression analysis and coefficients of part correlation

Dependent variable	Independent variables (R^2)				
	Total R^2	Age (years)	GEC[a] (mmoles/min)	HVI (units)	Body weight (kg)
GEC (mmoles/min)	82.2[b]	10.9[b]		0.5	27.8[b]
Estimated liver volume (units)	36.7[b]	5.8[c]	0.5		5.4[c]

The second column (Total R^2) indicates the percentage amount of variance of the dependent variable which is explained by the interaction of the three independent variables; the following columns indicate the percentage amount of variance of the dependent variable which is explained by adding each dependent variable to the regression already containing the other independent variables (part correlation analysis).

[a] GEC = galactose elimination capacity.

[b] $p < 0.001$.

[c] $p < 0.05$.

use to detect such small abnormalities because of the functional reserve which compensates for decreased liver function. This is the reason why galactose elimination was impaired in subjects whose routine liver function tests were within the normal limits. Bilirubin was repeatedly shown to be normal in the elderly (3, 6, 16, 17). Albumin may be low in the elderly (18, 19), but mainly in association with disease and malnutrition in hospitalized old people (20). Also, prothrombin activity may be reduced only in severely sick and malnourished patients with vitamin K deficiency (21). Since normal routine liver function tests were among the selection criteria, no conclusion can be drawn from the present study.

Cholesterol levels were surprisingly reduced in the older age groups. In longitudinal studies a progressive increase in plasma cholesterol is usually observed (22), while in cross-sectional studies cholesterol levels are somewhat reduced in the older age groups (23). This conflicting result might arise from the natural selection. Subjects with low cholesterol might survive longer, being the majority in older age groups.

Circulatory changes were also reported in the elderly. Hepatic blood flow decreases with age (24), this reduction being responsible for decreased clearance of drugs whose removal mainly depends on effective blood flow. Under our experimental conditions, the removal of galactose is independent from hepatic flow and a decreased elimination reflects a reduced hepatic cell mass (2).

In the subjects under study, the impaired functional liver cell mass in the elderly is associated with reduced liver size, measured by ultrasound.

The measurement of liver size by means of ultrasonography has been validated recently by a comparative study of ultrasonography and CT vs. the actual size of the liver in subjects undergoing liver transplantation (13). Complex ultrasonographic techniques, based either on the measurement of several section areas obtained during parallel scans (25) or on complex formulas following angular scans (26), may give a direct estimate of the actual size of the liver. However, these methods require manual equipment, which is technically out of date. The new real-time ultrasonographic instruments, equipped with linear or sectorial probes, are unsuitable to carry out parallel scans. Simpler methods, based on the evaluation of the maximum diameters of the liver, can be carried out with real-time probes. A single maximum diameter (cranio-caudal) proved to give a rough estimation of the actual volume of the liver, measured at autopsy (27). The simple method we used gives an almost accurate estimate of the actual size of the liver, as proved by correlation with CT measurements. Moreover, the figure derived from this simple calculation has been validated in subjects undergoing partial liver resection (28).

Changes in liver volume in the elderly have been reported previously. Old necropsy studies revealed that the weight of the liver is reduced in subjects over 50 years (29, 30) and correlates directly with total body weight (3), as also confirmed in the present series. In extremely old healthy people the liver may be very small (31), and the reduction in liver volume is larger than expected on the basis of reduced body weight. Microscopic studies showed that minor changes in liver histology also occur in the elderly. Portal fibrosis is common (32), possibly in relation to increased collagen deposition (33), and is likely to alter hepatic metabolism.

These alterations, together with decreased hepatic volume, are likely to be responsible for the decreased liver function in the elderly.

Indeed, the main result of the present study is to show that the decrease in both liver function and liver volume in the elderly is larger than expected on the basis of reduced body weight. Although part of the decreased galactose elimination capacity is due to decreased body weight, age maintains an independent effect on galactose kinetics when the variance due to body weight is removed. This conclusion is in keeping with the results obtained by Schnegg and Lauterburg (8), who reported a decrease in galactose elimination per kg of body weight in the elderly. In addition, age itself has a role in decreased liver volume, although the variance due to age is small.

The finding that liver volume has no independent effect on liver function is intriguing. This conclusion is derived from the lack of any significant difference in galactose elimination per unit of estimated volume and by the low correlation coefficient for the association between galactose elimination per unit of volume and age. Finally, these data were confirmed by multiple regression analysis, which indicated that liver volume accounts for only 0.5% of the total variance of galactose elimination, when the volume is added in the equation

already containing age and body weight. The data suggest that the alterations in liver histology present in the elderly, and probably responsible for decreased liver function, may be largely variable in normal populations.

Finally, the finding of decreased galactose elimination capacity in relation to age raises the question whether the "normal limits" of galactose elimination should be age related.

Acknowledgment: The authors are indebted to Dr. Anna G. Rusticali for her skillful assistance in the statistical analysis.

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