

**Les amplificateurs du signal  
échographique**

**The contrast enhanced  
ultrasound**



Ombretta Martinelli – Roma

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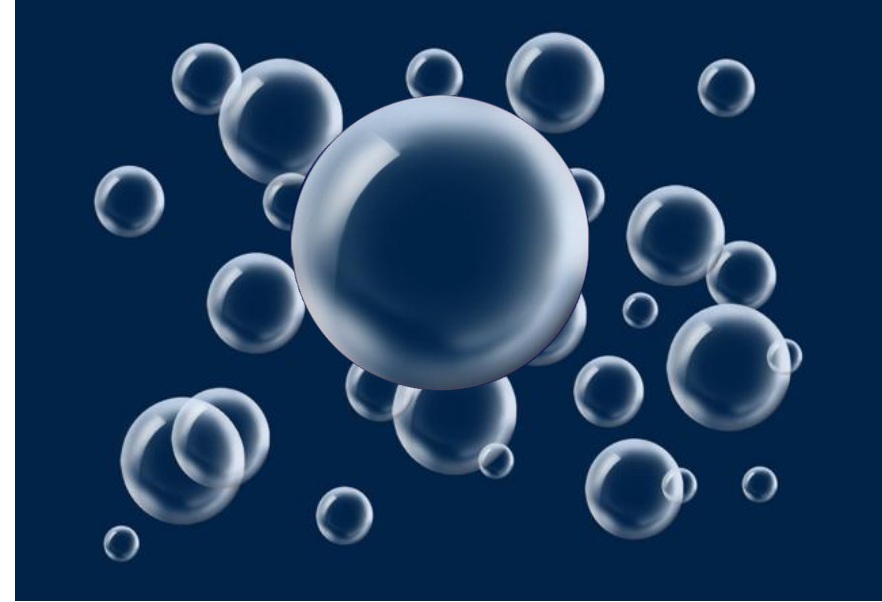
The use of **contrast enhanced ultrasound** (CEUS) has improved significantly the potentiality of standard duplex ultrasound (DUS) imaging in the last decade.

At present, 3 commercial agents, **Optison™** (GE Healthcare, Milwaukee, WI, U.S.A.), **Definity®** (Lantheus Medical Imaging, Billerica, MA, U.S.A.), and **SonoVue®** (Bracco SpA, Milano, Italy) are licensed for US applications.

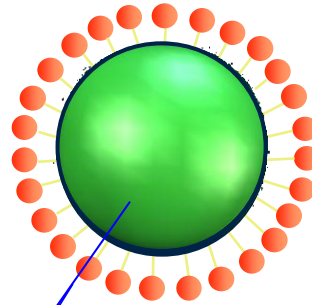
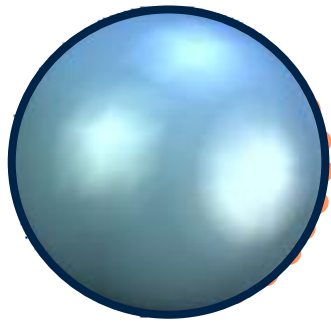
**Optison™ and Definity®** are available in both the United States and the European Union whereas **SonoVue®** is only available in the European Union.

Name	Manufacturer	Shell material	Gas	Mean size (µm)	Percentage less than 10 µm	Concentration (bubbles/mL)	Imaging time (minutes)
Optison™	GE Healthcare	Albumin	C <sub>3</sub> F <sub>8</sub>	2.0–4.5	95%	5.0–8.0 x 10 <sup>8</sup>	2.5–4.5
Definity® (Luminity® in the European Union)	Lantheus Medical Imaging	Phospholipid	C <sub>3</sub> F <sub>8</sub>	1.1–3.3	98%	1.2 x 10 <sup>10</sup>	2–10
SonoVue®	Bracco SpA	Phospholipid	SF <sub>6</sub>	2–8	99% (< 11 µm)	0.9–6 x 10 <sup>9</sup>	3–6
Homemade Microbubbles	Yeh Group at National Tsing Hua University	Phospholipid/Lipopolymer	C <sub>3</sub> F <sub>8</sub>	0.2–0.7	> 99.9%	1.4–3.0 x 10 <sup>10</sup>	10–20

Ultrasound contrast agents are highly echogenic microbubbles with many unique properties

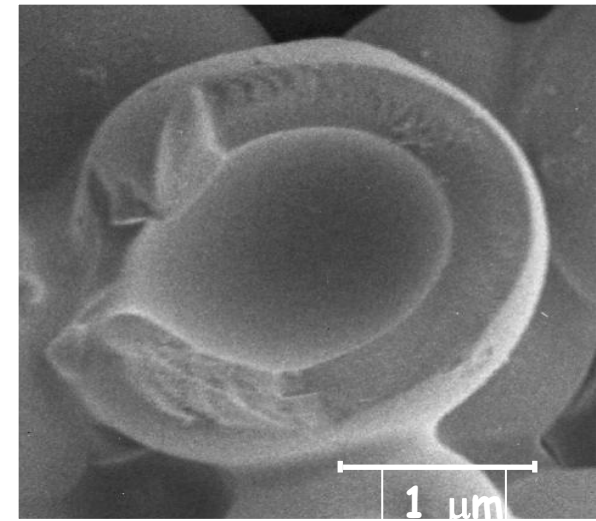
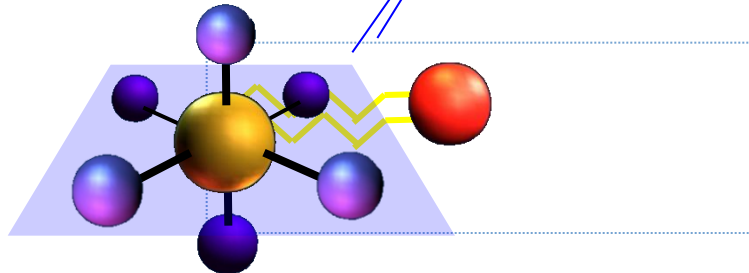
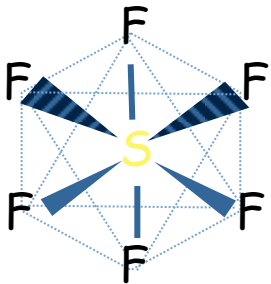


SonoVue<sup>®</sup> microbubbles structure



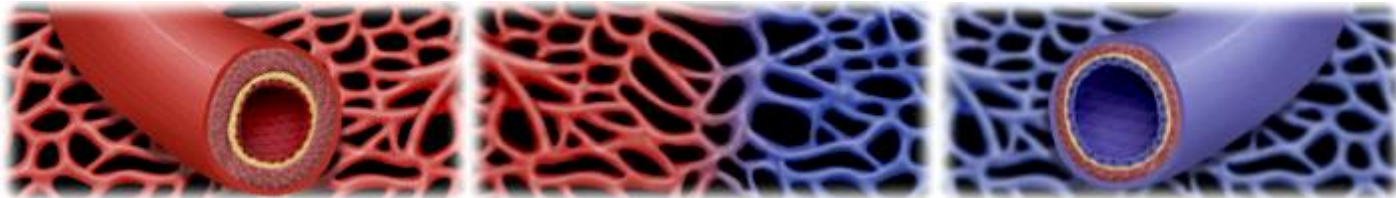
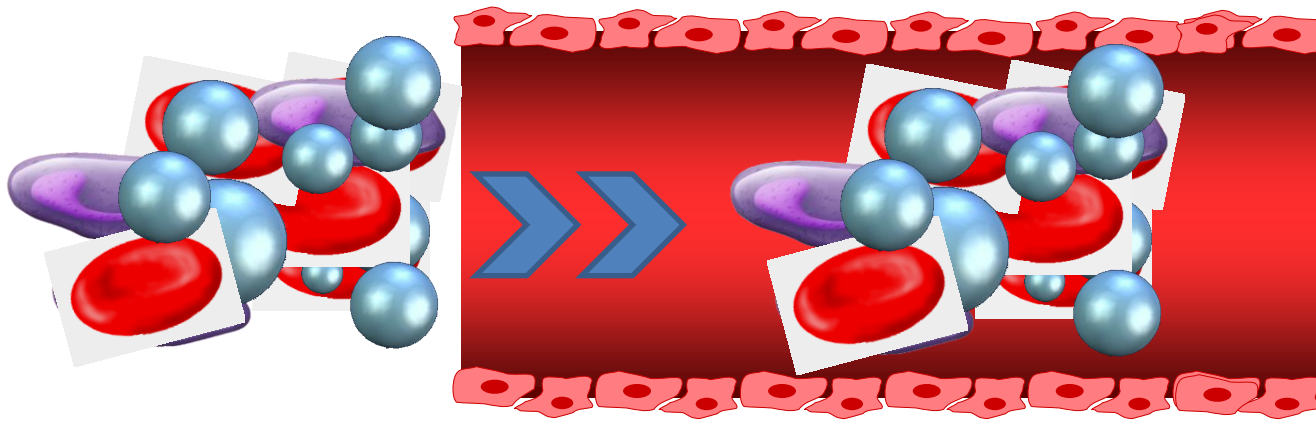
Shell material  
Phospholipids, polymers

Gas SF<sub>6</sub> Sulfur-hexafluoride

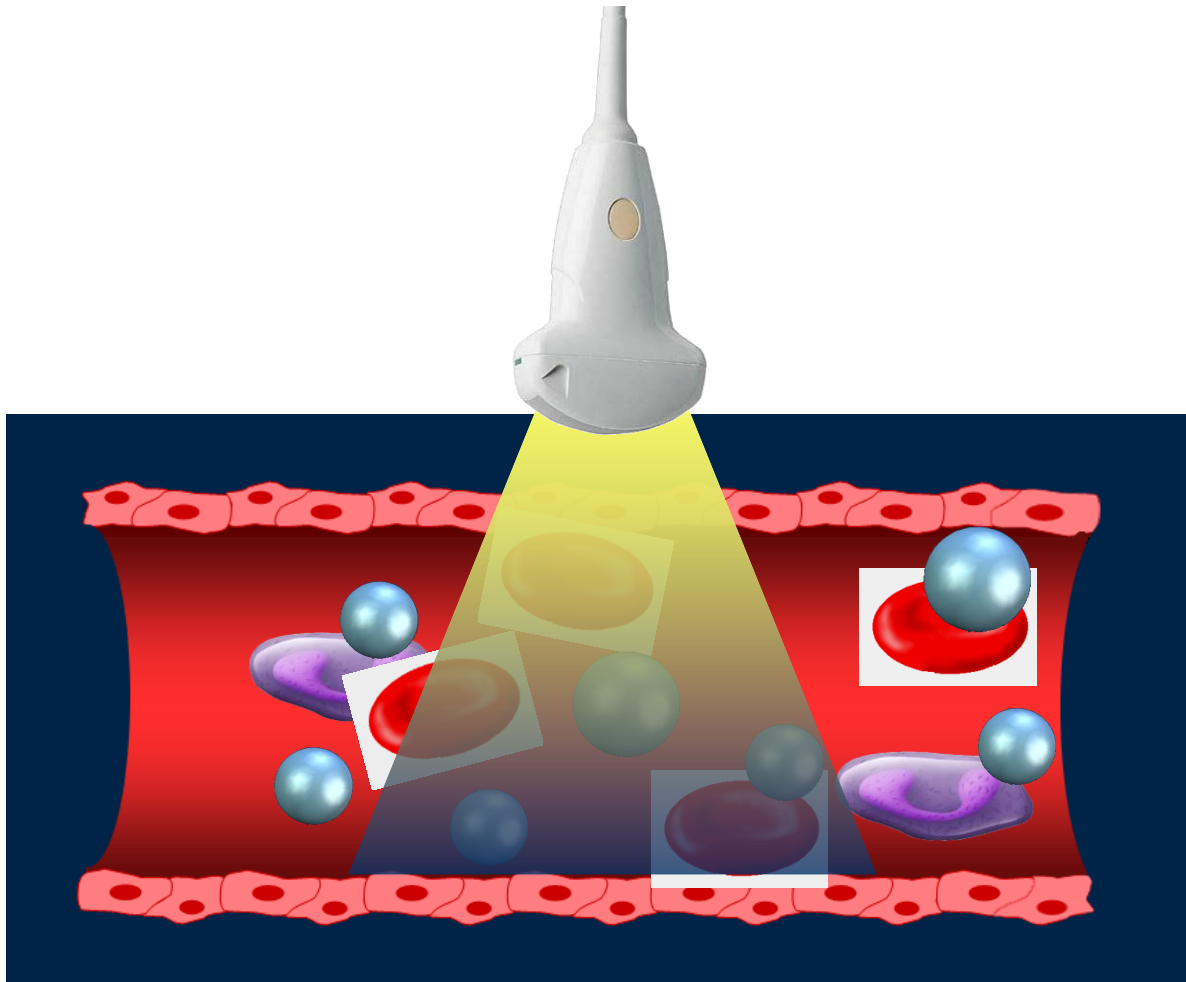


Ultrasound contrast agents are ***blood-pool agents***

After e.v. injection they remain intravascular without any diffusion to the tissue



