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Contrast-Enhanced Ultrasound Versus Doppler Ultrasound for Detection of Early Vascular Complications of Pancreas Grafts

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Abstract

OBJECTIVE.—The purpose of this study is to compare conventional duplex ultrasound and contrast-enhanced ultrasound (CEUS) for identifying vascular abnormalities in pancreas allografts in the immediate posttransplant setting. Identification of pancreas allografts at risk of failure may impact patient care because early intervention for vascular insufficiency can lead to graft salvage.

MATERIALS AND METHODS.—Two radiologists who were blinded to patient outcomes performed a retrospective analysis of the postoperative Doppler ultrasound and CEUS images of 34 pancreas grafts from transplants performed between 2017 and 2019. A total of 28 patients who did not require surgical reexploration were considered the control group. Six patients had surgically proven arterial or venous abnormalities on surgical reexploration. Each radiologist scored grafts as having normal or abnormal vascularity on the basis of image sets obtained using Doppler ultrasound only and CEUS only. Comparisons of both the diagnostic performance of each modality and interobserver agreement were performed.

RESULTS.—Both readers showed that CEUS had increased sensitivity for detecting vascular abnormalities (83.3% for both readers) compared with Doppler ultrasound (66.7% and 50.0%). For both readers, the specificity of CEUS was similar to that of Doppler imaging (81.6% and 78.9% for reader 1 and reader 2 versus 76.3% and 84.2% for reader 1 and reader 2). For both readers, the negative predictive value of CEUS was higher than that of Doppler ultrasound (96.9% and 96.8% for reader 1 and reader 2 versus 93.5% and 91.4% for reader 1 and reader 2). Interobserver agreement was higher for CEUS than for Doppler ultrasound ($\kappa = 0.54$ vs $\kappa = 0.28$).

CONCLUSION.—CEUS may provide radiologists and surgeons with a means of timely and effective evaluation of pancreas graft perfusion after surgery, and it may help identify grafts that could benefit from surgical salvage.

Keywords

contrast-enhanced ultrasound; Doppler ultrasound; pancreas transplant; postoperative

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Pancreas transplant is a surgical technique that may be used to restore euglycemia in certain patients with diabetes. It is most commonly performed as a simultaneous pancreas and kidney transplant or a pancreas-after-kidney transplant [1–3]. Data from the Organ Transplant Procurement Network show a slow increase in the number of such transplants performed over the past several years, with approximately 1000 transplants performed in the United States in 2018 [4].

In the immediate postoperative setting, pancreas allografts are at risk for vascular thrombosis, and vascular complications are responsible for 50% of grafts lost in the first 6 months after transplant [5, 6]. Duplex ultrasound currently is widely used as a method for evaluating pancreas allografts because of its availability, portability, and speed of acquisition and because it does not require the administration of contrast agents [7, 8]. In particular, Doppler ultrasound may be used to evaluate grafts for arterial and venous patency and to help guide surgical planning for reexploration in an attempt to salvage a hypoperfused graft.

CT and MRI can be used to evaluate pancreas graft vasculature and may provide excellent detail of the surrounding soft tissues and enteric anatomy [8]. At times, their role may be limited to second-line evaluation, however, because they are more time consuming and can require patient transport away from the operating room or clinical bed monitoring. CT and MRI contrast agents are excreted by the kidneys, which may also limit their use in patients who undergo simultaneous pancreas and kidney transplant.

Fewer data are available regarding the accuracy of ultrasound, CT, or MRI in evaluating pancreas grafts for vascular complications. Literature on Doppler ultrasound tends to describe qualitative findings for normal and abnormal grafts, with little information provided to guide radiologists in determining how effective the scan is for identifying abnormalities [9, 10]. The reported sensitivity for graft rejection varies from 13% to 82% [11].

