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ORIGINAL ARTICLE

Mechanisms of splenic hypertrophy following hepatic resection

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Abstract

Background: Following hepatic resection, liver regeneration has been associated with concurrent splenic hypertrophy. The mechanisms of this phenomenon are unknown, may be multiple and include: splanchnic sequestration caused by a reduction in the hepatic mass; hepatic growth factors that may indirectly act on the spleen, and the redistribution of the total reticuloendothelial system.

Methods: Seventy-five patients (40 males; median age: 60 years) who underwent minor (16%) or major (84%) hepatectomy between September 2004 and October 2009 were included. Prospective measurements of liver and spleen volumes were obtained preoperatively and postoperatively 1 month after hepatectomy using computed tomography (CT). The future remnant liver volume (RLV) was calculated on preoperative CT and the extent of resection was expressed as the RLV divided by total liver volume (TLV). Liver and spleen hypertrophy were expressed according to the absolute gain or relative increase in the initial volumes (%).The presence of fibrosis >F1, associated extrahepatic resection (except minor resections), and previous hepatectomy (major or minor) within 3 months represented exclusion criteria.

Results: Mean ± standard deviation (SD) liver volume at 1 month was higher than RLV (1187 ± 286 cm^3 versus 764 ± 421 cm^3; $P < 0.001$). Mean ± SD splenic volume increased from 252 ± 100 cm^3 preoperatively to 300 ± 111 cm^3 at 1 month ($P < 0.001$). Liver and splenic hypertrophy were significant after major hepatectomies (+100% and +26%, respectively; $P < 0.001$), but not after minor hepatectomies. Liver hypertrophy was inversely correlated to RLV/TLV ($r = –0.687$, $P < 0.001$). Splenic hypertrophy was not correlated to RLV/TLV. Liver and splenic hypertrophy were linearly correlated ($r = 0.495$, $P < 0.001$). Neoadjuvant chemotherapy ($n = 37$), preoperative portal vein embolization ($n = 10$) and postoperative complications (overall: $n = 25$; major: $n = 10$; infectious: $n = 6$) had no impact on hepatic or splenic hypertrophy.

Conclusions: Splenic hypertrophy occurred after major hepatectomy, but was not correlated to the extent of resection, by contrast with liver hypertrophy. Nevertheless, there was a linear correlation between splenic and liver hypertrophy. This correlation suggests the hypothesis of a splenic action of hepatic growth factors or a redistribution of the total reticuloendothelial system rather than an effect of reduction of the portal bed or hepatic outflow.

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Introduction

The spleen is capable of regeneration after partial splenectomy or autotransplantation of splenic fragments following splenectomy,[1–3] although the regenerative process in the spleen is not as important as that in the liver. Splenic hypertrophy has also been described following hepatic resections, mainly following living donor liver transplantation (LDLT), leading to postoperative hypersplenism and thrombocytopoenia in living liver donors.[4,5] Kamel *et al.* noted that in all their donors, the spleen increased in volume in the immediate postoperative period,

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reaching a peak of 45% at 1 month, followed by a plateau for up to 6 months, and then a gradual decline so that it returned to the preoperative volume after approximately 1 year.[6] In those compliant with full 1-year follow-up, five of 22 donors were noted to have persistent asymptomatic thrombocytopoenia beyond the perioperative period (90 days).[5] Similarly, in a study by Ishizawa *et al.*,[7] the ratio of splenic hypertrophy was 133% (range: 99–191%) and was associated with a platelet count decrease of 92% (range: 71–129%). Splenic hypertrophy has been less studied in the setting of hepatic resection for either malignant tumours or non-malignant disease.[8] The mechanisms of this phenomenon are unknown. Several hypotheses have been advanced to explain this splenic hypertrophy, including: splanchnic sequestration caused by a reduction in the hepatic mass;[9,10] hepatic growth factors that may indirectly act on the spleen,[4,11] and the redistribution of the total reticuloendothelial system.[12,13]

The aim of this study was to analyse splenic hypertrophy after liver resection. Secondly, the relationship between splenic hypertrophy and liver regeneration was analysed and factors predictive of postoperative splenic hypertrophy were investigated.

Materials and methods

Patients, surgical technique and indications

All clinical, biological and morphological information concerning patients who underwent hepatic resection in the Department of Digestive Surgery and Transplantation, University Hospital, Lille, France, were collected in a prospective database. Medical records for all hepatectomies performed between September 2004 and October 2009 were retrospectively analysed and all eligible patients were included in the study. All included patients had undergone computed tomography (CT) as part of their preoperative assessment. No patient had a background of chronic liver disease. Exclusion criteria were: liver fibrosis of >F1[14] on histopathological analysis; associated extrahepatic resection (except minor resections); previous hepatectomy (major or minor within 3 months of the study period), and lack of available preoperative volumetry (Fig. 1). After the inclusion of 40 patients, an intermediate analysis showed no significant change between the initial and final volumes (of the liver and spleen) in the group that had undergone minor hepatectomy. For this reason, only patients undergoing major hepatectomy were included in the present study.

