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● *Original Contribution*

IMAGE MONITORING OF THE IMPAIRED PHAGOCYTIC ACTIVITY OF KUPFFER CELLS AND LIVER OXYGEN SATURATION IN A MOUSE CHOLANGITIS MODEL USING CONTRAST-ENHANCED ULTRASOUND IMAGING AND PHOTOACOUSTIC IMAGING

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Abstract—Bile duct ligation (BDL) can cause cholangitis, which is known to induce impaired Kupffer cell (KC) function and increased oxygen consumption in a mouse model. It is important to monitor changes in KC function and tissue oxygen saturation, both of which are critical factors in the progression of cholangitis. The purpose of this study is to investigate the impaired phagocytic activity of KC and liver oxygen saturation (sO_2) in a mouse cholangitis model using contrast-enhanced ultrasound imaging (CEUS) and photoacoustic imaging (PAI). A mouse cholangitis model was created by ligation of the common bile duct (CBDL, n = 20), and the left intrahepatic bile duct (BDL-L, n = 19), both of which were compared with the non-ligation groups—right lobe measurement group after left intrahepatic bile duct ligation (BDL-R, n = 19) and the control group (n = 14). The echogenicity and sO_2 were measured by CEUS and PAI and the KC fraction was assessed at 1, 2 and 4 wk after ligation. We found a significantly lower echogenicity of the Kupffer phase in the CBDL and BDL-L groups compared with that in the control and BDL-R groups at 2 wk ($p < .01$). The CBDL and BDL-L groups showed a lower echogenicity than that of the BDL-R group at 4 wk ($p < .01$). We found a significantly lower sO_2 of the CBDL and BDL-L groups compared with that of the control and BDL-R groups at 4 wk ($p < .01$). The CBDL and BDL-L groups showed a higher KC fraction than that of the BDL-R and control groups at each time point ($p < .01$). In conclusion, our study suggests that the Sonazoid CEUS and PAI could be a useful tool for monitoring impaired KC phagocytic activity and the liver hypoxic state.
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Key Words: **Contrast-enhanced ultrasound, Photoacoustic imaging, Kupffer cells, Oxygen saturation, Cholangitis.**

INTRODUCTION

Cholangitis is caused by a combination of biliary obstruction and bacterial infection and is a major contributor to the systemic inflammatory response syndrome (Tomioka et al. 2000). Previous studies have postulated that cholangitis is caused by impaired reticuloendothelial system (RES) function or increased bacterial translocation into the systemic circulation (Clements et al. 1993; Deitch et al. 1990; Ding et al. 1992, 1994; Tomioka et al. 2000).

The impaired RES has been associated with Kupffer cells (KCs) dysfunction that occurs during the progression of bacteremia (Minter et al. 2005). Bile duct ligation (BDL) can cause cholangitis, which is known to induce proliferation of KCs, increased oxygen consumption and microvascular perfusion damage (Koeppel et al. 1997; Moon et al. 2009). The number of KCs increases in response to BDL, although the KC function may be impaired, as seen in the BDL animal model (Hoshino et al. 2003; Tomioka et al. 2000). An elevated expression of hypoxic-induced factors has been found in liver parenchyma in the BDL animal model after BDL (Moon et al. 2009; Rosmorduc and Housset 2010). Although these findings might be associated with important microenvironment changes after BDL, few reports exist regarding *in vivo* monitoring in a mouse cholangitis model.

Contrast-enhanced ultrasound imaging (CEUS) can assess KC phagocytic activity using the Kupffer-specific contrast agent Sonazoid (gaseous perflubutane; GE Healthcare, Chicago, IL, USA) (Miyata et al. 2011; Tsujimoto et al. 2008). The effect of the Sonazoid phagocytosis by KCs can provide a stable, late-stage CEUS imaging—Kupffer-phase imaging (Yanagisawa et al. 2007).

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The potential advantage of this CEUS is that the quantitative change in the contrast enhancement value would provide data that reflect the *in vivo* physiologic function of KC. On the other hand, photoacoustic imaging (PAI), a new functional imaging technology, can measure changes in tissue oxygen saturation (sO_2) because of microenvironment changes in real time (Eisenbrey et al. 2015; Hu and Wang 2010; Mallidi et al. 2011; Xu and Wang 2006). As the binding of oxygen to hemoglobin alters its absorption spectrum, comparing the photoacoustic signal at 750 and 850 nm allowed for measurement of the sO_2 within the detected blood or tissue (Hu and Wang 2010; Needles et al. 2013; Xu and Wang 2006).

Therefore, our study assessed the serial change of impaired phagocytic activity of KCs and liver sO_2 using CEUS and PAI in a mouse cholangitis model. We attempted to monitor changes in KC function and tissue sO_2 when the number of KCs increases or decreases.

