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● *Original Contribution*

EVALUATION OF EARLY KIDNEY DAMAGE CAUSED BY BRAIN DEATH USING REAL-TIME ULTRASOUND ELASTOGRAPHY IN A BAMA PIG MODEL

YING TANG, JINGWEN ZHAO, DONGYANG LIU, NINGNING NIU, and HUIMIN YU
Department of Ultrasound, Tianjin First Center Hospital, Tianjin, China

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Abstract—The aim of this study was to investigate the value of real-time tissue elastography (RTE) in the evaluation of early graft damage resulting from brain death. We performed RTE before and 0, 3, 6 and 9 h after brain death in a Bama pig model. Eleven RTE parameters were compared among time groups, and their correlations with electron microscopic findings were analyzed. Receiver operating characteristic curve analysis was used to find the RTE parameter cutoff values. The mean relative strain value within the region of interest (MEAN), standard deviation of the relative strain value within the region of interest (SD), percentage area of low strain within the region of interest (%AREA), complexity of low-strain area within the region of interest (COMP), kurtosis (KURT), skewness (SKEW), contrast (CONT) and entropy (ENT) and inverse difference moment (IDM) differed statistically significantly between groups ($p < 0.05$). Electron microscopy of kidney tissue revealed that irreversible damage gradually occurred with longer brain death duration and was marked at 9 h ($p < 0.05$). These findings correlated best with MEAN ($r = 0.632, p < 0.05$). Receiver operating characteristic curve analysis of RTE parameters identified a cutoff value of 63.43 for MEAN for optimal diagnostic performance. RTE allows non-invasive, preliminary evaluation of early renal graft damage resulting from brain death. (E-mail: doctortang2010@aliyun.com) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Brain death, Early damage, Electron microscopy, Kidney, Real-time elastography.**

INTRODUCTION

Since implementation of the pilot program for organ donation from deceased citizens in China in 2011, donations after brain death (DBDs) have increased significantly (Huang et al. 2012, 2013; Ye et al. 2014). Brain death is defined as the complete cessation of full function of the cerebrum, cerebellum and brainstem (Hershenov 2003). The state of brain death results in changes in hemodynamics, consumption of coagulation factors, pathologic changes in tissues, low body temperature, electrolyte disorders and changes in the endocrine system (Ranasinghe and Bonser 2011). All these effects can result in inflammatory damage to important organs, such as the kidneys. Such damage, if not detected before transplantation, might affect the prognosis of transplant recipients and graft survival (Jimenez-Castro et al. 2015). Currently, the mechanism underlying damage to solid organs caused by brain death is unclear (Watts et al. 2013). Moreover, an effective imaging method for evaluating the degree of this damage is lacking.

Address correspondence to: Ying Tang, No. 24 Fukang Road, Nankai District, Tianjin, China. E-mail: doctortang2010@aliyun.com

Real-time elastography (RTE) is a new functional ultrasonic technology that assesses tissue elasticity based on the physical strain created by external compression (Lin et al. 2017). The underlying principle relies on application of a limited force to selected regions with an ultrasonic probe or use of the patient's own cardiovascular pulsation (Schroder et al. 2016). Elasticity distribution is assessed by recording response to strain and stress within the tissue, and the result of the elastography is displayed in colors reflecting organ elasticity (Kalita et al. 2017). Those colors range from blue to red and represent different degrees of tissue stiffness (Wu et al. 2014). Specifically, hard tissue areas are displayed in *dark blue* or *blue*, and soft tissue areas are displayed in *red* or *green* (Dietrich et al. 2014). In practice, this functional ultrasound technology has played a key role in distinguishing between benign and malignant lesions in breast, thyroid and liver tissue (Kanamoto et al. 2009; Kumm and Szabunio 2010; Wang et al. 2012). Now, a new generation of RTE technology, aimed at assessing diffuse lesions, could provide quantitative results with 11 parameters—mean relative strain value (MEAN), standard deviation of the relative strain value (SD), percentage area of low strain (% AREA), complexity of low-strain area (COMP), kurtosis

(KURT), skewness (SKEW), contrast (CONT), entropy (ENT), inverse difference moment (IDM), angular second moment (ASM) and correlation (CORR)—describing three aspects of tissue elasticity (deformation, color histograms and texture) (Dietrich et al. 2014).

In this study, we used RTE for quantitative analysis of renal cortex elastic strain in Bama pigs in a state of brain death, and investigated the changes in morphology by electron microscopy, to determine whether RTE could assess the extent of kidney damage early in brain death.