Surgery for liver tumours was based on segment-oriented anatomical resection.[15] The extent of liver resection was defined according to the number of liver segments resected as minor (one or two Couinaud[16] segments were resected or a wedge resection was performed) or major (three or more segments were resected). Most resections were performed under low central venous pressure (3–5 cm H_2O) without hepatic inflow occlusion or with intermittent portal triad clamping (clamping periods of 15 min separated by 5 min of release). Liver transection was performed using an ultrasonic dissector (Dissectron®; Satelec Medical, Integra™, Mérignac, France).

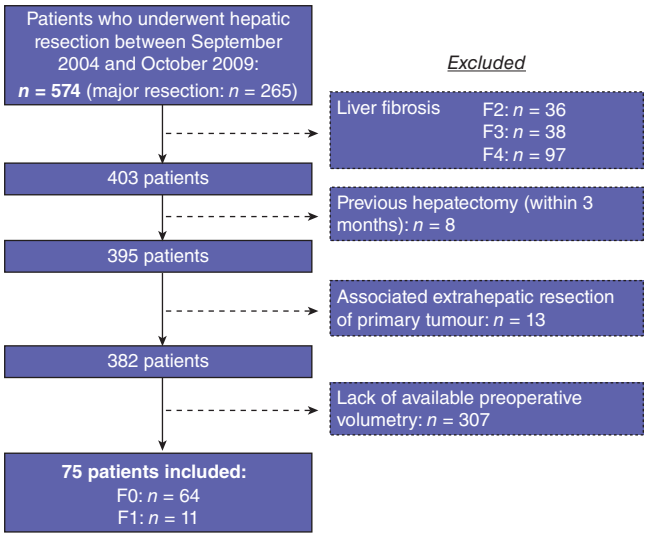

Figure 1 Flow chart showing details of the patient selection process

Liver and splenic volumetry

Volumetric measurements of the liver and spleen were obtained using methods previously reported.[17–20] Briefly, serial transverse images of the upper abdomen were obtained at intervals of 4.5–6.0 mm, with enhancement by i.v. bolus injection of contrast medium. On each slice of the preoperative CT, the total liver volume (TLV), the remnant liver volume (RLV) and the splenic volume (SV) were traced with the cursor and the sum of the slices was calculated using integrated software (Fig. 2). This preoperative CT was performed at ≤1 month prior to hepatectomy or after preoperative portal vein embolization (PVE) when the latter was performed. The RLV and SV were also measured after surgery within 4–6 weeks in all patients (RLV^{M1} and SV^{M1}).[7]

The extent of liver resection was evaluated according to either the ratio of RLV to TLV (RLV_{TLV}, expressed as a percentage of TLV) or by the ratio of RLV to body weight (RLV_{BW}, expressed as a percentage of body weight). Liver and spleen hypertrophy were calculated in two manners to show, respectively, absolute and relative increases. The absolute increase was defined as the difference between volume at 1 month and preoperative volume, expressed in cubic centimetres as $RLV_{increase} = RLV^{M1} - RLV$ for the liver, and $SV_{increase} = SV^{M1} - SV$ for the spleen. The relative increase was defined as the ratio between the absolute increase and preoperative volume, expressed as a percentage, as $RLV_{increase}\% = (RLV_{increase}/RLV) \times 100$ for the liver and $SV_{increase}\% = (SV_{increase}/SV) \times 100$ for the spleen. The ratios of SV to RLV before and after surgery were also calculated as SV/RLV and SV^{M1}/RLV^{M1}, respectively.[7]

Postoperative outcome and follow-up

Morbidity was defined as any perioperative complication occurring during the same hospital stay or within 3 months following resection. This category included surgical complications (bleeding from the surgical site or bile leak), hepatic, cardiovascular, respiratory or

