

Imagerie non linéaire & Produits de contraste

Ayache BOUAKAZ, PhD

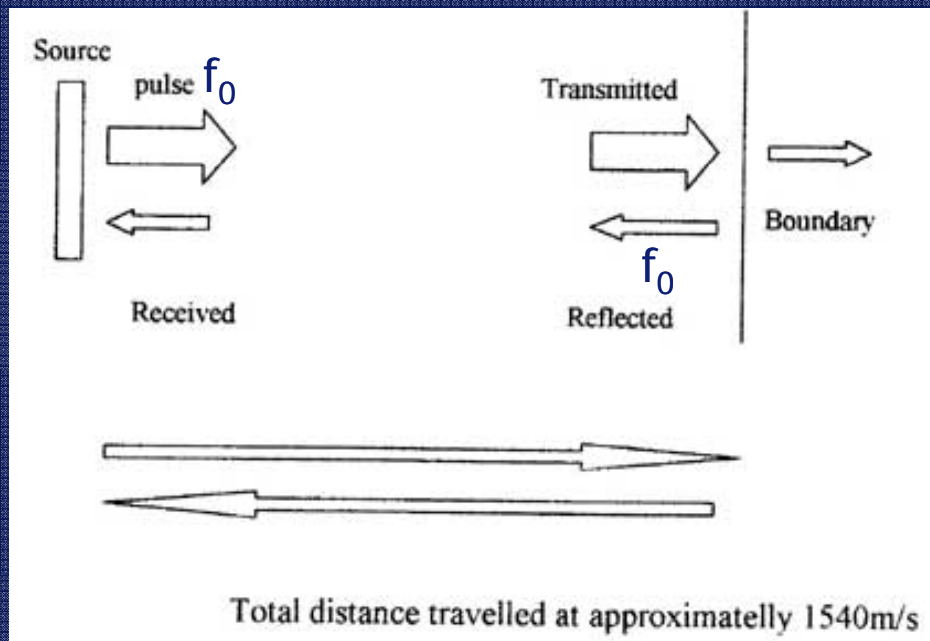
*UMR Imagerie et Cerveau
INSERM U930, Tours, France*

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 - 1. Tissulaire
 - 2. De Contraste
- II. Agents de contraste pour ultrasons: définitions
 - 1. Interaction bulles-Ultrasons
 - 2. Imagerie harmonique de contraste
- III. Imagerie harmonique tissulaire
- IV. Bulles et ultrasons en thérapie

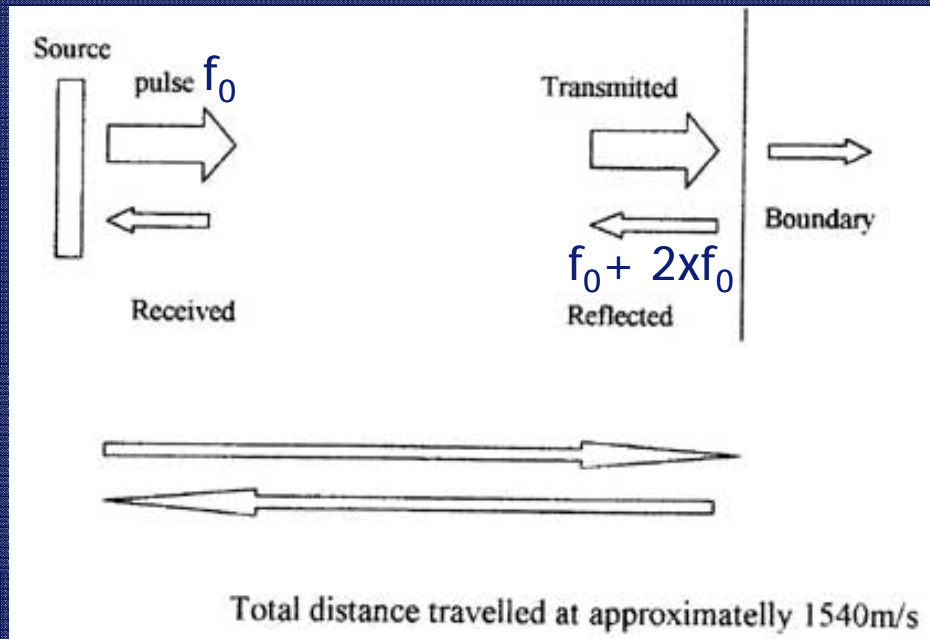
Formation de l'image et Imagerie conventionnelle (fondamentale)

- ➔ Impulsions ultrasonores émises à la fréquence de la sonde (f_0)
- ➔ Echos réfléchis à la fréquence (f_0)
- ➔ Image reconstruite à la fréquence (f_0)



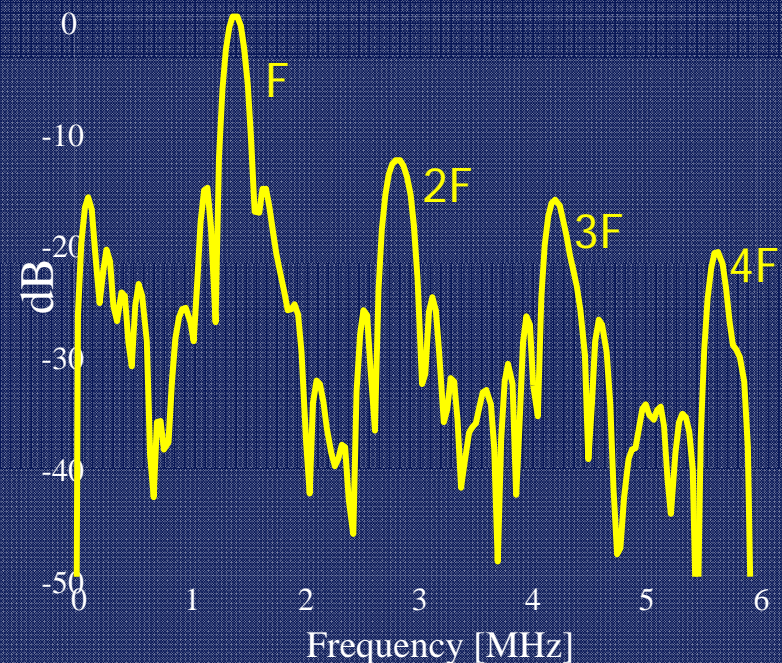
Formation de l'image et Imagerie harmonique (non linéaire)

- ➡ Impulsions ultrasonores émises à la fréquence de la sonde (f_0)
- ➡ Echos réfléchis sont composés de deux fréquences : $f_0 + 2xf_0$
- ➡ Image reconstruite à la 2 fois la fréquence émise : $2xf_0$



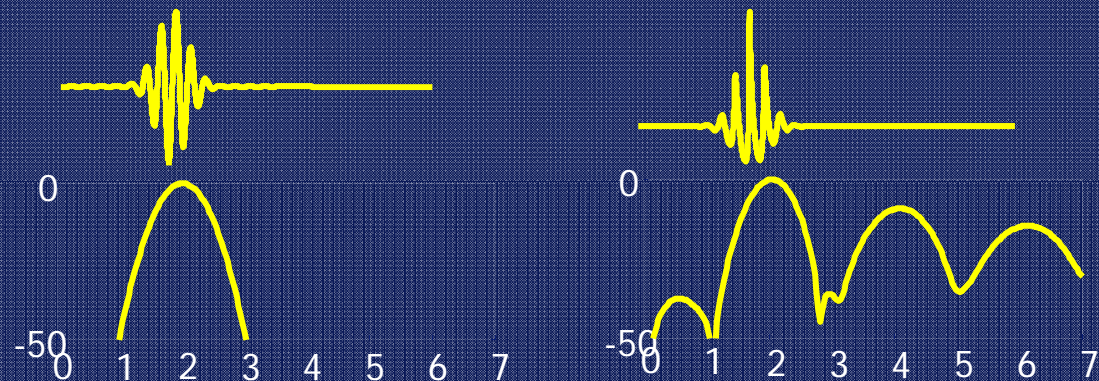
Formes de l'imagerie harmonique

➔ **Imagerie harmonique de contraste:** Les microbulles réémettent (réflexion) de l'énergie aux fréquences harmoniques (non linéaires), à des fréquences multiples de la fréquence d'émission.