The use of contrast-enhanced ultrasound (CEUS) for abdominal imaging has become more prevalent since the U.S. Food and Drug Administration approved CEUS for noncardiac imaging in 2016. CEUS contrast agents are microbubbles that are smaller than RBCs, which allows them to remain in the intravascular space. This property makes them ideal for evaluating organ perfusion. A previous study [12] reported the usefulness and feasibility of CEUS for routine postoperative evaluation of pancreas allografts. Specifically, it showed that CEUS has the ability to differentiate grafts that are perfused adequately from those with insufficient arterial flow, venous flow, or both.

Identifying allografts at risk of failure may greatly impact patient care because early intervention can lead to graft salvage in cases of vascular insufficiency [13]. The present study evaluates and compares the ability of conventional duplex ultrasound and CEUS to identify vascular abnormalities in pancreas allografts in the immediate postoperative setting.

Materials and Methods

After a waiver was granted by the institutional review board, a total of 34 consecutive patients who underwent pancreas transplant between 2017 and 2019 were retrospectively reviewed. These patients underwent a total of 51 postoperative ultrasound evaluations. Of

the 34 patients, there were 17 women (mean age, 41.3 years) and 17 men (mean age, 45.5 years). Of the images obtained, seven were excluded because Doppler sequences were not fully loaded to the PACS at the time of the examination, resulting in a total of 44 examinations available for review (Fig. 1).

A subset of patients (22 of 34) who were included in this study had been included in a previously published study [12]. This prior study was descriptive in nature and did not include any comparison of CEUS images with Doppler ultrasound images.

Pancreas grafts were retrieved, prepared, and ultimately transplanted using standard techniques previously described elsewhere [14–16], including creation of a vascular Y-graft for gland inflow and outflow. At our institution, two sonographers, each of whom had more than 10 years of experience, performed standard evaluation of pancreas allografts that consisted of gray-scale ultrasound, color and spectral Doppler imaging, and CEUS performed in the operative room immediately after surgical closure. Additional ultrasound images could also be obtained in the early postoperative period to assess changes in patient clinical status as determined by the transplant surgeons.

CEUS was performed after a 2.4-mL dose of sulfur hexafluoride lipid–type A microspheres (Lumason, Bracco Diagnostics) was injected through a central line and followed by a 10-mL saline flush [12]. The most readily visualized portion of the graft (usually the neck or body) was continuously imaged for 3–5 minutes. A second 2.4-mL dose of sulfur hexafluoride lipid–type A microspheres was administered to most patients either to confirm findings or to provide further visualization of the graft tail. No patients had adverse events related to contrast administration.

The reference standard of vascular insufficiency for abnormal Doppler ultrasound and CEUS results was determined on the basis of findings from surgical reexploration (for seven of 34 patients) and from the transplant surgeon’s report in the electronic medical record. At surgery, a total of six of seven patients were found to have either arterial or venous insufficiency that affected their grafts in the form of arterial spasm (two patients), arterial thrombus (two patients), venous thrombus (one patient), or venous compression by a lymph node (one patient).

The remainder of the patients (27 of 34) did not require surgical reexploration and were considered to have adequate perfusion. None of these patients had vascular insufficiency develop during their postoperative course, until disposition from the hospital.

The images were stored on a PACS workstation and were anonymized before undergoing review by two fellowship-trained abdominal radiologists with 3 and 20 years of experience respectively, who were blinded to the patient outcomes. For each patient, a set of gray-scale and Doppler images and a separate set of CEUS images were provided. The blinded radiologists were asked to score each set of images separately as showing adequate perfusion, arterial insufficiency, or venous insufficiency, according to previously published guidelines [12]. These data were then compared with the known surgical results for each patient, and the diagnostic performance of each modality was compared. A kappa test was used to determine interobserver agreement, with a score of less than 0.2 denoting poor

agreement; 0.2–0.4, fair agreement; 0.4–0.6, moderate agreement; and 0.6–0.8, good agreement. MedCalc software (version 19.1.3, MedCalc) was used for statistical analysis.

