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Microbubble contrast-enhanced ultrasound in the vascular evaluation after pancreas transplantation: a single-center experience

Audun E Berstad[1], Knut Brabrand[1], Rune Horneland[2], Trygve Syversveen[1], Håkon Haugaa[3,4], Trond G Jenssen[5,6,7] and Aksel Foss[2,7,8]

Abstract

Background: Arterial and venous thrombosis are feared complications of pancreas transplantation (PTx). Microbubble contrast-enhanced ultrasound (CEUS) is a non-invasive imaging technique that can augment diagnostic capabilities of transplant organ perfusion.

Purpose: To document the state to which CEUS can improve the vascular evaluation of PTx compared to conventional Doppler ultrasound (US) directly after surgery.

Material and Methods: A total of 129 consecutive PTx in 128 adult patients were eligible for inclusion. The duodenal segment of the graft was anastomosed to the native duodenum. Within 12 h postoperatively, graft-circulation was monitored by Doppler US in 116 PTx performed in 116 patients (69 men, 47 women; mean age ¼ 41 years). CEUS was performed with a sulfur hexafluoride-containing contrast agent (SonoVue) intravenously if the examiner was not able to confirm normal graft circulation. Image quality was documented by two independent observers on a 4-point scale: 1 ¼ excellent; 2 ¼ minor diagnostic limitations; 3 ¼ major diagnostic limitations; and 4 ¼ non-diagnostic.

Results: In the early postoperative phase, 79 (68%) of 116 PTx were examined with Doppler US only. Of these, 52 were of excellent quality (grade 1), 22 of good quality (grade 2), and five were of grade 3 or 4 quality. Thirty-seven (32%) examinations were supplemented by CEUS. CEUS significantly improved examination quality compared to Doppler US alone (median visualization score 1.5 vs. 2.5, respectively; $P < 0.0001$).

Conclusion: CEUS can significantly improve vascular evaluation of PTx compared to Doppler US alone in the early postoperative phase.

Keywords

Microbubble contrast-enhanced ultrasound, Doppler ultrasound, pancreas transplantation

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Introduction

Pancreas transplantation (PTx) is a well-established treatment option for patients with complicated type 1 diabetes mellitus with and without concomitant diabetic end-stage renal disease. PTx is associated with surgical complications such as bleeding, thrombosis, and exocrine leakage (1–3). In particular, arterial or venous thrombosis, partly due to use of oversized ves- sels (celiac trunk, superior mesenteric artery, and splenic/portal vein) in conjunction with the relatively low blood flow through an isolated PTx, is a feared complication. Therefore, PTx poses a delicate balance between thrombosis and bleeding complications. Imaging techniques should therefore be able to visualize the arterial and venous vasculature, parenchyma, and intestinal drainage pathway of the transplant (4).

Usually, conventional Doppler ultrasonography (US) is the initial imaging technique applied for the evaluation of the transplant (5). It is mobile, does not involve ionizing radiation or iodinated contrast material, and is non-invasive and inexpensive. However, overlying bowel gas may decrease the quality of US imaging. Intravenous contrast agent administration is especially useful for demonstrating intraluminal filling defects in the graft vessels and the lack of parenchymal enhancement. Contrast-enhanced US (CEUS) can provide additional, clinically relevant information in patients with early complications following pancreas transplantation and can obviate the need for computed tomography (CT) or magnetic resonance imaging (MRI) (6–8). The extent to which CEUS can improve the visualization of PTx after routine Doppler US in the early postoperative phase is not known.

We retrospectively examined the quality of routine US examination with or without CEUS directly after whole organ pancreas transplantation using duodeno-duodenostomy surgical technique.

