Calculation of Child and Adult Standard Liver Volume for Liver Transplantation

Koichi Urata,¹ Seiji Kawasaki,¹ Hidetoshi Matsunami,¹ Yasuhiko Hashikura,¹ Toshihiko Ikegami,¹ Shinpachi Ishizone, Yoshitaka Momose, Atsushi Komiyama, And Masatoshi Makuuchi

Despite refinements in surgical techniques for liver transplantation, liver size disparity remains one of the most common problems in pediatric patients. Optimal liver graft size remains unknown and the volume of diseased liver in the recipient is not indicative of the volume (standard liver volume [LV]) optimal for the recipient's metabolic demands. To establish a formula for calculating the standard LV in the pediatric and adult populations for liver transplantation, whole LVs were measured using computed tomography (CT) in 96 patients (65 pediatric and 31 adolescent or adult subjects) with normal liver whose disease conditions did not seem to affect body weight (BW) or LV. In the 96 subjects, the ratio of estimated LV to BW decreased gradually as age increased until approximately 16 years, when it started to level off. On the other hand, there seemed to be a directly proportional relationship between the estimated LV in vivo and body surface area (BSA) (r = .981; $r^2 = .962$; P < .0001) in the subjects as a whole, and the formula, LV (mL) = $706.2 \times BSA (m^2) + 2.4$, was established from the measured data by simple regression analysis. Another predicting equation, LV (mL) = $2.223 \times BW \text{ (kg)}^{0.426} \times body \text{ height (BH) (cm)}^{0.682}$, was produced by multiple regression analysis ($r^2 = .969$; P < .0001). Considering its simplicity of use, we adopted the first formula for predicting standard LV in an individual patient. (HEPATOLOGY 1995;21:1317-1321.)

Because of the shortage of grafts for pediatric recipients requiring liver transplantation, procedures using reduced-size grafts have been used with increasing frequency. 1-3 Based on clinical experience of such graft size modifications, new techniques using split-liver grafts⁴ and partial liver grafts from living adult donors^{5,6} have been introduced successfully for pediatric or partial grafts from living donors (Hashikura Y, et al, Lancet 1994;343:1233-1234, Correspondence) into adult patients has been reported. In these situations, some of the postoperative complications that occur are related to the disproportionate size of the liver graft in comparison with the recipient's native liver volume (LV). When a large-for-size graft is

liver transplantation. Furthermore, the transplanta-

tion of small liver grafts from cadaveric child donors⁷

transplanted into a small recipient, hepatic artery or portal vein thrombosis may occur caused by graft compression and poor perfusion.8-10 On the other hand, small-for-size grafts may cause primary nonfunction and graft dysfunction 11 and increase the risk of rejection. 12 To minimize these complications associated with graft size disparity, the LV (standard LV) optimal for the metabolic demands of an individual patient needs to be estimated preoperatively because accurate assessment of this parameter can provide useful information for selection of the graft reduction procedure in reduced-size liver transplantation or for selection of the type of donor hepatectomy in living-related liver transplantation (LRLT). 13,14

The aim of the present study was to establish a standard relationship between recipient body size and LV.

PATIENTS AND METHODS

LV and Weight Determinations in LRLT Recipients. Nine male and 10 female pediatric patients ranging in age from 5 months to 15 years with an average age of 5.3 ± 5.0 years underwent LRLT for end-stage liver disease (14 cases of biliary atresia, 4 cases of postnecrotic cirrhosis, and 1 case of postnecrotic cirrhosis with hepatocellular carcinoma) at the First Department of Surgery, Shinshu University, between June 1990 and May 1994.

These 19 children were subjected to the whole LV measurement using computed tomography (CT) before surgery. Serial abdominal transverse CT taken at 0.8- or 1.0-cm intervals including the segment between the dome of the liver and the most inferior part of the organ were used to calculate the LV by the method of Heymsfield et al¹⁵ with minor modifications. The perimeter of the whole liver was outlined on each slice using a track ball device, and the enclosed area was measured on an Apple Macintosh IIci computer (Apple Japan, Inc., Tokyo, Japan) using the National Institutes of Health Image 1.41 public domain program. We added these areas together and multiplied the total by the slice width to assess the total LV.