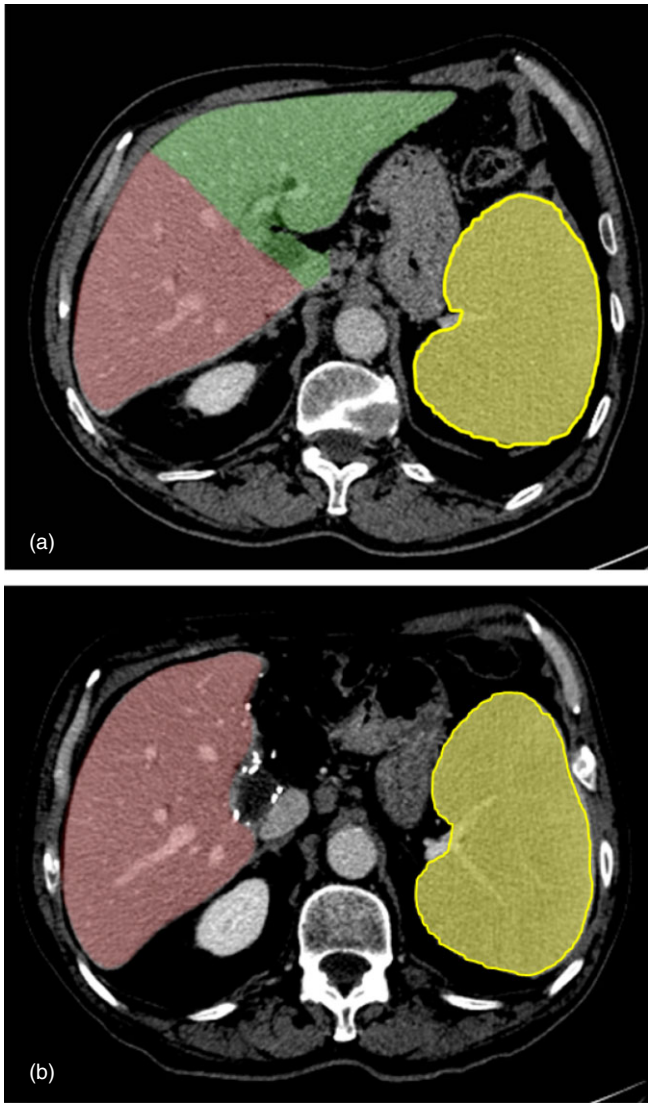

Figure 2 Computed tomography in a 46-year-old woman with metachronous colorectal cancer liver metastases. (a) Preoperative volumetry. The limits of the liver (resected liver in green, remnant liver in red) and spleen (yellow) were traced with the cursor and the sum of the 5-mm slices was calculated using integrated software. (b) Postoperative volumetry at 6 weeks after left hepatectomy shows an increase in spleen volume

renal dysfunction, and infection. Only clinically significant infections were taken into account; these were defined by coincident findings of a positive microbial culture and either local or general symptoms of inflammation.[21–23] Complications were categorized into five grades according to the Dindo–Clavien system of classification[24] and defined as major when they required interventional radiology or reoperation (Dindo–Clavien Grade III) or resulted in organ(s) failure (Dindo–Clavien Grade IV) or patient death (Dindo–Clavien Grade V). Common blood cell counts and liver function tests were examined before surgery and on postoperative days 1, 3, 5 and 7. The biochemical and clinical courses of patients were studied for their associations with liver and spleen volumes, and the respective extents of hypertrophy of these organs at 1 month.

Statistical analysis

Continuous variables are expressed as the median, mean and range; qualitative variables are expressed as frequencies (percentages). The Shapiro–Wilk normality test was used to choose between parametric and non-parametric tests. Parametric tests were used for normal distributions. Otherwise, non-parametric tests were chosen. The evolution in SV at 1 month after hepatectomy (SV^{M1}) and the evolution in liver volume at 1 month after hepatectomy (RLV^{M1}) were tested using a paired *t*-test and a Wilcoxon signed-rank test, respectively. Continuous variables were compared between type of resection (major or minor hepatectomy) and the resected portal branch (right or left) using the Mann–Whitney *U*-test. Correlations between continuous variables were measured using Pearson's correlation coefficient. To identify variables predictive of splenic hypertrophy within 4–6 weeks after surgery (SV^{M1}), all analyses were adjusted on SV. Preoperative, intraoperative and early postoperative (up to day 7) variables for all patients were analysed using a linear regression method for continuous variables and analysis of covariance (ANCOVA) for qualitative variables. In order to study whether the kinetics of biological parameters can influence changes in SV, this analysis included the extreme values (minimum and maximum) of these parameters. All variables with a *P*-value of <0.2 in the previous analysis were introduced in a multiple linear regression with stepwise selection to identify a subset of independent predictive factors of SV^{M1} adjusted on SV. Influential individuals were sought using Cook's distance estimates and the normality of standardized residuals was checked to validate the final regression model. All analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, USA). A *P*-value of <0.05 was considered to indicate statistical significance.