Material and Methods

The study was approved by the regional ethical committee and written informed consent was obtained from all patients. From October 2012 to March 2017, all consecutive PTx recipients aged > 18 years in our institution were eligible for the study. During the period, 129 consecutive whole organ PTx had been performed in 128 patients, all from deceased donors (Fig. 1). One female patient was transplanted twice during the inclusion period. Within 12 h postoperatively, graft circulation was monitored by Doppler US in 116 PTX performed in 116 patients (69 men, 47 women; mean age 41 years). Sixty patients were simultaneous pan- creas–kidney (SPK) recipients, 50 received pancreas transplantation alone (PTA), two received pancreas

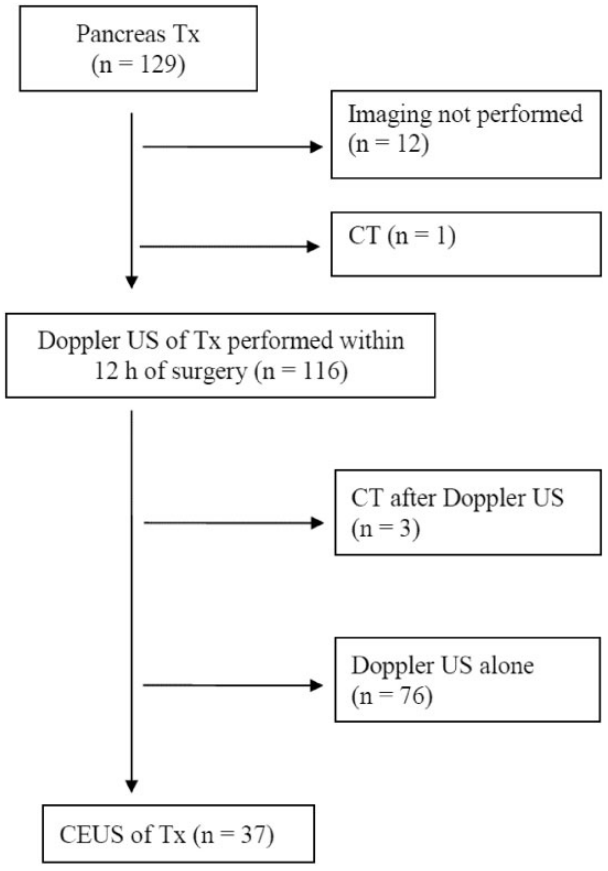

Fig. 1. Flow chart of patients (n = number of full organ pancreas transplantations). Contrast-enhanced ultrasound (CEUS).

after islets (PAI), two received pancreas after kidney transplantation (PAK) and two patients underwent pancreas after SPK transplantation (PASPK).

The pancreas was placed in an upright, right-sided, retrocolic position. The duodenal segment of the graft was anastomosed side-to-side to the native duodenum at its lower knee (1). The pancreatic arteries were anastomosed end to side to the right common iliac artery through a preserved aortic patch or through a reconstruction with an iliac-Y-allograft. The portal vein was elongated in most patients using an iliac allograft vein that was anastomosed end-to-side to the lowermost part of the inferior caval vein (Fig. 2). The electronic radiological archives and journal files of patients during the postoperative period were reviewed.

Ultrasound

All patients were routinely examined according to our post-surgical protocol with Doppler US within 12 h on the first postoperative day, preferably within 4 h. In several cases, a written description or a hand-drawn draft of the post-surgical anatomy, including vascular