Abbreviations: LV, liver volume; LRLT, living-related liver transplantation; CT, computed tomography; BW, body weight; BH, body height; BSA, body surface area; DRWR, donor-to-recipient weight ratio.

From the 'First Department of Surgery, 'Department of Pediatrics, Shinshu University School of Medicine, Matsumoto; 3Department of Surgery, Nagano Children's Hospital, Toyoshina, Japan.

Received June 13, 1994; accepted December 9, 1994.

Address reprint requests to: Seiji Kawasaki, MD, First Department of Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390, Japan.

Copyright © 1995 by the American Association for the Study of Liver Diseases.

^{0270-9139/95/2105-0014\$3.00/0}

1318 URATA ET AL HEPATOLOGY May 1995

The recipient's liver was weighed after the attached ligaments and gallbladder had been dissected and removed. The weight determination was performed without knowledge of the previously estimated volume calculated from the CT images. The absolute value of liver weight was considered to be equivalent to the actual volume because the density of the liver is nearly the same as that of water. ¹⁶

LV Determinations in Subjects With Normal Liver. A total of 61 male and 35 female patients, ranging in age from 1 month to 27 years with an average age of 11.1 ± 8.8 years, were investigated retrospectively for this study. During the period between April 1989 and February 1994, these patients had undergone serial abdominal CT scans at Shinshu University Hospital or affiliated hospitals for the following reasons: abdominal pain, fever, constipation, or macrohematuria of unknown cause; abdominal trauma; localization of tumors in patients showing increased levels of urinary vanillylmandelic acid; screening and staging of malignancies; determination of segmental LV for preoperative assessment as LRLT donors. None of the patients studied showed any liver abnormalities at CT examination or at follow-up (Table 1).17,18 All of the children were between the 5th percentile and the 95th percentile on the standard physical growth chart. 19 Patients with malignant tumors that appeared to weigh more than 0.5% of total body weight (BW) were excluded. For patients with malignancies, we calculated the LV using CT films taken before surgical treatment or chemotherapy.

BW and body height (BH) recorded at the time of CT examination were used for calculating the body surface area (BSA). Because the DuBois formula tends to underestimate BSA in infants, 20 BSA was calculated using the equation of Haycock et al 21 : BSA (m²) = BW (kg) $^{0.378} \times$ BH (cm) $^{0.3964} \times$ 0.024265 for children who weighed less than 15 kg, and that of DuBois and DuBois 22 for children and adults who weighed 15 kg or more: BSA (m²) = BW (kg) $^{0.425} \times$ BH (cm) $^{0.725} \times$ 0.007184, as used by Whitington et al. 23

LVs were measured from CT scan films using the technique described above. Moreover, the ratio of LV to BW (LV/BW ratio) and the ratio of LV to BSA (LV/BSA ratio) in the infant group (<2 years) were compared with those in the adolescent/adult (\geq 16 years) group. The LV/BSA ratio was also compared between males and females.

TABLE 1. Reasons for Abdominal CT Scanning in 96 Patients

Condition	No. of Patients
Abdominal trauma	33
Abdominal pain	20
Neuroblastoma (stage 1, 2A, 4S)*	16
Increased urinary VMA level	9
Abdominal mass	4
Constipation	3
LRLT donor	2
Macrohematuria	2
Fever	2
Non-Hodgkin's lymphoma (stage I)†	2
Teratoid tumor	2
Total	96

NOTE. In all of the cases, hepatic involvement was excluded. Abbreviation: VMA, vanillylmandelic acid.

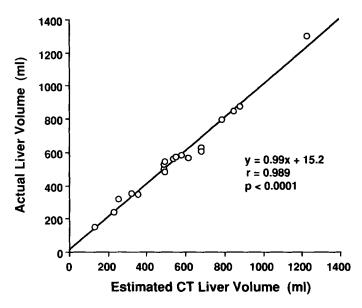


FIG. 1. Relationship between CT-estimated and actual LVs in LRLT recipients.

Statistical Analysis. The actual LVs were plotted against the estimated CT liver volumes in the 19 LRLT recipients. The calculated CT LVs were plotted against age, BH, BW, and BSA in the 96 subjects. The LV/BW ratios were also plotted against age. A microcomputer-based program of least-squares regression was used to establish possible linear relationships between the dependent and individual independent variables. Then, analysis of residuals was used to evaluate the fit of the regression equations, and multiple regression analysis was used in the prediction equation for independent variables as necessary. The significance of regressions was determined by F test. The significance of differences between means was determined by Student's t-test for unpaired populations. The null hypothesis was rejected at a P value of less than .05. Data are presented as means \pm SD except where indicated.