METHODS

Animals

The specimen pigs used were Chinese Bama miniature pigs (*Sus scrofa domestica*), which are genetically stable, share anatomic and physiologic similarities with humans and are commonly used in studies of the renal system (Cai et al. 2006; Liu et al. 2008; Yu et al. 2007). Nine healthy adult Bama pigs (seven females and two males), average weight 30.32 ± 0.7 kg, were provided by the Tianjin Ji Xian Experimental Animal Center. The pigs were fasted for 24 h and had no access to water for 12 h. This study received ethical approval from the Department of Clinical Laboratory, First Central Hospital of Tianjin.

Brain death model

Animals were each administered 10 mg/kg ketamine, 0.4 mg/kg diazepam and 0.03 mg/kg atropine intramuscularly to induce basal anesthesia. Pigs were placed in a supine position, and anesthesia was maintained by injection of 1 mg/kg ketamine and 1 mg/kg suxamethonium chloride and inhalation of 2.5%–3% sevoflurane (Fig. 1). Cannulas were inserted into the pig's femoral artery and vein to record mean arterial pressure, heart rate and central venous pressure. Another cannula was opened and connected to a microrespirator for respiratory wave monitoring; electrodes were inserted to monitor electroencephalographic and electrocardiographic activity. Then the parietal central area of the skull was perforated, and normal saline was injected with a transcatheter progressively, at a speed of 0.5 mL/min; intracranial pressure (ICP) and mean arterial pressure (MAP) were monitored during this procedure. Pressurization was started when MAP > ICP and then stopped when MAP < ICP. The pressure adjustment was continued until MAP no longer increased with increasing ICP.

Brain death was confirmed when the model had met six criteria (Pratschke et al. 2000): (i) deep shock; (ii) disappearance of the papillary light reflex and corneal reflection; (iii) absence of spontaneous respiration; (iv) electroencephalograph display of resting potential; (v) negative atropine test; (vi) absence of change in characteristics i–v over a 12-h period. In addition, transcranial Doppler revealed that the anterior and posterior circulation consisted of oscillatory waves and sharp and small contraction waves ("t-waves") (Fig. 2). Then a median abdominal incision for laparotomy was made, and an abdominal retractor was used to allow ultrasound to be performed directly on the kidney. This was done to mimic clinical conditions for procurement of a kidney from a brain-dead confirmed donor; RTE was performed directly on the kidney to evaluate its quality.

Apparatus and method

A single sonographer with 5 y of ultrasound experience and at least 3 y of RTE experience performed 2-D and RTE examinations using a HITACHI Noblus portable ultrasound system (Hitachi Noblus, Tokyo, Japan) with a C5-1 convex probe (1–5 MHz) for the 2-D examination and an L7-3 linear probe (3–7 MHz) for the RTE examination.

Renal ultrasound elasticity imaging measurement. At 0, 3, 6 and 9 h after brain death, ultrasound elasticity imaging of the kidney tissue was performed; these findings were compared with those obtained before brain death (control group). RTE commenced with a

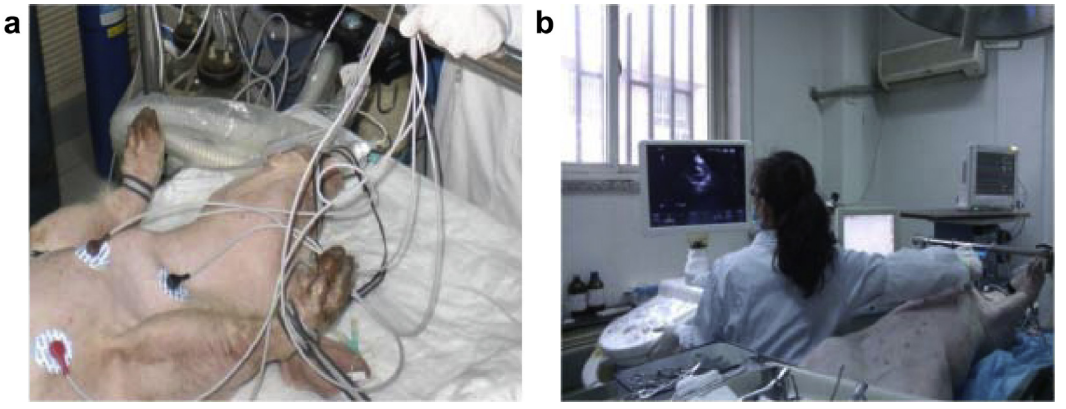

Fig. 1. (a) Establishment of brain death model in a Bama pig. (b) Transcranial Doppler ultrasound detection of the brain-dead state.