

Recovery of Hepatic Asialoglycoprotein Receptors After Major Hepatic Resection

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Although morphological restoration of the hepatic mass after partial hepatectomy has been well studied, fewer reports have appeared on the change of functional hepatic capacity during liver regeneration. Asialoglycoprotein receptor (ASGP-R) is a hepatic cell surface receptor specific for galactose-terminated glycoprotein. Kinetic modeling of ^{99m}Tc -labeled diethylenetriamine pentaacetic acid-galactosyl-human serum albumin (TcGSA) time-activity data yields estimates of ASGP-R concentration $[R]_0$ and amount R_0 , which are directly related to functional liver mass. We have investigated the changes in ASGP-R status as well as liver volume in regenerating human liver after major hepatic resection. **Methods:** Twenty-two patients (18 noncirrhotic, 4 cirrhotic) had a TcGSA study before and 3 wk after major hepatic resection, with a mean hepatic parenchymal resection rate of 36.0%. **Results:** $[R]_0$ was significantly decreased from $0.683 \pm 0.024 \mu\text{mol/L}$ to $0.565 \pm 0.032 \mu\text{mol/L}$ ($P < 0.001$) after resection. The decrease in $[R]_0$ was more prominent in cirrhotic patients. Recovery of ASGP-R was observed as a significantly increased R_0 3 wk after the operation. Subsequent (long-term) restoration of ASGP-R appeared to be slower when compared with the volume restoration. **Conclusion:** ASGP-R concentration of the liver significantly decreased after major hepatic resection. Subsequent recovery of ASGP-R amount was shown by TcGSA study. By estimating hepatic functional reserve expressed by ASGP-R amount and concentration, one may detect a delayed or impaired liver regeneration with higher sensitivity.

Key Words: ^{99m}Tc GSA; asialoglycoprotein receptor; hepatic resection; liver regeneration

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Since the classic work of Higgins and Anderson (1), liver regeneration after partial hepatic resection has been extensively studied in animals (1,2) and humans (3-7). In human noncirrhotic liver, restoration of liver volume after major hepatic resection is completed within 6-12 mo (5,6). In contrast to the number of investigations of morphological restoration after hepatic resection, there have been fewer reports on the functional changes in regenerating liver (2,7). It has been reported that the metabolic activity of the remaining parenchyma increases in the early postoperative

phase and subsequently returns to the preoperative level during the course of regeneration (7). With the exception of the early phase after partial hepatectomy (-4 h), hepatic metabolic capacity directly correlates with liver mass (2). In previous studies, aminopyrine demethylation capacity (2), antipyrine clearance (8) or galactose elimination capacity (7,9,10) have been selected as parameters that are directly proportional to the functional hepatic mass.

Asialoglycoprotein receptor (ASGP-R) is a hepatic cell surface receptor specific for galactose-terminated glycoprotein (11,12). ^{99m}Tc -labeled asialoglycoprotein analogs, ^{99m}Tc -diethylenetriamine pentaacetic acid (DTPA)-galactosyl-neoglycoalbumin (TcNGA) (13) and ^{99m}Tc -DTPA-galactosyl-human serum albumin (TcGSA) (14) have been applied to human hepatic receptor imaging. Tc-GSA scintigraphy is unique and provides information totally independent from previously known liver function tests such as aminopyrine demethylation capacity (2), antipyrine clearance (8,15) or galactose elimination capacity (7,9,10). Vera et al. (16) developed an automated kinetic analysis that transforms heart and liver time-activity data into ASGP-R concentration ($[R]_0$), amount (R_0), and other physiological parameters. Previous studies showed that the determination of $[R]_0$ is a reproducible, sensitive and bilirubin-independent method for evaluating hepatic functional reserve (17,18).

Using these new parameters, which are directly related to functional liver mass, we analyzed the changes in ASGP-R status in the regenerating human liver. These data were compared with CT liver volume measurements. To the best of our knowledge, this is the first report on the changes in ASGP-R concentration and amount in the human liver after major hepatic resection.

MATERIALS AND METHODS

Patients

From December 1995 to July 1997, 22 patients underwent major hepatic resection at the Department of Surgery, Cancer Institute Hospital (Tokyo, Japan). The extent of all resections was more than one segment of Healey (19). The group comprised 16 men and 6 women, 40-77 y old (mean, 63.0 y). Clinical diagnoses were metastatic liver cancer in 13, hepatocellular carcinoma in 5, cholangiocellular carcinoma in 3 and giant hemangioma in 1. Histological diagnosis of the hepatic underlying parenchyma was liver cirrhosis in 4 and almost normal liver in the remaining 18.