RESULTS

Relationship Between Actual Volume and Estimated CT Volume of Pediatric Recipients' Livers. The weight of the 19 livers removed at surgery averaged 568 ± 260 g with a range of 151 to 1,300 g. The estimated CT volume of these 19 livers averaged 560 ± 261 mL, and ranged from 131 to 1,230 mL. The differences between radiographically determined and actual organ volumes, expressed as percentage of actual volume, ranged from -12.4% to 20.5%, with a mean of $2.4 \pm 7.8\%$. The relationship between actual volume and CT-estimated volume for the 19 livers is shown in Fig. 1 (r = .989; P < .0001). As a whole, the CT-calculated LV was considered to have been estimated with acceptable accuracy on comparison with the actual LV in the pediatric population.

Standard LV in Children and Adults. The calculated CT volume of the 96 normal livers averaged 764 ± 380 mL (range, 138 to 1,544 mL), with an average BW of 33.8 ± 21.6 kg (4.0 to 78.0 kg), an average BH of 126.6 ± 40.9 cm (53.6 to 178.0 cm), and an average BSA of

^{*} Staging in accordance with Brodeur et al. 17

 $[\]dagger$ Staging in accordance with Murphy et al. 18

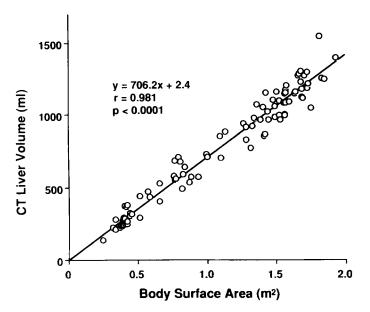


Fig. 2. Relationship between BSA and CT-estimated LV in 96 subjects with normal livers.

 1.078 ± 0.528 m 2 (0.248 to 1.935 m 2). The estimated CT LV $in\ vivo$ was significantly related to age (r=.905; P<.0001), BW (r=.972, P<.0001), BH (r=.968; P<.0001), and BSA (r=.981; P<.0001). The analysis of residuals demonstrated that liver size $in\ vivo$ was correlated most linearly with BSA among the four parameters. On the basis of these results, the following equation was derived from our data by linear regression analysis (Fig. 2) to predict the LV for normal children and adults:

$$LV (mL) = 706.2 \times BSA (m^2) + 2.4.$$

The value of the coefficient of determination, " r^2 ," was .962. The size of the coefficient of determination, "adjusted R squared," which one would expect to see in another group of application, was .962.

Another equation for predicting the liver size *in vivo* was established from our data by multiple regression analysis. BH and BW were taken as independent variables, and calculated CT LV as the dependent; the relationship was analyzed in the form:

log (liver volume) = x log BW + y log BH

+ log z (equivalent to: liver volume = $BW^x \times BH^y \times z$).

The least squares best fit for this equation yielded the formula:

liver volume (mL) = BW (kg) $^{0.426}$ × BH (cm) $^{0.682}$

$$\times$$
 2.223 (r^2 = .969; adjusted R² = .968; P < .0001).

A plot of LV/BW ratio versus age is shown in Fig. 3. The LV/BW ratio decreased as age increased, until approximately 16 years, when it began to level off. There was a significantly negative correlation between LV/BW ratio and age in subjects younger than 16 years

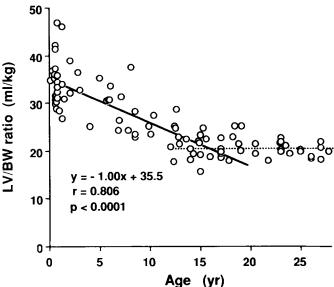


FIG. 3. Relationship between age and LV/BW ratio in 96 subjects with normal liver. A significant negative correlation was observed in subjects younger than 16 years of age.

of age with normal liver (r=.806; P<.0001). The mean value of LV/BW ratio was 34.5 ± 5.1 mL/kg in infants (younger than 2 years of age), which was significantly larger than the value in adolescents and adults (≥16 years of age; 20.5 ± 1.9 mL/kg; P<.001) (Table 2).

