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Grant ID: 041



College of Radiographers Industrial Partnership Research Grants

1. Principal Investigator	Benjamin Stenberg
2. Project Title	3D contrast enhanced ultrasound in perfusion studies of early renal transplants
3. Amount of Grant	£8,230
4. Did you spend the money as indicated in your proposal (if not why)?	
Yes	
5. Did you reach your intended project outcomes (if not why)?	
Yes	
6. What are your significant findings?	
<p>I have shown that 3D CEUS is possible in early kidney transplants. This is shown to be more sensitive than DTPA in the detection of infarction and allows accurate quantification of the volume of sub-total infarction. The degree of infarction correlates with subsequent renal function, particularly at 1 and 3 months after surgery with a significant increase in creatinine and reduction in eGFR per percentage of total renal volume infarcted. The enhancement patterns measured in the cortex, medulla and main renal artery show a degree of correlation with subsequent renal function but this is multifactorial and does not appear to be a useful clinical tool in predicting outcomes. The enhancement patterns also correlate with the presence of histologically proven rejection although this is not more sensitive than measuring resistance indices which is the current standard practice.</p>	
7. Have you submitted the work for publication (if so where)?	
<p>Stenberg B, Elliott S, Wilkinson M, Caplan N, The prevalence and significance of renal perfusion defects in early kidney transplants quantified using 3D contrast enhanced ultrasound (CEUS), <i>European Radiology</i>, 2017, DOI: 10.1007/s00330-017-4871-3</p> <p>Mafeld S., Stenberg B., Elliott ST. Intrarenal arteriovenous shunts in kidney transplants demonstrated by contrast-enhanced ultrasound, <i>Clinical Imaging</i>, 2014, 39(1):144-51</p> <p>Stenberg B, Chandler C, Wyrley-Birch, Elliott ST, Post-Operative 3-Dimensional Contrast-Enhanced Ultrasound (CEUS) Versus Tc99m-DTPA in the Detection of Post-Surgical Perfusion Defects in Kidney Transplants – Preliminary Findings. <i>Ultraschall in Med.</i> 2013 35(3):273-8</p> <p>Stenberg B, Elliott St, Can Live Bi-Plane Sonography Reduce Work-Related Musculoskeletal Disorders of the Wrist? <i>J Clin Ultrasound</i>, 2012, 41(3):140-4</p> <p>Stenberg B, Talbot D, Arslan M, A New Technique for Assessing Renal Transplant Perfusion Preoperatively Using Contrast-Enhanced Ultrasound (CEUS) and Three-Dimensional Ultrasound (3DUS) – A Porcine Model Pilot Study, <i>Ultraschall in Med</i> 2011; 32: E8–E13</p>	

8. Have you presented the work at a national/international event (if so where)?

1. (Oral) WFUMB, 2015, Stenberg B, McNeill A, Renal Transplant-Early Post-Surgical CEUS in The Detection of Rejection and in Predicting Subsequent Kidney Function, Ultrasound in Medicine and Biology, 2015, 41 (4), S77
2. (Oral) WFUMB, 2015, Stenberg B, McNeill A, Contrast Enhanced Ultrasound Vs Renal DTPA in the Detection of Perfusion Defects In Early Renal Transplants-Preliminary Findings. Ultrasound in Medicine and Biology, 2015 41 (4), S78
3. (Oral) BMUS (Manchester) 2014- CEUS haemodynamics in early kidney transplants and its effect on subsequent function
4. (Oral) RSNA (Chicago) 2013- 3D CEUS in kidney transplants
5. (Oral) BMUS (Gateshead) 2013- The significance of CEUS detected perfusion defects in kidney transplantation.
6. (Poster) Stenberg B, Elliott S, The potential impact of live bi-plane ultrasound on work related musculoskeletal disorders (WRMD) of the wrist, BMUS, 2012

9. Please provide an executive summary of your work (two sides of A4 maximum)

N.B. If you already have a draft or final version of the proposed publication can you please attach.

