Data in brief 25 (2019) 104170

Contents lists available at ScienceDirect

Data in brief

journal homepage: www.elsevier.com/locate/dib

Data Article

The biological response of rodent kidneys to low frequency, full volume diagnostic contrast-enhanced ultrasound imaging: Pilot data

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ARTICLE INFO

Article history:
Received 17 May 2019
Received in revised form 13 June 2019
Accepted 14 June 2019
Available online 5 July 2019

Keywords:
Contrast enhanced ultrasound
Ultrasound contrast agents
Microbubble
Bioeffects

ABSTRACT

With the growth of contrast-enhanced ultrasound (CEUS) clinically, there are concerns about histologic bioeffects in regards to the implementation of high mechanical index (MI) imaging, such as the imaging sequence used for a specific CEUS technique known as flash-replenishment. The data presented are results from a pilot study, which explored flash-replenishment with high and moderate MI imaging sequences at time points of 24 hours and 2 weeks post imaging. This pilot study was followed by a larger study, which can be found in a journal article entitled "Histological and Blood Chemistry Examination of the Rodent Kidney After Exposure to Flash-Replenishment Ultrasound Contrast Imaging" Nyankima et al., 2019.

DOI of original article: https://doi.org/10.1016/j.ultras.2019.05.003.
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https://doi.org/10.1016/j.dib.2019.104170

Specifications table

Subject area	*Biomedical Engineering*
Specific subject area	*Contrast-enhanced ultrasound imaging*
Type of data	*Histopathology, blood clinical chemistry*
How data was acquired	*Microscopy (Olympus BX46) and blood chemistry test*
Data format	*Raw data collected in Microsoft Excel*
Experimental factors	*Transmitted acoustic mechanical index and final time point*
Parameters for data collection	*Rodent kidneys were exposed to contrast-enhanced ultrasound, and kidneys were analyzed for signs of hemorrhage by histopathology and blood clinical chemistry. Imaging was conducted at an MI of 1.9 and 1.0, clinically high and moderate intense acoustic pulses respectively. Each MI was assessed at a final time point of 24 hours or 2 weeks in order to assess differences in short-term and long-term bioeffects.*
Description of data collection	*Animals were sacrificed at 24 hours or 2 weeks, and kidneys were stained for histopathology assessment. Blood samples were also collected at the time of imaging and sacrifice and analyzed for blood urea nitrogen (BUN) levels.*
Data source location	*Chapel Hill, NC, USA*
Data accessibility	*Data submitted with paper*
Related research article	A. G. Nyankima, S. K. Kasoji, R. Cianciolo, P. A. Dayton, and E. H. Chang, "Histological and Blood Chemistry Examination of the Rodent Kidney After Exposure to Flash-Replenishment Ultrasound Contrast Imaging," *Ultrasonics*, vol. in press, 2019. "in press" [1]

Value of the data

- For flash-replenishment imaging, a useful technique in contrast-enhanced ultrasound (CEUS), it is necessary to transmit acoustic waves at moderate to high mechanical indices (MIs) to destroy contrast agents in the field, and image new contrast flow into visualized vessels. We observed the in vivo bioeffects of flash-replenishment across the rodent kidney volume at a clinically-relevant frequency by evaluating histopathology and clinical chemistry 24 hours after exposure to the clinical maximum MI.
- We report these findings to inform both researchers using CEUS imaging and medical communities, of the parameters that may induce bioeffects from high MI flash pulses during flash-replenishment imaging. This data can be used to better guide safe and effective imaging parameters for clinical translation of CEUS, by carefully choosing acoustic parameters to minimize risk.
- The value of this data comes from the presence of long-term bioeffect assessments and the histopathologic assessments using clinically relevant imaging parameters.

1. Data

Data demonstrates the histopathologic and blood urea nitrogen (BUN) changes after the use of flash-replenishment contrast-enhanced ultrasound (CEUS) in the rodent kidney. Fig. 1 frames the bioeffect indicators and time table of the data presented. Fig. 2 presents the results of histopathology assessment. Histopathology, the standard for assessing kidney bioeffects, was quantified as red blood cells (RBCs) in the glomeruli or tubules, which denote signs of hemorrhage in kidney tissue at the final time point. Lastly, BUN levels were measured as a global indication of kidney health, and were measured in serum isolated prior to imaging and at the time of necropsy. Fig. 3 depicts these results in graphical format. Table 1 and Table 2 present the raw values of BUN levels through several time points before and after flash-replenishment imaging. Table 1 includes the raw values of data presented in Fig. 3. Table 3 and Table 4 report raw values of the histopathology assessment at different time points before and after CEUS. Table 3 presents values presented in Fig. 2. Tables 2 and 4 present data published in Nyankima et al. [1].