Ultrasound contrast agents contribute to high enhance the ultrasound blood signal



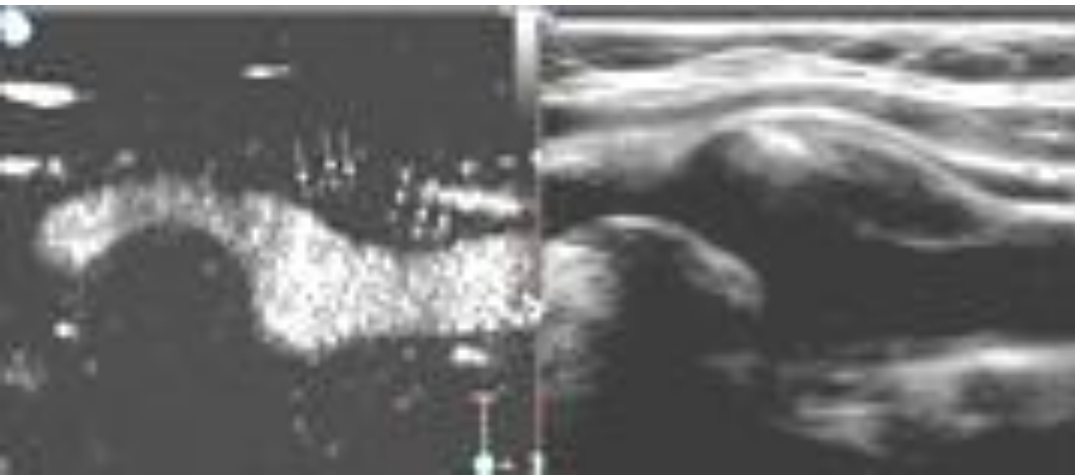
# After disruption by US



Microbubbles gas is removed through the lung

Microbubbles structures (phospholipids, membranes, etc) are metabolized by the liver and are removed by the kidney

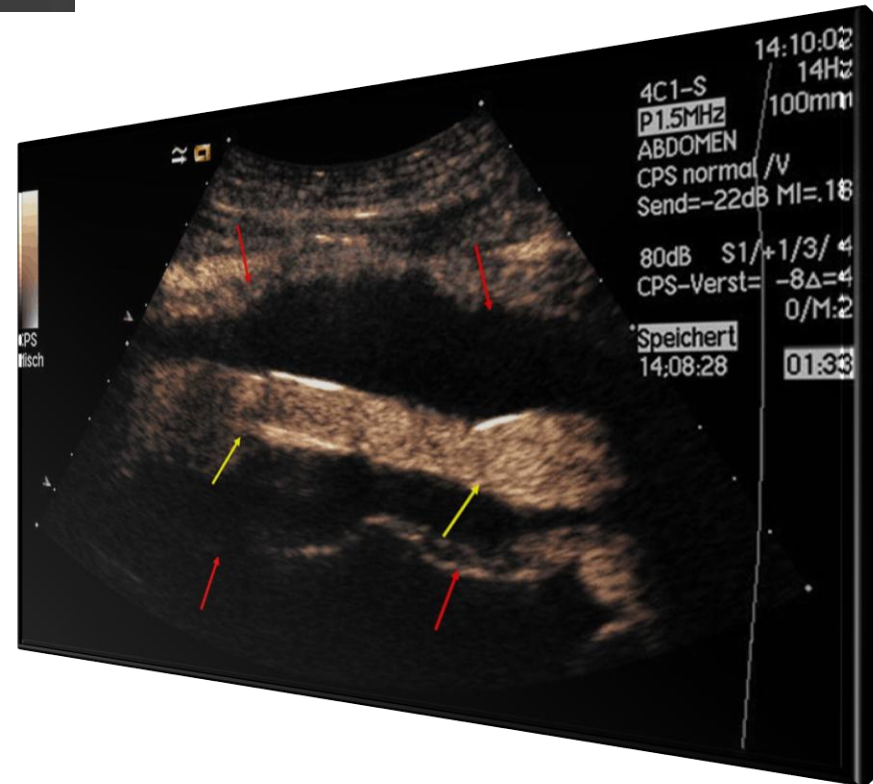




**Contrast-Enhanced Ultrasound Imaging  
of the Vasa Vasorum:  
From Early Atherosclerosis to the  
Identification of Unstable Plaques**

*J Am Coll Cardiol Img.* 2010;3(7):761-771

**CEUS** is currently used  
in many different vascular  
fields; particularly  
as far as the evaluation  
of **carotid plaques** and  
the **follow-up  
after aneurysm  
repair** (EVAR).



**Endoleak detection and classification after endovascular treatment of  
abdominal aortic aneurysm: value of CEUS over CTA**

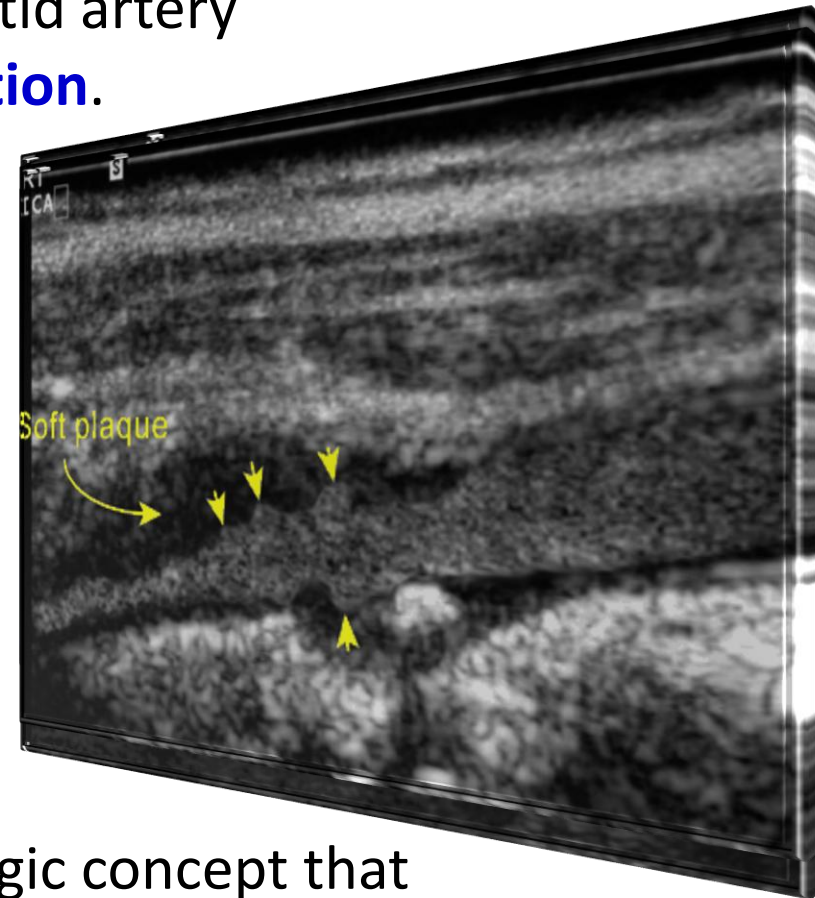
[Abdominal Imaging](#) May 2008, Volume 33, [Issue 3](#), pp 357-362



# Evaluation of carotid plaques

Many studies have shown a correlation between echolucency on standard DUS of the carotid artery and grade of **intraplaque neovascularization**.

**More echolucent lesions had significantly higher degree of neovascularization** compared with more echogenic ones

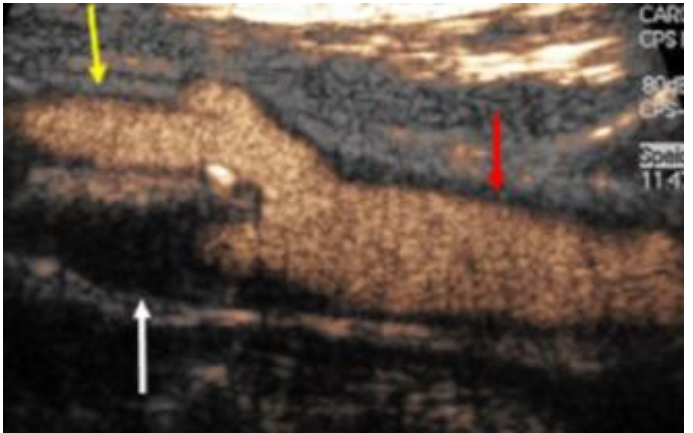
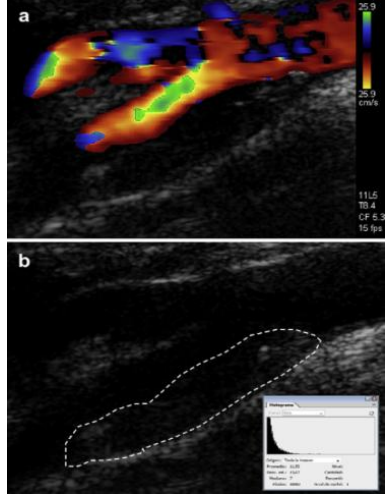
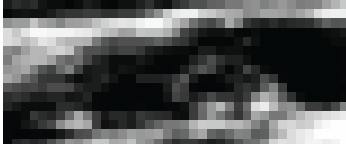


This is consistent with the pathophysiologic concept that neoangiogenesis is associated with **more rapidly progressive and unstable vascular disease**

Many stroke-related features of the carotid plaques can be assessed by:

# Basic carotid duplex ultrasound (CDU)

- plaque echolucency (>40% of area)
- discrete white areas (DWAs) without acoustic shadowing
- thin cap/ulceration
- stenosis degree → wall shear stress → cap disruption
- motion of intraplaque content



# CEUS

- intraplaque inflammation
- vasa vasorum network within the plaque

*Falkowski A Med Sci Mon 2007  
 Nicolaides An J Vasc Surg 2011  
 Makris GC Atherosclerosis 2011  
 Kashiwazaki D J Neurosurg 2012  
 Byrnes KR Int J Vasc Med 2012*

# Contrast enhanced ultrasound – CEUS

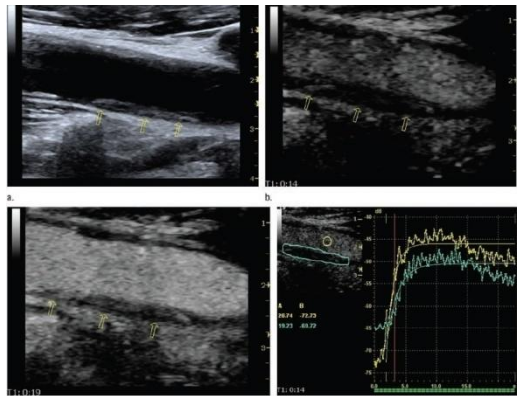
can be used to quantify plaque morphology by identifying intraplaque inflammation and or neovascularization that is directly related to the risk of cardiovascular events (myocardial infarction, TIA, stroke)

Radiology

## Correlation of Carotid Plaque Neovascularization Detected by Using Contrast-enhanced US with Clinical Symptoms<sup>1</sup>

