Enhancement of liver regeneration and liver surgery
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CHAPTER 6

Use of an absorbable embolization material for reversible portal vein embolization in an experimental model

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ABSTRACT

**Background:** Portal vein embolization (PVE) is used to increase future remnant liver size in patients requiring major hepatic resection. PVE using permanent embolization, however, predisposes to complications and excludes the use of PVE in living donor liver transplantation. In the present study, an absorbable embolization material containing fibrin glue and different concentrations of the fibrinolysis inhibitor aprotinin was used in an experimental animal model.

**Methods:** PVE of the cranial liver lobes was performed in 30 New Zealand White rabbits, which were divided into five groups: fibrin glue + 1000, 700, 500, 300 or 150 kunits/ml aprotinin, and were compared with a previous series of permanent embolization using the same experimental set-up. Caudal liver lobe hypertrophy was determined by CT volumetry and portal recanalization was identified on contrast-enhanced CT images. Animals were killed after 7 or 42 days, and the results were compared with those of permanent embolization.

**Results:** PVE using fibrin glue with aprotinin as embolic material was effective, with 500 kunits/ml providing the optimal hypertrophic response. Lower concentrations of aprotinin (150 and 300 kunits/ml) led to reduced hypertrophy owing to early recanalization of the embolized segments. The regeneration rate over the first 3 days was higher in the group with 500 kunits/ml aprotinin than in the groups with 300 or 150 kunits/ml or permanent embolization. In the 500-kunits/ml group, four of five animals showed recanalization 42 days after embolization, with minimal histological changes in the cranial lobes following recanalization.

**Conclusion:** Fibrin glue combined with 500 kunits/ml aprotinin resulted in reversible PVE in 80 per cent of animals with a hypertrophy response comparable to that achieved with permanent embolization material.
INTRODUCTION

Liver resection is the only curative treatment for patients with a primary or secondary liver malignancy. Liver resection can be performed safely only when the future remnant liver (FRL) is of sufficient size. To limit the risk of postoperative liver failure, FRL volume is preferably 25 per cent or more of total liver volume in healthy livers and at least 35–50 per cent in compromised livers, as measured before surgery by CT volumetry. When the FRL is too small, portal vein embolization (PVE) is the standard procedure used to increase FRL volume. By occluding the portal vein branch to the tumour-bearing segments, compensatory hypertrophy of the contralateral segments is induced. Makuuchi and colleagues were the first to describe PVE in patients, and since then PVE has made curative liver resection with acceptable postoperative complications possible for many patients.

There is ongoing discussion on the optimal embolization material to be used for PVE. Generally, permanent embolization materials are used because of the higher hypertrophy response compared with that achieved with absorbable embolization materials. However, permanent embolization has several disadvantages. First, 20–30 per cent of patients who undergo preoperative PVE are shown to have non-resectable disease at exploration. In these patients, the permanently deportalized liver segments are prone to complications and reversible PVE would hypothetically be safer. The potential risk of permanent embolization of portal segments should thus be avoided in the setting of complex palliative treatment in a patient with unresectable disease after PVE. Second, CT becomes troublesome after permanent embolization owing to stardust formation based on the radio-opaque materials used, which reduces the diagnostic value of these scans. Furthermore, an effective and safe reversible PVE method might have clinical benefit in living donor transplantation, in which the functional volume of the future donor liver can be increased without causing permanent damage to the residual liver segments.

The aim of this study was to evaluate the use of fibrin glue with addition of different concentrations of aprotinin, which inhibits clot lysis, to achieve controllable dissolution of the obstruction and thereby reversible PVE in a standardized rabbit model.

MATERIALS AND METHODS

In vitro clot lysis

The effect of aprotinin on in vitro clot lysis was determined in a purified system consisting of fibrinogen, plasminogen, thrombin and tissue plasminogen activator (tPA). In a volume of
60 µl, fibrinogen (2.5 mg/ml, Haemocomplettan® P; Aventis Behring, Haywards Heath, UK), plasminogen (200 µg/ml, tPA (5 µg/ml, Actilyse®; Boehringer Ingelheim, Ingelheim am Rhein, Germany), thrombin (10 nmol/l; gift from W. Kisiel, University of Albuquerque, New Mexico, USA) and aprotinin (0–1000 kunits/ml; Roche, Basle, Switzerland) were incubated in buffer containing 10 mmol/l Hepes, 20 mmol/l calcium chloride, 150 mmol/l sodium chloride and 0.1 per cent bovine serum albumin (pH 7.4). Clot formation and subsequent clot lysis were followed by measuring changes in turbidity at 405 nm at 37°C in a microplate reader. Absorbance results were expressed in optical density units.