Results

Study population

Seventy-five patients were included in the study; their principal characteristics are shown in Table 1. Hepatectomy was performed for malignant tumours in 69 patients (92%); diagnoses in these patients referred to colorectal cancer liver metastases in 44 (59%) patients, other secondary malignancies in six (8%) patients, hepatocellular carcinoma in eight (11%) patients, cholangiocarcinoma in nine (12%) patients, sarcoma in one (1%) patient and gallbladder cancer in one (1%) patient. Other indications for hepatectomy were focal nodular hyperplasia in two (3%) patients, adenoma in three (4%) patients and haemangioma in one (1%) patient. Additional procedures were performed in seven (9%) patients. These included adrenalectomy in one patient, eventration repair in two patients, colorectal anastomosis in one patient, small intestine suture in one patient, embolectomy for thrombosis of an arterio-

Table 1 Principal characteristics of the study population (n = 75)

Age, years, median, mean (range)		60, 60 (34–85)
Body mass index, kg/m^2, median, mean (range)		25.1, 26.1 (17.0–38.6)
Gender, *n* (%)	Female	35 (46.7%)
	Male	40 (53.3%)
ASA physical status, *n* (%)	1	25 (33.3%)
	2	38 (50.7%)
	3	12 (16.0%)
Preoperative chemotherapy, *n* (%)		37 (49.3%)
Indications, *n* (%)	Metastases	50 (66.7%)
	Liver cancer[a]	19 (25.3%)
	Non-malignant	6 (8.0%)
Portal vein embolization, *n* (%)		10 (13.3%)
Major hepatectomy, *n* (%)		63 (84.0%)
Resected nodules/patient, median, mean (range)		1, 2 (1–10)
Resected segments/patient, median, mean (range)		4, 4 (0–6)
Clamping, *n* (%)		33 (44.0%)
Total ischaemia, min, median, mean (range)		0, 15 (0–96)
Blood loss, ml, median, mean (range)		525, 657 (50–3500)
Intraoperative blood transfusion, *n* (%)		4 (5.3%)
Operative time, min, median, mean (range)		285, 294 (60–580)
Morbidity, *n* (%)	Overall	25 (33.3%)
	Major (Clavien Grades III, IV)	10 (13.3%)
	Infectious	6 (8.0%)
Duration of ICU stay, days, median, mean (range)		2, 4 (0–97)
Duration of hospitalization, days, median, mean (range)		8, 12 (4–97)

[a]Includes hepatocellular carcinoma, cholangiocarcinoma, sarcoma and gallbladder cancer.
ASA, American Society of Anesthesiologists; ICU, intensive care unit.

venous fistula for haemodialysis in one patient, and subcutaneous lipoma removal in one patient. Three (4%) patients died, all after the 1-month volumetric evaluation.

Overall volumetric data

Volumetric data for all patients are shown in Table 2. There was a statistically significant increase in SV at 1 month after hepatectomy, with a mean increase of 24% of the initial volume ($P < 0.001$). Similarly, there was a statistically significant increase in liver volume at 1 month, with a mean increase of 85% of the initial volume ($P < 0.001$). The ratio of SV to RLV measured on preoperative CT was significantly greater than the ratio of SV to RLV at 1 month ($P < 0.001$).

Significant increases in spleen ($P < 0.001$) and liver ($P < 0.001$) volumes were noted in patients after major hepatectomies (Table 2). In the minor hepatectomy group, there was no significant difference between preoperative volume and volume at 1 month in either the spleen or liver ($P = 0.158$ and $P = 0.182$, respectively).

Stratification by portal branch resection (right or left)

Patients who underwent a major hepatectomy were divided into two groups according to whether the left or right portal branch had been resected. The increase in liver volume was significantly higher ($P < 0.001$) in patients subjected to right portal branch resection (median: 102%; mean: 117%; range: 14–395%) than in those submitted to left portal branch resection (median: 19%; mean: 15%; range: −17% to 59%), which relates to a smaller RLV in the former group. By contrast, despite the disparity in RLV, there was no significant difference in spleen hypertrophy between patients undergoing right portal branch resection (median: 18%; mean: 26%; range: −48% to 186%) and those undergoing left portal branch resection (median: 29%; mean: 30%; range: −14% to 95%) ($P = 0.473$).

Correlation with the extent of resection

Liver hypertrophy, expressed as the $RLV_{increase}$%, was inversely correlated to postoperative RLV_{TLV} (Pearson's correlation coefficient: −0.687; $P < 0.001$) (Fig. 3). Splenic hypertrophy ($SV_{increase}$%) was not correlated to the extent of liver resection (Pearson's correlation coefficient: −0.142; $P = 0.224$) (Fig. 4). However, liver and splenic hypertrophy were linearly correlated to one another (Pearson's correlation coefficient: 0.495; $P < 0.001$) (Fig. 5).