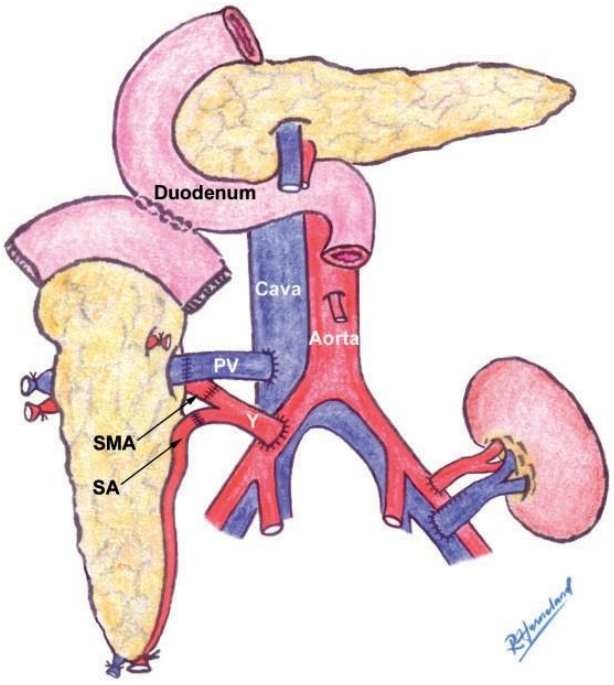

Fig. 2. Schematic drawing of PTx (duodeno-duodenostomy). PV, portal vein; SMA, superior mesenteric artery; SA, splenic artery; Y, common arterial trunk.

and intestinal anastomoses, was provided to the US operator before the examination. A transplant surgeon was available for consultation regarding surgical issues. Several radiologists performed the examinations with routine gray-scale, color, and spectral Doppler US using a Siemens Acuson Sequoia 512 (Siemens Acuson, Mountain View, CA, USA) with a 4C1 or 4V1 transducer or a GE Logiq E9 (GE Healthcare, Milwaukee, WI, USA) with a C1-6 probe. During off-duty hours, the examination was performed by the radiologists on call, who had > 2 years of experi- ence with abdominal US. The radiologists had all been trained to examine pancreas transplanted patients with respect to localization, fluid accumulation, size of the transplant and echogenicity of parenchyma, state (open or not) of the pancreas artery including measurement of resistive index (RI, normal range 0.5–0.7) of the head and body (4). The normal arterial Doppler wave- form should have a rapid systolic upstroke and contin- uous diastolic flow. Patency and flow direction of the pancreatic veins were also evaluated in both the head and the body.

If in doubt about the circulatory state of the PTx, including incomplete evaluation of major vessels, the US operator consulted a radiologist experienced in transplant imaging and CEUS. The Doppler US was reviewed and/or repeated by the more experienced radiologist before deciding if CEUS should be performed.

CEUS with the same scanner using one or more doses (a dose is regarded as 2.4 mL) of a sulfur hexafluoride-containing second-generation contrast agent (SonoVue, Bracco, Milan, Italy) given intravenously in an antecubital vein with a 5–10 mL 0.9% saline flush (9).

Contrast programs with low mechanical index imaging and pulse inversion technique were used. The operator could choose to display the contrast information in different ways; either as an image exclusively based on contrast echoes or as an overlay on a low mechanical B-mode image (mixed mode). A dual screen display with the contrast images and low mechanical gray-scale image side-by-side was instructive and often used. The images were saved as still images and/or video clips. Patients were under medical supervision during and then for at least 30 min following the administration of the contrast agent.

Retrospectively, image quality, including vascular evaluation was documented on a 4-point scale: 1 excellent, 2 minor diagnostic limitations; 3 major diagnostic limitations; and 4 non-diagnos- tic, as has been reported previously (8). The grading was performed by two independent observers experi- enced in CEUS. Separate scores of Doppler US and CEUS of the same session were acquired.

Statistical analysis

Inter-rater agreement of two independent observers was performed by weighted kappa (**j**) (10). A **j** value < 0.20 was regarded as poor agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as good, and ≤0.81 for excellent agreement. In case of disagreement between observers, the average value of examination quality was used. US image quality before and after contrast enhancement was compared using Wilcoxon test for paired data using MedCalc statistical software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Two-tailed probability $P < 0.05$ was regarded as significant.

Results

Of 116 PTx, 79 (68%) were examined with Doppler US only in the early postoperative phase (Fig. 1). Of examinations with Doppler US only, 52 were of excellent quality (grade 1), 22 of good quality (grade 2), and five were of grade 3 or 4 quality. Bowel air caused the major diagnostic limitations or non-visualization in the five PTx of grade 3 or 4 imaging quality.