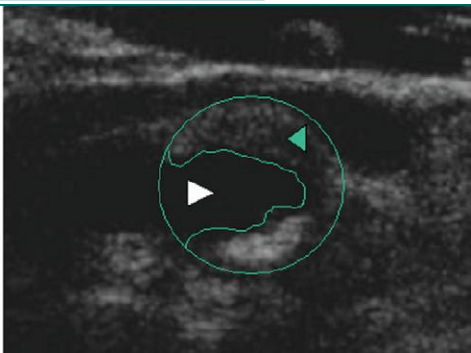
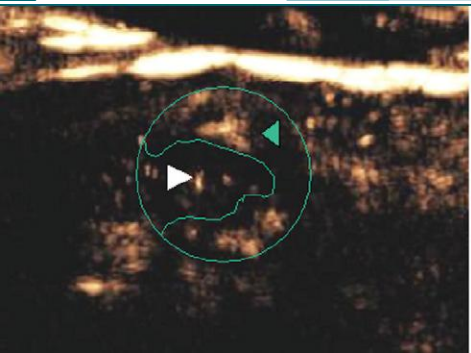
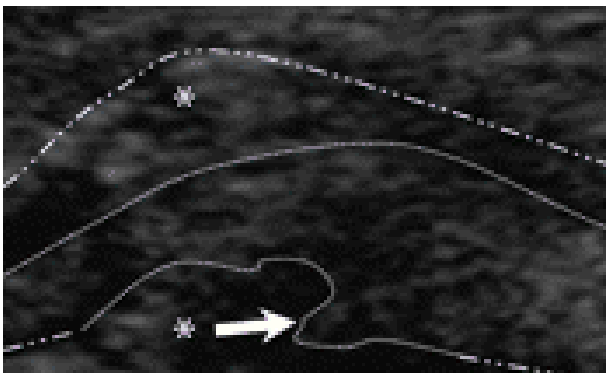
Li Xiong, MD  
You-Sin Deng, MD  
Ying Zhu, MD  
Ya-Ni Liu, MD  
Xiao-Jun Si, MD

**Purpose:** To determine the correlation between the degree of plaque enhancement with contrast agent microbubbles and clinical symptoms in patients with carotid atherosclerotic plaque.



## Inflammation within Carotid Atherosclerotic Plaque: Assessment with Late-Phase Contrast-enhanced US<sup>1</sup>

Radiology

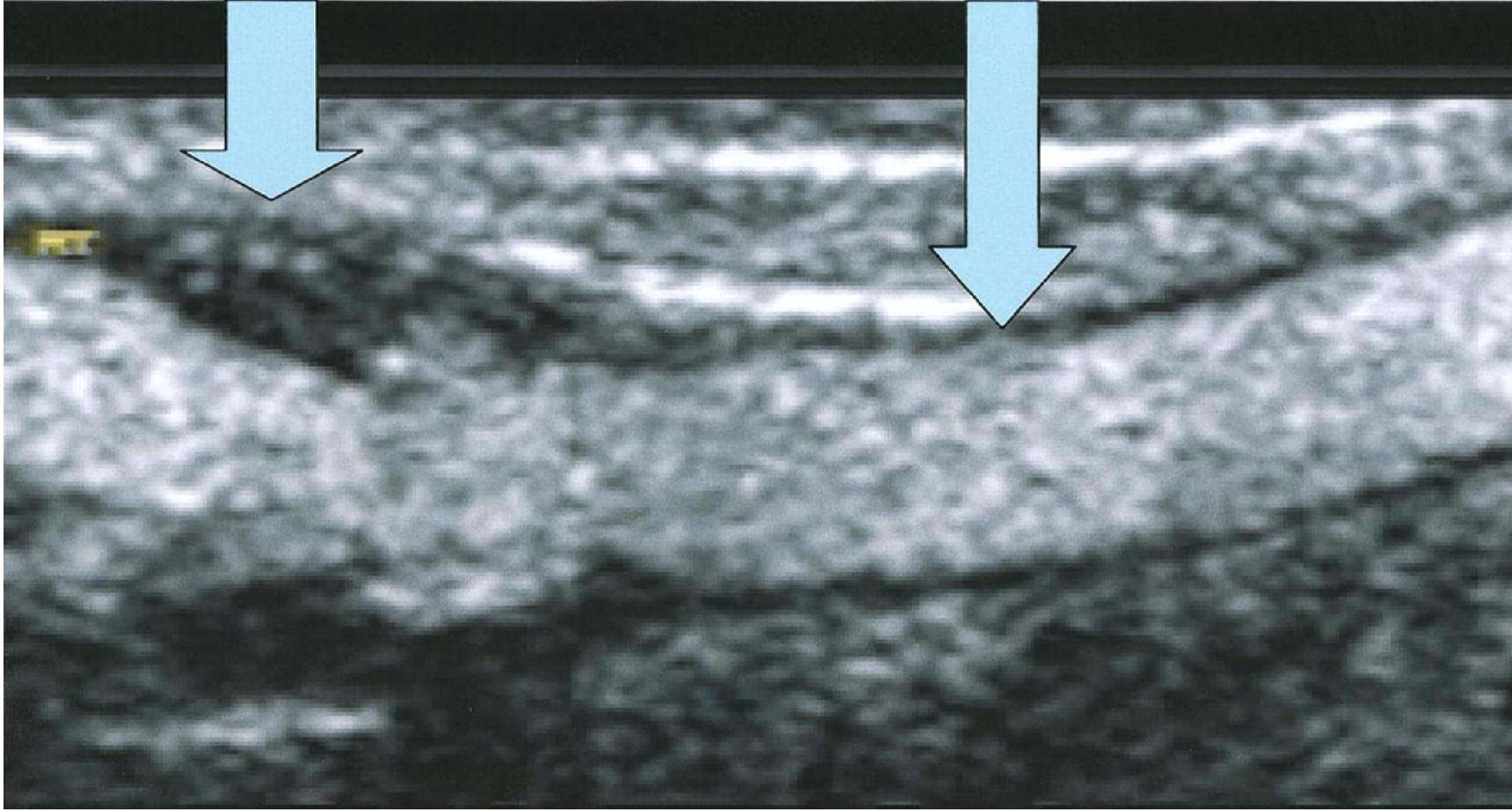


Staub D. *Stroke*. 2010  
Faggioli GL *Eur J Vascular and Endovascular Surgery*. 2011  
Clevett DA *Eur J Radiology*. 2011