Animals
Thirty female New Zealand White rabbits (mean(s.d.) weight 3084(241) g) were obtained from Harlan (Gennat, France). Animals were housed individually with a 12-h dark–light cycle and fed standard chow ad libitum. All animals were allowed to acclimatize for 2 weeks before initiation of experiments. The institutional animal ethics and welfare committee approved all animal experimental protocols. The experiments were reported according to the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Experimental design
The rabbit liver is divided into four lobes: three cranial and one caudal. Because the cranial lobes are isolated from the caudal lobe, the rabbit is ideally suited for selective portal vein occlusion (Figure S1, supporting information). PVE was performed in five groups (n = 5 rabbits per group) using fibrin glue (Beriplast® P Combi-Set; Nycomed, Hoofddorp, The Netherlands) with different concentrations of aprotinin (1000, 700, 500, 300, 150 kunits/ml). Aprotinin was mixed with fibrin glue according to the manufacturer’s protocol and was reduced for non-standard aprotinin concentrations (all concentrations except 1000 kunits/ml, which is the standard aprotinin concentration in Beriplast® fibrin glue).

Results were compared with those of a previous PVE series in which permanent embolization material (polyvinyl alcohol (PVA) particles and coils; P and C) was used (n = 5 rabbits); this comprised a combination of PVA (90–180 µm in diameter followed by 300–500 µm in diameter; Cook, Bloomington, Indiana, USA) and three fibred platinum coils (PVAc, 4.0, 5.0 and 6.0 mm; Boston Scientific, Natick, Massachusetts, USA). The methods and technique of PVE were identical to those of the present study. Before death, digital subtraction portography was performed to confirm recanalization of the portal vein.

Rabbit model of portal vein embolization
Anaesthesia was induced by intramuscular injection of 25 mg/kg ketamine (Nimatek; Eurovet, Bladel, The Netherlands) and 0.2 mg/kg medetomidine (Dexdomitor®; Orion,
Espoo, Finland). Anaesthesia was maintained using 1–2 per cent isoflurane (Forane®; Abbott Laboratories, Sittingbourne, UK) mixed with oxygen : air (0.5 : 1, 1.5 l/min). All animals received a subcutaneous injection of 0.03 mg/kg buprenorphine (Temgesic®; Reckitt Benckiser Healthcare, Hull, UK) as preoperative analgesia, and 0.2 mg/kg Baytril® (Bayer Healthcare, Berlin Germany) was administered daily as antibiotic prophylaxis until the third postoperative day.

Following a midline laparotomy, a branch of the inferior mesenteric vein was cannulated with an 18-G catheter (Hospira Venisystem, Lake Forest, Illinois, USA). A Renegade 3-Fr microcatheter (Boston Scientific) with a Transend®-ex 0.36-mm × 182-cm guidewire (Boston Scientific) was subsequently introduced into the portal vein. Visualization of the individual portal vein branches by digital subtraction portography was carried out using a mobile C-arm Exposcop 8000 (Ziehm Imaging, Nurnberg, Germany). The microcatheter was placed in the main portal branch to the cranial lobe. The embolization material (fibrin glue with aprotinin) was infused through the catheter to achieve embolization of the portal branches of the cranial liver lobes. Afterwards, the catheter was flushed with 10 ml saline to avoid occlusion. After the embolization procedure, portal occlusion was confirmed by digital subtraction portography. Subsequently, the catheter was extracted and a ligature was used to close the mesenteric vein. The abdomen was closed in two layers using a running Vicryl® 4/0 suture (Ethicon, Johnson & Johnson, Somerville, New Jersey, USA) and interrupted Mersilene 3/0® U-sutures (Ethicon).