Of 116 PTx, 37 (32%) were examined by Doppler US and CEUS during the same session (Figs. 3–7). Rapid enhancement of the parenchyma corresponding to nearby arteries was noted in normal PTx (Figs. 4 and 5). CEUS was performed in three PTx with

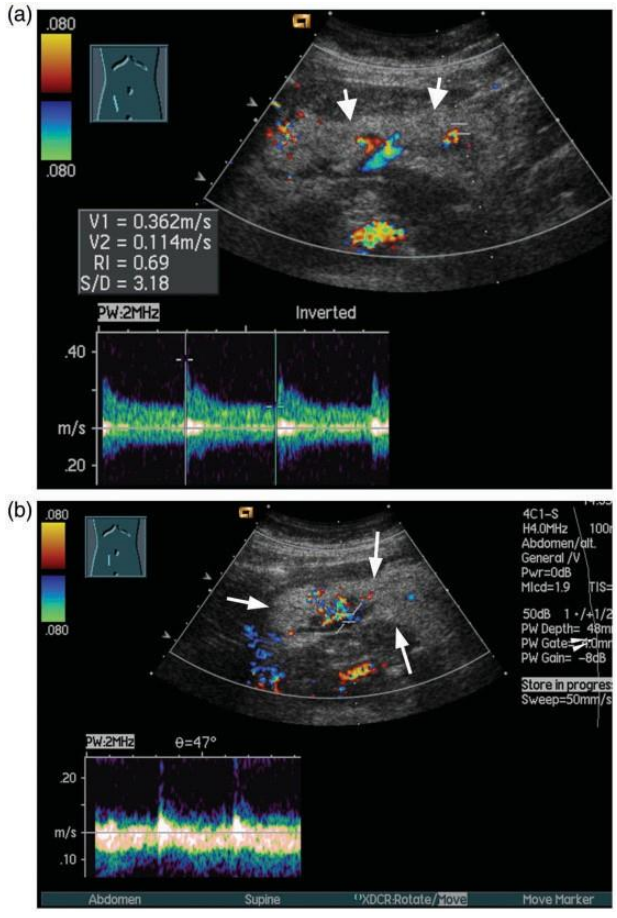

Fig. 3. Doppler US of normal pancreas transplant (white arrows) in right fossa in a 46-year-old woman at the first post-operative day shows an open artery (a) in body and tail as well as an open donor splenic vein (b). The transplant appears hyperechoic in B-mode. The resistive index (RI) was 0.7.

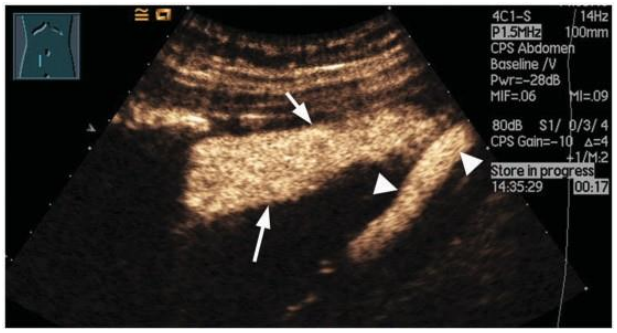

Fig. 4. CEUS 17 s after intravenous injection of contrast medium shows normal, marked parenchymal contrast enhancement of body and tail (white arrows) in the same patient as in Fig. 3. Note the contrast enhancement in the recipient's external iliac artery (arrowheads) close to the tip of the transplant's tail.