On the other hand, the LV/BSA ratio averaged 707.6 \pm 79.8 mL/m² in the subjects as a whole. It was 687.9 \pm 98.6 mL/m² in infants (younger than 2 years of age), and 712.0 \pm 51.2 mL/m² in adolescents and adults (\geq 16 years of age) (Table 2). The ratios in males and females were 709.2 \pm 73.8 mL/m² and 705.0 \pm 90.5 mL/m², respectively. No significant differences in the LV/BSA ratio were observed between the infant and adolescent/adult groups (P > .1) or between males and females (P > .1).

The mean LVs in adolescent/adult (≥ 16 years of age) males and females were 1,225 \pm 124 mL and 1,057 \pm 108 mL, respectively.

TABLE 2. Volumetric Data in the Infant and Adolescent/Adult Groups

	Infant (<2 yr)	Adolescent/ Adult (≥16 yr)
No.	26	31
Sex (male/female)	19/7	17/14
BW (kg)*†	8.0 ± 1.4	56.5 ± 8.5
BH (cm)*†	69.4 ± 5.9	164.8 ± 8.1
BSA (m ²)*†	0.398 ± 0.049	1.613 ± 0.513
CT liver volume (mL)*†	274 ± 53	1149 ± 142
LV/BW ratio (mL/kg)*†	34.5 ± 5.1	20.5 ± 1.9
LV/BSA ratio (mL/m²)*	687.9 ± 98.6	712.0 ± 51.2

^{*} Data expressed as mean ± SD.

 $[\]dagger$ SD (P < .001) between the two groups.

1320 URATA ET AL HEPATOLOGY May 1995

DISCUSSION

For reduced-size liver transplantation, the donor-torecipient weight ratio (DRWR) has been widely used as a criterion for roughly estimating the graft size to fit the recipient's abdominal cavity. 2,3,24-26 However, whole-liver weight based on autopsy data is reported to be approximately 5% of BW at birth but only 2% in adults.²⁷ As described in this article, the LV/BW ratio was found not to be constant during the growing period. The ratio decreased gradually as age increased until approximately 16 years, and then reached a plateau (Fig. 3). Patients who require liver transplantation are often outside standard physical growth range for the corresponding age because various degrees of nutritional deficit are usually associated with end-stage liver disease. 28,29 Under these circumstances, liver size cannot be predicted only on the basis of the recipient's BW and/or age.

BSA is another parameter used frequently in physiology and clinical medicine to normalize measures of biological function with respect to variations in body size and conformation. Its use is based on some metabolic principles that can also apply to children. Caloric needs, total body water, and extracellular water are more closely related to BSA than to BW.30,31 Therefore. we considered that the liver mass required to meet the metabolic demands of the patient should correlate more closely with BSA than with other parameters such as BW, BH, or age. In spite of the significant disparity between the infant and adolescent/adult groups in BH, BW, BSA, LV, and LV/BW ratio, there was no difference in LV/BSA ratio between them (Table 2). Another finding was that males and females had essentially the same LV for a given value of BSA. This is in agreement with the results of autopsy measurements in adults reported by DeLand et al. 32

To predict liver size in proportion to body size, we first computed a simple regression model for BSA:

$$LV (mL) = 706.2 \times BSA (m^2) + 2.4.$$

We then calculated another formula for predicting liver volume using multiple regression analysis with two independent variables, BW and BH, without considering age:

$$LV (mL) = 2.223 \times BW (kg)^{0.426} \times BH (cm)^{0.682}$$
.

As described by Haycock et al 21 and DuBois and DuBois, 22 BSA can also be calculated from two independent control variables for body size, i.e., BW and BH, and thus our two models remain essentially the same. And yet the values of " r^2 ," the coefficient of determination, and adjusted R^2 , the size of the coefficient of determination one would expect to see in another group of application, are almost the same in the two models. Considering its simplicity of use, we adopted the first formula for predicting the standard LV for liver transplantation.

Most previous reports based on autopsy measurements give the range of liver weight for males or females and the ratios of organ weight to BW according to age. ³³⁻³⁵ To our knowledge, there has been only one report describing the relationship between liver weight and BSA in adults, ³² and no data are available on the definitive relationship between liver size and BSA in a pediatric population.