Results

Each reader's interpretations of the Doppler ultrasound and CEUS findings are listed in Table 1. Both readers showed a higher sensitivity for vascular abnormalities when using CEUS compared with Doppler imaging (83.3% and 83.3% for readers 1 and 2 versus 66.7% and 50.0% for readers 1 and 2, respectively). CEUS and Doppler ultrasound showed a similar specificity (81.6% and 78.9% for readers 1 and 2 versus 76.3% and 84.2% for readers 1 and 2, respectively). The negative predictive value for each modality was high, with values for CEUS reaching 96.9% and 96.8% for readers 1 and 2, respectively, and those for Doppler ultrasound reaching 93.5% and 91.4% for readers 1 and 2, respectively. Interobserver agreement was moderate for CEUS ($\kappa = 0.54$) and fair for Doppler ultrasound ($\kappa = 0.28$).

Images of adequately perfused pancreas grafts that were obtained using CEUS showed rapid progressive enhancement of the graft, leading to a uniform appearance of contrast distribution less than 30 seconds after contrast injection (Fig. 2). Grafts with arterial abnormalities showed heterogeneous and diminished enhancement of the graft or complete nonenhancement of the graft in more severe cases (Fig. 3). Venous abnormalities in pancreas grafts manifested as delayed washout of contrast medium, often with the graft retaining at least a moderate amount of contrast medium 90 seconds or more after injection (Fig. 4).

Discussion

CEUS contrast agents provide intravascular contrast in a way that allows investigation of organ perfusion. Although Doppler imaging is well established as a technique for the evaluation of individual vessels, it is limited in its ability to examine organ perfusion. Our study shows that CEUS has better sensitivity for detecting vascular abnormalities than does Doppler imaging and that interobserver agreement is also improved with CEUS.

This ability of CEUS to provide a more complete evaluation of the pancreas graft may explain some of the difference in performance between CEUS and Doppler imaging. Doppler evaluation relies on examination of individual vessels within and around organs. In pancreas grafts, this often refers to small intraparenchymal arterial and venous branches because it can be technically challenging and time intensive to find and examine each branch of the traditional Y-graft. The presence of Doppler signal within these smaller branches can then be used as a marker of graft perfusion.

Because CEUS images show enhancement of the entire graft, they may possibly identify perfusion derangements that might be missed using the spot-check approach inherent in Doppler imaging (Figs. 5 and 6). In addition, the ability of CEUS to examine grafts continuously over several minutes leads to a much higher temporal resolution than that provided by Doppler imaging, and it may allow real-time visualization of delayed washout of contrast medium in patients with venous thrombus or other abnormalities.

The present study also showed improved interobserver agreement with CEUS compared with Doppler imaging. Moderate agreement between readers suggests that CEUS may be a more reproducible method for identifying vascular abnormality and thus is attractive for implementation in pancreas graft imaging protocols. The uniform signal seen in a normally perfused organ on CEUS is similar to that seen on CT and MRI. Radiologists are familiar with this pattern of enhancement, and it is possible that evaluating pancreas graft perfusion in this manner explains some of this improved agreement among radiologists.

The present study adds to the scarce literature describing the use of CEUS for imaging pancreas grafts. CEUS has been described as improving the subjective quality and visualization of pancreas grafts [17]. Other studies examining the use of CEUS for identifying graft dysfunction have focused on evaluating grafts for rejection [18] or have described graft perfusion in fewer patients without providing a comparison with Doppler imaging [19, 20].

Another study [9] examined the Doppler findings that are most commonly associated with graft failure, and it showed that Doppler imaging has relatively low sensitivity, with higher specificity observed for vascular abnormalities associated with graft loss, similar to the findings of our study.

The findings of the present study suggest that CEUS may provide an improved method for evaluating pancreas grafts postoperatively to identity vascular complications. In clinical practice, the improved sensitivity of CEUS and its high negative predictive value may make it a useful modality for vascular screening examinations. The improved interobserver agreement observed with CEUS suggests that it can serve as a reproducible technique that can be integrated into a boarder clinical practice. Further work to validate and reproduce the technique could focus on larger patient populations and multiple institutions. Correlation between CEUS and clinical and laboratory findings after surgery may also be of assistance, as may the use of perfusion quantification software to evaluate differences between normally and abnormally perfused grafts.