Table 2 Volumetric data

Variables	Total sample (n = 75) Median, mean (range)	Major hepatectomy (n = 63) Median, mean (range)	Minor hepatectomy (n = 12) Median, mean (range)
SV, cm^3	242, 252 (87–551)	242, 250 (87–551)	228, 258 (130–463)
TLV, cm^3	1646, 1827 (845–5650)	1670, 1877 (1023–5650)	1521, 1567 (845–2923)
TLV/BW, %	2.2, 2.4 (1.2–7.6)	2.2, 2.5 (1.2–7.6)	2.1, 2.3 (1.5–4.4)
SV/RLV, %	39.1, 40.7 (11.0–128.0)	41.8, 44.5 (11.0–128.0)	17.6, 20.2 (13.0–42.0)
SV/TLV, %	13.9, 14.5 (3.4–32.2)	13.5, 14.1 (3.4–32.2)	15.9, 17.1 (8.5–31.6)
SV/BW, %	0.3, 0.3 (0.1–0.7)	0.3, 0.3 (0.1–0.7)	0.3, 0.4 (0.2–0.7)
RLV, cm^3	607, 763 (158–2024)	562, 663 (158–2024)	1292, 1291 (799–1784)
RLV/TLV, %	36.9, 43.9 (13.9–98.1)	31.7, 36.2 (13.9–76.7)	87.7, 84.5 (60.6–98.1)
RLV/BW, %	0.8, 1.0 (0.2–2.7)	0.7, 0.8 (0.2–2.6)	1.7, 1.9 (1.4–2.7)
RLV^{M1}, cm^3	1142, 1186 (545–1878)	1098, 1154 (545–1781)	1357, 1356 (888–1878)
SV^{M1}, cm^3	290, 300 (83–610)	302, 304 (83–610)	233, 277 (145–520)
SV^{M1}/RLV^{M1}, %	22.7, 25.9 (9.7–57.5)	24.2, 27.0 (9.7–57.5)	19.5, 20.4 (12.7–39.4)
RLV^{M1}/BW, %	1.5, 1.6 (0.8–2.7)	1.5, 1.5 (0.8–2.7)	2.1, 1.9 (1.5–2.4)
SV^{M1}/BW, %	0.4, 0.4 (0.1–0.8)	0.4, 0.4 (0.1–0.8)	0.4, 0.4 (0.2–0.8)
$RLV_{increase}$, cm^3	467, 422 (–243 to 1018)	502, 491 (–243 to 1018)	93, 64 (–219 to 325)
$RLV_{increase}$%	82.1, 85.5 (–17 to 395)	94.8, 100.3 (–17 to 395)	7.0, 7.1 (–12 to 33)
$SV_{increase}$, cm^3	41, 48 (–197 to 225)	44, 53 (–197 to 225)	24, 19 (–71 to 106)
$SV_{increase}$%	17.8, 23.8 (–48 to 186)	18.2, 26.5 (–48 to 186)	12.1, 9.7 (–23 to 26)

SV, spleen volume; TLV, total liver volume; BW, body weight; RLV, remnant liver volume, M1, at 1 month.

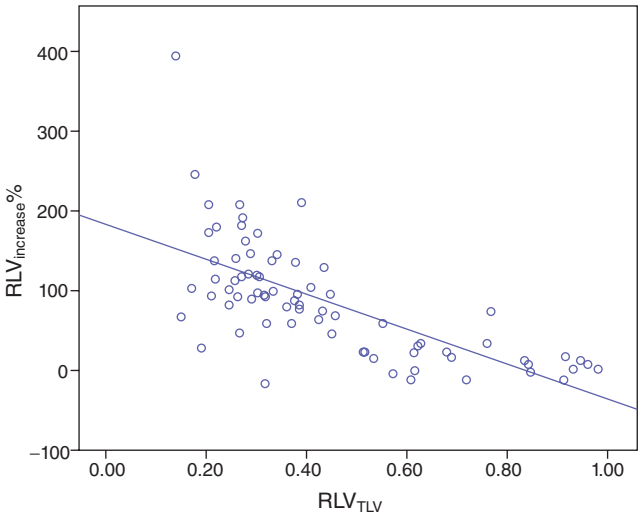

Figure 3 Correlation between liver hypertrophy ($RLV_{increase}$%) and the extent of liver resection [as reflected by the remnant liver volume (RLV)] expressed as a percentage of total liver volume (TLV). Pearson's correlation coefficient: –0.687 ($P < 0.0001$)