2. Experimental design, materials, and methods

A pilot study was conducted with an N of 15 (n = 3–4/group) as a first round assessment of microbubble-induced bioeffects during CEUS imaging. This study was conducted with the same instrumentation and animal subjects as the final study presented in Nyankima et al. (2019) [1], but with a few differences in parameters. Female Fischer 344 rat kidneys were chosen as the in vivo model for the study. All procedures were approved by the University of North Carolina at Chapel Hill Animal Care and Use Committee board prior to beginning the study. Animals were separated into groups as demonstrated in Fig. 1.

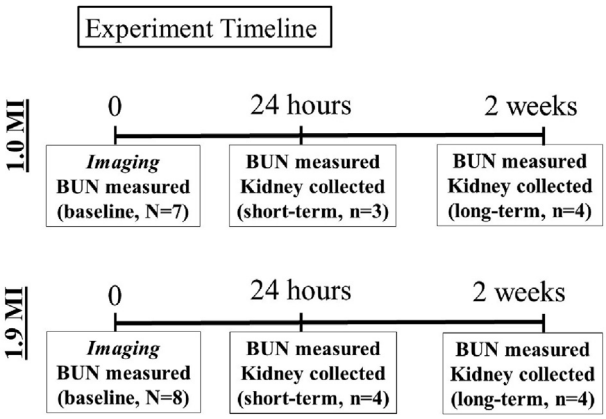

Fig. 1. Experiment Timeline. Prior to imaging, BUN levels were measured (t = 0). Short term bioeffect assessments were quantified 24 hours after imaging. Blood and kidneys were collected for BUN and histopathology analysis. Long term bioeffect assessments were quantified 2 weeks post imaging. This timeline was followed for animals exposed to 1.0 MI and 1.9 MI microbubble destructive pulses. This figure was made in likeness of Fig. 1 of Nyankima et al. [1] and captures the difference in time points assessed.

Imaging was conducted using an Acuson Sequoia 512 (Mountain View, CA, USA), with a 4C1 curved array transducer. Definity microbubbles were purchased from Lantheus (North Billerica, MA, USA), and used for the study. Animals were anesthetized with isoflurane, and placed on their side while imaging in the sagittal plane. Microbubbles were administered in a tail vein at a dose of 200 μL of Definity in 400 μL of 0.9% saline. The solution was continuously infused into the animal at a rate of 40 μL/min.

Flash-replenishment imaging was conducted across the kidney volume in 1mm step sizes across a 1.5cm volume. In each plane, a microbubble destructive pulse was conducted at 3 MHz, a frame rate of 10 Hz, and an MI of either 1.9 or 1.0. This flash pulse was followed by low MI imaging pulses at 1.5 MHz, 14 Hz frame rate, and an MI of 0.2. Low MI imaging was completed for 1 second, before moving to the subsequent plane, to allow for microbubble perfusion after destructive pulses. Animals were euthanized at either a time point of 24 hours or 2 weeks. At this time, kidneys were prepared for histopathology assessment.

In this set up, the control kidney was exposed to ultrasound and bioeffects were observed in both. To address these issues, changes were made for the full study, including re-positioning the rat to reduce control kidney exposure.

2.1. Preliminary observation: histopathology at 24-h and 2 weeks

Histopathologic assessments were conducted on hematoxylin and eosin (H&E) stained tissue. Quantitative analysis was conducted by counting RBCs in glomeruli or tubules, a sign of hemorrhage, in both the experimental and control kidneys. No RBCs were identified in the glomeruli. The total number of RBCs in tubules, or RBC casts, for both control and experimental kidneys are presented in Fig. 2.