Kidney transplantation is the most common form of transplant surgery worldwide and there have been great advances both surgically and medicinally to improve peri- and post-operative care. Despite this, complication rates are still relatively high and focal/global infarction, rejection, acute tubular necrosis and poor function are still common outcomes. Contrast enhanced ultrasound (CEUS) is a technology which allows for high resolution, real-time analysis of the vasculature of the kidney but there is still limited research into its clinical usefulness. The aim of this research is to assess the usefulness of 2D and 3D CEUS in early post-operative kidney transplants in the detection and quantification of focal/global infarction, the detection and prediction of episodes of rejection and acute tubular necrosis, and the prediction of renal function up to 3 months after surgery.

This new 2D/3D technique was initially developed using a porcine model on cold perfusion machines prior to patient studies, highlighting the potential for pre-operative use of CEUS. The 3D technique was also assessed biomechanically, demonstrating a reduction of wrist movements by 70% in abdominal examinations using 3D technology, which could reduce the incidence of repetitive strain injury in radiologists.

Subsequently, 105 consecutive kidney transplant patients were scanned around the first post-operative day capturing 60 seconds of continuous contrast filling and then 3D volume of the whole organ in contrast specific mode. The patients also underwent a renogram (Tc-DTPA) as standard care in the author's institution and received regular blood tests to monitor renal function. Analysis of 3D CEUS demonstrated a superior detection rate of focal infarction compared to Tc-DTPA. Nine perfusion defects were detected by Tc-DTPA. These were all detected using CEUS with a further 14 cases identified (up to 17% of total renal volume). Perfusion defects also correlated with subsequent renal function with those with a perfusion defect have significantly raised Creatinine at 3 months ($t = -2.2$) and reduced estimated Glomerular Filtration Rate (eGFR) at 1 month ($t = 2.2$) and 3 months ($t = 2.03$) post-surgery. Magnitude-based analysis showed that this was also likely to be clinically beneficial at the same time points.

Multiple linear regression of the perfusion curves in the renal artery, cortex and medulla demonstrated good correlations with subsequent function at all time points ($R > 0.5$), but most noticeably at two weeks post-procedure ($R = 0.765$, $p < 0.0005$) with donor age ($t = 3.552$) and cortical area under the curve ($t = -3.246$) contributing most highly. These perfusion curves also correlated with episodes of rejection, the difference in cortex and medulla rise time correlating most strongly ($t = 2.586$), however, measuring resistance index (standard care) had greater correlation ($t = 3.611$). Similar correlations were not shown with episodes of acute tubular necrosis.

In conclusion, 2D/3D CEUS is a straightforward technique which provides an accurate and detailed map of renal vasculature. This is beneficial in the detection and quantification of focal infarction and informing clinicians' expectations regarding subsequent renal function of the transplanted kidney. It is a promising tool in the detection of rejection but in this study did not exceed the current standard technique of measuring resistance index.

Contribution to knowledge base

- This current study is the largest reported study of the use of contrast enhanced ultrasound in kidney transplants (see chapter 2).
- As part of the early design of the study, two small scale, initial studies were performed. The first describes a novel use of pre-operative CEUS while kidney transplants are in cold storage as a proof of concept for the first time in the literature (Chapter 4). The second was the paper to describe the ergonomics of using a biplane imaging protocol in abdominal imaging demonstrating a dramatic reduction in high risk movements by the operator, potentially reducing repetitive strain injury (Chapter 5).
- In chapter 6, this study makes the first description of a direct comparison with DTPA in the detection of perfusion defects, significantly increasing the detection rate from the current standard practice. Also demonstrated in this chapter was the first use of kidney transplant perfusion defect quantification with 3D contrast enhanced ultrasound in human participants.
- Because this level of detection has not been present previously, the consequences of these tiny perfusion defects were unknown or unreported in the literature. Therefore, in chapter 8 there is the first analysis of the clinical significance of small perfusion defects in kidney transplants.
- An interesting incidental discovery was the visualisation of junctional cortical shunting with CEUS, a controversial phenomenon previously debated and never previously reported as being seen with CEUS (chapter 7).
- This study also describes the first multiple regression analysis on the haemodynamic variables to demonstrate the prognostic value of CEUS providing evidence that early measurement of the renal blood flow does provide information regarding how well it will go on to function (chapter 9).
- Chapter 10 provides an analysis of the ability of CEUS perfusion curves in the detection of rejection and acute tubular necrosis (ATN) using CEUS, showing that it does not provide information regarding ATN but the rise time in the cortex and medulla correlates well with the presence of rejection but does not provide a greater predictive tool than the current practice of measuring the resistance index.