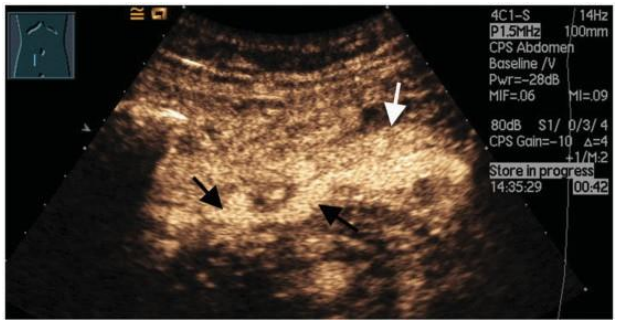

Fig. 5. CEUS 42 s after intravenous injection of contrast medium in the same patient as in Fig. 3 shows contrast enhancement of parenchyma (white arrow) and filling of the somewhat tortuous donor splenic vein (black arrows).

imaging score grade 1 at Doppler US. Twenty-six patients got 2.4 mL and eight patients got 1.2 mL per dose of Sonovue. The numbers of doses were 1–3. The dose of microbubble contrast medium was not specified in three patients.

Visualization

The median grade of image quality was improved from 2.5 to 1.5 ($P < 0.0001$, n ¼ 37) after the addition of CEUS (Fig. 8).

Inter-rater agreement (weighted kappa) of two observers was 0.57 (moderate ¼ SE 0.11, 95% confidence interval [CI] ¼ 0.36–0.78) for Doppler US and 0.50 (moderate ¼ SE 0.12, 95% CI ¼ 0.26–0.73) for CEUS. Three Doppler US examinations were graded as non-diagnostic (grade 4) by both observers, mainly due to overlying bowel gas. As expected, CEUS did not provide additional information in two of these procedures. However, in the third patient, the anatomy was visualized to some extent with CEUS, but the examination still had major limitations (grade 3 by both observers) and a CT was recommended. The contrast-enhanced CT performed showed extensive, non- occlusive venous thrombosis extending into the IVC (Fig. 6). Pathological findings with regard to circulation were noted in five patients (Table 1). The findings were confirmed by graftectomy (n ¼ 2), contrast-enhanced CT (n ¼ 2), or invasive venography (n ¼ 1).

Discussion

In the present study, a two-step approach for PTx vascular evaluation was applied. First, we did a conventional Doppler US and then, in case of uncertainty regarding the circulation, including incomplete evaluation of major vessels, CEUS with an intravenously administered, second-generation contrast agent was performed. The microbubbles were used as contrast