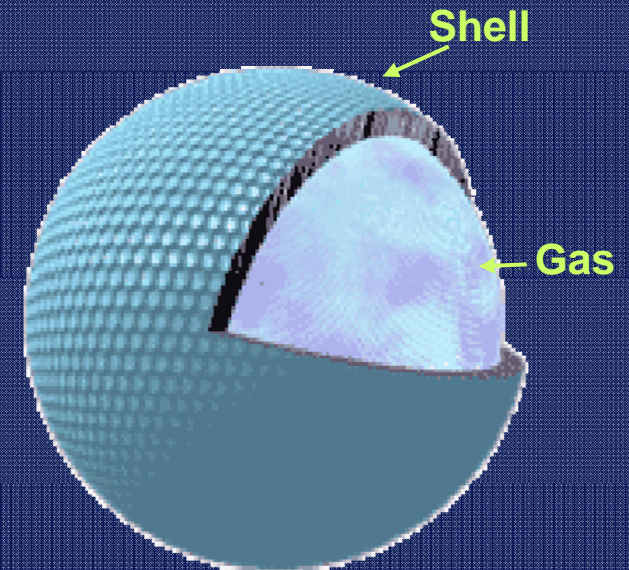
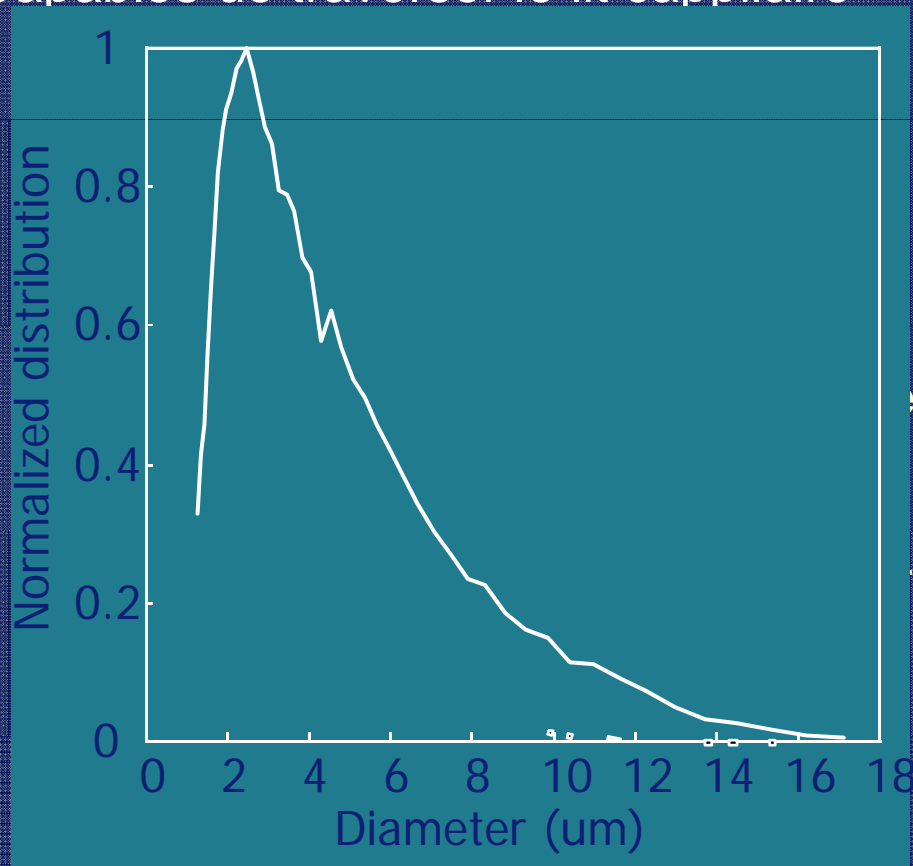
Formes de l'imagerie harmonique

- ➔ **Imagerie harmonique de contraste:** Les microbulles re-émettent (réflexion) de l'énergie aux fréquences harmoniques (non linéaires), à des fréquences multiples de la fréquence d'émission.
- ➔ **Imagerie harmonique tissulaire:** Des composantes fréquentielles harmoniques (non linéaires) sont générées lors de la propagation dans les tissus.



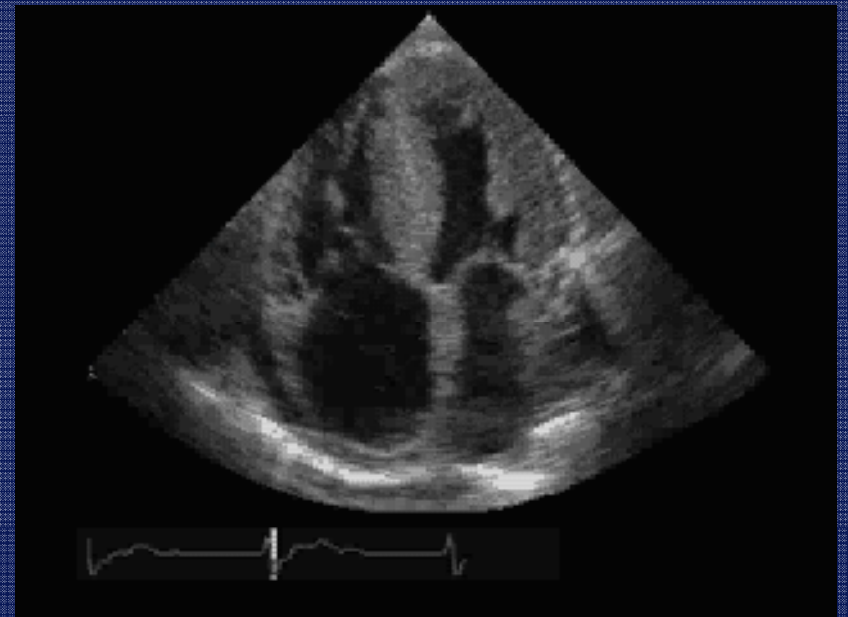
Agents de contraste US

- Suspension de microbulles de gaz pour injection intraveineuse.
- Capables de traverser le lit capillaire



Pourquoi un agent de contraste US?

- Le sang réfléchit très peu les ultrasons
- Les vaisseaux sanguins ont un fort coefficient de réflexion
- Aux fréquences ultrasonores, les petits vaisseaux (<2 mm) ne sont pas visibles



Pourquoi un agent de contraste US?

Pour amplifier la réflexion de la circulation sanguine

- L'écho US (image) est basé sur la différence d'impédances acoustiques
- L'amplitude de l'écho est proportionnelle à la différence d'impédances acoustiques
 - $Z = \rho c$; ρ =densité, c =vitesse de propagation
 - $Z_{\text{tissus}} \approx 1.55 \times 10^6$ [kg.m⁻² s⁻¹]
 - $Z_{\text{air}} \approx 4 \times 10^2$ [kg.m⁻² s⁻¹]
- Air-eau (tissus) est le réflecteur idéal des ultrasons

List of US contrast agents

Manufacturer	Name	Gas	Shell	Status
Acusphere	AI-700	Decafluorobutane	Polymer	Pre-clinical
Alliance/Schering	Imavist	Perfluorohexane	Surfactant	Approved
Bracco	Sonovue	Sulfurhexafluoride	Phospholipid	Available EU
Bracco	BR14	Perfluorocarbon	Phospholipid	Clinical
Byk-Gulden	BY963	Air	Lipid	Research only
Dupont-/(Bristol-Myers)	Definity	Octafluoropropane	Liposome	Available USA/CA
IMARx	Aerosomes	Perfluoropropane	Lipid bilayer	Clinical
Mallinckrodt	Albunex	Air	Albumin	Available
Mallinckrodt	Optison	Octafluoropropane	Albumin	Available
Nycomed	Sonazoid	Perfluorocarbon	Lipid	Late clinical
Point Biomedical	BiSphere	Air	Polymer bilayer	Late clinical
Porter	PESDA	Perfluorocarbon	Albumin	Research
Quadrant	Quantison	Air	Albumin	Clinical/hold
Schering	Echovist	Air	No	Available
Schering	Levovist	Air	Fatty acid	Available
Schering	Sonavist	Air	Polymer	Clinical
Sonus	Echogen	Dodecafluoropentane	Surfactant	Withdrawn 2000

List of US contrast agents

Manufacturer	Name	Gas	Shell	Status
Bracco	Sonovue	Sulfurhexafluoride	Phospholipid	Available EU
Dupont-/(Bristol-Myers)	Definity/Luminity	Octafluoropropane	Liposome	Available USA/CA
Mallinckrodt	Optison	Octafluoropropane	Albumin	Available
Nycomed	Sonazoid	Perfluorocarbon	Lipid	Japan 2007
			Fatty acid	Available

- Sonovue Europe 2001
- Definity USA, Australia
- Sonazoid Japan 2007

Interaction bulle-Ultrasons

MODELE LINEAIRE

Réflexion passive

$$P_d = I_i \sigma_p \quad \Sigma_p = \text{Section efficace de diffusion}$$

$$\Sigma_p = \frac{4\pi}{9} k^4 R^6 \left[\left(\frac{\kappa_p - \kappa}{\kappa} \right)^2 + \frac{1}{3} \left(\frac{3(\rho_p - \rho)}{2\rho_p + \rho} \right)^2 \right]$$

$$\Sigma_p \propto f^4; \quad \Sigma_p \propto R^6$$

$$(R = 1.5 \mu\text{m}, f = 3 \text{ MHz})$$

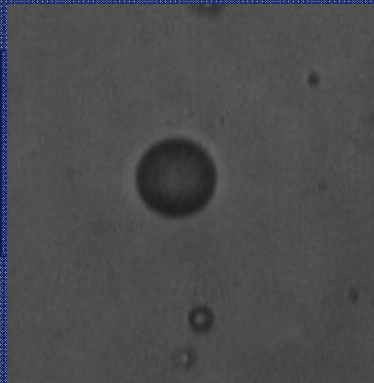
	particule air	Particule métal
$\Sigma_p (\mu\text{m}^2)$	113	$6 \cdot 10^{-7}$