The present study is limited by its retrospective design as well as the relatively small number of examinations that showed vascular abnormalities (six of 44 examinations). The use of findings from surgical reexploration as a reference is somewhat subjective, but in all cases considered to have abnormal findings, thrombosis or true morphologic changes of the artery or vein were found. Finally, the study relied on qualitative evaluation of graft perfusion by the radiologist, which allows subjectivity but is also more realistic in terms of current radiology practice.

Conclusion

CEUS can be used to identify vascular abnormalities in pancreas grafts with greater sensitivity, similar specificity, and improved interobserver agreement compared with conventional Doppler ultrasound. CEUS with normal findings also has a high negative predictive value for identifying grafts not requiring reexploration. The use of CEUS therefore may provide radiologists and transplant surgeons with a timely and effective

method of evaluating pancreas graft perfusion after surgery and may help identify grafts that could benefit from surgical salvage.

Acknowledgments

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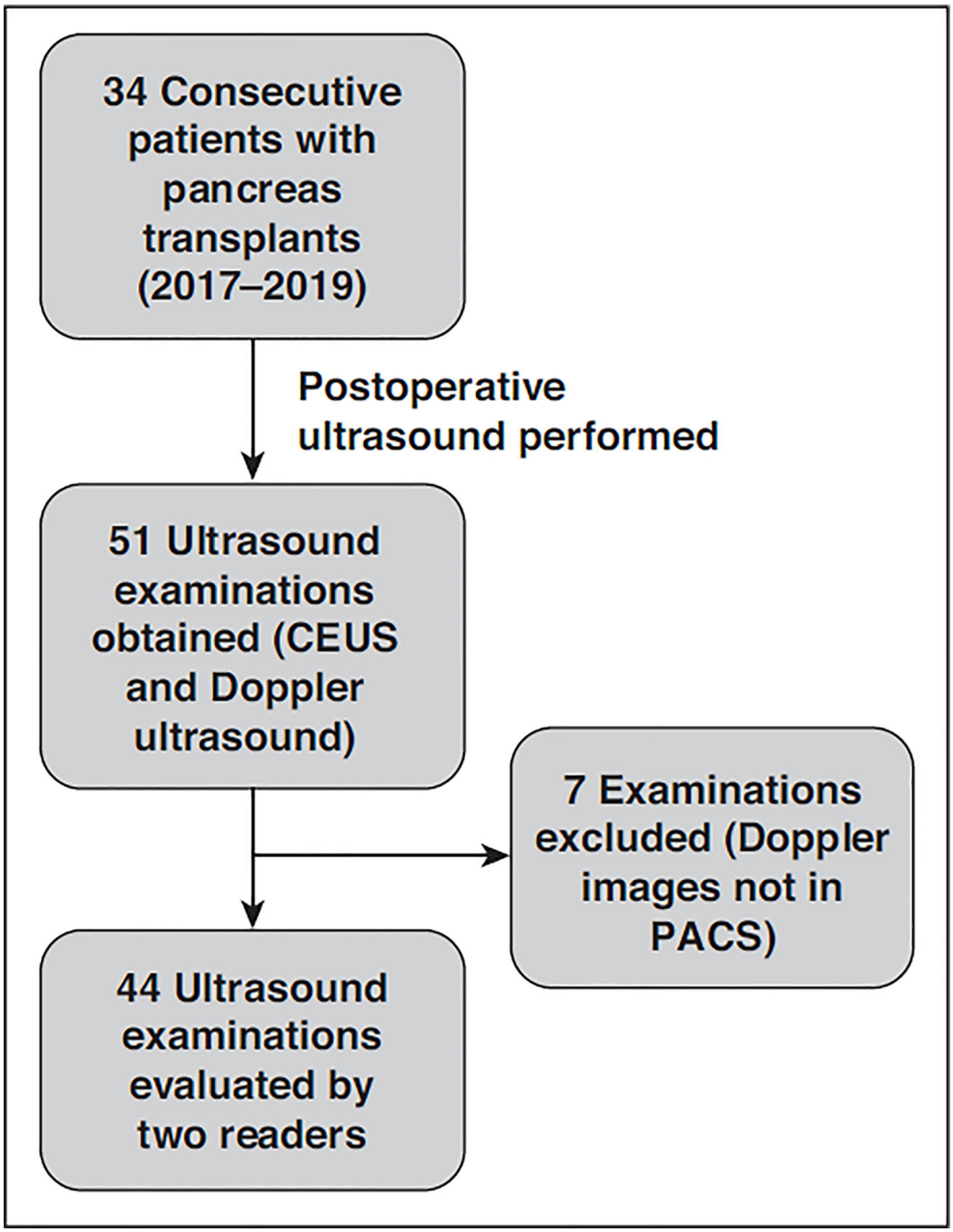