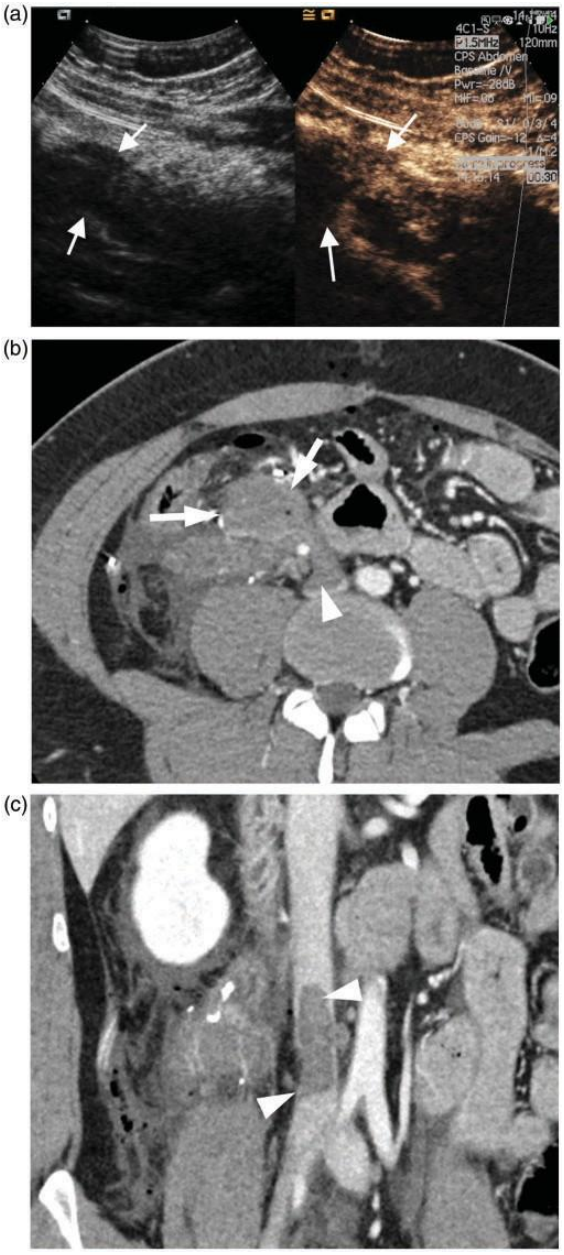

Fig. 6. B-mode (left) and CEUS (right) of a 34-year-old man at postoperative day 1 after pancreas transplantation. Thepancreas transplant (white arrows) appears hypoechoic relative to the surrounding fatty tissue. Thirty seconds after intravenous injection of Sonovue, there is insufficient contrast enhancement of transplant parenchyma (white arrows) indicating venous outflow obstruction (a). Axial (b) and coronal (c) images of contrast-enhanced CT performed immediately after shows poorly enhancing transplant (white arrows) and extensive venous thrombus extending into the inferior vena cava (arrowhead).

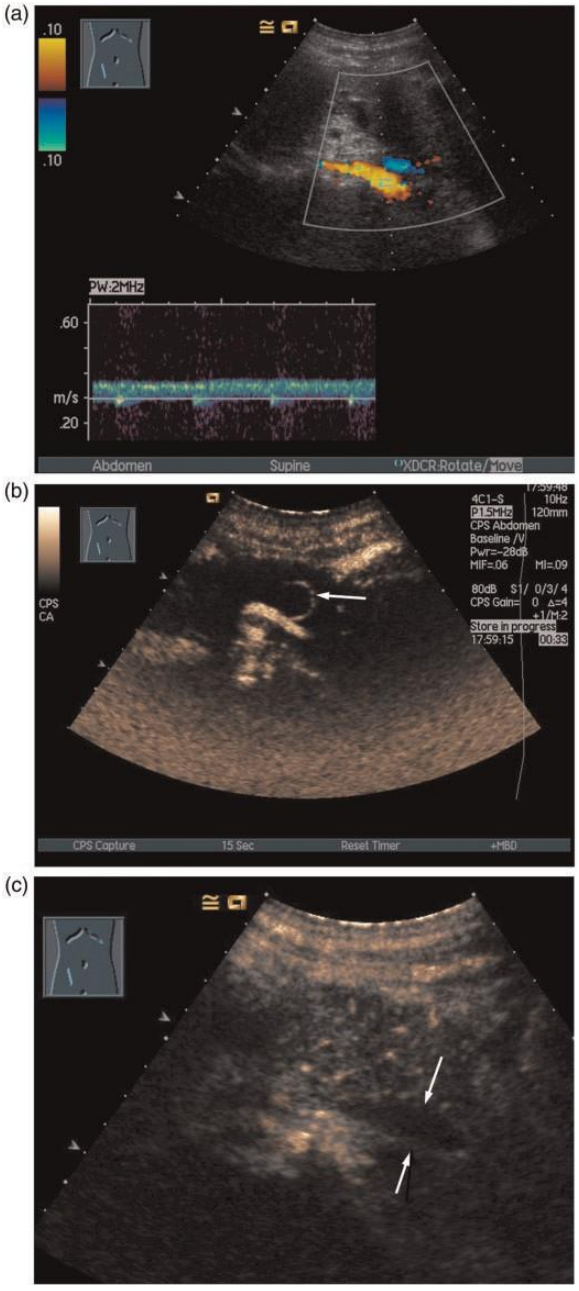

Fig. 7. Pitfall in imaging. A 36-year-old man at postoperative day 1 after simultaneous pancreas and kidney transplantation.
(a) Spectral Doppler US shows venous flow in the iliac vein and should not be mistaken as the splenic vein of the transplant.
(b) CEUS shows an open main transplant artery and branch (arrow), but parenchymal enhancement is not present.
(c) A mixed B-mode/CEUS image shows limited parenchymal enhancement and luminal filling defect of donor splenic vein compatible with an occlusive thrombus (arrows).