One autopsy study showed that liver weight in Japanese adults was lower than in European and American adults, whereas the liver weight to BW ratio in Japanese adults was slightly higher.³³ The investigators suggested that these findings might be caused by differences in body proportion between the two groups.

The values of LV we obtained from CT scans in vivo are somewhat small in comparison with those of liver weight in previous autopsy studies. The values of organ weight at autopsy in normal Japanese adolescent/adult (16 to 25 years of age) males and females averaged 1,483 and 1,159 g, respectively,³³ whereas in our study (16 to 27 years of age), they were 1,225 and 1,057 mL, respectively. The ratio of liver weight to BW in Japanese adolescents and adults (17 to 25 years of age) is approximately 26 g/kg from autopsy measurements, 33 compared with 20.5 mL/kg from our present data (Table 2). The reason for this is not clear, but the following factors may be significant. Usually in a legal postmortem examination, data from autopsy studies include the weight of the gallbladder, the attached ligaments, and the hepatic vena cava, whereas in our study these were excluded; also previous autopsy studies dealt with subjects who had died of acute causes involving some cases of shock such as cardiac failure and traffic accidents, which might have altered the liver weight through mechanisms associated with shock-related hepatic congestion. 36,37 Blood accumulation in the liver, which represents one of these postmortem alterations, may affect the weight of the organ in autopsy measurements.

In summary, total LV was estimated from CT scan images with acceptable accuracy in comparison with the actual volume of the organ obtained in a pediatric population. The liver volume to BW ratio is not constant during the growth period. However, the relationship between total LV and BSA in the pediatric and adult population can be established, and should provide useful information for preoperative estimation of standard LV in recipients and help the planning of liver transplantation.

Acknowledgment: We thank Drs A. Yafune and C. Hamada (Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo) for their help with statistical analysis, and Dr K. Shimizu (Department of Pediatric Surgery, Nagano Red Cross Hospital) for assistance in the preparation of this manuscript.

REFERENCES

- Bismuth H, Houssin D. Reduced-size orthotopic liver graft in hepatic transplantation in children. Surgery 1984;95:367-370.
- 2. de Hemptinne B, de Ville de Goyet J, Kestens PJ, Otte JB. Volume reduction of the liver graft before orthotopic transplanta-

- tion: report of a clinical experience in 11 cases. Transplant Proc 1987; 19:3317-3322.
- 3. Strong R, Ong TH, Pillay P, Wall D, Balderson G, Lynch S. A new method of segmental orthotopic liver transplantation in children. Surgery 1988;104:104-107.
- 4. Pichlmayr R, Ringe B, Gunbernatis G, Hauss J, Bunzendahl H. Transplantation einer Spenderleber auf zwei Empfanger (Splitting-Transplantation)-Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation. Langenbecks Arch Chir 1988;373:127-130.
- Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. N Engl J Med 1990;322:1505-1507.
- Makuuchi M, Kawasaki S, Noguchi T, Hashikura Y, Matsunami H, Hayashi K, Harada H, et al. Donor hepatectomy for living related partial liver transplantation. Surgery 1993; 113:395-402.
- Adam R, Castaing D, Bismuth H. Transplantation of small donor livers in adult recipient. Transplant Proc 1993;25:1105-1106.
- Kasai H, Makuuchi M, Kawasaki S, Ishizone S, Kitahara S, Matsunami H, Kawarazaki H. Intraoperative color Doppler ultrasonography for partial-liver transplantation from the living donor in pediatric patients. Transplantation 1992;54:173-175.
- Payen DM, Fratacci MD, Dupuy P, Gatecel C, Vigouroux C, Ozier Y, Houssin D, et al. Portal and hepatic arterial blood flow measurements of human transplanted liver by implanted Doppler probes: interest for early complications and nutrition. Surgery 1990;107:417-427.
- Stevens LH, Emond JC, Piper JB, Heffron TG, Thistlethwaite JR, Jr, Whitington PF, Broelsch CE. Hepatic artery thrombosis in infants. Transplantation 1992;53:396-399.
- 11. Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, Sasaki T, et al. Risk factors for primary dysfunction after liver transplantation: a multivariate analysis. Transplantation 1993;55:807-813.
- Shiraishi M, Csete ME, Yasunaga C, Drazan KE, Jurim O, Cramer DV, Busuttil RW, et al. Regeneration-induced accelerated rejection in reduced-size liver grafts. Transplantation 1994;57:336-340.
- Kawasaki S, Makuuchi M, Matsunami M, Hashikura Y, Ikegami T, Chisuwa H, Ikeno T, et al. Preoperative measurement of segmental liver volume of donors for living related liver transplantation. Hepatology 1993; 18:1115-1120.
- Kawasaki S, Makuuchi M, Ishizone S, Matsunami H, Terada M, Kawarazaki H. Liver regeneration in recipients and donors after transplantation. Lancet 1992;339:580-581.
- Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. Ann Intern Med 1979;90:185-187.
- Van Thiel DH, Hagler NG, Schade RR, Skolnick ML, Pollitt Heyl A, Rosenblum E, Gavaler JS, et al. In vivo hepatic volume determination using sonography and computed tomography. Gastroenterology 1985;88:1812-1817.
- Brodeur GM, Seeger RC, Barrett A, Berthold F, Castleberry RP, D'Angio G, De-Bernardi B, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. J Clin Oncol 1988;6:1874-1881.