MODELE LINEAIRE

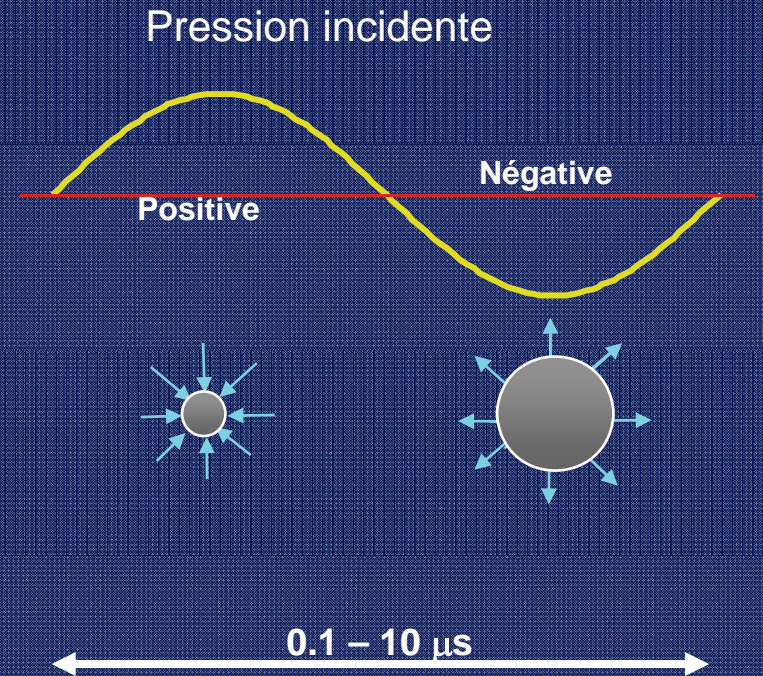
Réflexion active: vibration & résonance

La bulle agit comme un oscillateur harmonique

US 2MHz ==> 2 millions oscillations / sec



La taille change avec la pression

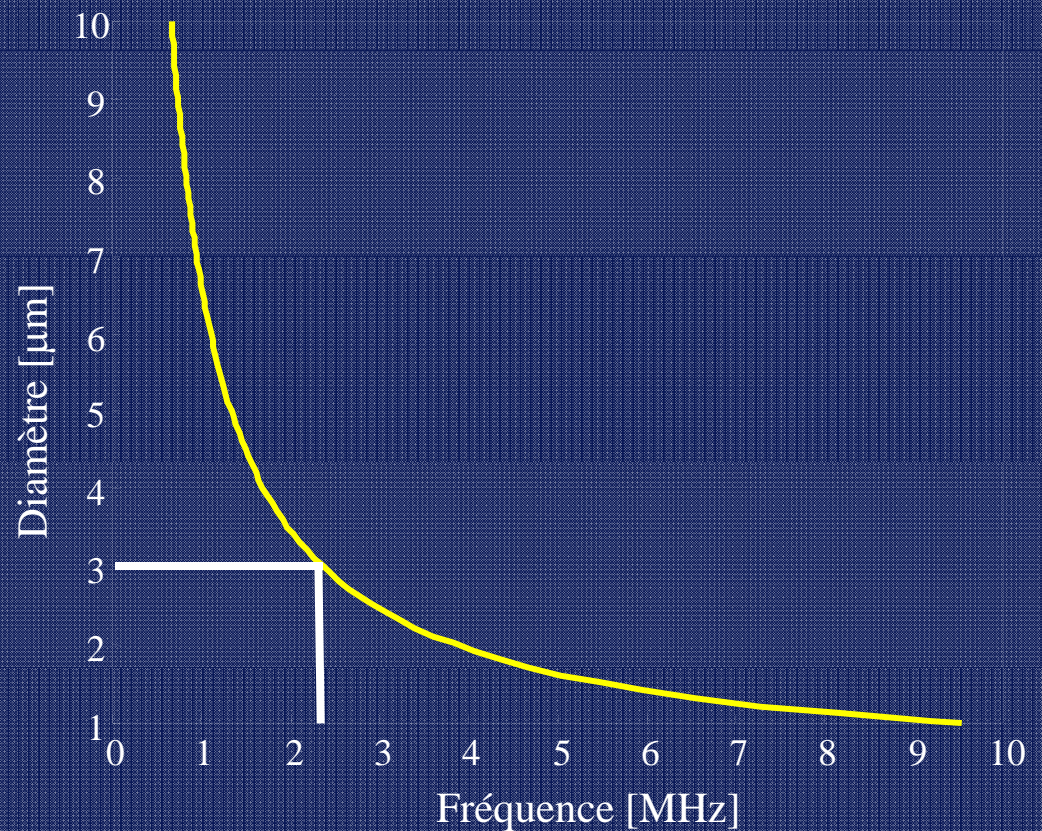


Fréquence de Résonance

Bulle nue

$$f_o = \frac{1}{2\pi R} \sqrt{\frac{3 \kappa P_o}{\rho}}$$

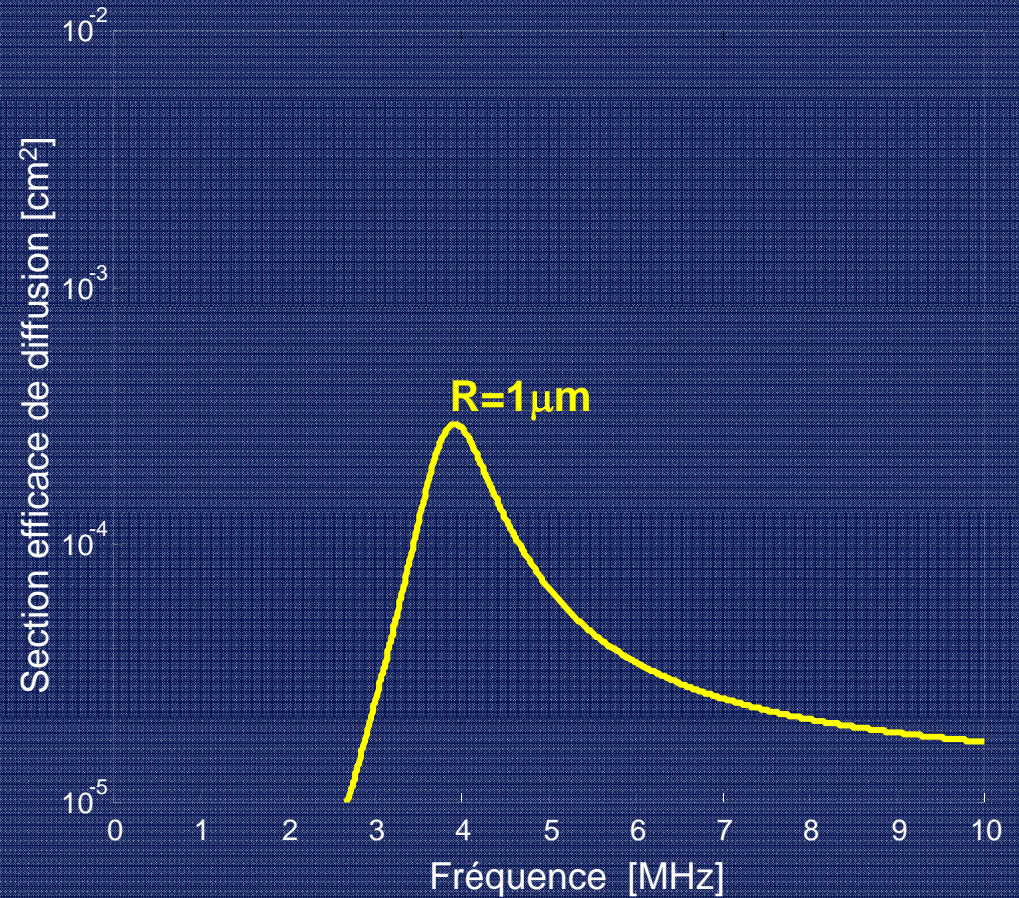
$\Phi = 3 \mu\text{m}$, $f_r = 2.5\text{MHz}$



Efficacité en réflexion

Section efficace de diffusion

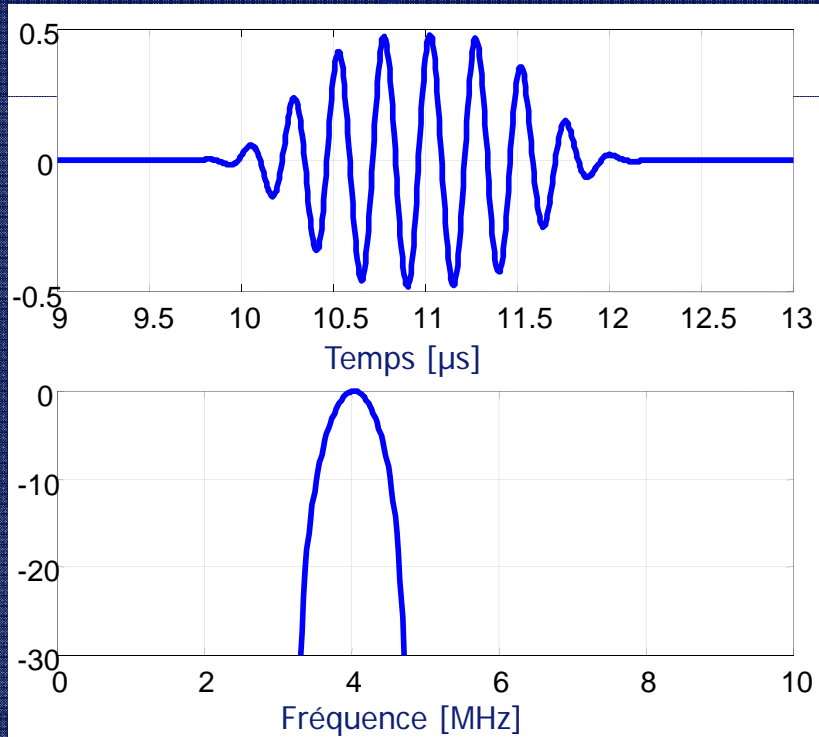
$$\Sigma_p = \frac{P_s}{I_i} = \frac{4\pi R^2}{\left(\frac{f_r^2}{f^2} - 1\right)^2 + \delta^2}$$



