

Double Embolization for Rapid Liver Hypertrophy: The Endovascular ALPPS

A review of how an interventional double embolization procedure developed from the surgical ALPPS procedure and discussion of the initial results.

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Portal vein embolization (PVE) with gelatin sponge and cyanoacrylate is a well-established approach to divert portal flow from one side of the liver to the future liver remnant (FLR) to prepare the liver for extended resections.¹ When more than 70% of the liver has to be removed, most often due to extensive tumor load, PVE can help to prepare the small FLR to tolerate the hemodynamic stress of the portomesenteric blood flow and metabolic requirements of the organism and increase the liver volume of the FLR by up to 50%.^{2,3}

This process of conditioning the FLR usually takes about 6 weeks but is not successful in all patients. In some patients, the FLR fails to grow in volume, or cancer progression during the waiting period makes the planned resection impossible. Overall, up to 27% of patients fail to achieve resectability using this strategy, even in the most experienced centers.⁴ Due to its unreliability and the necessary waiting period, PVE is not a popular option at some centers. Randomized studies have not been able to consistently prove an outcome advantage for all patients, but some subgroups, such as those with cirrhosis undergoing extensive resections, have had improved outcomes over extended resections without preconditioning.⁵

In 2012, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), a surgical procedure, was proposed to replace interventional PVE.⁶ In ALPPS, the portal vein is ligated but not embolized, and the liver parenchyma is transected to separate the deportalized liver and the FLR.⁷ ALPPS both accelerates the time the liver takes to hypertrophy and increases

the amount of liver volume achieved when compared to PVE.⁸ The novel operation was hailed to increase the resectability of liver tumors and expand the indications for surgical resection.⁶ Not surprisingly, complications and mortality were higher in a surgical procedure requiring laparotomy instead of a radiologic intervention,⁹ but in bilobar multifocal liver metastases, which require two surgical procedures for resection anyway, the ALPPS procedure continued to garner support.¹⁰

A Scandinavian randomized study recently showed that the complication rate associated with resection of bilobar colorectal liver metastases in a two-stage hepatectomy, using PVE in between, is comparable to that of the two ALPPS stages.¹¹ However, more patients proceed to complete resection with the ALPPS procedure than with PVE.¹¹ In contrast, reports of high complication rates for most other indications for liver resection such as hepatocellular carcinoma and biliary tumors have challenged the potential of ALPPS to replace PVE.¹²⁻¹⁴ ALPPS remains a second-line intervention behind PVE for all indications for liver resection to increase the function and volume of the FLR except for very extensive colorectal liver metastases.^{15,16}

To maintain the advantages of rapid hypertrophy while reducing the high morbidity and mortality rate of ALPPS, attempts have been made to return to the interventional paradigm. ALPPS reformists proposed interventional embolization of the portal vein instead of ligation (also called hybrid ALPPS),¹⁷ as well as interventional transection of the parenchyma using transcatheter radiofrequency ablation combined with PVE (also called radiofrequency-assisted ALPPS or RALPPS)¹⁸



Figure 1. Angiogram showing two Amplatzer plugs in the middle hepatic vein. The second one is still connected to the delivery system from a jugular approach (A). A marked decreased of filling of the portal vein system of the right lobe is seen on digital subtraction angiography after previous embolization of the right and middle hepatic vein (B). After glue embolization of the right portal vein, a cast of Lipiodol-Glubran mixture is seen (C).

as the first stage of these modified ALPPS procedures. Other authors have proposed a laparoscopic modification of the first stage or even the entire procedure to reduce the complication rate.¹⁹ However, it appeared that rapid hypertrophy requires some kind of transection of the parenchyma.

ANIMAL STUDIES

Our group recently showed that after portal vein ligation (PVL) in pigs, extensive collaterals develop within 1 week between the deportalized liver and the liver supplied by the portal vein, whereas these collaterals are abrogated by transection of the parenchyma.²⁰ These collaterals draw portal vein blood from the side supplied by the portal vein to the deportalized side and thereby steal hepatotrophic factors in portal vein blood from the FLR that is supplied with portal vein blood. This phenomenon of portal vein steal after PVL was first described in experiments by Rous and Larimore in 1929, who observed that after PVL in rabbits, certain areas of the deportalized liver that received portal vein blood from small collaterals, which had developed from the side supplied by the portal vein over time, did not atrophy but kept their size and vitality.²¹ Since then, the literature has documented that collaterals to the deportalized liver weaken the hypertrophic effect on the side supplied by the portal vein not only in PVL, but also in PVE.²²⁻²⁴

DEVELOPMENT OF DOUBLE EMBOLIZATION

Given the results of animal studies, the question arose as to whether collateralization could be prevented without going to the extreme of parenchymal surgi-

cal transection.²⁰ One possible interventional strategy was to avoid collateralization by obstructing hepatic vein outflow from the deportalized side. If there is no venous outflow, there should be resistance to portal vein collateralization and thereby to the stealing of hepatotrophic factors.

Attempts to simultaneously embolize both the portal and hepatic veins did not appear very promising based on the existing literature, because it had been shown that sequential portal vein and hepatic vein ligation does not enhance the kinetic growth of the FLR very much.^{25,26} Sequential portal and hepatic venous embolization was the preferred method in these studies due to the concern about liver necrosis with simultaneous embolization. Likely, this concern was unjustified and underestimated the ability of the liver to develop outflow collaterals across the watersheds in the parenchyma. It appears now that the arterial pressure and flow to the deportalized and hepatic vein-occluded liver are high enough to keep a simultaneously deportalized and hepatic vein-deprived liver alive without necrosis.