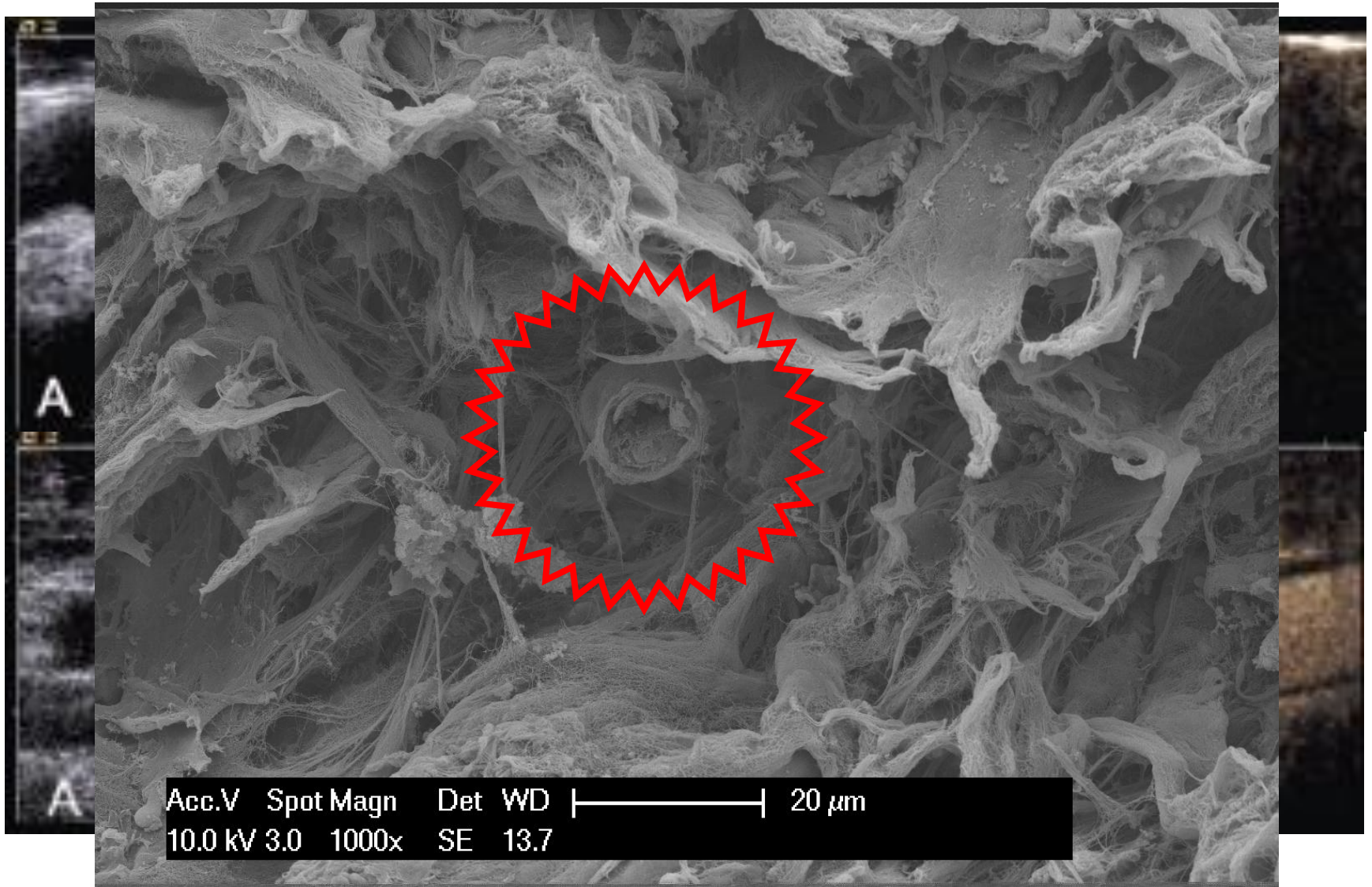
# Evaluation of carotid plaques

Plaque neovascularization highlighted with ultrasound contrast agents

Contrast-enhanced, common carotid artery lumen

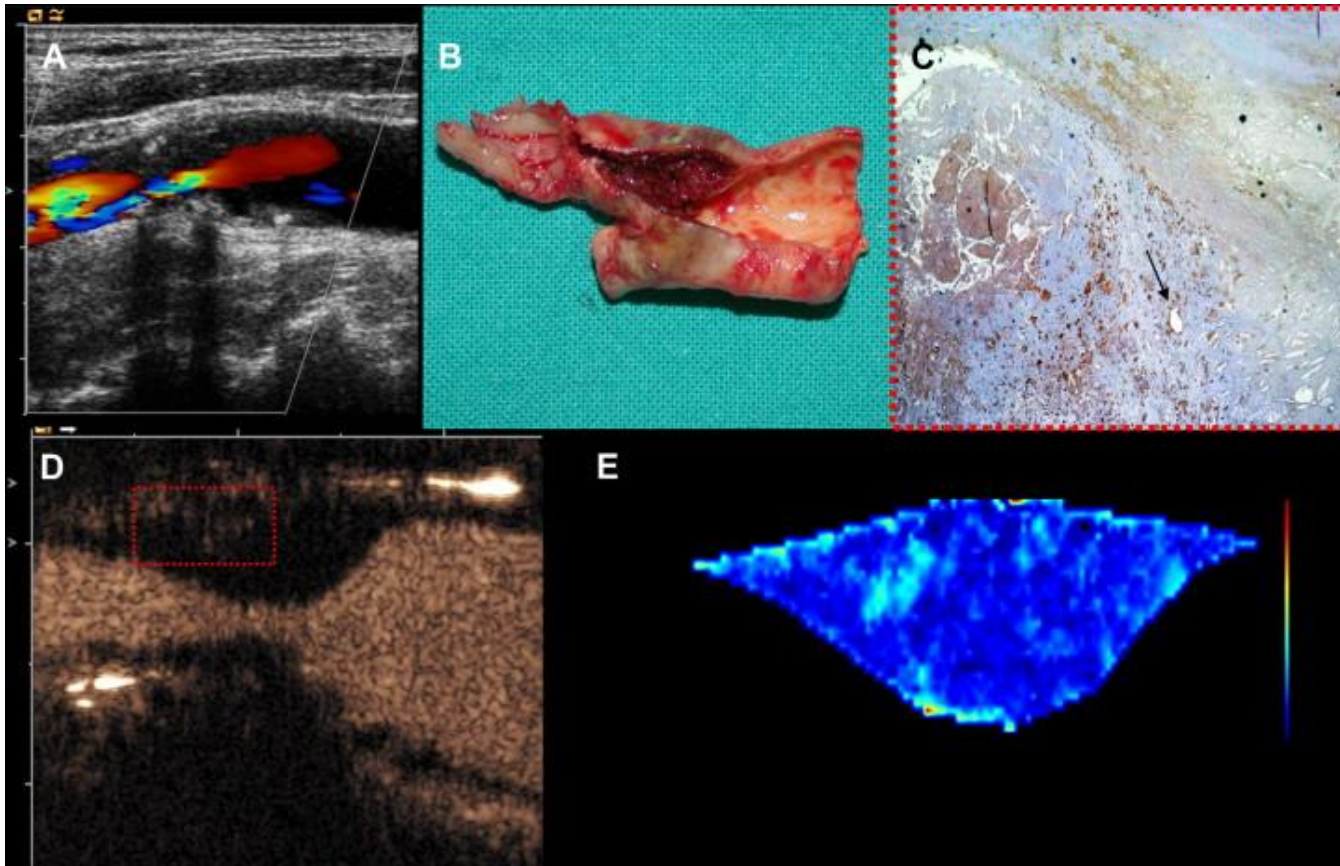


# Plaque Neoangiogenesis



# Plaque Neoangiogenesis

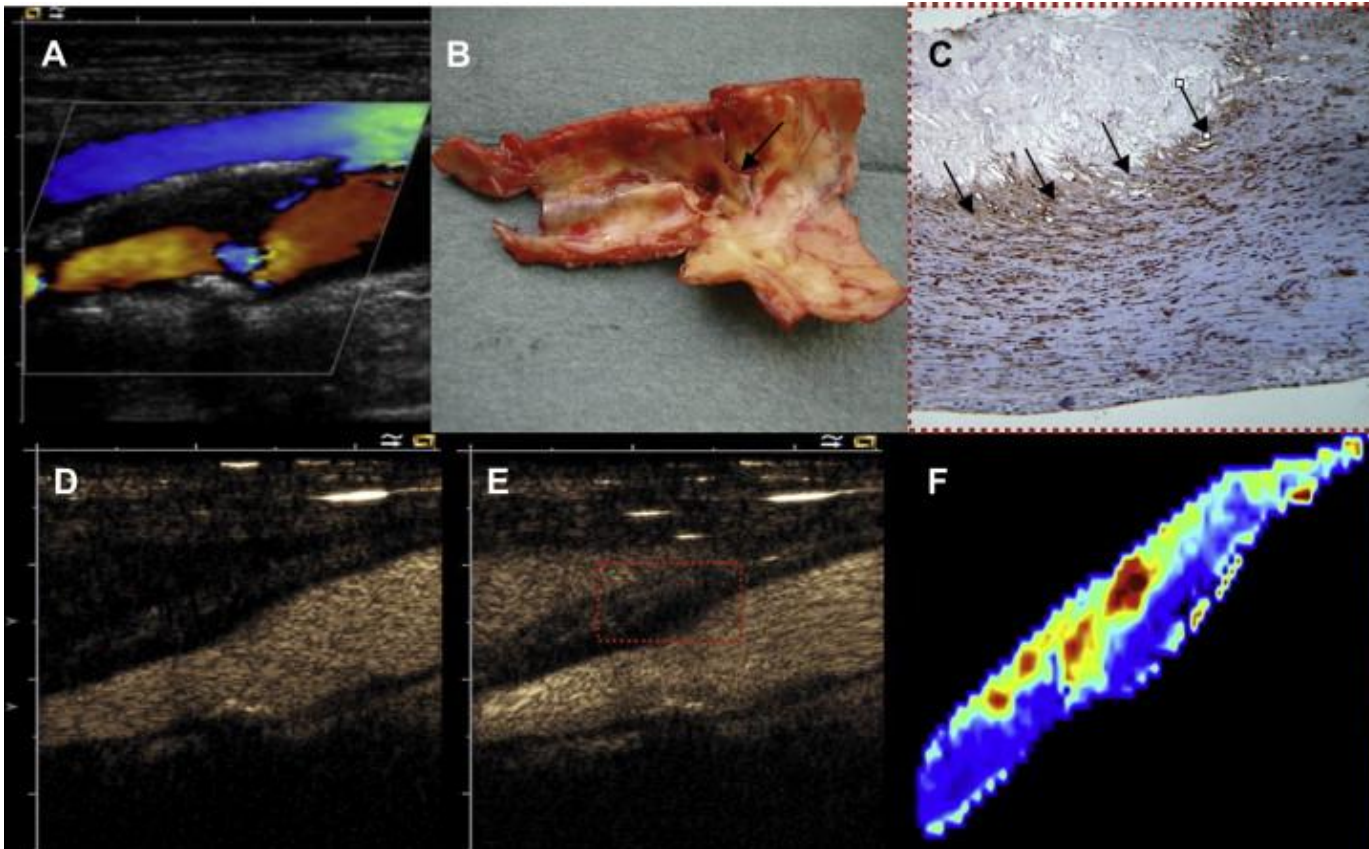
**Asymptomatic Patient**  
**Lower angiogenesis**



**A: colorDoppler – B; emorragic plaque - C: immuno-histochemical image VEGF (vascular endotelial growth factor) e MMP3 (Matrix Metallo Proteinasi) - D: Contrast cadense CPS - E: Contrast software of imaging analysis**

# Plaque Neoangiogenesis

## Symptomatic Patient Higher angiogenesis

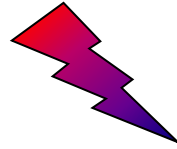


**A: colorDoppler - B: emorragic plaque - C: immuno-histochemical image for VEGF (vascular endotelial growth factor) e MMP3 (Matrix Metallo Proteinasi) - D/E: Contrast cadense CPS - F: Contrast software of imaging analysis**

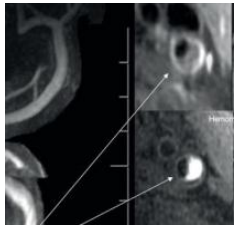
Giannoni MF Eur J Vasc Endovasc Surg 2009;37(6);722-727

[Am J Cardiol.](#) 2013 Jul 15;112(2):292-8. Usefulness of contrast-enhanced ultrasound for detection of carotid plaque ulceration in patients with symptomatic carotid atherosclerosis.

The assessment of plaque vulnerability by CEUS is not routinely available and is not the current standard of practice



CDU may be considered the initial modality of choice to identify patients with suspicion of vulnerable plaques to be further studied with serum inflammatory and proteolytic markers



(PCR, IL-6, MMP-2, MMP-9, Tissue inhibitors of MMP -1 e -2)

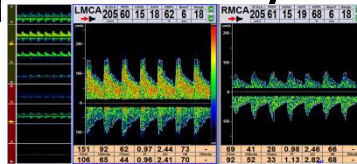


contrast-enhanced MRA



CTA

PET/CT



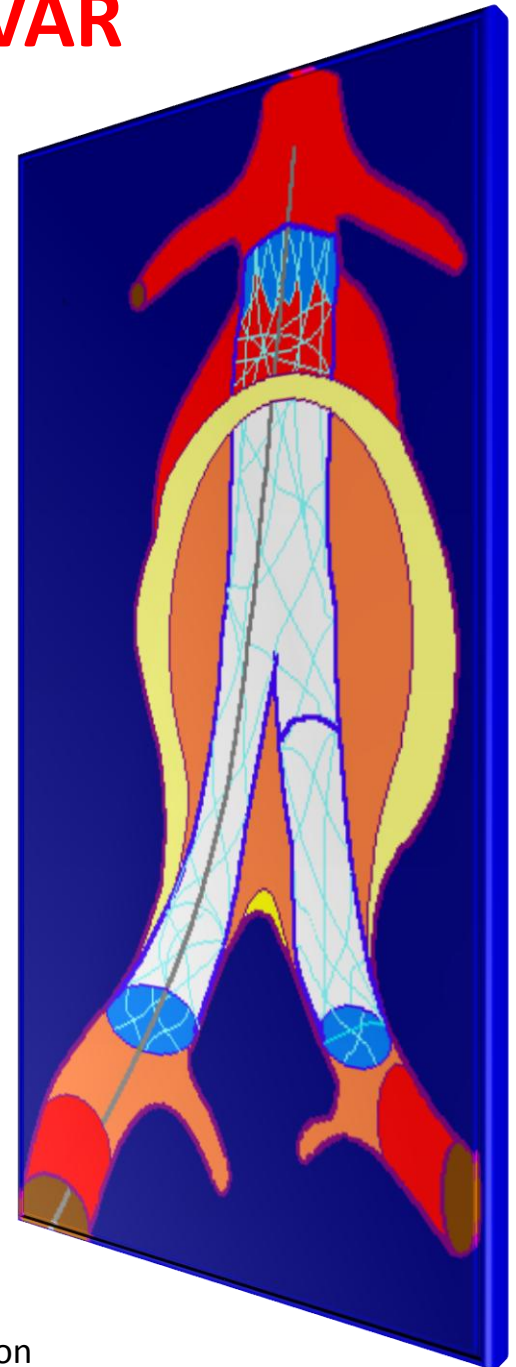
Transcranial Doppler



# Follow-up after aneurysm repair EVAR

## Types of endoleak

- Type 1: perigraft or graft related
- Type 2: retrograde or non graft related
- Type 3: fabric tear or modular disconnections
- Type 4: graft porosity
  
- Undefined origin
- Endopression or endotension



[D.A. Clevert a, N. Minaifar a, S. Weckbach a, R. Koppb, G. Meimarakis b, D.A. Clevert c and M. Reiser](#)

**Color duplex ultrasound and contrast-enhanced ultrasound in comparison to MS-CT in the detection of endoleak following endovascular aneurysm repair**

[Clinical Hemorheology and Microcirculation](#) 39 (2008) 121–132 121

**In many studies the utility of CEUS in the follow up after Endovascular aortic aneurysm Repair is remarked**

[Kopp R, Zürn W, Weidenhagen R, Meimarakis G, Clevert DA.](#)

**First experience using intraoperative contrast-enhanced ultrasound during endovascular aneurysm repair for infrarenal aortic aneurysms.**

[J Vasc Surg.](#) 2010 May;51(5):1103-10

[Giannoni MF, Citone M, Rossini M, Speziale F, David V.](#)