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The extent of liver resection was right bisegmentectomy in 11, left bisegmentectomy in 5, one segmentectomy in 3, median bisegmentectomy in 2 and left trisegmentectomy in 1. At time of discharge, all patients had an uneventful postoperative course. Liver scintigraphy and hepatic volumetry were performed in all patients before and 3 wk after surgery. Four patients had a third scintigraphy study 35–139 d after surgery. Informed consent was obtained from all patients. Because there is no formal ethical committee for human research in our institute, the protocol was preapproved by the senior staff committee of the department.

TcGSA Functional Imaging

Liver scintigraphy using a ^{99m}Tc -labeled asialoglycoprotein analog, TcGSA (Nihon Medi-Physics, Nishinomiya, Japan), was performed as previously described (14,20). Briefly, after injection of TcGSA (3 mg, 185 MBq), dynamic imaging was performed with the patient supine under a large-field-of-view gamma camera. Liver and heart time-activity curves were generated by identifying the entire heart and liver using standard software.

To evaluate the receptor concentration $[R]_0$ ($\mu\text{mol/L}$), TcGSA data were analyzed on a three-compartment, bimolecular kinetic model (16). An automated computer program (NGAFIT version 6.1 [17]), running on a personal computer (Power Macintosh; Apple Computer Inc., Cupertino, CA), repeatedly adjusts $[R]_0$ and other kinetic parameters representing hepatic plasma flow F (L/min), hepatic plasma volume V_h (L), extrahepatic plasma volume V_e (L) and the receptor-TcGSA forward-binding rate constant k_b ($\mu\text{mol/L}\cdot\text{min}$). NGAFIT automatically stops the adjustments when the computer simulations match the shape of the liver and heart time-activity curves. If the curve-fit results meet a set of prescribed criteria (16), the program outputs the estimate and standard error of each kinetic parameter. Total hepatic receptor amount R_0 ($\mu\text{mol/liver}$) was calculated by $[R]_0 \times V_h$.

The following modification to the protocol was used to replace the counting standard: immediately after the withdrawal of 1.0 mL TcGSA into a 3-mL syringe from the labeling vial, the activities in the syringe and vial were measured in a dose calibrator. After injection, the residual activity within the syringe was measured in the same dose calibrator as the previous measurements. These values and the time at which they were measured were entered into the NGAFIT computer program; the time of the injection and a conversion factor also were entered. The conversion factor was determined by measuring the activity of [^{99m}Tc]pertechnetate sample (~ 5 mCi, ~ 1 mL in a 3-mL syringe) in the dose calibrator and measuring in the gamma counter the cpm of a 0.10-mL sample from a 5000-fold dilution of the same [^{99m}Tc]pertechnetate solution.

The clearance index (HH15) was calculated by dividing radioactivity of the heart region of interest (ROI) at 15 min by that at 3 min. The receptor index (LHL15) was calculated by dividing radioactivity of the liver ROI by the radioactivity of the liver plus heart ROIs at 15 min postinjection (21,22).

CT Hepatic Volumetry

Serial transverse CT scans of the whole liver were taken pre- and postoperatively (3 wk after resection). Liver volume (LV_{pre} or LV_{post}) was calculated by multiplying the area of each cross-sectional liver image by the slice thickness (1 cm in most of the cases) (23). Volume of the tumor (TV) was similarly estimated by manually tracing each tumor border. When there were multiple tumors, TV was a sum of all tumor volumes. Preoperative hepatic parenchymal volume (HPV_{pre}) was calculated by subtracting TV from LV_{pre} . HPV_{post} is equal to LV_{post} . Volume of resected specimen

(SpV) was converted from weight of resected liver. The resected fraction (Rf) and the resected parenchymal fraction (RPf) were calculated as follows:

$$Rf = SpV/LV_{\text{pre}} \quad \text{Eq. 1}$$

$$RPf = (SpV - TV)/HPV_{\text{pre}} \quad \text{Eq. 2}$$

Volume of the remnant liver on day 0 (LV_{day0}) was estimated by subtracting SpV from LV_{pre} .