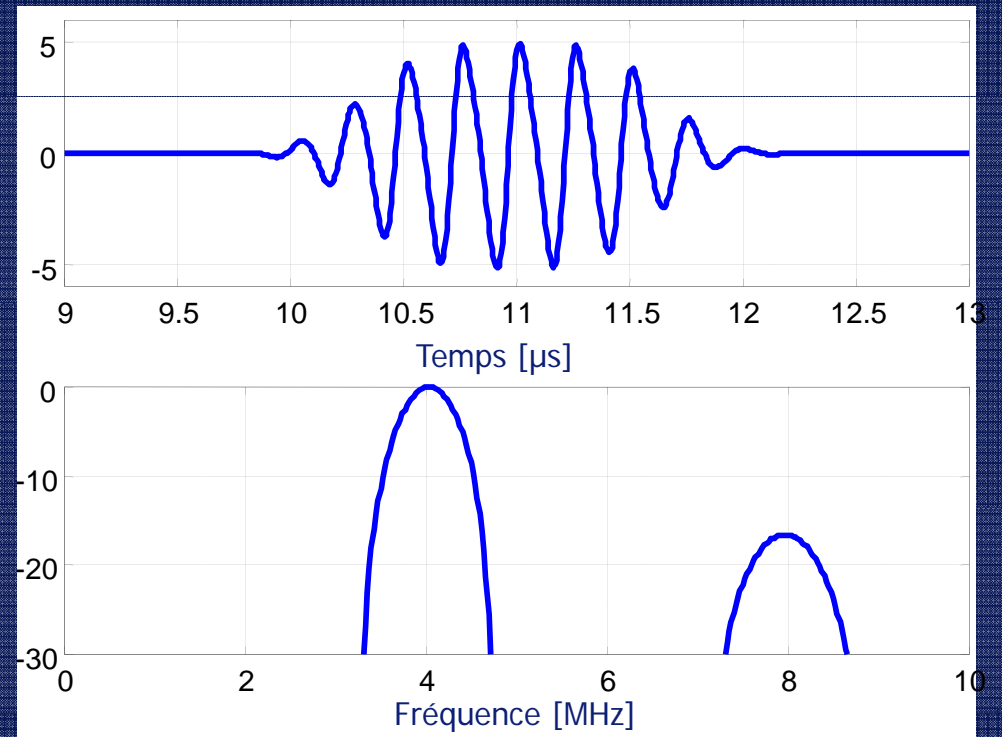
Modèle non linéaire et Harmoniques

$r=1\mu\text{m}$; $f=f_0$ [4MHz]

Amp=5kPa

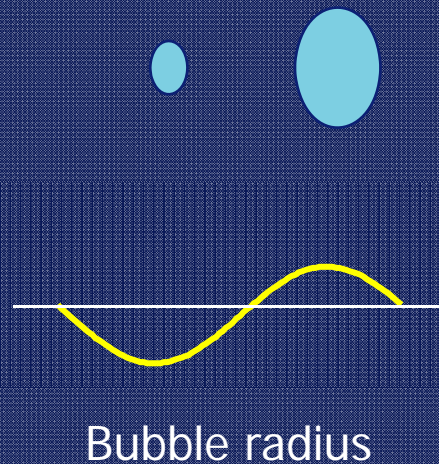
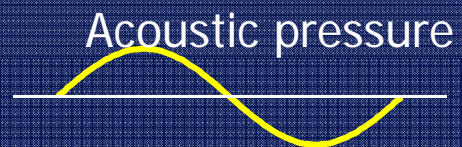


Amp=50kPa

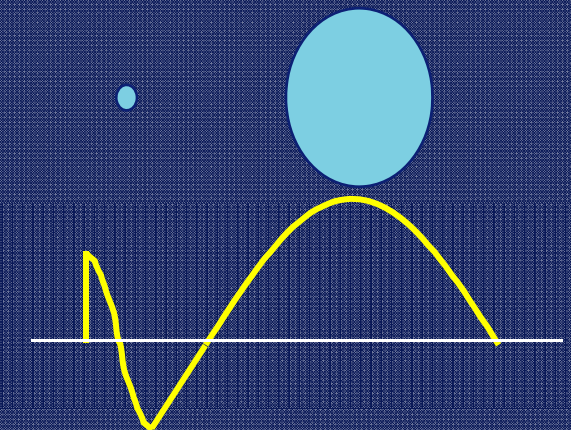
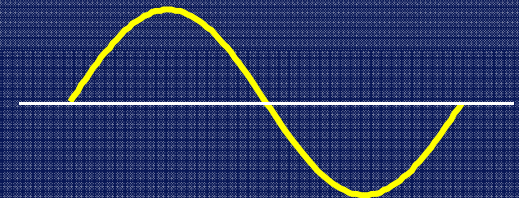


Harmoniques

Linear oscillation:
Fundamental imaging



Nonlinear oscillation
Harmonic imaging



Caractérisation optique: régime linéaire

US: $f=1.8\text{MHz}$, 50kPa ($\text{IM}<0.1$)

Optic: Frame rate 16MHz

Soft-shelled agent (Sonovue Bracco, Italy)

Soft-shelled agent

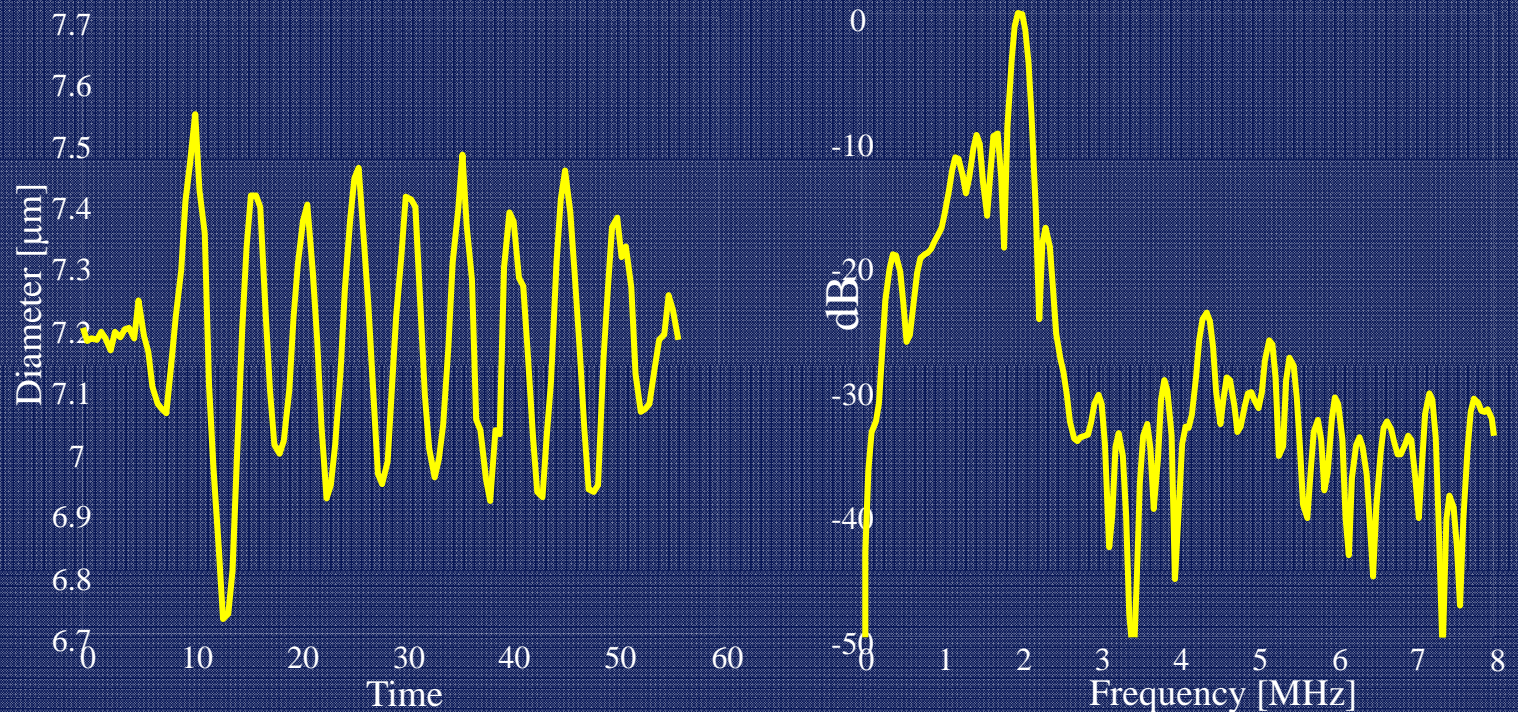


Caractérisation optique: régime linéaire

US: $f=1.8\text{MHz}$, 50kPa ($\text{IM}<0.1$)