Fig. 1—.
Flow diagram of patient enrollment in study.
CEUS = contrast-enhanced ultrasound.

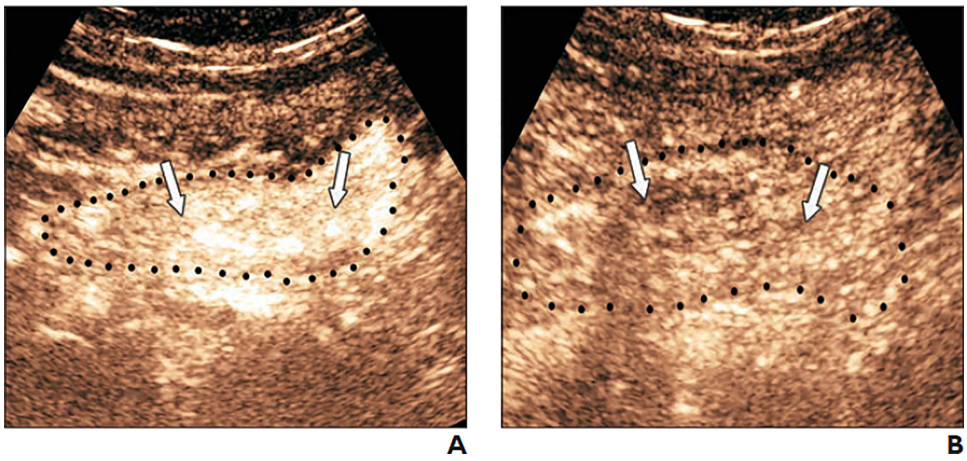

Fig. 2—.

44-year-old man with adequate early enhancement of pancreas graft.

A, Contrast-enhanced ultrasound image interpreted by reader as showing uniform robust enhancement (*arrows*) throughout pancreas graft (area within *dotted outline*) at 10 seconds after injection of contrast medium. Patient did not undergo reexploration and was successfully discharged from hospital.

B, Contrast-enhanced ultrasound image interpreted by reader as showing contrast signal (*arrows*) that became more heterogeneous and less robust throughout pancreas graft (area within *dotted outline*) at 30 seconds after injection of contrast medium, suggesting intact venous washout of microbubbles. Patient did not undergo reexploration and was successfully discharged from hospital.