Estimation of TcGSA Hepatic Function Immediately After Liver Resection

Total hepatic receptor amount on day 0 ($R_{0\text{-day0}}$) was calculated as:

$$R_{0\text{-day0}} = R_{0\text{-pre}} \times (1 - Rpf/100), \quad \text{Eq. 3}$$

where $R_{0\text{-pre}}$ is preoperative R_0 . Receptor concentration on day 0 ($[R]_{0\text{-day0}}$) is theoretically equal to preoperative $[R]_0$.

Volume Regeneration Rate and Receptor Regeneration Rate

Volume regeneration rate (%RegR-vol) was calculated by dividing LV_{post} by LV_{day0} . Receptor regeneration rate (%RegR-rec) was calculated by dividing $R_{0\text{-post}}$ by $R_{0\text{-day0}}$.

Statistical Analysis

Statistical difference between preoperative and postoperative values were tested by means of paired Student t test.

RESULTS

Change of Liver Parenchymal Volume Before and After Hepatic Resection

HPV_{pre} , TV, Rf and RPf are summarized in Table 1 according to the surgical procedures. Overall, HPV was reduced by 36.0% (from 1109 ± 72 mL to 710 ± 77 mL) after liver resection. In 3 wk, HPV increased by 6.3%, regaining 68.1% of HPV_{pre} . In a subgroup of patients who had right bisegmentectomy ($n = 11$), in whom the mean RPf was 55.2%, HPV significantly increased by 20.7% at 3 wk ($P < 0.001$), regaining 61.3% of HPV_{pre} . Changes in HPV are shown in Figure 1.

Change of ASGP-R Concentration $[R]_0$ and ASGP-R Amount R_0 Before and After Hepatic Resection

ASGP-R concentration $[R]_0$, which theoretically does not change immediately after hepatic resection, significantly decreased from 0.683 ± 0.024 $\mu\text{mol/L}$ to 0.565 ± 0.032 $\mu\text{mol/L}$ ($P < 0.001$) 3 wk after the operation. Changes in $[R]_0$ are depicted in Figure 2. Three of the four cirrhotic patients showed marked decreases in $[R]_0$ (0.680–0.380 μmol , 0.590–0.292 μmol and 0.712–0.365 μmol).

ASGP-R amount R_0 was estimated to decrease from 0.164 ± 0.012 μmol to 0.101 ± 0.010 μmol per liver after the hepatic resection. At 3 wk, R_0 significantly increased to 0.130 ± 0.009 μmol ($P < 0.05$). This increase was more prominent in the 18 noncirrhotic patients (from 0.093 ± 0.011 μmol to 0.136 ± 0.010 μmol , $P < 0.01$). Overall, R_0 regained 79.3% of preoperative value 3 wk after hepatic resection (Fig. 3).

TABLE 1
Preoperative Hepatic Parenchymal Volume, Tumor Volume, Resected Fraction and Resected Parenchymal Fraction According to Surgical Procedure

Surgical procedure	No. of patients	HPV _{pre} (mL)	TV (mL)	Rf (%)	RPf (%)
Right bisegmentectomy	11	1018 ± 103*	120 ± 36	55.2 ± 3.0	50.2 ± 3.2
Left bisegmentectomy	5	1078 ± 216	775 ± 584	47.8 ± 12.6	27.0 ± 16.0
Median bisegmentectomy	2	1280 ± 194	317 ± 100	37.8 ± 3.7	22.6 ± 7.1
Segmentectomy	3	1386 ± 30	19 ± 4	21.4 ± 7.6	20.3 ± 7.8
Left trisegmentectomy	1	1071	—†	46.7	46.7
Overall	22	1109 ± 72	243 ± 117	46.9 ± 3.8	38.7 ± 3.8

*Mean ± SE.

†Hepatic hilar carcinoma.

HPV_{pre} = preoperative hepatic parenchymal volume; TV = tumor volume; Rf = resected fraction; RPf = resected parenchymal fraction.

Rmax (= kb [R]₀ [R]₀ / tbw) significantly decreased from 29.5 ± 3.2 to 18.3 ± 2.2 nmol/L/1 min/kg (*P* < 0.001) after surgery.

Comparison Between Cirrhotic and Noncirrhotic Patients

Comparison between cirrhotic and noncirrhotic patients is summarized in Table 2. The postoperative decrease of [R]₀ was more prominent in cirrhotic patients. In contrast to significant volume or receptor regeneration in noncirrhotic patients, neither volume regeneration nor receptor regeneration was evident in the cirrhotic patients.