Quantification of liver regeneration

Multiphase contrast-enhanced CT was performed using a multislice helical CT scanner (Philips Medical Systems, Eindhoven, The Netherlands) on postoperative days 0, 3 and 7, and weekly thereafter when applicable. Briefly, contrast solution (3 ml Visipaque™; GE Healthcare, Waukesha, Wisconsin, USA) was injected in the lateral ear vein under anaesthesia. Following injection, arterial, portal and venous phase CT images were acquired. Three-dimensional reconstructions of the liver were made by superimposing sequential 2-mm axial slices, and the volumes of the total liver, caudal and cranial lobes were calculated using integrated software (MX-View 3.52; Philips Medical Systems, Best, The Netherlands). Caudal liver volume (CLV) was correlated with caudal liver lobe weight at time of death in order to validate volumetric measurements. The increase in CLV and the CLV regeneration rate were calculated using the following formulas:

\[
\text{Increase in CLV} (\%) = \frac{\text{CLV}_{\text{post-PVE}} - \text{CLV}_{\text{pre-PVE}}}{\text{CLV}_{\text{pre-PVE}}} \times 100\%
\]
Regeneration rate (%/day) = \frac{\text{Increase in CLV}_{\text{post-PVE}}}{\text{Days}_{\text{post-PVE}}}

On every CT scan, recanalization of the embolized portal branches was evaluated by analysing ipsilateral portal perfusion. At death, portography was performed to confirm the recanalization status as determined by CT. In all rabbits, portography results corresponded to the recanalization status determined by CT analysis (Figure S2, supporting information).

To exclude congestive hypertrophy as a contributor to the measured increases in liver volume, the wet/dry weight ratio was examined on liver biopsies from all rabbits. Biopsies were weighed, stored at 60°C for 4 weeks, and then weighed again.

Biochemical parameters
Plasma alanine aminotransferase (ALT) was measured by the Department of Clinical Chemistry using a Cobas® 8000 modular analyser (Roche). Plasma total bile acids were measured using a Total Bile Acids Assay Kit (Diazyme, Poway, California, USA) according to the manufacturer’s instructions on a Synergy™ HT microplate reader (Biotek, Winooski, Vermont, USA).

Histology
Liver tissue was fixed in formalin and embedded in paraffin. Liver sections (5 µm) were stained using standard haematoxylin and eosin, and van Gieson staining to visualize collagen. Cranial liver lobe histology of the groups treated with 300 and 500 kunits/ml apoprotin was assessed in a descriptive manner by an experienced liver pathologist, who was blinded to the group assignment.

Statistical analysis
Data are expressed as mean(s.d.). Differences in liver hypertrophy between groups were tested by means of the Mann–Whitney U test at individual time points, using values obtained by area under the curve (AUC) analysis. Differences between groups in ALT and total bile acid levels were tested using Kruskal–Wallis tests. Correlations were investigated by Pearson’s product-moment correlation. \( P < 0.050 \) was considered statistically significant. All data analysis was performed using Graphpad Prism® version 5.0 (GraphPad Software, La Jolla, California, USA).
RESULTS

In vitro clot lysis
To select the optimal aprotinin dose for in vivo experiments, the effect of aprotinin on lysis of a preformed clot by tPA was investigated in a purified system in vitro. In the presence of 5 µg/ml tPA, clot lysis was inhibited by aprotinin, whereas at higher tPA concentrations no effect of aprotinin was observed (data not shown). When clot turbidity (increased turbidity reflects increased clot formation) was measured over time, aprotinin had a dose-dependent effect on clot lysis in the presence of 5 µg/mL tPA (Figure 1). In the absence of aprotinin, the clot was immediately degraded. With 250 kunit/ml aprotinin, the clot remained stable for 42 h. Further lowering the concentration of aprotinin resulted in rapid clot lysis, whereas in this set-up increasing concentrations did not provide additional clot stability. Therefore 150, 300, 500, 700 and 1000 kunit/ml aprotinin were selected for the in vivo experiments.

![Figure 1](image-url)  
**Figure 1** In vitro clot lysis in a purified system in the presence of varying concentrations of aprotinin; 250–1000 kunit/ml aprotinin resulted in a stable clot for 42 h in the presence of 5 µg/ml tissue plasminogen activator.

Liver regeneration following portal vein embolization
Volumetric measurements of CLV correlated significantly with caudal liver lobe weight at time of death (r = 0.965, P < 0.001) (Figure S3, supporting information). At baseline, there was no difference between the groups in either total liver volume and CLV (data not shown). PVE was successful in all but one rabbit in the 1000-kunit/ml aprotinin group, determined by direct postprocedural recanalization on the portogram and confirmed by an inadequate hypertrophy response. This rabbit was excluded from further analysis.
All groups showed increases in CLV compared with baseline on days 3 and 7 after PVE (Figure 2a). The effect of aprotinin was optimal in the group that received 500 kunits/ml (Figure 2b); this group showed the greatest increase in CLV on day 7, which did not differ from that of the group treated with P and C, the standard embolization material \((P = 0.962)\). Both lower and higher concentrations of aprotinin conferred a smaller degree of hypertrophy. A CLV increase exceeding 50 per cent was observed only in all rabbits in the 300-, 500- and 700-kunits/ml aprotinin groups, and the P and C group. In the 700-kunits/ml group, however, a decrease in regeneration rate was observed on day 7 compared with day 3 (Figure 2c), on the basis of which only the 300- and 500-kunits/ml groups were analysed further over time until day 42.