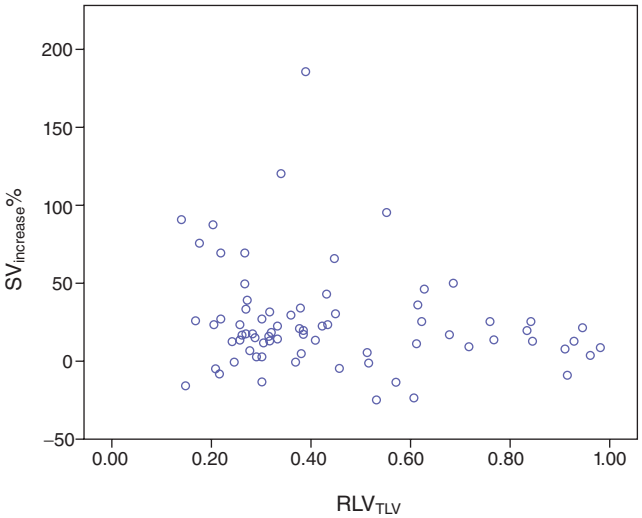

Figure 4 Correlation between spleen hypertrophy ($SV_{increase}$%) and the extent of liver resection [as reflected by the remnant liver volume (RLV)] expressed as a percentage of total liver volume (TLV). Pearson's correlation coefficient: –0.142 ($P = 0.224$)

Predictors of splenic hypertrophy

Factors associated with splenic hypertrophy on bivariate analysis are shown in Tables 3 and 4.

In multivariate analysis, the independent predictive factors of postoperative splenic hypertrophy were: preoperative haemoglobin ($P = 0.047$); intraoperative blood loss ($P < 0.001$), and postoperative maximum bilirubin ($P < 0.001$).

Discussion

The present study described a significant increase of 24% in SV after partial hepatectomy that occurred only after major hepatec-

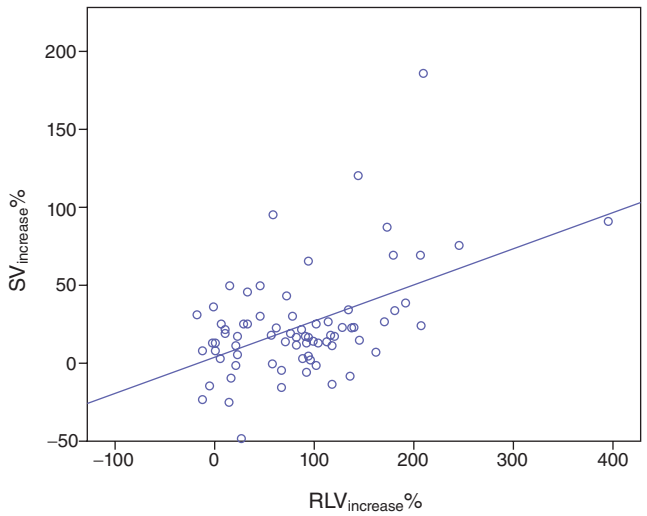

Figure 5 Correlation between spleen hypertrophy ($SV_{increase}$%) and liver hypertrophy ($RLV_{increase}$%) in the 75 patients. Pearson's correlation coefficient: 0.495 ($P < 0.0001$)

tomy and was linearly correlated to hepatic hypertrophy. By bivariate analysis, predictors of splenic hypertrophy included preoperative SV/TLV and haemoglobin level, intraoperative blood loss and transfusion requirements, and, postoperatively, the main indicators of liver function (bilirubin, albumin, factor V and platelet count). By contrast, splenic hypertrophy was not influenced by the extent of resection, preoperative chemotherapy or PVE, or postoperative complications. In a multivariate analysis, only preoperative haemoglobin, intraoperative blood loss and the postoperative peak of bilirubin were independent predictors of splenic hypertrophy.

The spleen has been shown to be capable of regeneration after partial splenectomy or autotransplantation.[1–3,25] Nevertheless, the mechanism for its growth is unknown and may differ from that observed after hepatic resection. This study demonstrates a mean ± standard deviation (SD) increase in SV of 23.8 ± 33.9% of the original volume after hepatic resection. Accordingly, previous studies in LDLT reported increases in spleen volume of 30–50% from baseline at 1–6 months postoperatively.[6,26–28] There have also been a few reports of splenic hypertrophy after partial hepatectomy in small patient cohorts.[11] In 41 patients with colorectal liver metastases, Jacobs *et al.*[8] showed an increase in SV of 26% on the first postoperative CT ($P < 0.0001$). In 24 patients with biliary cancer, Ando *et al.*[11] showed that SV increased to a mean ± SD of 155 ± 40% of preoperative volume by 14 days after hepatectomy and to a mean ± SD of 179 ± 41% of preoperative volume by 28 days. In the current series of 75 patients, the biggest series to have been reported to date, the rate of splenic hypertrophy was comparable with that found by Jacobs *et al.*,[8] but weaker than that observed by Ando *et al.*[11] In this latter study of extended hepatectomies (more than four segments), splenic hypertrophy may have been accentuated by some degree of hepatic fibrosis secondary to preoperative cholestasis, although this was not specified by the authors. Consequently, a significant negative correlation was found between SV and platelet counts at 1 year after hepatectomy.[11] Because of its retrospective pattern, the current series did not allow for an analysis of platelet count during the first postoperative year as this was not measured in all patients.