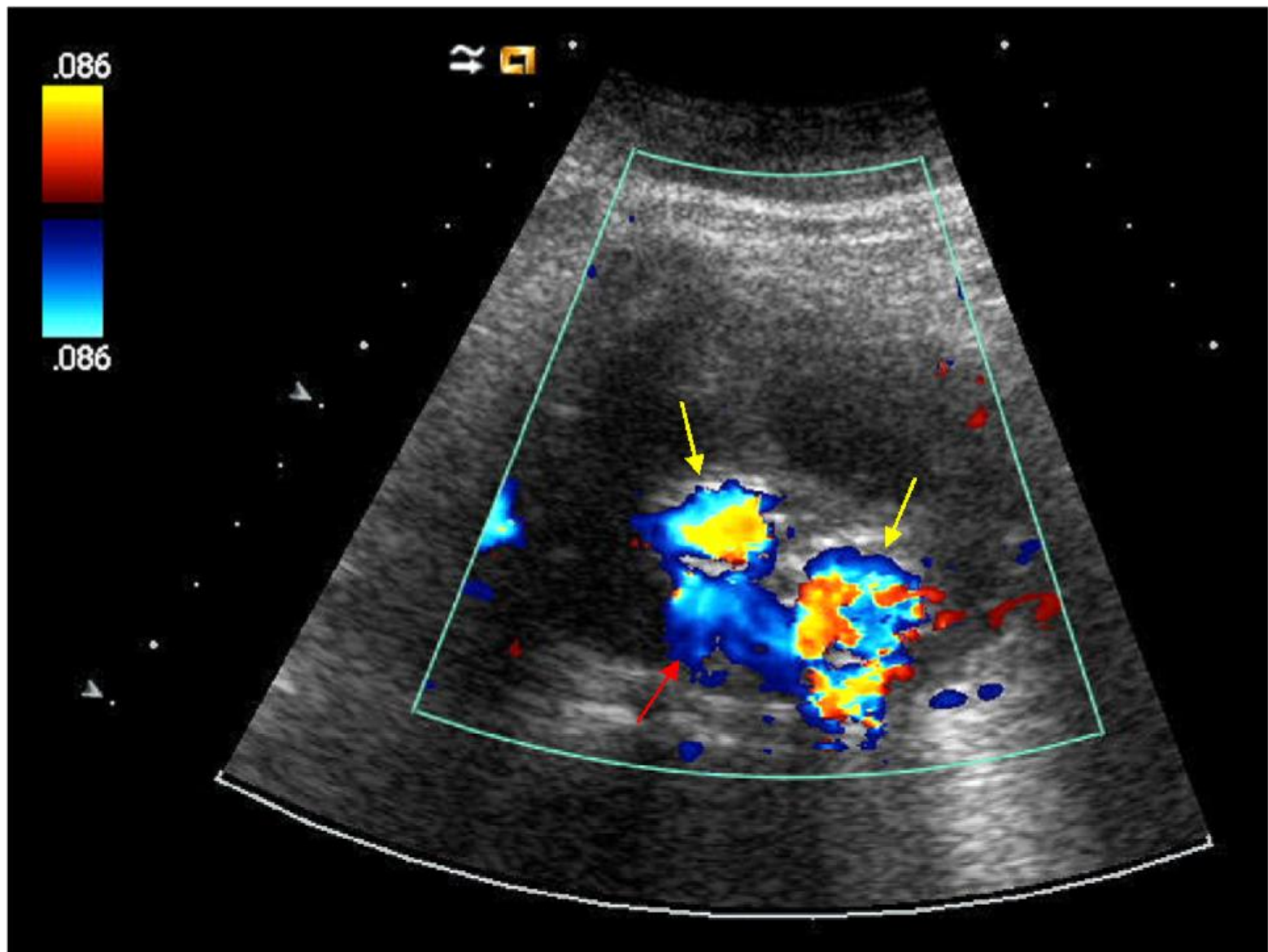
**Role of contrast-enhanced ultrasound in the follow-up of endo-vascular aortic aneurysm repair: an effective and safe surveillance method.**

[Curr Pharm Des.](#) 2012;18(15):2214-22.

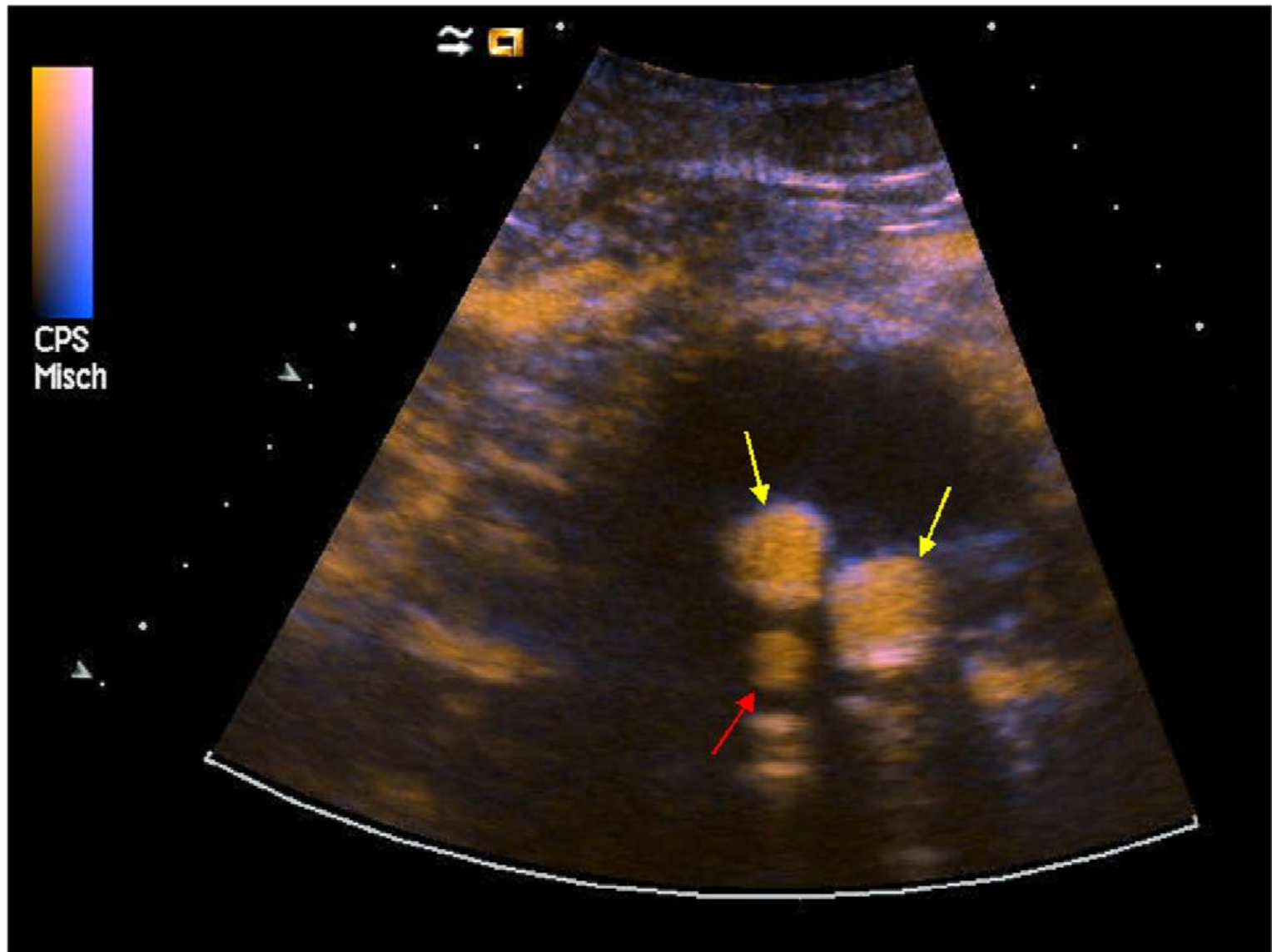
[Marijke Vroomen Durning, RN](#)