Correlation Between Regeneration Rate and Parenchymal Resection Rate or Preoperative Values of Hepatic Functional Indicators

There was a significant correlation between RPf and %RegR-vol (*r* = 0.770, *P* < 0.001, Fig. 4). Correlation between RPf and %RegR-rec was also significant (*r* =

0.607, *P* < 0.01, Fig. 5). The preoperative [R]₀, Rmax, HH15, LHL15 and 15-min retention rate of indocyanine green did not correlate with %RegR-vol (*r* = -0.163, -0.156, 0.196, 0.059, -0.026, respectively).

Long-Term Changes in Liver Volume and ASGP-R After Major Hepatic Resection

Long-term changes in liver volume and ASGP-R were observed in 4 noncirrhotic patients who had right bisegmentectomy. Liver parenchymal volume gradually but steadily recovered with time after surgery (Fig. 6A). Change of ASGP-R, however, varied; after an initial increase, R₀ remained at the same level for more than 3 mo in 3 patients, whereas R₀ continued to increase in the other (Fig. 6B).

DISCUSSION

There have been few reports on the changes of liver function using TcGSA scintigraphy after liver resection (24,25). Yumoto et al. (25) reported a slight decrease in [R]₀ in four cirrhotic patients after hepatic resection. A consistent fall in [R]₀ is consistent with the current understanding of hepatic regeneration. Competition between hepatocellular proliferation and activities of specialized functions including ASGP metabolism explains the observed decrease in [R]₀. A striking drop in [R]₀ observed in cirrhotic patients may indicate an exaggerated postoperative change in the

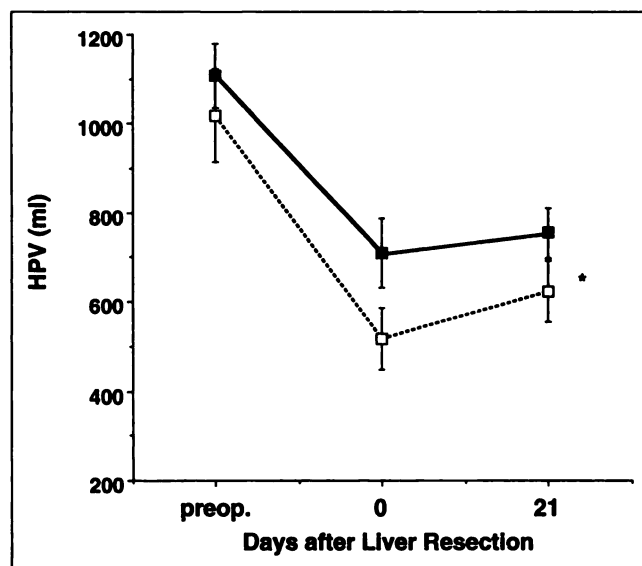


FIGURE 1. HPV (mean ± SE) before, immediately after and 3 wk after liver resection: all patients (solid line, n = 22), and patients who underwent right bisegmentectomy (dashed line, n = 11, **P* < 0.001).

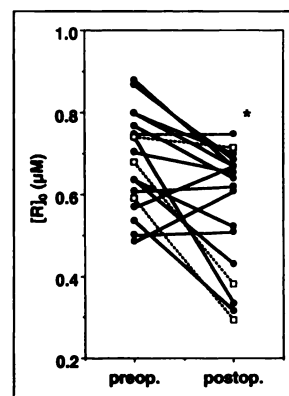


FIGURE 2. Individual changes in ASGP-R concentration [R]₀ before and 3 wk after liver resection. [R]₀ was significantly decreased at 3 wk (**P* < 0.01). Three of four cirrhotic patients showed marked decreases in [R]₀ (dashed lines).