In the current study, the increase in SV occurred only after major hepatic resection and reached as much as a mean ± SD of 26.5 ± 35.9% of the original volume. In this subgroup of patients, liver volume at 1 month increased to a mean ± SD of 100.4 ± 69.9% of RLV. By contrast, no significant liver or spleen hypertrophy was noted after minor hepatectomies. Similarly, in the study by Jacobs *et al.*,[8] the subgroup of patients who demonstrated no increase or even a slight decrease in SV postoperatively tended to have undergone hepatectomies of smaller volumes than patients who demonstrated an increase in SV.[8] However, in the current series, splenic hypertrophy was not significantly correlated to the extent of liver resection. By contrast, there was a significant linear correlation between rates of splenic and liver hypertrophy in favour of common regulatory factors. Similarly, Ando *et al.*[11] reported a strong correlation between rates of increase in liver and spleen volumes at 14 days after major hepatectomy. Interestingly, two experimental studies[3,29] reported that hepatectomy stimulates DNA synthetic activity in the spleen, compatible with the hypothesis of common stimulating growth factors.[30–34]

Alternatively, the increase in SV after hepatectomy may reflect a mechanism that maintains the total body reticuloendothelial system (RES),[11] for which the liver and spleen are important components.[3] In a lymphatic translocation model of endotoxinaemia, the liver was shown to play an important role in ensuring the clearance of bacteria and their products from systemic circulation.[35] After a liver resection, gut bacterial translocation increases the demands on the hepatic RES to keep the systemic circulation sterile.[36,37] In addition, significant increases in phagocytosis capacity have been shown at extrahepatic sites such as the spleen and lungs.[12,13] Such findings have been accompanied by a change in cytokine gene induction in the liver and spleen: for example, tumour necrosis factor-α (TNF-α), an immune activator, was induced at the transcriptional level in the spleen of partially hepatectomized rats.[38] In the current study, the fact that the main indicators of liver function were predictors of spleen hypertrophy supports this hypothesis as there is a strong relationship between liver function and risk for postoperative sepsis.[39] Although the present authors found no relationship between spleen hypertrophy and septic complications, it can be assumed that liver RES may be deficient – and insufficiently compensated by spleen RES, resulting in sepsis – in extended hepatectomies only.[40,41]

A last hypothesis for post-hepatectomy splenic hypertrophy is splanchnic sequestration caused by a reduction in the hepatic mass available for the egress of splanchnic flow or in the hepatic outflow. However, only 60% of sinusoids are functioning in the steady state.[42] After major hepatectomy, portal venous pressure

Table 3 Bivariate analysis of factors associated with spleen hypertrophy, adjusted on baseline

Categorical variables		*n*	Spleen volume$_{increase}$%Median, mean (range)	*P*-value[a]
Gender[b]	Female	35	20, 23 (–48 to 185)	0.167
	Male	40	17, 24 (–15 to 121)	
ASA physical status	Class 1	25	18, 18 (–23 to 69)	0.377
	Class 2	38	17, 24 (–48 to 186)	
	Class 3	12	24, 36 (–1 to 121)	
Preoperative chemotherapy	Yes	37	21, 25 (–25 to 121)	0.384
	No	38	15, 23 (–48 to 186)	
Indications: metastases	Yes	50	19, 25 (–25 to 121)	0.537
	No	25	16, 22 (–48 to 186)	
Portal vein embolization	Yes	10	9, 18 (–48 to 91)	0.967
	No	65	18, 25 (–25 to 186)	
Preoperative splenomegaly	Yes	18	7, 10 (–48 to 66)	0.695
	No	57	20, 28 (–25 to 186)	
Clamping	Yes	33	18, 28 (–48 to 186)	0.691
	No	42	18, 21 (–25 to 95)	
Intraoperative blood transfusions[b]	Yes	4	–15, –11 (–48 to 32)	0.001
	No	71	18, 26 (–25 to 186)	
Resected portal branch	Left	10	29, 30 (–14 to 95)	0.336
	Right	52	18, 26 (–48 to 186)	
	No	13	13, 10 (–23 to 26)	
Major hepatectomy[b]	Yes	63	18, 27 (–48 to 186)	0.120
	No	12	12, 10 (–23 to 26)	
Liver steatosis of >30%[b]	Yes	11	17, 51 (7–186)	0.013
	No	64	18, 19 (–48 to 95)	
Overall complications	Yes	25	18, 27 (–48 to 121)	0.577
	No	50	18, 22 (–25 to 186)	
Major complications	Yes	10	20, 26 (–48 to 95)	0.885
	No	65	17, 23 (–25 to 186)	
Infectious complications	Yes	6	14, 14 (–48 to 87)	0.296
	No	68	18, 25 (–25 to 186)	
Postoperative hyperbilirubinaemia[b]	Yes	38	23, 33 (–15 to 186)	0.012
	No	31	13, 16 (–25 to 95)	
Increased INR[b]	Yes	6	46, 48 (5–91)	0.003