**Figure 2**

*Figure 2a* Increase in caudal liver volume (CLV) on days 3 and 7 after portal vein embolization (PVE) in groups with varying concentrations of aprotinin added to the fibrin glue. Values were normalized to baseline CLV using CT volumetry. *Figure 2b* Increase in CLV at 7 days after PVE. *Figure 2c* Differences in regeneration rate between groups on days 3 and 7 after PVE. Values are mean(s.d.) \((n = 4–5\) per group). *\(P < 0.050\) (Mann–Whitney U test)
The regeneration rate was calculated for all groups on days 3 and 7 after PVE (Figure 2c). On day 3, the regeneration rate in the 500-kunits/ml group was higher than in the groups that received 300 or 150 kunits/ml aprotinin, or P and C. On day 7, the regeneration rate in the 500-kunits/ml group was higher than that in the 700-kunits/ml group. These results demonstrated a rapid and effective hypertrophy response following PVE when fibrin glue was used in combination with 500 kunits/ml aprotinin.

**Recanalization**

After establishing PVE efficacy over an aprotonin concentration range of 300–500 kunits/ml, recanalization of portal branches of the embolized liver lobes was assessed by examining portal flow on CT. On day 7 after PVE, all rabbits in the 150-kunits/ml group showed recanalization, whereas no recanalization was seen in the dose range of 300–1000 kunits/ml. Because it was probable that recanalization was inversely related to the aprotinin concentration used, animals in the 300- and 500-kunits/ml groups were scanned weekly until day 42 to examine recanalization dynamics. On day 42, four of five animals in the 500-kunits/ml group and three of five in the 300-kunits/ml group showed recanalization of the occluded portal system of the cranial lobes (Figure 3a,b).

With respect to recanalization dynamics, two of five animals in the 300-kunits/ml group already had patent portal vein branches to the cranial liver lobes in the first 10 days after PVE (rabbit 1 and 5; Figure 3a), which hampered CLV hypertrophy (Figure 3c). In contrast, earliest recanalization in the 500-kunits/ml group was evident on day 21 after PVE, which did not affect CLV hypertrophy (Figure 3b,d). Therefore, 500 kunits/ml appeared to be the optimal concentration of aprotinin for effective hypertrophy, while allowing recanalization after a sufficiently extended period.

Recanalization had significant effects on the volume of the cranial liver lobes. When recanalization occurred, an increase in cranial liver volume (CrLV) was observed in both groups (Figure 3e,f). In both 300- and 500-kunits/ml groups, there was a significant difference in the decrease in CrLV on day 35 between animals with non-recanalized portal branches versus those with recanalized portal branches ($P = 0.024$).
Figure 3  

**a,b** Recanalization of embolized liver lobes in 300-kunits/ml (a) and 500-kunits/ml (b) aprotinin group determined by examining portal flow on CT images. Numbers 1–5 represent individual animals in each group. Closed circles indicate portal vein obstruction and open circles represent portal vein recanalization.  

**c,d** Increase in caudal liver volume (CLV) in 300-kunits/ml (c) and 500-kunits/ml (d) aprotinin group.  

**e,f** Decrease in cranial liver volume (CrLV) in 300-kunits/ml (e) and 500-kunits/ml (f) aprotinin group. In c–f numbers 1–5 represent the same animals in each aprotinin group as in a–b.
Biochemical parameters
After establishing an adequate hypertrophy response using fibrin glue and aprotinin, with 80 per cent recanalization, serum ALT and total bile acids were measured to ensure the safety of the procedure. Serum ALT levels increased following PVE with a peak on day 1. No significant differences were measured between groups, but there was a trend towards lower peak ALT levels in the aprotinin groups compared with the P and C group (Figure 4a).

Serum total bile acid levels were measured in all rabbits. No significant intergroup differences were seen (Figure 4b). Serum bile acid levels correlated significantly with regeneration on both days 3 and 7 (data not shown).