Optic: Frame rate 16MHz

Soft-shelled agent (Sonovue Bracco, Italy)

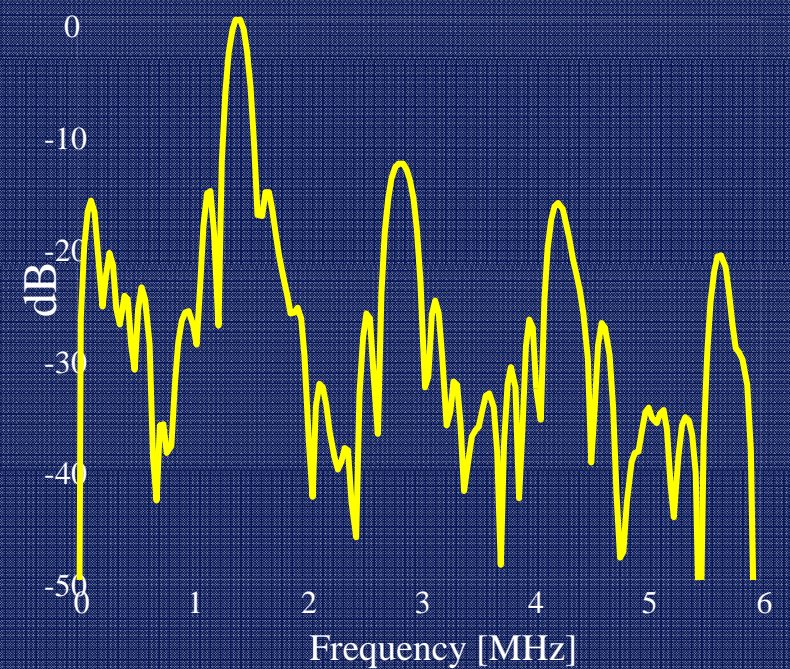
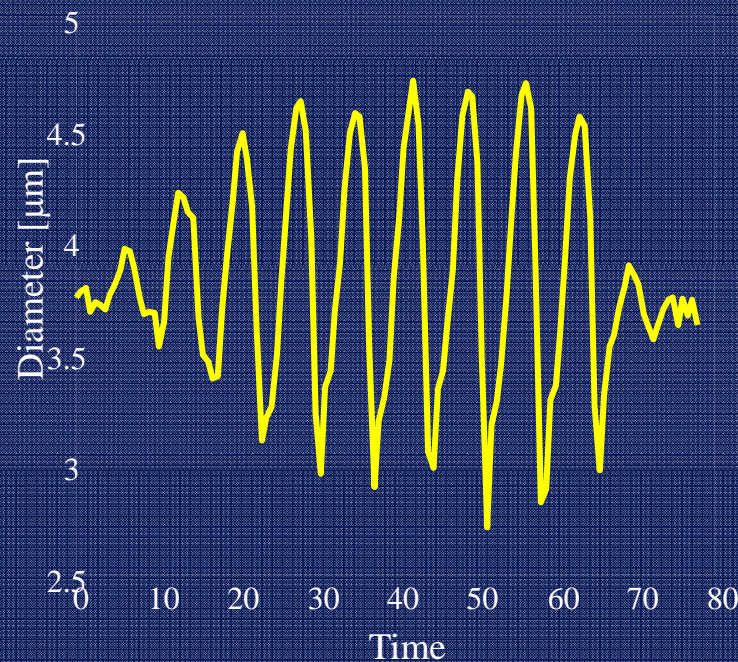
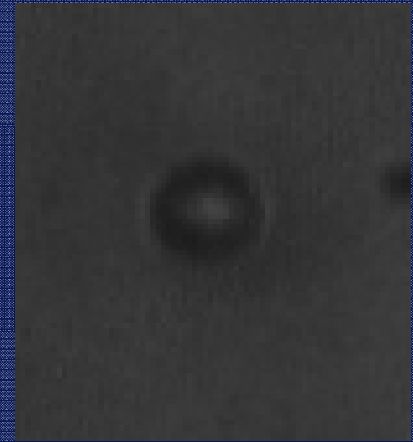


Caractérisation optique: régime non linéaire

US: $f=1\text{MHz}$, 200kPa ($\text{IM}=0.2$)

Optic: Frame rate 16MHz

Soft-shelled agent (Sonovue Bracco, Italy)



Caractérisation optique: destruction

US: $f=1.7\text{MHz}$, 1.7MPa ($MI=1.3$)

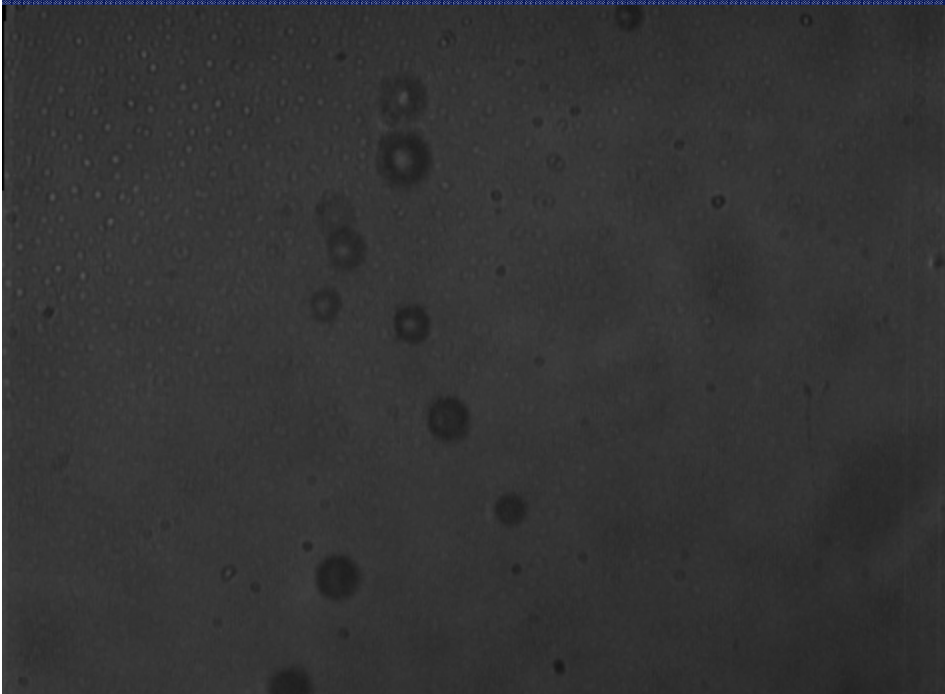
Optic: Frame rate 14.69MHz



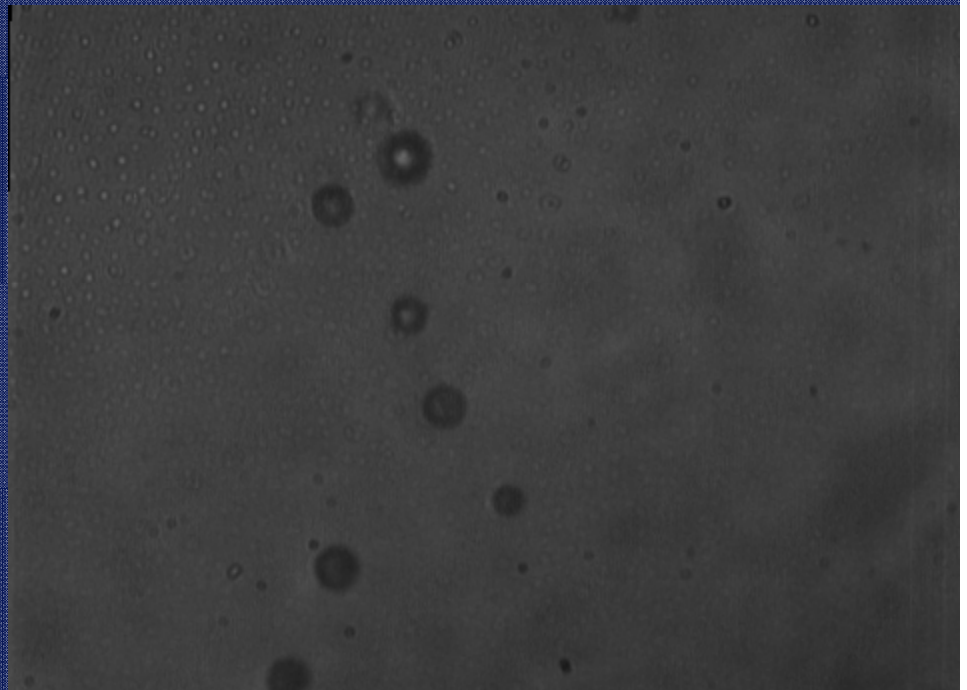
M1212

M1212 Hard shell bubble
1MPa (MI=0.8), $f=1.7\text{MHz}$, frame rate $\approx 15\text{Mfps}$