MATERIALS AND METHODS

Animal preparation and study design

All protocols were approved by Seoul National University Hospital's Institutional Animal Care and Use Committee. We used 6-wk–old, male, C57 BL/6 mice, each weighing 30 g, for the experiments. In our study we used the BDL technique described in previous studies (Clements et al. 1993; Deitch et al. 1990; Ding et al. 1992, 1994). The mice were given local anesthesia and a midline incision was made through the skin and peritoneum. After lifting the entire liver, the common bile duct (CBD) was identified, gently dissected using moistened cotton gauze and microforceps and ligated using 7-0 Prolene (Ethicon, Somerville, NJ, USA). The left intrahepatic bile duct (IHD) was ligated in a similar way before the left and median IHD were merged. Sham-operated mice had the peritoneal incision, but not the ligated bile duct. The peritoneum was closed using a 7-0 Prolene.

The mice were divided into 4 groups as follows: CBD ligation group (CBDL, n = 20); left lobe measurement group after left IHD ligation (BDL-L, n = 19); right lobe measurement group after left IHD ligation (BDL-R, n = 19); and the control group (n = 14). The evaluation of the BDL-R group was regarded as the non-ligation group, similar to the control group. The study design was as outlined in Figure 1.

Contrast-enhanced ultrasound imaging with Sonazoid

CEUS was performed at 1, 2 and 4 wk after the BDL. The ultrasound scans were obtained by a radiologist (JHK) experienced in the use of Aplio-500 (Toshiba Medical Systems Corp, Otawara, Japan) with a PLT-120 linear transducer centered at 12–MHz, using the following parameters: a dynamic range of 65 dB, a mechanical index of 0.9, a gain of 95 dB and a field of view depth of 1.5 cm. First, a morphologic examination of the entire liver was performed in the B-mode.

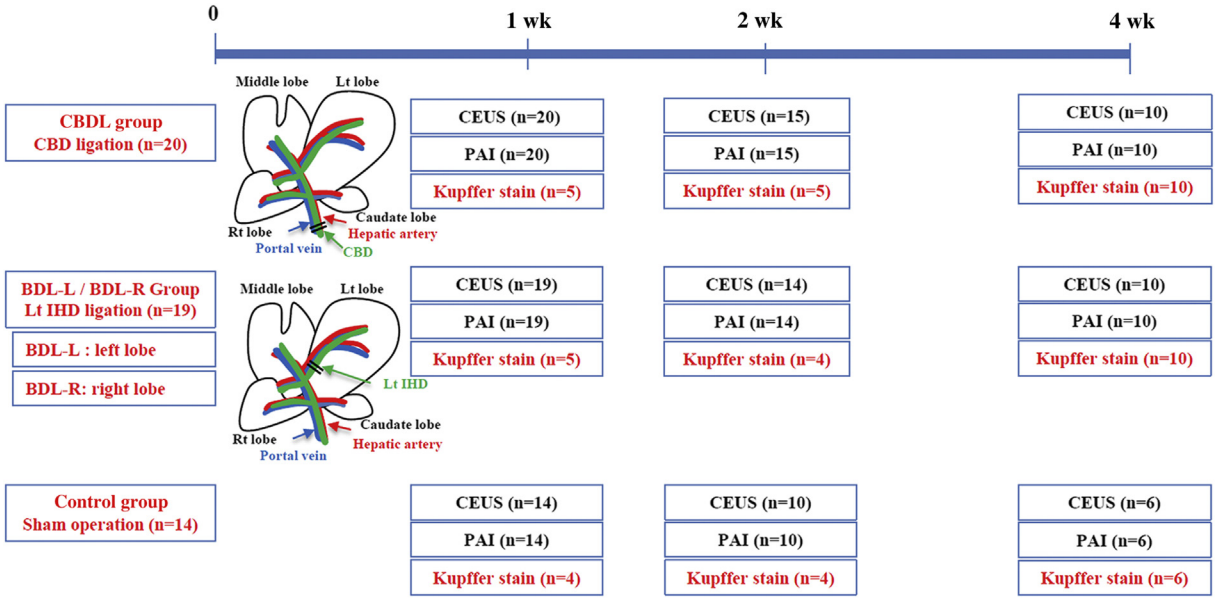

Fig. 1. Study design of a mouse cholangitis model. The mice were divided into 4 groups, including the ligation group of CBD (CBDL, n = 20), the ligation group of left IHD (BDL-R or BDL-L, n = 19), and the control group (n = 14). The CEUS and PAI were performed at 1, 2 and 4 wk after bile duct ligation. In total 14 specimens were available for Kupffer cell staining at 1 wk, 13 specimens at 2 wk and 26 specimens at 4 wk. CBD = common bile duct; CBDL = common bile duct ligation; IHD = intrahepatic bile duct; BDL-R = bile duct ligation, right lobe; BDL-L = bile duct ligation, left lobe; CEUS = contrast-enhanced ultrasound; PAI = photoacoustic imaging.

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