**Contrast-enhanced US Monitors Aortic Aneurysm Repair**

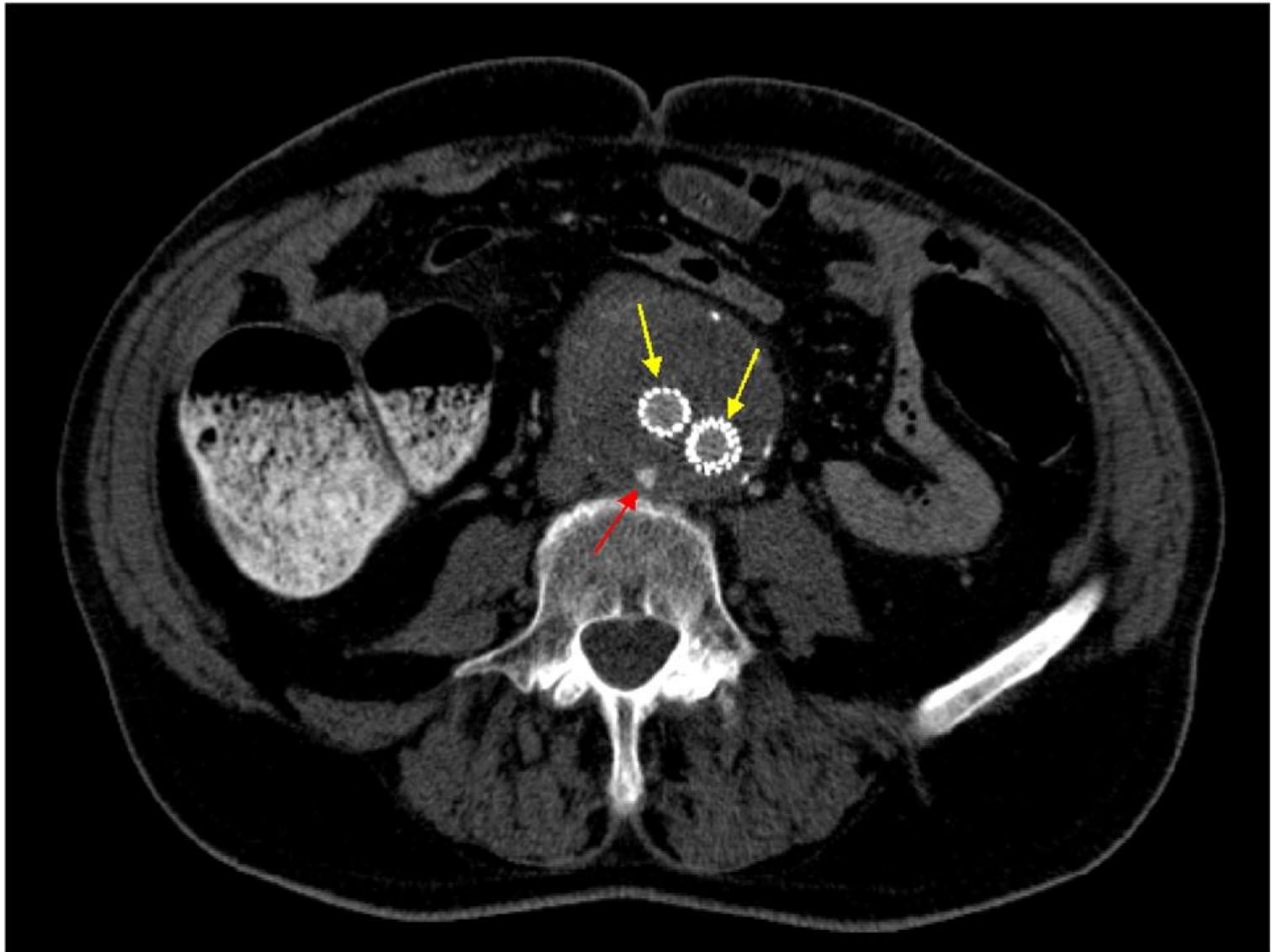
[Ultrasound](#) May 15, 2012



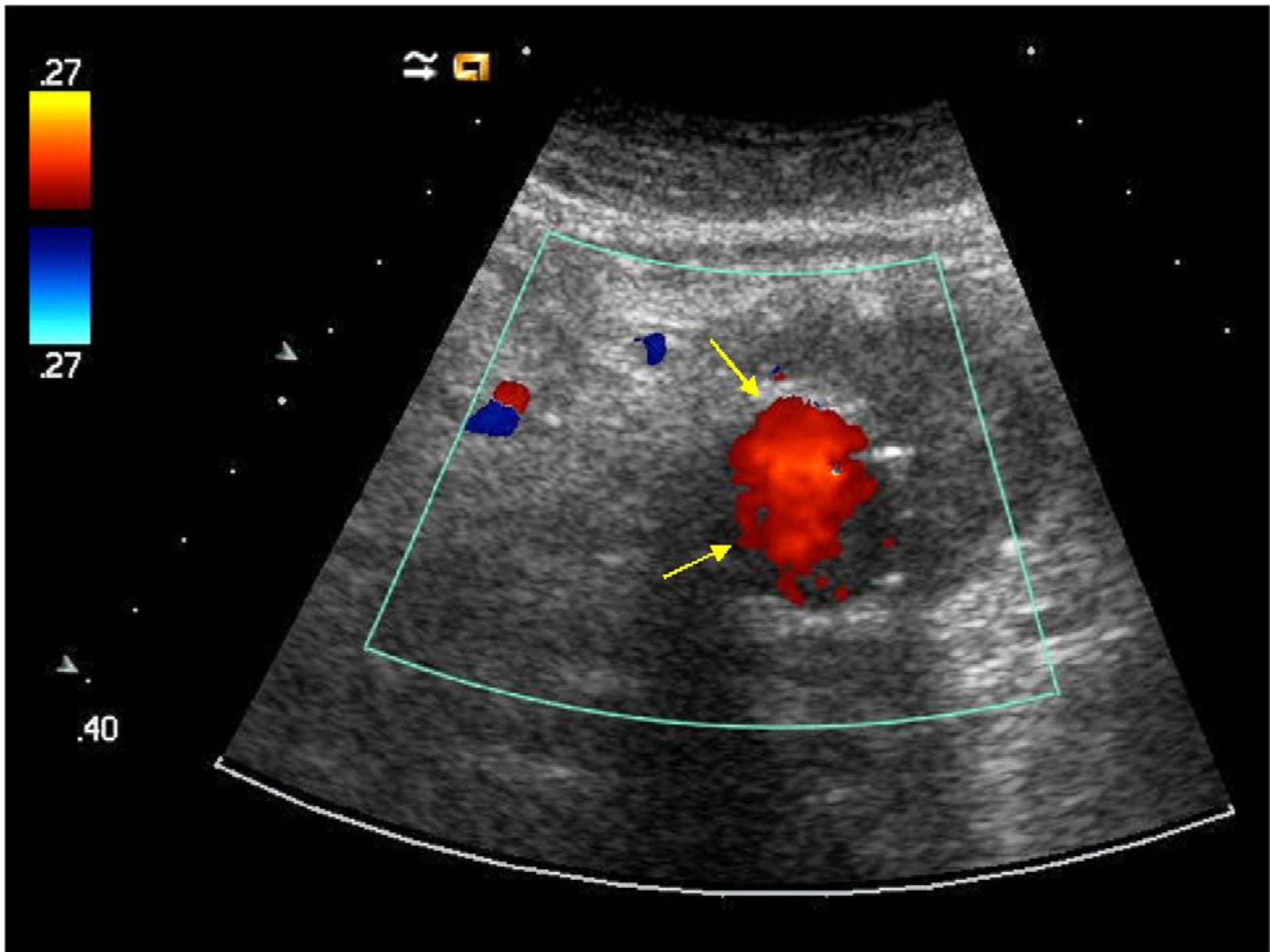
Type II endoleak detected by CDU (red arrow).  
The yellow arrows mark the stentgraft.



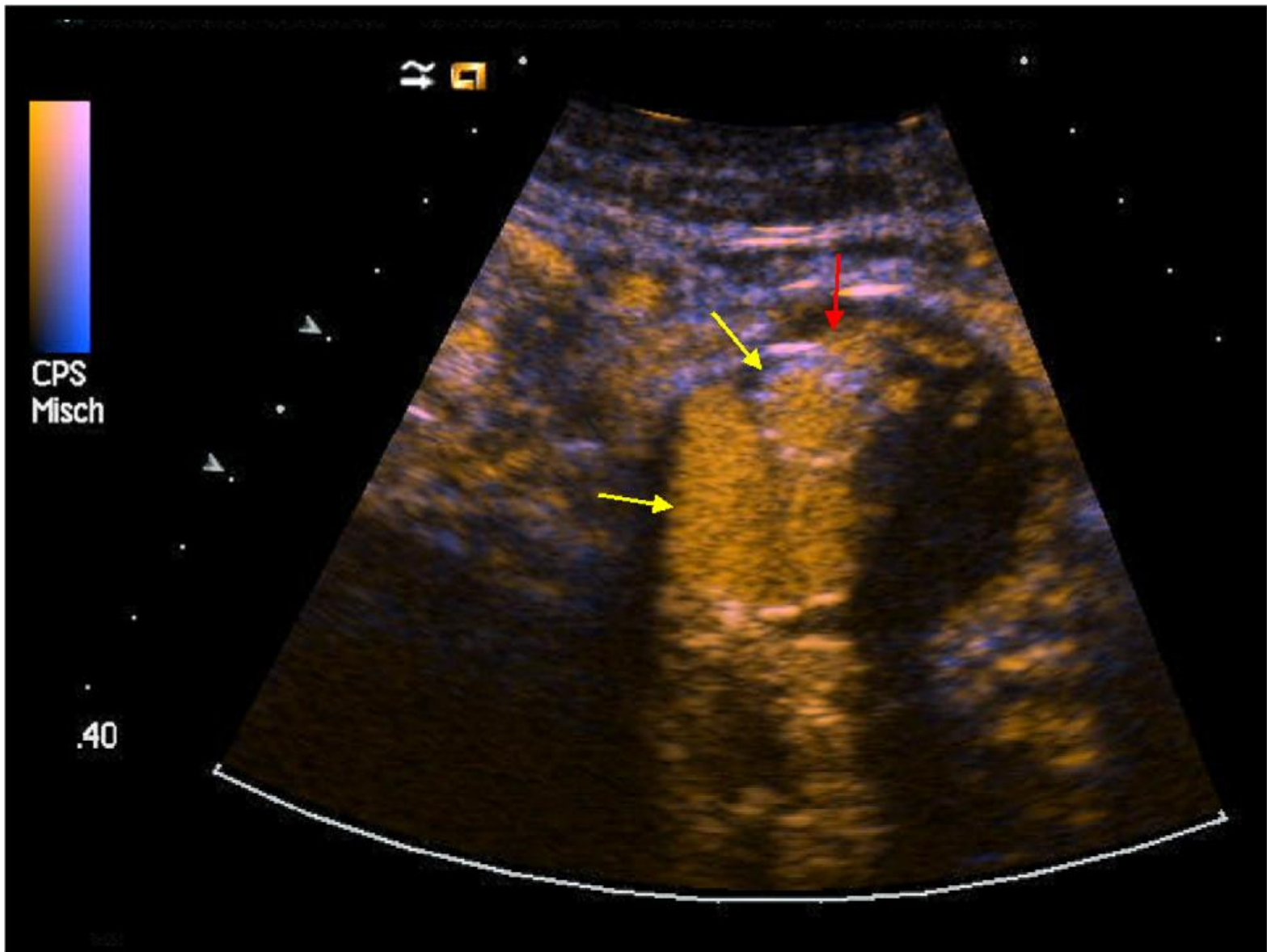
The type II endoleak is confirmed by CEUS (red arrow).  
The well-perfused stentgraft is delineated by the (yellow) arrows.



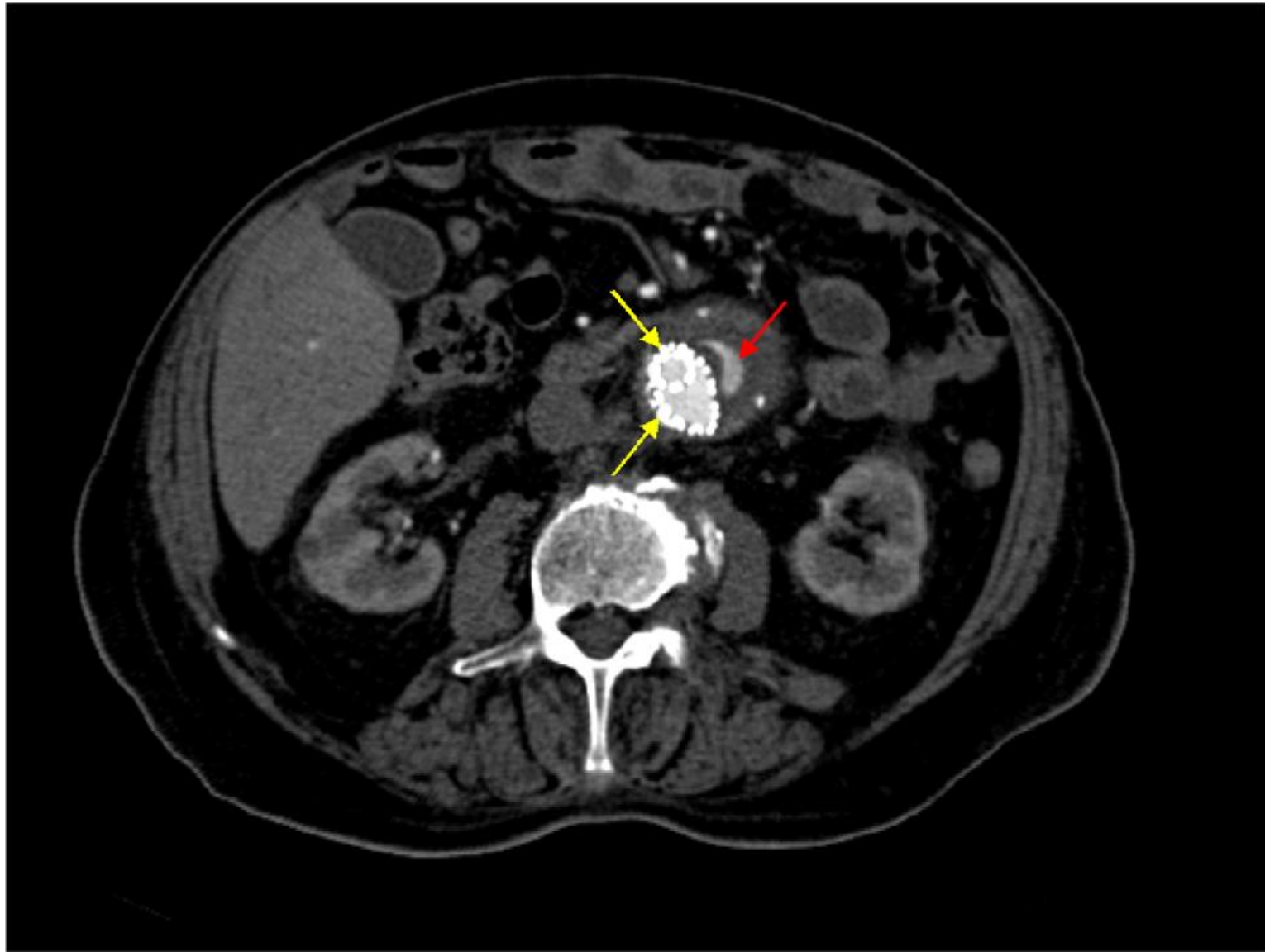
MS-CT demonstration of the type II endoleak (red arrow) and the contrast enhanced stentgraft (yellow arrows).



CDU does not show any presence of an endoleak.  
The bright (yellow) arrows mark the stentgraft.