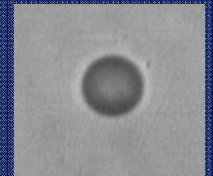
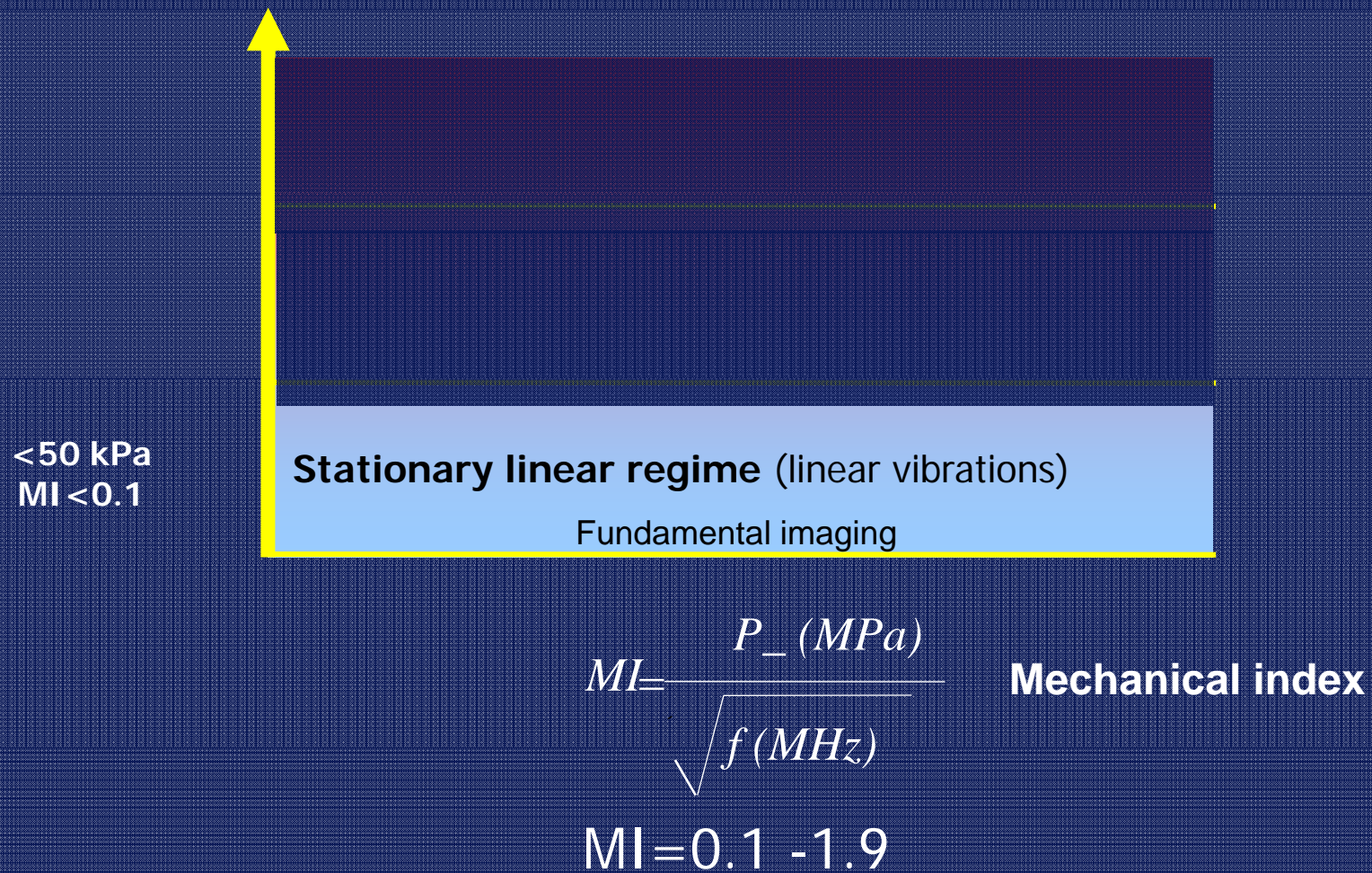
1st US pulse



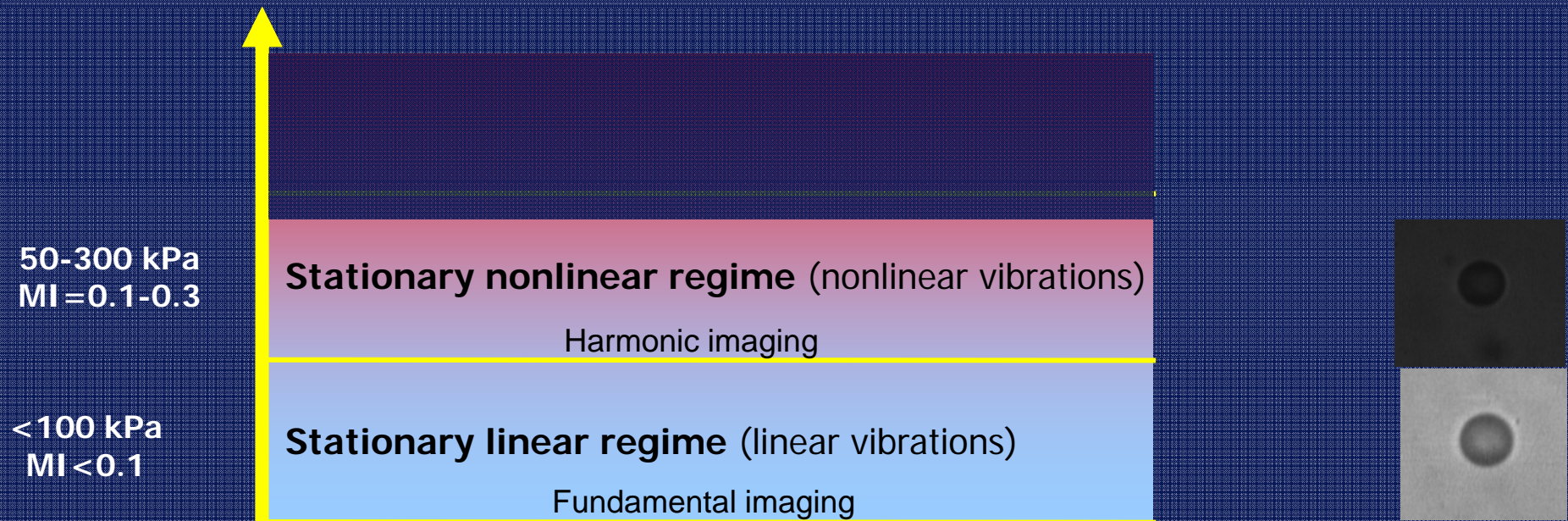
2nd US pulse (100ms later)