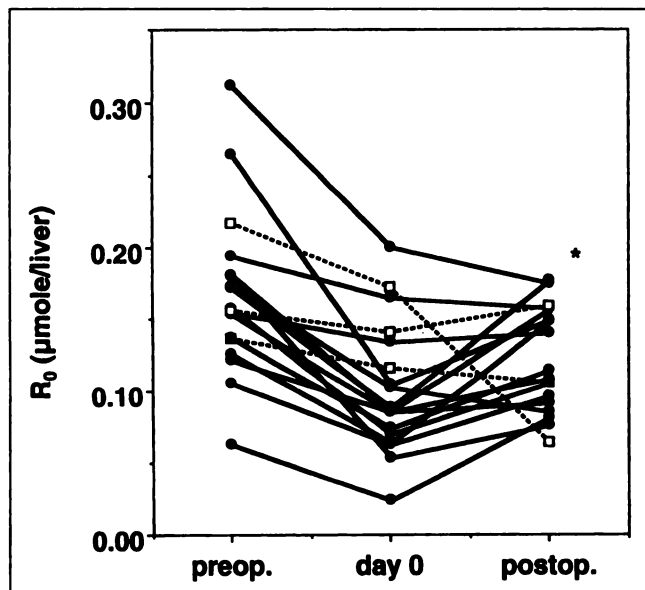


FIGURE 3. Individual changes in total hepatic ASGP-R amount R_0 before, immediately after and 3 wk after liver resection. Postoperative increase in R_0 was statistically significant ($*P < 0.01$) in noncirrhotic patients (solid lines, noncirrhotic patients; dashed lines, cirrhotic patients).

cirrhotic liver, which is known to be slow in regeneration after liver resection (5,6,26).

Because the percentage of the resected liver parenchyma is one of the most important factors governing liver regeneration (4), the RPf should always be precisely estimated, which has not been the case in most of the previous studies (5–7,27). We selected patients who had major hepatic resections, in whom RPf was as high as 38.6% and most of whom were noncirrhotic. The significant correlation between RPf and the receptor regeneration (%RegR-rec) shown in Figure 5 indicates that RPf also regulates receptor regeneration. The observation that the volume and receptor restoration are not simultaneous indicates that receptor regeneration could be an independent event and have a unique clinical importance.

We observed the liver parenchymal volume gradually but steadily recovering with time after surgery, which was consistent with other studies (5,6). Change of ASGP-R, however, varied; after the initial postoperative increase at 3

TABLE 2
Comparison Between Cirrhotic and Noncirrhotic Patients

	Cirrhotic (n = 4)	Noncirrhotic (n = 18)
$\Delta[R]_0$ ($\mu\text{mol/L}$)*	-0.243 ± 0.073	-0.100 ± 0.031
%RegR-vol	97.4 ± 11.5	$120.6 \pm 5.9^\dagger$
%RegR-rec	88.1 ± 17.7	$154.6 \pm 15.6^\dagger$

*Postoperative $[R]_0$ minus preoperative $[R]_0$.

†Postoperative gains were statistically significant ($P < 0.01$).

$[R]_0$ = asialoglycoprotein receptor concentration; %RegR-vol = volume regeneration rate; %RegR-rec = receptor regeneration rate.

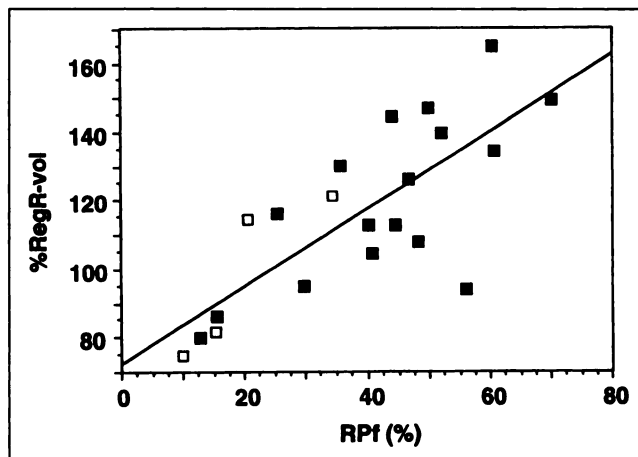


FIGURE 4. Correlation between resected parenchymal fraction (RPf) and volume regeneration rate (%RegR-vol; closed squares, noncirrhotic patients; open squares, cirrhotic patients). There was significant correlation between RPf and %RegR-vol ($r = 0.778$, $P < 0.001$).

wk, R_0 remained stable for 3 mo in 3 patients, whereas R_0 increased in the other. Long-term restoration of ASGP-R appears to be slower, compared with the volume restoration, again indicating the competition between cellular proliferation and hepatocellular differentiation. Decreased ASGP-R may be a common characteristic of the regenerating or regenerated liver.