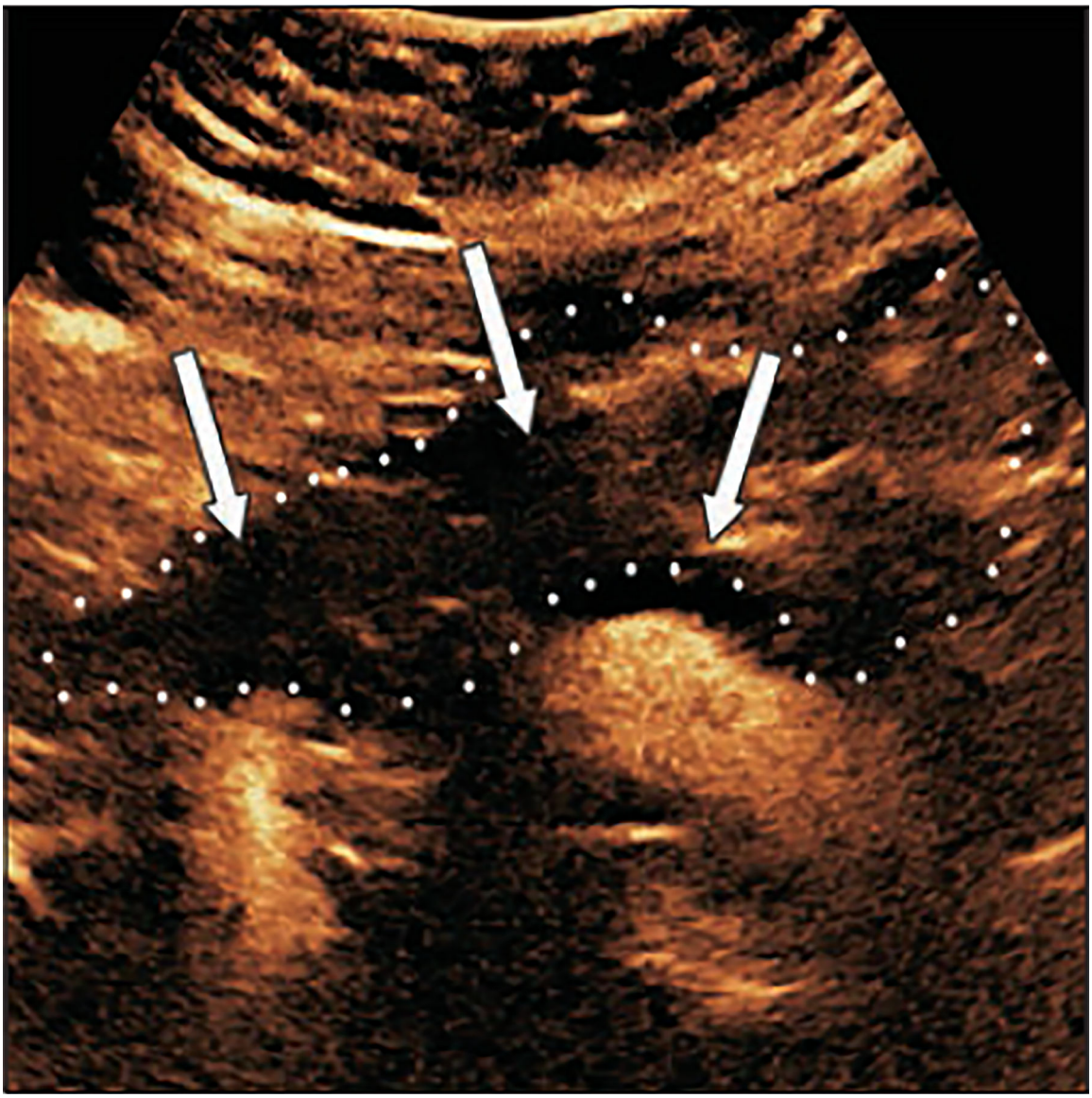

Fig. 3—.

35-year-old woman with pancreas graft with arterial insuffi ciency. Contrast-enhanced ultrasound image interpreted by reader as showing that pancreatic parenchyma (*arrows*) had minimal internal contrast signal at 20 seconds after injection of contrast medium. Patient was found to have arterial thrombosis on surgical reexploration. Area within dotted outline denotes pancreas graft.