Microbubble – Ultrasound interaction



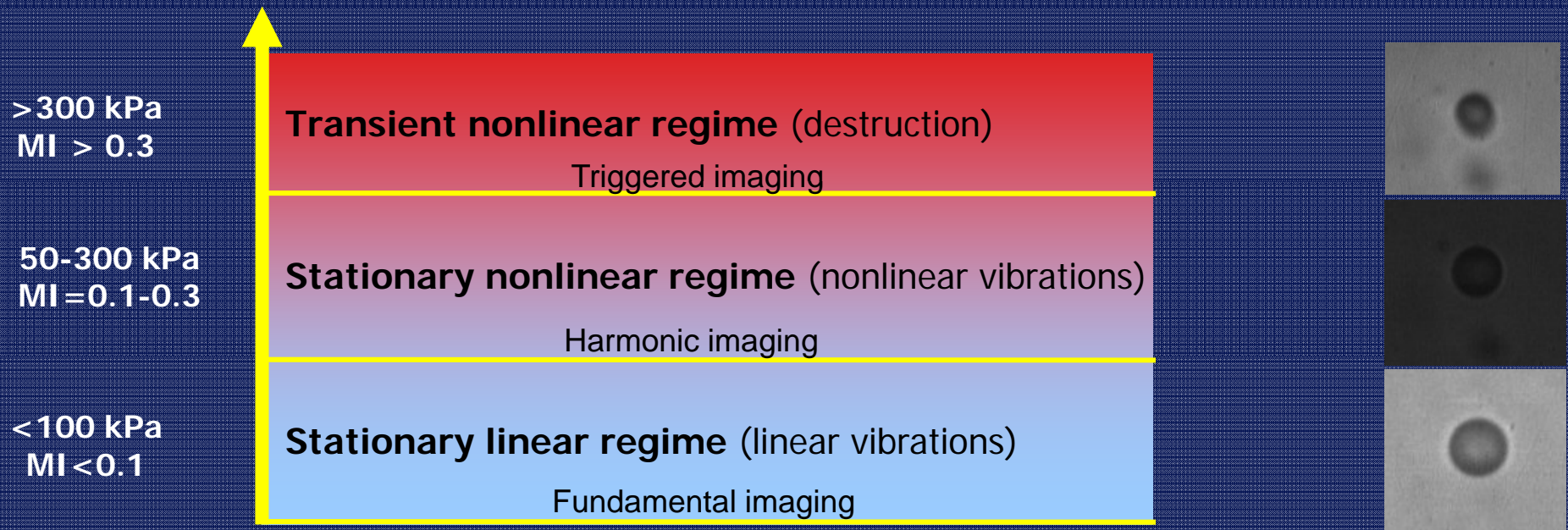
Microbubble – Ultrasound interaction



$$MI = \frac{P_- (MPa)}{\sqrt{f (MHz)}}$$

$$MI = 0.1 - 1.9$$

Microbubble – Ultrasound interaction



$$MI = \frac{P_{-} (MPa)}{\sqrt{f (MHz)}}$$

$$MI = 0.1 - 1.9$$

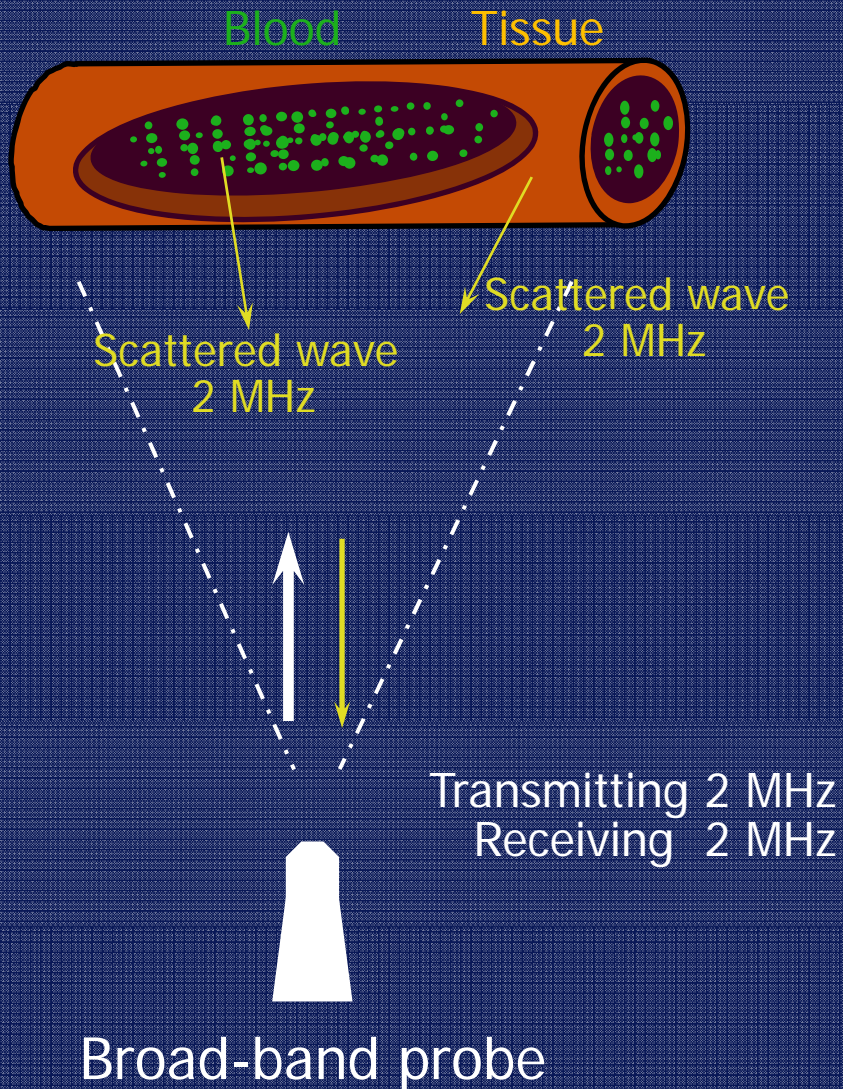
Contrast Imaging Methods

Méthodes d'imagerie de contraste

- Second harmonic imaging (filtering)
- Pulse inversion imaging (Pulse inversion Doppler) \Rightarrow ATL (Philips)
- Power modulation imaging \Rightarrow Agilent (Philips)
- Pulse inversion/power modulation
- Contrast Pulse Sequence (CPS) \Rightarrow Acuson (Siemens)

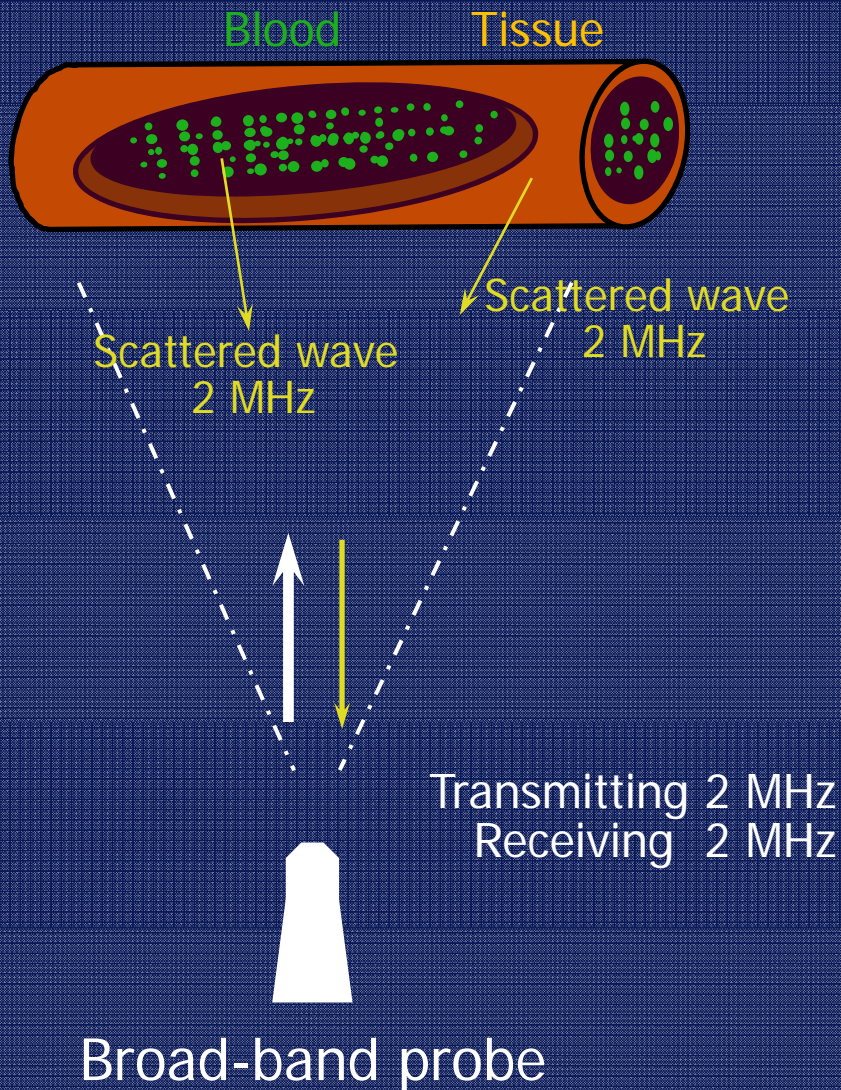
Principe de l'imagerie harmonique de contraste