[a]Factors that achieved a *P*-value of <0.05 are statistically significant.
[b]Factors that achieved a *P*-value of <0.2 were introduced in a multiple linear regression with stepwise selection (R^2 = 0.83).
ASA, American Society of Anesthesiologists; INR, international normalized ratio.

has been shown to increase,[9,10] but the increase was reported to be small, at <4–5 cm H_2O. Furthermore, in serial measurements, portal pressure was temporarily elevated at 3–5 days after surgery and returned to preoperative values at an early stage after hepatectomy.[43,44] Because there are fewer sinusoidal vascular beds in the hepatic islands at the beginning of the regeneration process, transient narrowing of the sinusoids caused by the increasing number of hepatocytes was assumed to contribute to this change.[44] Thus, passive congestion arising from increased portal venous pressure may be of only limited importance as a mechanism of splenic hypertrophy.[11] In addition, a recent study showed that tissue stiffness of the remnant liver after donor hepatectomy, as assessed by virtual touch tissue quantification (VTTQ), increased until postoperative days 3–5, and values in patients with a small RLV were significantly higher than those in patients with a large RLV.[45] It was assumed by the authors that the formation of hepatic islands leads to an increase in cellular density.[46] The VTTQ values of the spleen also increased and were similarly more pronounced in the group of patients with a small RLV.[45] A significant positive correlation was observed between the postoperative

Table 4 Bivariate analysis of factors associated with spleen hypertrophy, adjusted on baseline

Continuous variables	*P*-value[a]
Age, years	0.528
Body mass index	0.883
TLV[b]	0.063
TLV/BW[b]	0.019
SV/TLV[b]	0.027
SV/BW	0.338
Preoperative platelet count[b]	0.074
Preoperative AST	0.919
Preoperative ALT	0.910
Preoperative ALP[b]	0.175
Preoperative GGT	0.338
Preoperative bilirubin	0.248
Preoperative prothrombin time[b]	0.075
Preoperative coagulation factor V[b]	0.082
Preoperative blood urea nitrogen[b]	0.028
Preoperative creatinine	0.924
Preoperative haemoglobin[b]	0.002
Preoperative albumin	0.840
Number of resected nodules[b]	0.018
Number of resected segments	0.461
Total ischaemia, min	0.945
Blood loss, ml[b]	0.002
Operative time, min	0.235
RLV[b]	0.098
RLV/TLV	0.379
RLV/BW[b]	0.055
Duration of ICU stay, days	0.347
Duration of hospitalization, days	0.711
Postoperative minimal platelet count[b]	0.002
Postoperative maximum AST	0.209
Postoperative maximum ALT	0.267
Postoperative maximum ALP	0.838
Postoperative maximum GGT	0.920
Postoperative maximum bilirubin[b]	<0.001
Postoperative maximum INR[b]	0.001
Postoperative maximum blood urea nitrogen	0.357
Postoperative maximum creatinine	0.319
Postoperative minimum haemoglobin	0.389
Postoperative minimum coagulation factor V[b]	0.013
Postoperative minimum albumin[b]	0.014

[a]Factors that achieved a *P*-value of <0.05 are statistically significant.
[b]Factors that achieved a *P*-value of <0.2 were introduced in a multiple linear regression with stepwise selection (R^2 = 0.83).
TLV, total liver volume; BW, body weight; SV, spleen volume; RLV, remnant liver volume; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; ICU, intensive care unit; INR, international normalized ratio.

maximum value of remnant liver VTTQ and postoperative peaks in bilirubin,[45] presumably because the bile canalicular networks are initially disrupted at the beginning of the regeneration process.[47] Interestingly, in the current study, the postoperative peak in bilirubin was an independent predictor of splenic hypertrophy, suggesting that the disorganization of the hepatic lobular architecture may play a role in spleen enlargement. This may also explain why the spleen increases in volume in the first postoperative months and returns to a normal volume at the end of the liver regeneration process.[8]

In conclusion, the current study showed that splenic hypertrophy was a common finding after liver resection, but occurred only after major hepatectomy. This splenic enlargement was not linearly correlated to the extent of liver resection, whereas there was a linear correlation between spleen and liver hypertrophy. This correlation supports the hypothesis of a splenic action of hepatic growth factors or a redistribution of total RES, rather than an effect of reduction of the portal bed or hepatic outflow. A last hypothesis was that splenic hypertrophy might reflect a disorganization of the hepatic lobular architecture at the beginning of the liver regeneration process.

Conflicts of interest

None declared.

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