Recently, an interventional radiology group in France showed for the first time that simultaneous embolization of the right portal vein and the right hepatic vein, called liver venous deprivation (LVD), is not only feasible without liver necrosis, but it also achieves volume increase comparable to ALPPS.^{27,28} This group performed 10 LVD procedures before liver surgery. They embolized the right and the middle hepatic vein in some cases with Amplatzer vascular plugs (Abbott Vascular, formerly St. Jude Medical) and cyanoacrylate. Surgery was successfully performed in nine of 10 patients after a median of

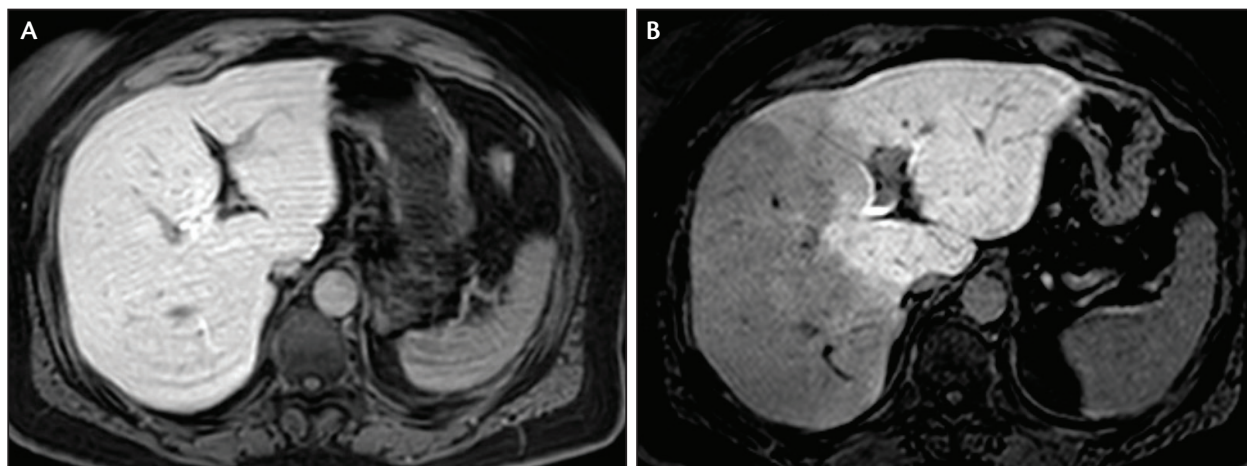


Figure 2. Equilibrium-phase, T1-weighted axial MRI before (A) and after (B) double embolization showing hypertrophy of the left lobe and a marked decrease of gadoteric acid in the right lobe, indicating a reduction of functional hepatocytes. Normal excretion is seen on the left lobe.

31 days (range, 22–45 days) after LVD. LVD and “double embolization” are synonymous.²⁹

LIVER FUNCTION AFTER ALPPS AND LVD

Additional interest in double embolization arose from the fact that liver function assays have demonstrated that ALPPS does not lead to a congruent increase in liver function, despite the volume gains. Regional liver function tests, such as the mebrofenin or hepatobiliary iminodiacetic acid scan, are able to give an estimate of regional liver function based on technetium-labeled mebrofenin uptake kinetics.³⁰ Meticulous studies in ALPPS patients showed that although the right liver lobe grew in volume by a median of 78% with ALPPS, its functional increase was only 29%.³¹ These data have also been confirmed in animal models.³² The reason for this functional deficit is unknown, but the observation may explain the high morbidity and mortality of ALPPS since the initial reports.³³ In contrast, Guieu et al showed that LVD leads to a symmetric increase in volume and function in a very small series of patients.²⁸

The reason that rapid liver growth leads to a significant functional deficit with one method to induce rapid hypertrophy and to a normally functioning liver using another method to induce rapid hypertrophy may be explained by the liver’s ability to regulate the negative trophic effects of increased portal blood, pressure, and shear stress; in double embolization, the parenchyma is left intact and decompressive shunts can develop inside the parenchyma and to small hepatic veins. This is likely not the case with ALPPS. Further studies are needed to support this hypothesis.

OUR EXPERIENCE WITH DOUBLE EMBOLIZATION

Thus far, three patients have been treated by our group with simultaneous embolization of the right portal vein and the right hepatic vein (two cases) and the right and middle hepatic vein (one case). All patients had colon cancer with simultaneous liver metastasis. Double embolization was performed as an outpatient procedure. First, the hepatic vein(s) were embolized from a jugular vein approach (Figure 1A). Amplatzer plugs should be placed centrally without prolapsing into the inferior vena cava. Then, the right portal vein was accessed under ultrasound guidance. Portography showed an impressive reduction of portal flow into the right liver lobe secondary to prior hepatic vein embolization (Figure 1B). The right portal vein was then occluded with a mixture of Lipiodol (Guerbet LLC) and Glubran (GEM Srl) in a 1:1 ratio (Figure 1C). T1-weighted, postcontrast, late-phase liver MRI with gadoteric acid (Primovist, Bayer) showed hypertrophy of the left liver lobe and a markedly decreased contrast uptake into the right liver lobe after double embolization (Figure 2). Right hepatectomy, including segment IV in two cases, was performed 41, 21, and 8 days, respectively, after double embolization, with > 30% FLR in all cases without complications and no posthepatectomy liver dysfunction. After a follow-up of 1, 4, and 5 months, no residual or recurrent liver metastases were found.

CONCLUSION

Preliminary results after double embolization show consistent and rapid growth of the FLR comparable to

ALPPS but without severe complications. This novel approach has the potential to improve PVE, especially by reducing the waiting period prior to surgery. The approach allows rapid hypertrophy by endovascular means, particularly for two hepatectomies required for bilobar colorectal liver metastases, which remains the most common indication for liver resection in the Western world. ■

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