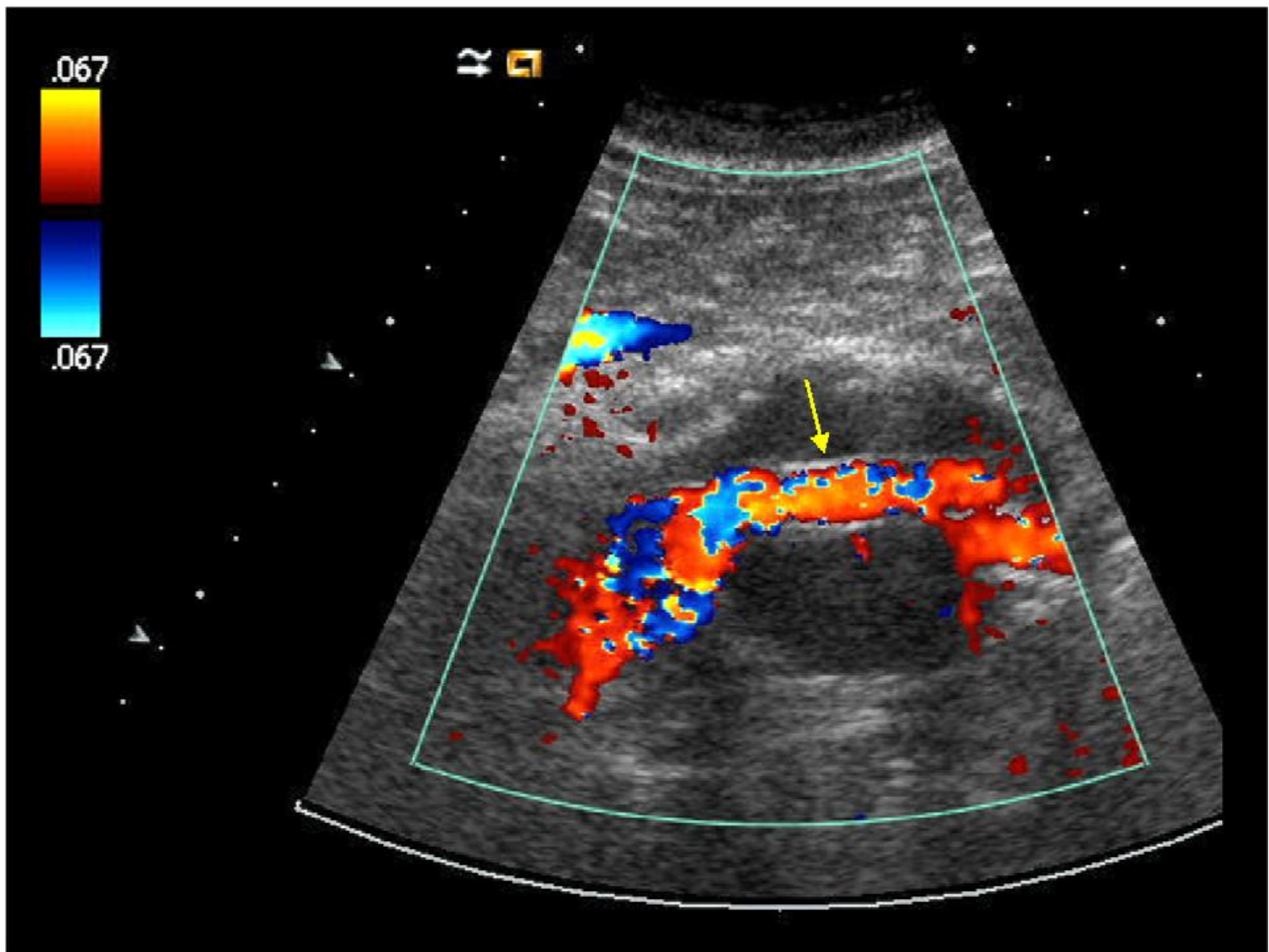


CEUS demonstrates a type III endoleak (red arrow) and the perfused stentgraft (yellow arrows).

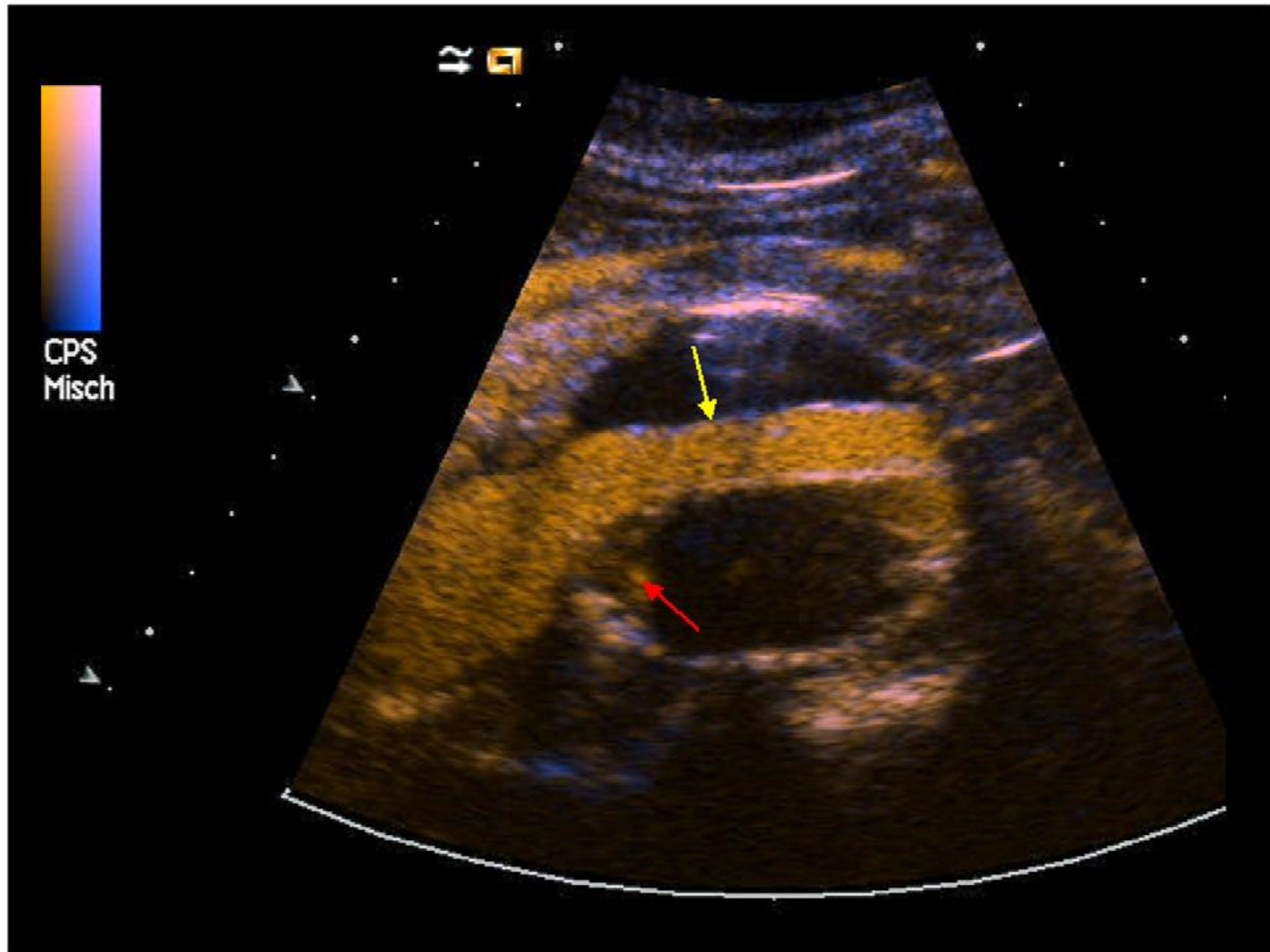


MS-CT confirms the finding of CEUS by showing a type III endoleak (red arrow). The stentgraft is marked by (yellow) arrows.

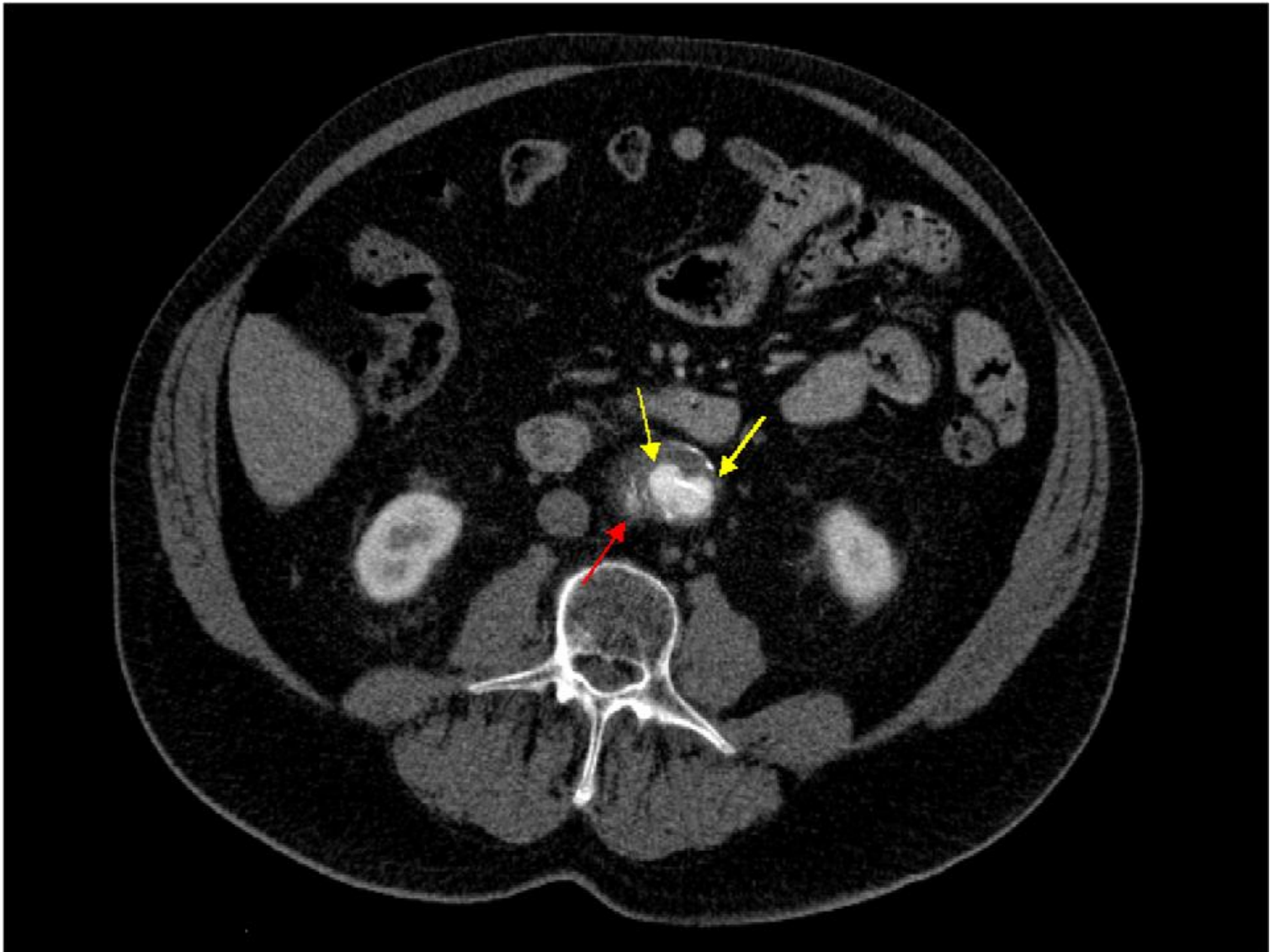




In CDU no endoleak is seen. There is perfusion of the stentgraft (yellow arrows).

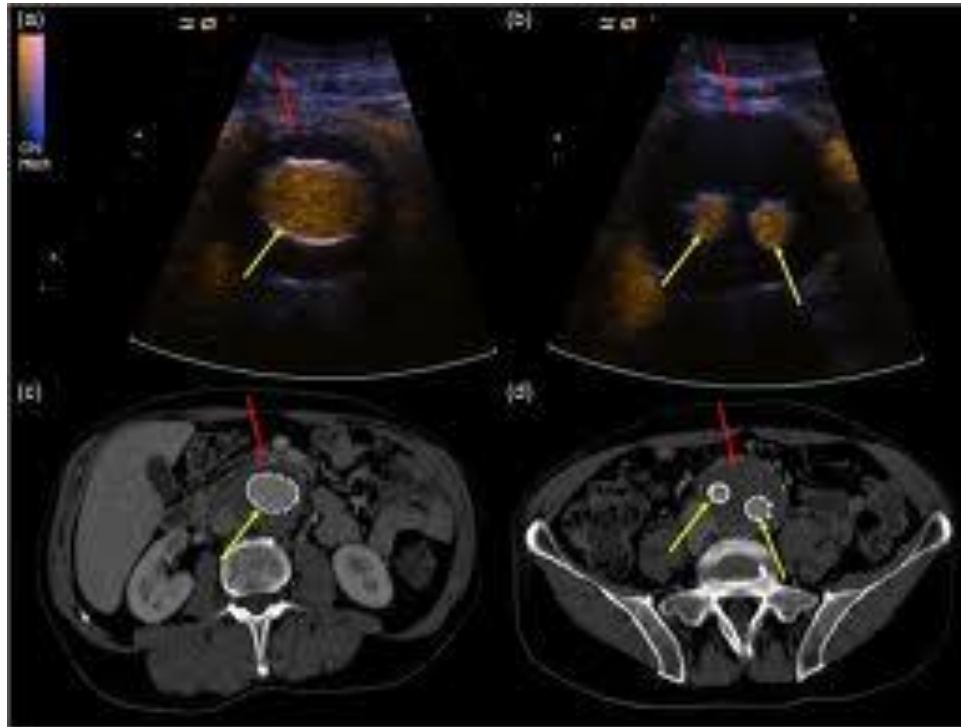


CEUS demonstrates a type IA endoleak (red arrow) and the well-perfused stentgraft (yellow arrows).