CONCLUSION

$[R]_0$ was significantly decreased 3 wk after major hepatic resection. The decrease in $[R]_0$ was more prominent in cirrhotic patients. Recovery of ASGP-R was observed as an increase in R_0 3 wk after surgery. There was a significant correlation between RPf and ASGP-R regeneration. Long-term restoration of ASGP-R appeared to be slower compared with volume restoration. To the best of our knowledge, this

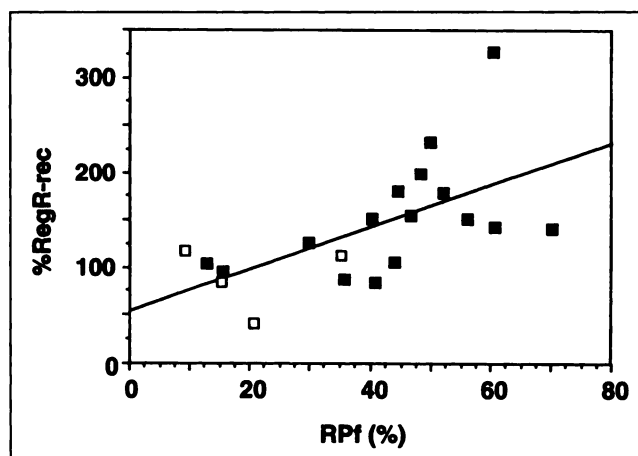


FIGURE 5. Correlation between resected parenchymal fraction (RPf) and receptor regeneration rate (%RegR-rec; closed squares, noncirrhotic patients; open squares, cirrhotic patients). There was a significant correlation between %RegR-vol and %RegR-rec ($r = 0.607$, $P < 0.01$).

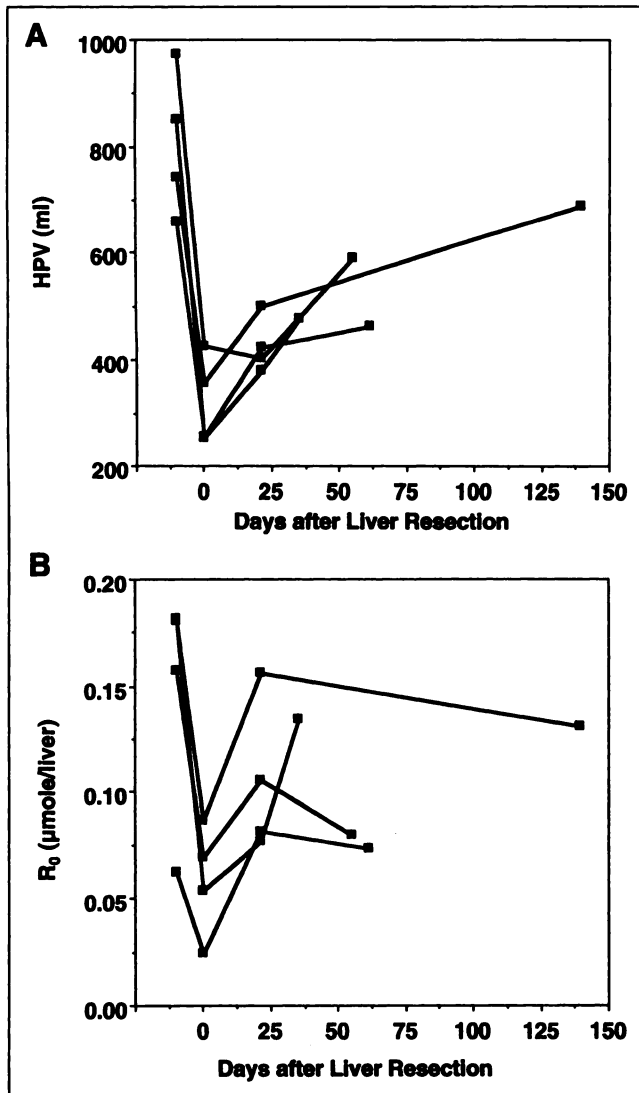


FIGURE 6. Long-term changes in hepatic parenchymal volume (HPV, A) and ASGP-R (R_0 , B) after major hepatic resection. Long-term changes in liver volume and ASGP-R were observed in four noncirrhotic patients who underwent right bisegmentectomy.

is the first report on the changes in ASGP-R concentration and amount in the human liver after major hepatic resection, with detailed HPV data. These results expand our knowledge on the sequence of events during liver regeneration in the clinical setting. By estimating hepatic functional reserve expressed by ASGP-R amount, one may detect an impaired liver regeneration with higher sensitivity.

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