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Research review

# A review of animal models for portal vein embolization

*Floor Huisman, MD,*[a,*] *Krijn P. van Lienden, MD, PhD,*[b] *Samantha Damude, MD,*[a] *Lisette T. Hoekstra, MD, PhD,*[a] *and Thomas M. van Gulik, MD, PhD*[a]

[a] *Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands*
[b] *Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands*

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ABSTRACT

*Background:* Portal vein embolization (PVE) is a preoperative intervention to increase the future remnant liver (FRL) through regeneration of the non-embolized liver lobes. This review assesses all the relevant animal models of PVE available, to guide researchers who intend to study PVE.

*Materials and methods:* We performed a systematic literature search in Medline and Pubmed, from 1993–June 2013, using search headings "PVE" and "portal vein ligation". Articles were included when meeting the selection criteria: experimental animal study on PVE or portal vein ligation and experiments described in 5 animals or more.

*Results:* Sixty-one articles were selected, describing six different animal models. Most articles reported experiments with rats, rabbits, and pigs. In rats, the increase in wet-weight ratio of the non-occluded liver or total liver weight is greatest in the first 7 d with values ranging from 75%–80.5% on day 7. The volume increase of FRL in the rabbit model is greatest in the first 7 d with values ranging from 33.6%–80% on day 7. In pigs, the largest gain in volume of the FRL was seen in the first 2 wk.

*Conclusions:* The choice of the model depends on the specific aim of the study. Evaluating the increase in liver volume and liver function after PVE, larger animals as the pig, rabbit, or the dog is useful because of the possibility to apply computed tomography volumetry. To evaluate mechanisms of regeneration after PVE, the rat model is useful, because of the variety of antibodies commercially available.



## 1. Background

Surgical resection of primary or secondary tumors in the liver remains the only curative therapy. The great majority of patients are however, not candidates for surgery because of tumor burden or too small liver remnant leading to increased risk of post hepatectomy liver failure. To undergo a major liver resection, the future remnant liver (FRL) volume in humans has to be at least 25% based on computed tomography (CT) volumetric studies to avoid post resectional liver failure [1]. In

* *Corresponding author*. Department of Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands. Tel.: +31 20 566 5569; fax: +31 20 697 6621.
E-mail address: floor_huisman@hotmail.com (F. Huisman).
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livers with compromised parenchyma due to cirrhosis, steatosis or recent chemotherapy, the minimum volume should be at least 30%. Preoperative portal vein occlusion by embolization or ligation is a method to stimulate growth of the non-occluded liver segments, thereby increasing the volume of the FRL [2].

The concept of the atrophy–hypertrophy complex following unilateral portal vein occlusion has initially been demonstrated in a rabbit model by Rous and Larimore in 1920 [3]. They discovered in rabbits that ligation of the portal branches to part of the liver caused atrophy of that part of the liver and concomitant hypertrophy of the non-ligated part of the liver. This phenomenon has already been used in a clinical setting for many years. Although clinical portal vein embolization (PVE) has shown effective, several issues need further investigation. The mechanism of induction of liver regeneration after PVE is still poorly understood, the optimal technique and choice of embolization materials can be improved and (pharmaceutical) interventions to stimulate liver regeneration in addition to PVE must be further investigated. As a downside, PVE not only induces liver regeneration but it also promotes tumor growth [2,4,5]. Strategies to control this potential drawback need to be explored in animal studies. In this review, we describe all relevant animal models, used to study PVE, in relation to the species-specific anatomy techniques and the induced hypertrophy response.

## 2. Materials and methods

We performed a systematic literature search in Medline and Pubmed, from 1993–June 2013. The applied search headings were “PVE” and “portal vein ligation”. Limitations were set to English language and animal studies. The abstracts were screened to identify potentially relevant articles and were evaluated by two of the authors (F.H., S.D., and L.T.H.), using a predetermined scoring list. Full text articles of potentially relevant articles were screened and were included in this study when meeting the following selection criteria:

- experimental animal study on PVE or portal vein ligation (PVL)
- experiments described in at least five animals.

## 3. Results

### 3.1. Types of animals

Sixty-one articles were selected, describing six different animal models; that is, in monkeys, pigs, dogs, rabbits, rats, or mice (Table 1). One article discussed both dogs and rats. Two articles described both PVL and PVE in a rat model, rabbit model, and pig model.

**Table 1 – Animal models used for PVE.**

| Animal | Number of articles PVL | Number articles PVE | Total number of articles |
|---|---|---|---|
| Monkey | 0 | 1 | 1 |
| Pig | 5 | 9 | 13 |
| Dog | 1 | 7 | 8 |
| Rabbit | 2 | 8 | 9 |
| Rat | 20 | 8 | 27 |
| Mouse | 3 | 0 | 3 |

### 3.2. Mice

Only three articles described the procedure of PVL in a murine model and no reports of PVE in the mouse have been published [6–8]. The diameter of the portal branches of the mouse is small; therefore, it is not an ideal animal model to perform PVE.

### 3.3. Monkeys

One article described the use of a monkey model to observe the regeneration response after PVE with an absorbable embolization material [9]. The use of monkeys for research is in many countries restricted or forbidden.

### 3.4. Rats

Twenty-seven articles described PVE or PVL in a rat model.

#### 3.4.1. Anatomy of the rat liver

The liver of the rat consists of four lobes. The left part of the liver part consists of the median lobe (ML) and the left lateral lobe (LLL). The right part of the liver consists of the superior (SRL) and inferior right lobe, the anterior and posterior caudate lobe. Each lobe has its own blood supply consisting of branches of the portal vein and hepatic artery (Fig. 1).

#### 3.4.2. Technical procedure in the rat

In seven of the eight articles describing PVE in rats, the left liver lobe was embolized, corresponding to 70% of total liver volume (Fig. 2; [10–16]). The main portal trunk was dissected and punctured with a needle ranging from 20–30-gauge and a

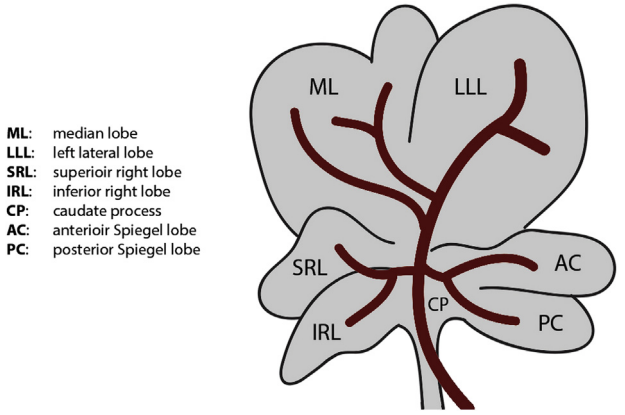


**Fig. 1 – Anatomy of the rat liver. (Color version of figure is available online.)**