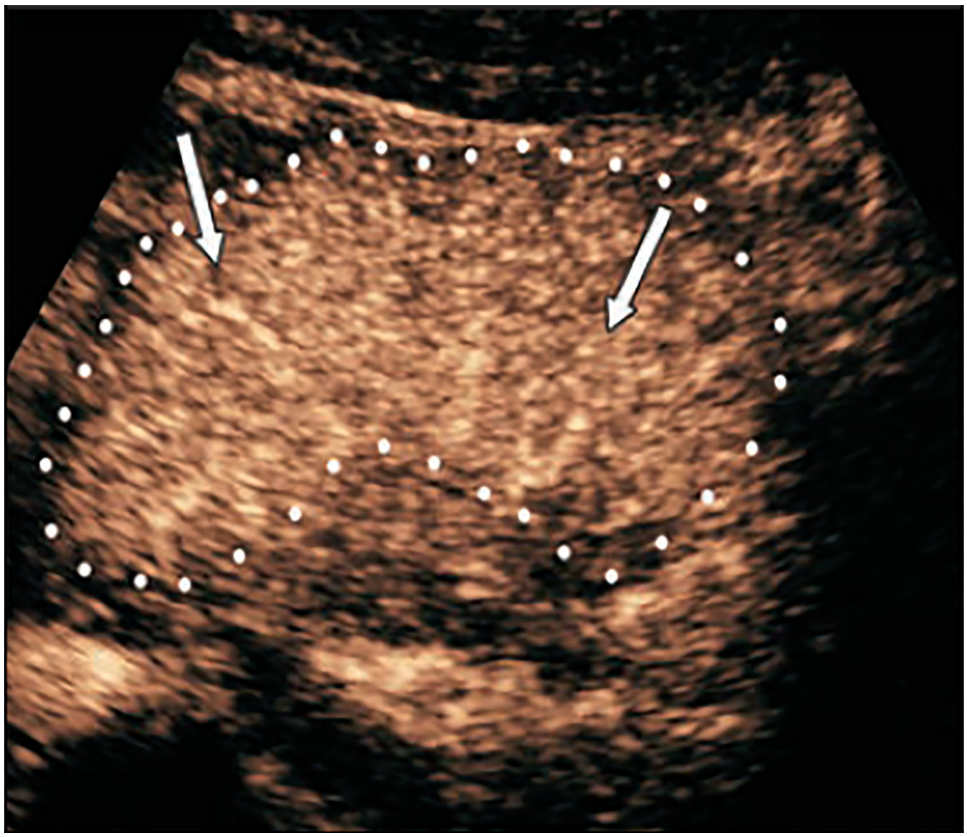

Fig. 4—.

26-year-old man who had pancreas graft (area within *dotted outline*) with venous insufficiency. Contrast-enhanced ultrasound image interpreted by reader as showing that pancreatic parenchyma (*arrows*) had persistent homogeneous enhancement at 2 minutes 30 seconds after injection of contrast medium, suggesting impaired venous washout of contrast medium. Patient was found to have large splenic vein thrombus.

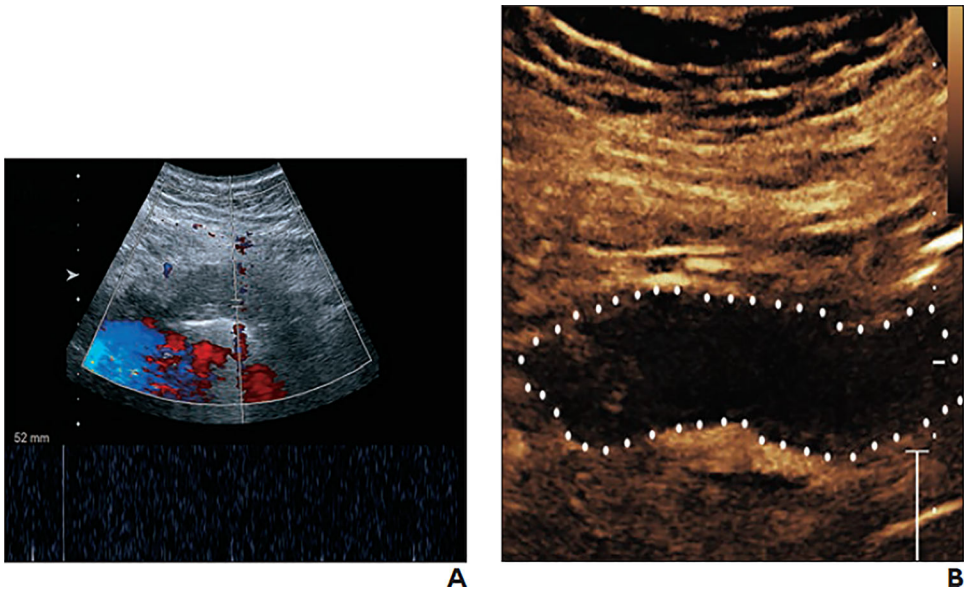

Fig. 5—.