In rats exposed to 1.0 MI pulses for CEUS imaging, no evidence of hemorrhage was found at either the 24-h or 2-week time points (see Fig. 2). In the 1.9 MI group, total RBC cast score averaged 13 ± 9 (mean ± SEM) when assessed after 24 hours. These signs of hemorrhage were absent on histopathologic examination after 2 weeks (see Fig. 2). As a result of the imaging setup, the signs of hemorrhage were observed in both the right and left kidney, removing a control from this study. It was this finding in the 1.9 MI at 24 hours that led to the final (and larger) round of data collection. To eliminate the chance of ultrasound exposure in the control kidney, the animals were imaged on their back, and the transducer mechanically-steered over the chosen imaging side. To determine if RBCs were originating from the glomeruli as a result of glomerular capillary hemorrhage, an earlier time point of 4 hours was chosen since urine progresses from the glomeruli to the tubules.

Group	Animal Number	No. RBC casts (in ten 10X fields)	No. glomeruli with RBC (out of 100 glomeruli)
1.0 MI at 24 hours	3	0 ± 0	0 ± 0
1.0 MI at 2 weeks	4	0 ± 0	0 ± 0
1.9 MI at 24 hours	4	13 ± 9	0 ± 0
1.9 MI at 2 weeks	4	0 ± 0	0 ± 0

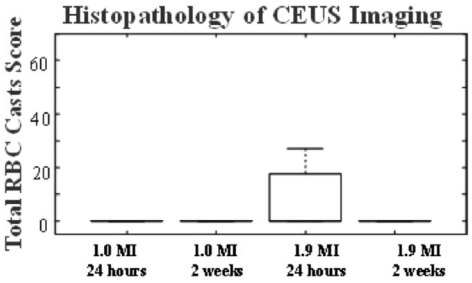

Fig. 2. Histopathology Results. Histopathologic kidney examination for RBCs after both moderate and high destructive pulses at 24 hours and 2 weeks. Data is displayed as the mean ± standard error of the mean (SEM). This figure was made in likeness of Figure 4 of Nyankima et al. [1].

2.2. Preliminary observation: kidney clinical chemistry at 24-h and 2-weeks

Blood samples prior to imaging (baseline) and at the time of necropsy (endpoint) were measured for BUN. For subjects exposed to an MI of 1.0, there was no significant change in the BUN levels from baseline to their endpoint (Fig. 3).

In the 1.9 MI group, no significant change was observed after 24 hours. At the 2-week endpoint, the BUN of the 1.9 MI group had significantly increased from 17 ± 1 mg/dL at baseline to 23 ± 2 mg/dL at 2 weeks ($P = 0.002$).

The normal BUN range for female Fischer rats is 19.18 ± 2.39 mg/dL (95% confidence internal ~15–24 mg/dL) [2]. As indicated in Fig. 3, mean BUN levels of all four groups remained in this range.

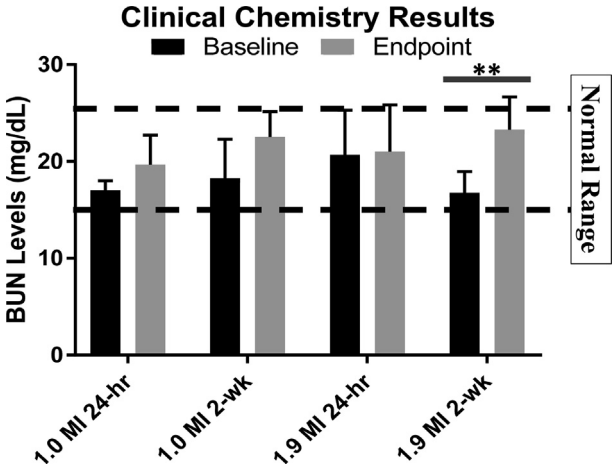

Fig. 3. Clinical Chemistry Results. BUN levels are grouped by imaging parameters and endpoint. Results of paired T-test indicate a statistically significant increase in BUN levels for subjects in the high MI group after 2 weeks (p-value from 0.001 to 0.01 is marked with a '**'). No statistical significance was observed in the low MI groups. Average BUN values remained within normal range for female Fischer rat (15–24 mg/dL, dashed lines).

2.3. Raw data: kidney histopathology and clinical chemistry

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Table 1
Clinical Chemistry Results. Raw data of blood urea nitrogen measurements taken from groups exposed to an MI of 1.9 or 1.0 (N = 15). Blood was collected prior to contrast imaging (baseline) and at the final time point of either 24 hours or 2 weeks.