Histology
Cranial liver lobe sections from the 300- and 500 kunits/ml aprotinin groups were examined to determine parenchymal viability following temporary portal occlusion. Marked differences were observed between recanalized (Figure 5a,c) and embolized (Figure 5b,d) liver lobes. In the animals with no recanalization (Figure 5b,d), severe histomorphological changes were evident with severe perivenular and periportal fibrosis and formation of fibrotic portal-portal bridges. Sinusoidal congestion was noted, as well as extensive macrophage influx. Variable venous occlusion was seen in the non-recanalized animals.

Only minor histological changes were found in the cranial liver lobes of recanalized animals (Figure 5a,c). Discrete sinusoidal congestion with minimal inflammation was observed, and in the larger portal tracts mild oedema with none to minimal periportal and perivenular fibrosis.
Figure 5 Representative cranial lobe sections from livers harvested on day 49 after portal vein embolization. a, b Haematoxylin and eosin-stained sections from a recanalized animal (a) and a non-recanalized animal (b). c, d Van Gieson-stained sections from a recanalized animal (c) and a non-recanalized animal (d). Macrophages (arrows), fibrotic changes (asterisks) and occluded vein (triangle) are shown, PT, portal triad (original magnification × 200).

DISCUSSION

This study sought to establish a novel reversible PVE method in a standardized rabbit model by modulating clot lysis with aprotinin. Fibrin glue-based PVE in combination with 500 kunits/ml aprotinin resulted in an adequate hypertrophy response, while providing recanalization in four of five animals after 42 days. These results demonstrate that reversible PVE can be performed safely while preserving procedure efficacy.

Preoperative PVE is part of standard care to prevent postoperative liver failure in patients undergoing major hepatic resections when the FRL volume and/or function is deemed insufficient before surgery. However, using P and C to embolize liver segments severely impairs
the diagnostic accuracy of subsequent diagnostic CT. Therefore, absorbable embolization materials hold a potential benefit over the currently used permanent embolization materials. The challenge is to achieve reversible occlusion of the portal branches, while maintaining a regenerative response that is sufficient to allow safe liver resection.

Lainas and colleagues\textsuperscript{12} found a sufficient hypertrophy response after PVE with gelfoam in monkeys. Recanalization of the embolized portal branches had taken place after 12–16 days, while adequate volume increase of the non-embolized liver lobes was noted. Van den Esschert and co-workers\textsuperscript{11}, however, concluded that gelfoam in a rabbit model of PVE was absorbed within 7 days and resulted in clinically insufficient hypertrophy of the non-embolized lobes. In the same study, Beriplast\textsuperscript{®} (fibrin glue with 1000 kunits/ml aprotonin) was evaluated as potential absorbable embolic material. Beriplast\textsuperscript{®}, however, permanently obstructed portal flow, which was attributed to excessive antifibrinolytic activity of aprotonin.

Fibrin glue is a two-component surgical haemostatic agent consisting of the blood coagulation factors fibrinogen, factor XIII, thrombin, an antifibrinolytic agent (aprotinin) and calcium chloride. It mimics the final stages of secondary haemostasis to produce a stable fibrin clot and is commonly used to achieve haemostasis of the resection surface of the liver after parenchymal transection\textsuperscript{13}. Fibrin glue has been used routinely for PVE and appears to be safe and effective, yet it is not absorbable and therefore acts as a permanent embolic material\textsuperscript{14,15}. The hypothesis of the present study was that lowering the aprotonin concentration would accelerate absorption of the embolic material and hence allow fibrin glue to be used as an absorbable embolic agent.

The \textit{in vitro} experiments demonstrated that aprotonin effectively inhibits fibrinolysis. Unlike 125 kunits/ml aprotonin, doses of 250–1000 kunits/ml in the presence of 5 µg/ml tPA resulted in stable clots for more than 42 h. Based on these results, the efficacy of the higher aprotonin concentrations were evaluated further \textit{in vivo}.