agent to demonstrate blood flow and tissue perfusion to improve observer confidence about the vascular state of the transplants. This setting provided an opportunity to compare the two methods with regard to visualization quality and diagnostic gain. Doppler US alone was able to evaluate the PTx vasculature with excellent or good results in a substantial propor- tion of the patients. In a subgroup, approximately

one-third of the patients, CEUS significantly improved the visualization of the graft circulation by, on average, 1 grade point which is likely clinically relevant. The patients with normal enhancement pattern of arteries, parenchyma, and veins did not have to be transported to the CT or MRI department. Therefore, CEUS can supplement and increase observer confidence in clinical situations where the PTx is accessible by, but incompletely evaluated by, Doppler US.

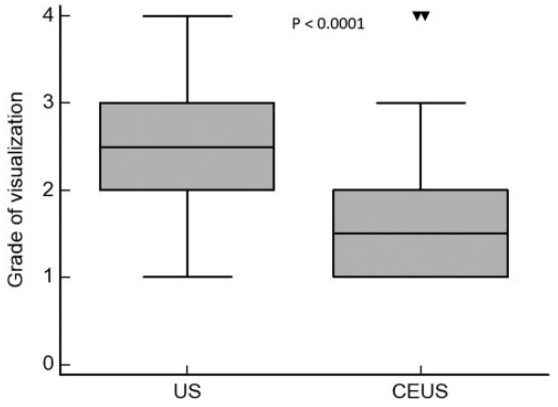

Fig. 8. Box-and-whiskers plot of image quality of 37 pancreas transplants examined with Doppler US and CEUS. Quality was scored on a 4-point scale: 1 ¼ excellent; 2 ¼ minor diagnostic limitations; 3 ¼ major diagnostic limitations; 4 ¼ non-diagnostic. Contrast enhancement significantly improved visualization.

Our study has several limitations. First, CEUS was given to a subset of patients only. The indication to perform CEUS was not standardized according to protocol but was carried out according the preference or uncertainty of the observer who was experienced in transplant imaging. Microbubble contrast was only given to the patients in whom the observer was not confident about the state of the transplants. The clinical state of patients and input from the clinicians could have influenced the radiologist's decision to proceed to CEUS. Second, several observers were involved in the initial examinations of the transplants. However, two experienced radiolog- ists familiar with CEUS performed the retrospective analyses for this study. Time-intensity curves were not available in the present study. Interestingly, the paren- chymal contrast enhancement was subjectively assessed and described as absent or delayed in the PTx with exten- sive venous thrombosis. Two different US systems were used and the dose of intravenous contrast media was not standardized, but within recommended values (9). The value of retrospective evaluation of US examinations has major limitations as these are dynamic, operator- dependent studies. Inter-observer agreement for imaging quality was moderate, without any apparent difference for Doppler US and CEUS. The various grades of visu- alization are not defined in detail and the stored images had limitations. For instance, standardized cine loops of the PTx were not recorded but should be used more extensively in the future together with structured reports of circulatory parameters.

Table 1. Patients with pathological findings of pancreas transplant (PTx) at CEUS.