- 18. Murphy SB. Prognostic features and obstacles to cure of child-hood non-Hodgkin's lymphoma. Semin Oncol 1977;4:265-271.
- The Ministry of Health and Welfare. National Nutrition Survey of Japan (1980). Tokyo: Dai-ichi-Shuppan, 1983.
- Brion L, Fleischman AR, Schwartz GJ. Evaluation of four lengthweight formulas for estimating body surface area in newborn infants. J Pediatr 1985; 107:801-803.
- 21. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 1978;93:62-66.
- 22. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863-871.
- Whitington PF, Emond JC, Whitington SH, Broelsch CE, Baker AL. Small-bowel length and the dose of cyclosporine in children after liver transplantation. N Engl J Med 1990;322:733-738.
- Kalayoglu M, D'Alessandro AM, Sollinger HW, Hoffman RM, Pirsch JD, Belzer FO. Experience with reduced-size liver transplantation. Surg Gynecol Obstet 1990;171:139-147.
- Houssin D, Soubrane O, Boillot O, Dousset B, Ozier Y, Devictor D, Bernard O, et al. Orthotopic liver transplantation with a reduced-size graft: an ideal compromise in pediatrics? Surgery 1991;111:532-542.
- Tan KC, Malcolm GP, Reece AS, Calne RY. Surgical anatomy of donor extended right trisegmentectomy before orthotopic liver transplantation in children. Br J Surg 1991;78:805-808.
- 27. Balistreri WF. Liver and biliary system: development of hepatic and biliary structure and function. In: Behrman RE, Kliegman RM, eds. Nelson textbook of pediatrics. Ed 14. Philadelphia: Saunders, 1992:1001-1004.
- 28. Martinez-Ibañez V, Boix-Ochoa J, Lloret J, Broto J. Paediatric liver transplantation: life after portoenterostomy in biliary atresia. J Pediatr Surg 1992;27:830-832.
- Chin SE, Shepherd RW, Thomas BJ, Cleghorn GJ, Patrick MK, Wilcox JA, Ong TH, et al. The nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation. Am J Clin Nutr 1992;56:164-168.
- Lewis RC, Duval AM, Iliff A. Standards for the basal metabolism of children from 2 to 15 years of age, inclusive. J Pediatr 1943;23:1-18.
- 31. Friis-Hansen B. The extracellular fluid volume in infants and children. Acta Paediatr 1954;43:444-458.
- 32. DeLand FH, North WA. Relationship between liver size and body size. Radiology 1968;91:1195-1198.
- 33. Tanaka G, Kawamura H. Reference Japanese man: I. Mass of organs and other characteristics of normal Japanese. Health Phys 1979;36:333-346.
- International Commission on Radiological Protection, "Report of the Task Group on Reference Man," ICRP Publication 23. Oxford: Pergamon Press, 1975.
- 35. Schulz DM, Giordano DA, Schulz DH. Weights of organs of fetuses and infants. Arch Pathol 1962;74:244-250.
- Cook GC. Hepatic changes associated with shock. Int Anethesiol Clin 1969;7:883-894.
- Sherlock S. The liver in heart failure: relation of anatomical, functional, and circulatory changes. Br Heart J 1951;13:273-293