In rabbits, PVE using fibrin glue with 500 kunits/ml aprotonin induced the optimal hypertrophy response in the non-embolized liver lobe. During the first 3 days the regeneration rate was significantly higher than in the group embolized with standard P and C. Embolization using less than 500 kunits/ml aprotonin resulted in reduced caudal lobe hypertrophy. This was probably due to early lysis of the embolization material and rapid reperfusion of the embolized portal branches, as demonstrated by recanalization of all portal branches in the 150-kunits/ml aprotonin group by day 3 after PVE. However, the use of aprotonin concentrations exceeding 500 kunits/ml also reduced regeneration, despite stable clot formation. This may be explained by inhibitory effects of aprotonin on liver regeneration
pathways. Aprotinin inhibits plasmin, which is required for hepatocyte growth factor expression during liver regeneration\textsuperscript{16}, as well as for extracellular matrix proteolysis and clearance of cellular debris\textsuperscript{17}. In addition, plasminogen mediates liver regeneration by regulating angiogenesis\textsuperscript{18}. In high doses, aprotinin also inhibits the kallikrein–kinin system, which in turn reduces plasmin formation\textsuperscript{19}. All these effects of increased aprotinin levels probably contributed to the reduced hepatic regenerative capacity observed at higher concentrations.

The clinical potential of reversible PVE is only substantial when the recanalized liver lobes show functional viability. Recanalization of the embolized segments resulted in the regrowth of the atrophied cranial liver lobes, suggesting viability and return of function of the embolized segments upon recanalization. This was supported by lower decreases in CrLV on day 35 in non-recanalized animals compared with those not showing recanalization in the 300- and 500-kunits/ml groups (Figure 3e,f). However, as liver volume does not necessarily reflect liver function\textsuperscript{20}, functional recovery of recanalized liver segments should be confirmed using quantitative, dynamic liver function tests\textsuperscript{21}. Nevertheless, histological analysis showed marked differences between recanalized and embolized cranial liver lobes. Following recanalization, liver histology showed only minor changes, attesting to the hypothesis that the embolized lobes contribute to liver function following recanalization.

Considering the minor histological changes in the embolized lobes of rabbits following recanalization, reversible PVE might have potential application in living donor liver donation. However, the technique must be optimized to obtain maximal hypertrophy with an optimal time span to recanalization before clinical introduction.

Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) combines parenchymal transection and portal vein ligation in patients with a small FRL volume and function, and results in a rapid hypertrophic response\textsuperscript{22}. ALPPS resulted in 74 per cent (median) hypertrophy in a median of 9 days, which was faster than similar hypertrophy in a median of 34 days after PVE\textsuperscript{23}. Most likely, the parenchymal transection prevents collateral perfusion of the deportalized segments thereby enhancing liver regeneration. Furthermore, with ALPPS, 97 per cent\textsuperscript{24} of patients completed liver resection compared with 72 per cent of patients treated with PVE\textsuperscript{23}. ALPPS might be an alternative technique to reduce the number of patients treated with PVE who do not progress to surgery; however, its effectiveness is counterbalanced by increased morbidity and mortality compared with PVE\textsuperscript{23,25}. No ALPPS models have been developed in rabbits. In mice, ALPPS induces more rapid and increased hypertrophy compared with portal vein ligation alone. The regeneration obtained in the present study is comparable to that in the authors’ previous reports of PVE in rabbits using
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permanent embolization materials; however, it is most likely slower than the hypertrophy response after ALPPS\textsuperscript{11}. Although ALPPS might result in superior hypertrophy compared with (permanent) PVE, the procedures have distinct indications. In the present study, using a standardized rabbit model of PVE, in which fibrin glue was combined with 500 kunits/ml aprotinin, reversible PVE was obtained in 80 per cent of animals (four of five) while inducing a hypertrophy response comparable with that achieved with standard (permanent) embolization materials. These results pave the way for the clinical evaluation of a fibrin glue-based, reversible PVE technique.
REFERENCES


SUPPORTIVE INFORMATION

**Figure S1:** Anatomy of the rabbit liver. Four main lobes: caudal liver lobe and three cranial lobes: left lateral (LL), left medial (LM), and the right liver lobe (RL). CT volumetric assessment is facilitated by the rabbit liver anatomy in which the cranial and caudal lobes are separated. The lobes above the black line represent the cranial liver volume (CrLV), the lobes below the line represent the caudal liver volume (CLV). The coils represent the position of portal catheter placement during PVE and the position of the coils in the Particles & Coils group.
**Figure S2:** Portography before sacrifice to confirm correctness of recanalization status based on portal perfusion on contrast-enhanced CT-scans. **A.** Portography demonstrating an occluded portal system of the cranial lobes. **B.** Portography demonstrating perfusion of the portal system of the cranial liver lobes in a previously embolized animal.

**Figure S3:** Correlation between CLV determined by CT-volumetric analysis on the CT scan directly before sacrifice and caudal liver weight at sacrifice. Correlation was tested using Pearson’s correlation coefficient for 20 animals. $r = 0.9647$ and $p < 0.0001$. 