Patient no.	Age (years)	Sex	PTx	CEUS finding	Further action, CPAT
1	36	Male	SPK	No contrast enhancement of PTx. One open artery, RI ¼ 0.99. No contrast enhancement of donor portal or splenic vein	Graftectomy; grade 3 venous thrombosis and tissue necrosis
2	34	Male	PAI	Delayed contrast enhancement of PTx parenchyma. Open artery, RI ¼ 0.89. Absent contrast filling of donor splenic vein. Portal vein not visualized	CT showed grad 3 venous thrombosis extending into the IVC
3	53	Female	PTA	Contrast enhancement of PTx regarded as normal. Open artery, RI ¼ 0.95. Filling defect ¼ 3 cm (thrombus) of donor splenic vein	CT showed non-occlusive, grade 2 thrombus in splenic vein and narrowing of main vein
4	34	Male	PTA	No contrast enhancement of PTx paren- chyma. Arteries and veins not visualized	Graftectomy; grade 3 venous thrombosis extending into the IVC
5	36	Male	PTA	Open artery, RI ¼ 0.87. Delayed contrast enhancement of PTx parenchyma. No contrast enhancement of donor portal or splenic vein	Invasive venography showed grade 3 venous thrombosis

SPK, simultaneous pancreas and kidney; IVC, inferior vena cava; PAI, pancreas after islets; PTA, pancreas transplantation alone; CPAT, Cambridge Pancreas Allograft Thrombosis grade of venous thrombosis; RI, resistive index.

For SonoVue, an intravenous dose of 2.4 mL (half a vial) is recommended for most indications in the liver, but 1.2 mL may suffice for the pancreas, spleen, and kidney (9). It is plausible that less contrast medium is necessary for PTx than in liver examinations as the transplant is generally quite close to the transducer and the relative fragile microbubbles do not have to pass through the portal venous system before reaching the target organ. The optimal dosage of contrast medium in PTx examinations is not established and should be explored in future studies. Our stored image material was extensive and quite complete. However, a reference standard such as CT or MRI was not regularly performed during the same session, so we could not calculate the diagnostic accuracy of pathological findings using CEUS.

CT angiography evaluates the graft effectively in the immediate post-transplantation period but involves radiation and the use of potentially nephrotoxic con- trast media (11). Interestingly, thromboses that do not involve the central vessels (portal vein or Y-graft) of pancreatic grafts (Cambridge Pancreas Allograft Thrombosis, CPAT grade 1 or grade 2 thrombus) can be managed without anticoagulation (12). In a clinical setting, CEUS may often be sufficient to detect inter- mediate non-occlusive or central occlusive thrombosis that are clinically important and obviate the need for more expensive imaging methods. It is not yet known if CEUS can safely monitor the natural course of a thrombus once detected. US contrast agents are admin- istered safely with minimal risk to patients (13). The contrast medium of CEUS is not excreted through the kidneys and can be safely administered to patients with renal insufficiency, attractive features after PTx (14). The examination can be performed bedside, so patients do not have to be moved to the radiological depart- ment. Patients were examined within the first day of surgery in our study. The clinical value of using CEUS, such as limiting the number of CT scans and early salvage of pancreas glands, should be explored in future studies. However, there are obstacles to exten- sive use of CEUS as it is operator-dependent; 24-h ser- vice may be difficult as the operator must gain sufficient knowledge and training using con- trast agents.

Doppler US is an established, valuable tool in the assessment of kidney transplants (15). At present, most PTx internationally are performed as SPK (16). The US examination of both the PTx and kidney transplant during the same session can harmlessly evaluate the vascular state of both transplant organs rapidly and inexpensively during follow-up. Microbubbles can be used when intravenous contrast material is necessary but iodine and/or gadolinium-based contrast agents are contraindicated, mostly in patients with kidney failure (17).

Our study documented that the PTx can be obscured by bowel air, thus degrading the quality of the US examination. If the transplant is substantially obscured by bowel air, it is unlikely that CEUS will provide additional information in most cases, as was noted in our study. In such cases, other imaging modalities, such as CT should be considered. CEUS may make the observer more confident by demonstrating the anatom- ic localization of the arteries and veins, facilitating the application of spectral flow analysis. Doppler US and CEUS should therefore be considered as complementary rather than competitive methods.

In conclusion, conventional Doppler US proved sufficient to document open vessels after whole body PTx in most cases in the early postoperative phase after PTx. CEUS significantly improved vascular evaluation compared to Doppler US alone in a subset of patients.

Declaration of Conflicting Interests

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