Subject	High MI				Moderate MI			
	Baseline	1.9 MI 24 hours	Baseline	1.9 MI 2 weeks	Baseline	1.0 MI 24 hours	Baseline	1.0 MI 2 weeks
1		19	18	26	18	23	16	24
2	26	28	19	26	17	19	23	25
3	18	20	14	19	16	17	14	22
4	18	17	16	22			20	19

Table 2
Clinical Chemistry Results. Raw data of blood urea nitrogen measurements taken from groups exposed to an MI of 1.9 or 1.0 (N = 31). Blood was collected prior to contrast imaging (baseline) and at the final time point of either 4 hours or 2 weeks. Data can also be found in Nyankima et al. [1].

Subject	High MI				Moderate MI			
	Baseline	1.9 MI 4 hours	Baseline	1.9 MI 2 weeks	Baseline	1.0 MI 4 hours	Baseline	1.0 MI 2 weeks
1	21	21	18	21	23	25	27	21
2	20	24	20	18	24	27	25	25
3	17	20	15	18	24	25		21
4	17	18	15	18	21	24	21	21
5	18	18	15	20	24	24		
6	17	17	15	18	21	21	17	20
7	17	20	17	18	21	24	18	20
8	15	17	18	18	24	25	20	

Table 3
Histopathology Results. Counts of total RBCs were collected for groups exposed to an MI of 1.9 or 1.0 (N = 15). Histology was assessed 24 h or 2 weeks after imaging.

Subject	Kidney Location	High MI		Moderate MI	
		1.9 MI 24 hours	1.9 MI 2 weeks	1.0 MI 24 hours	1.0 MI 2 weeks
1	R	0	0	0	0
	L	0	0	0	0
2	R	0	0	0	0
	L	0	0	0	0
3	R	8	0	0	0
	L	27	0	0	0
4	R	72	0		0
	L	0	0		0

Table 4
Histopathology Results. Counts of total RBCs were measured for groups exposed to an MI of 1.9 or 1.0 (N = 31). Histology was assessed 4 hours or 2 weeks after imaging. Data can also be found in Nyankima et al. [1].

Subject	Kidney Location	High MI		Moderate MI	
		1.9 MI 4 hours	1.9 MI 2 weeks	1.0 MI 4 hours	1.0 MI 2 weeks
1	R	0	0	0	0
	L	0	0	0	0
2	R	0	0	0	0
	L	0	0	0	0
3	R	0	0	0	0
	L	0	0	0	0
4	R	0	0	0	0
	L	0	0	0	0
5	R	0	0	0	0
	L	0	0	0	0
6	R	0	0	0	0
	L	0	0	0	0
7	R	0	0	0	0
	L	0	0	0	0
8	R	0	0	0	
	L	0	0	0	

Acknowledgments

Authors would like to thank the UNC Animal Histopathology Core and UNC Animal Clinical Chemistry Core for their work on processing tissue and blood for histopathology assessment. Animal histopathology was performed in the LCCC Animal Histopathology Core Facility at the University of North Carolina at Chapel Hill with special assistance from Traci Raley and Amanda Brown. The LCCC Animal Histopathology Core is supported in part by an NCI Center Core Support Grant (2P30CA016086-40) to the UNC Lineberger Comprehensive Cancer Center. This work was partially funded by the North Carolina Translational & Clinical Sciences Institute via the NC TraCs IHHAR11503. The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number TraCs UL1TR002489. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Finally, during the time of the study, A. Gloria Nyankima was supported by the NIH F31 grant (5 F31 CA206602-03).

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. Chang is supported by a research grant (CG#16013) sponsored by Lantheus Medical Imaging, the distributor of the Definity microbubbles used in this study, though she was not supported during the time of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dib.2019.104170.

References

[1] A.G. Nyankima, S.K. Kasoji, R. Cianciolo, P.A. Dayton, E.H. Chang, Histological and blood chemistry examination of the rodent kidney after exposure to flash-replenishment ultrasound contrast imaging, Ultrasonics 98 (2019) 1–6.
[2] M.J. Derelanko, M.A. Hollinger, Handbook of Toxicology 124 (14) (2002).