39-year-old woman with pancreas graft arterial thrombus found at surgery. Concordant results were found on Doppler ultrasound and contrast-enhanced ultrasound images.

A, Doppler ultrasound image was interpreted by reader as lacking definite color signal, and spectral waveforms were either absent or severely diminished.

B, Contrast-enhanced ultrasound image was interpreted by reader as showing no contrast signal throughout graft (area within *dotted outline*)

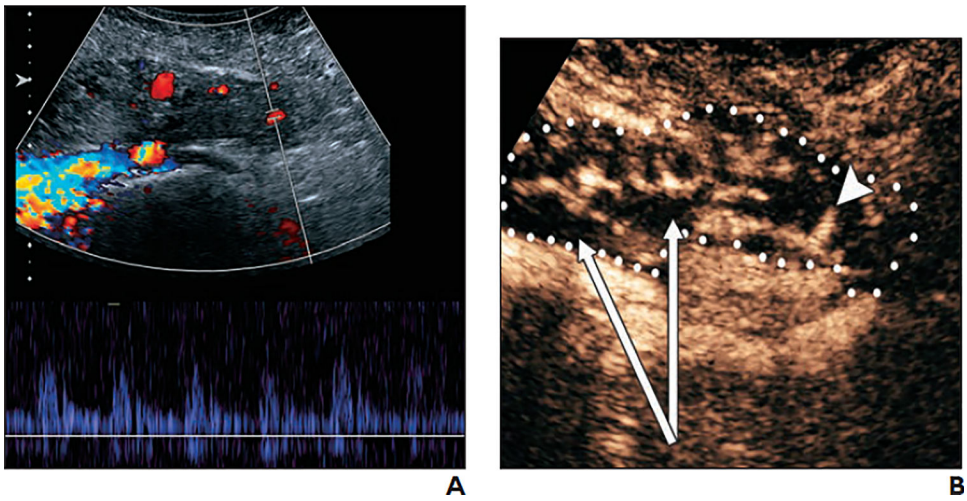

Fig. 6—.

26-year-old man with pancreas graft arterial spasm found at surgery. Discordant results were found on Doppler ultrasound and contrast-enhanced ultrasound images.

A, Doppler ultrasound image interpreted by reader as showing intact arterial color and spectral signal in graft tail, suggesting normal graft perfusion.

B, Contrast-enhanced ultrasound image interpreted by reader as showing heterogeneous hypoenhancement of graft (*arrows*) suggesting arterial insuffi ciency. Small perfused intraparenchymal arterial branch (*arrowhead*) correlated with area of intact Doppler signal. Case was scored as normal on Doppler ultrasound and abnormal on contrast-enhanced ultrasound by both readers. Area within dotted outline denotes pancreas graft.

TABLE 1:

Comparison of Contrast-Enhanced Ultrasound (CEUS) Versus Doppler Ultrasound for Identifying Vascular Abnormalities in Pancreas Grafts

Value	CEUS		Doppler Ultrasound	
	Reader 1	Reader 2	Reader 1	Reader 2
Sensitivity (%)[a]	83.3 (5/6)	83.3 (5/6)	66.7 (4/6)	50.0 (3/6)
Specificity (%)[b]	81.6 (31/38)	78.9 (30/38)	76.3 (29/38)	84.2 (32/38)
Positive predictive value (%)	41.7	38.5	30.8	33.3
Negative predictive value (%)	96.9	96.8	93.5	91.4

[a]Data in parentheses are the number of examinations on which the reader identified vascular abnormalities/total number of surgically proven vascular abnormalities.

[b]Data in parentheses are the number of examinations on which the reader did not identify vascular abnormalities/total number of cases without vascular abnormalities.