MS-CT confirms the type IA endoleak (red arrow) in the follow-up. The stentgraft is indicated by the bright (yellow) arrows.

CEUS **has a number of advantages** to conventional color duplex ultrasound.



**It has high spatial resolution**

**It can simultaneously detect high and slow velocities**

**It can assess blood flow and tissue**

**It doesn't use X-ray**

Nonetheless, CEUS **has some limitations.**

Obesity and bowel gas can interfere with US scanning,  
and **patient compliance is always required.**

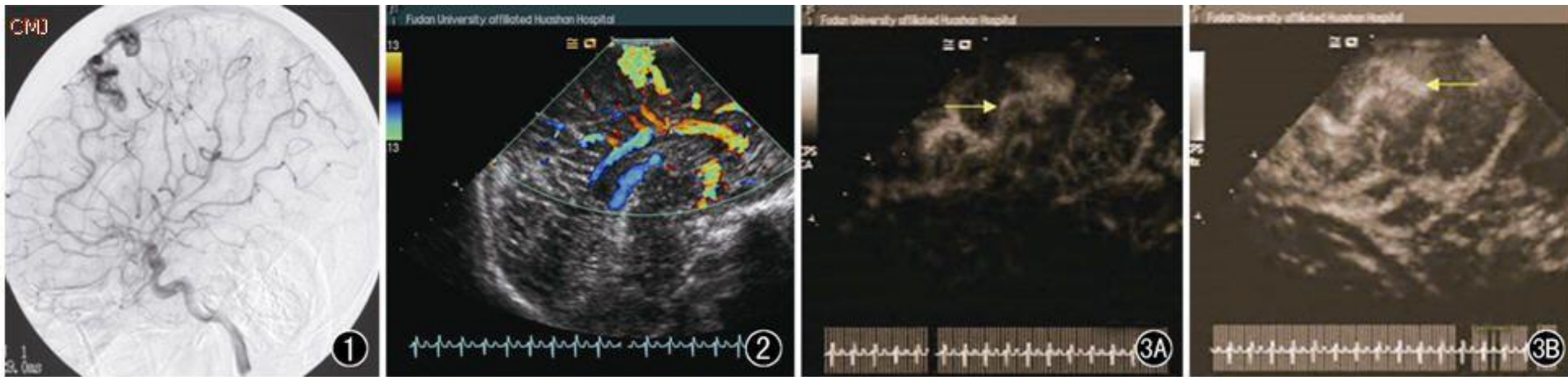
The equipment, including the contrast agent, is expensive,  
**highly specific and not yet widely available.**

The examination is operator-dependent and requires  
**specific skills and training.**

Finally, CEUS may seem very sensitive in the depiction of  
per graft flow but is not appropriate for the evaluation of  
other factors such as **graft anchorage and integrity**  
and **changes in aneurysm morphology,**  
for which CTA is the modality of choice

# Other indications for CEUS

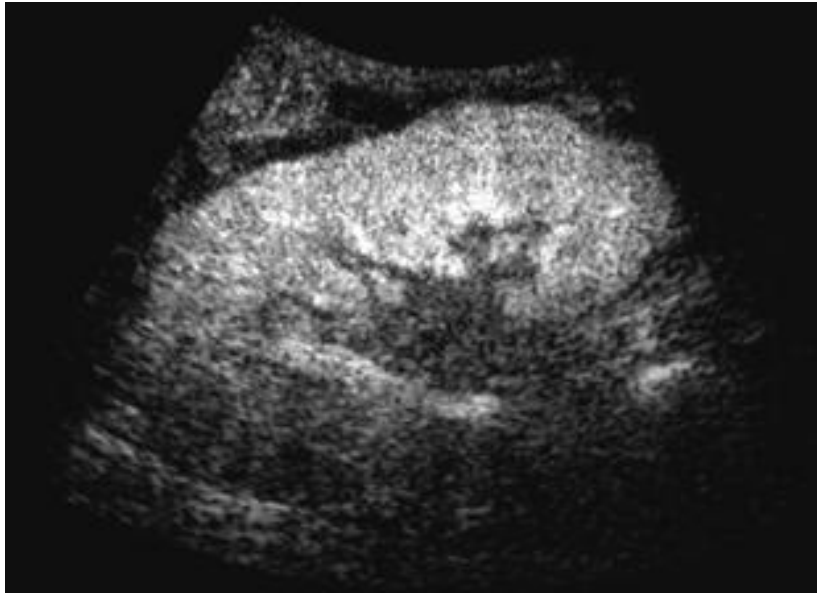
Color-coded transcranial Doppler



**Diagnostic value of contrast-enhanced intraoperative Doppler sonography for cerebral arteriovenous malformations compared with angiography . [Chinese Medical Journal 2010;123\(20\):2812-2815](#)**

## Other indications for CEUS

## Kidney



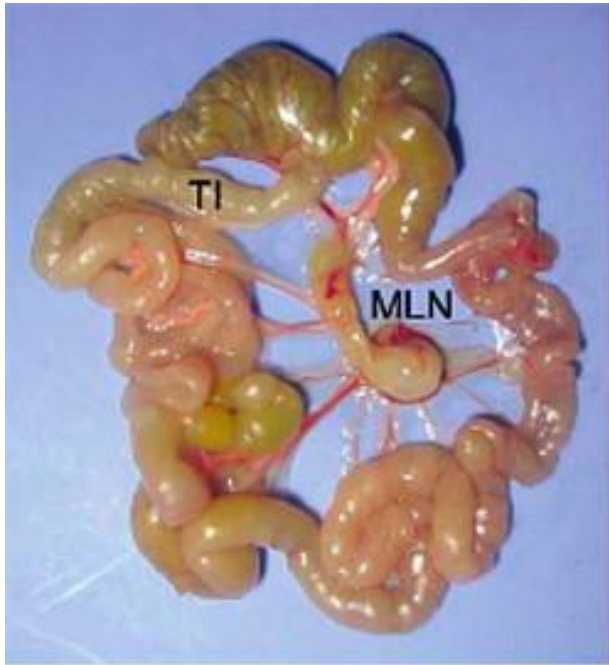
Perfusion study of transplanted kidney



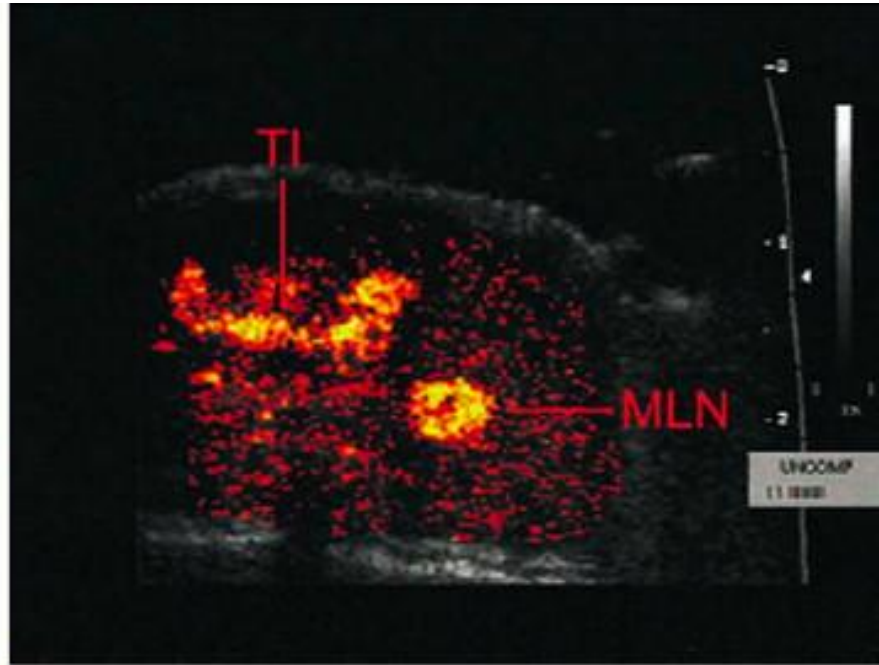
Detection of kidney masses

## Other indications for CEUS

Contrast enhanced ultrasound may be used also in oncology to identify neo-vascularized areas

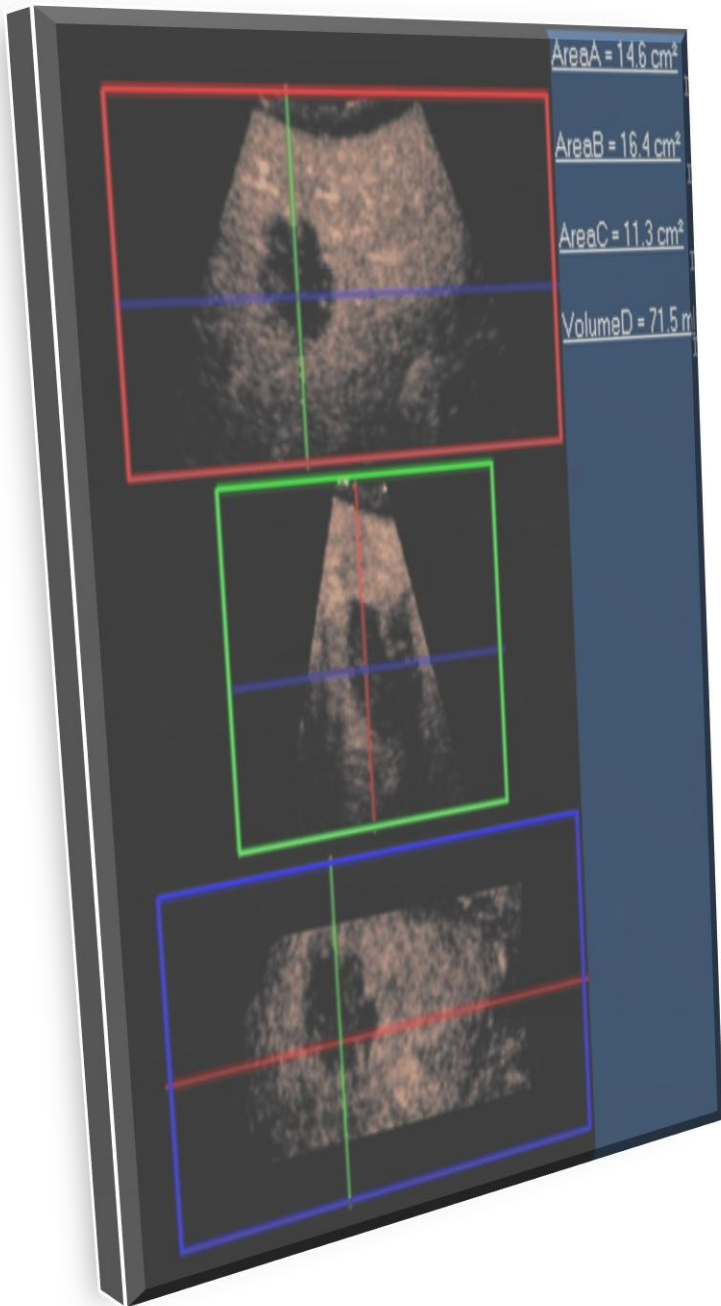


(a)



(b)





## The future

3D Contrast enhanced ultrasound  
for a better definition  
of the structures in study

Microbubbles have been proposed as a new vehicle for carrying drugs and genes

Shih-Tsung Kang, Chih-Kuang Yeh

**Ultrasound Microbubble Contrast Agents for Diagnostic and Therapeutic Applications: Current Status and Future Design**  
Chang Gung Med J Vol. 35 No. 2 March-April 2012

**Lipophilic chemotherapeutic drugs** can be incorporated into the lipid layer of microbubbles.

**Genetic materials** (e.g., plasmid DNA) can be electrostatically attached to the surface of positively charged microbubbles

The payload of drugs or DNA can be locally released by the destruction of microbubbles within the ultrasound-treated region, with a simultaneous increase in the permeability of the tissues.

This suggests the potential of microbubble technology in aiding drug or gene therapy, **with reduced side effects to normal tissues.**

# Arrivederci

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