Fundamental Imaging

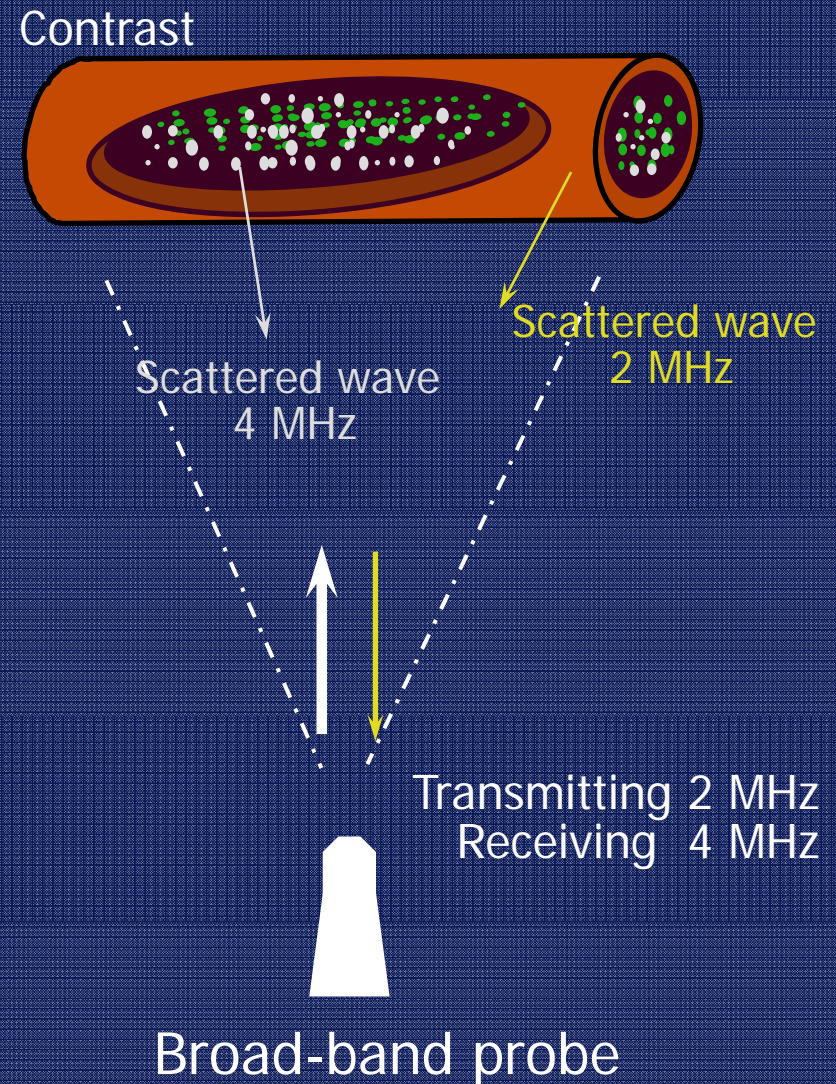


Principe de l'imagerie harmonique de contraste

Fundamental Imaging

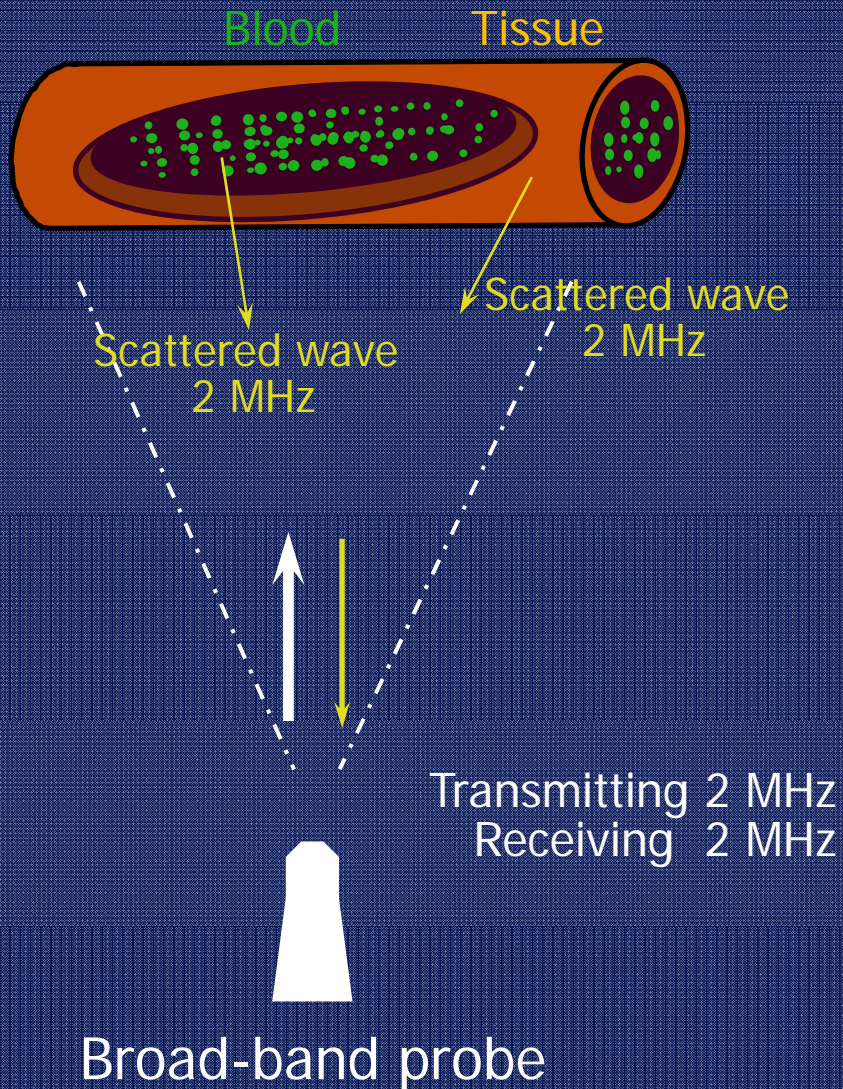


Contrast Harmonic Imaging



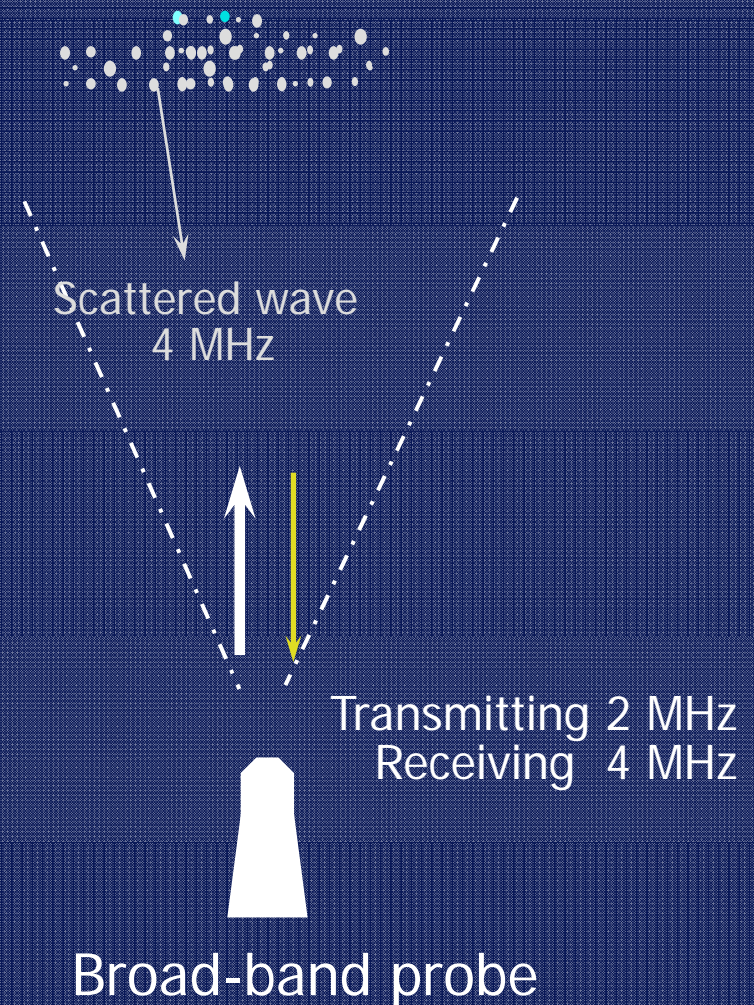
Principe de l'imagerie harmonique de contraste

Fundamental Imaging



Contrast Harmonic Imaging

Contrast

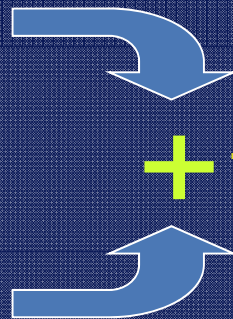
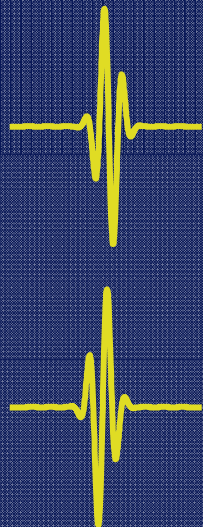
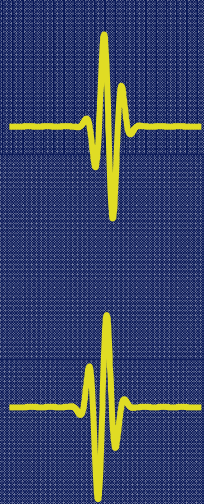


PULSE INVERSION

transmit

receive

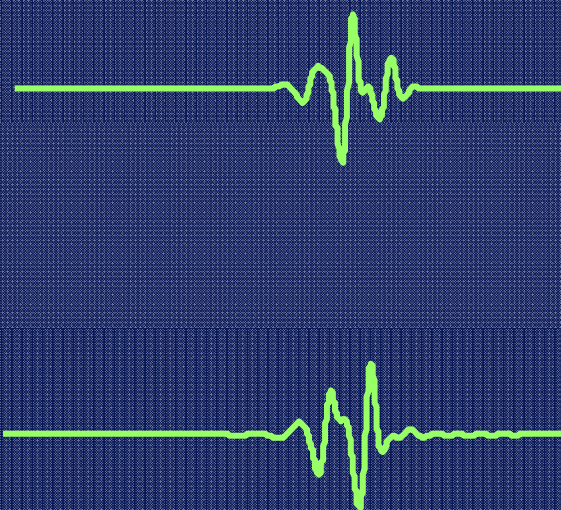
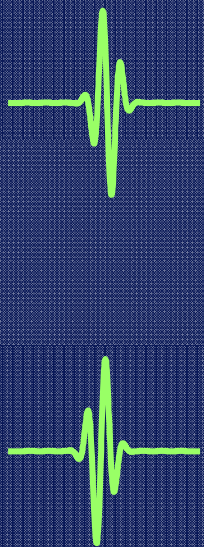
Display



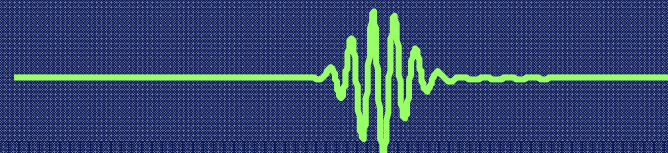
+



Linear reflector (tissue)



+



Nonlinear reflector (bubble)

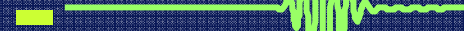
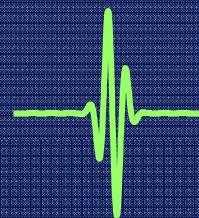
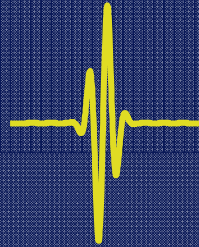
POWER MODULATION

transmit

receive

Scale x2

Display



Linear reflector (tissue)

Nonlinear reflector (bubble)

Microbulles en imagerie

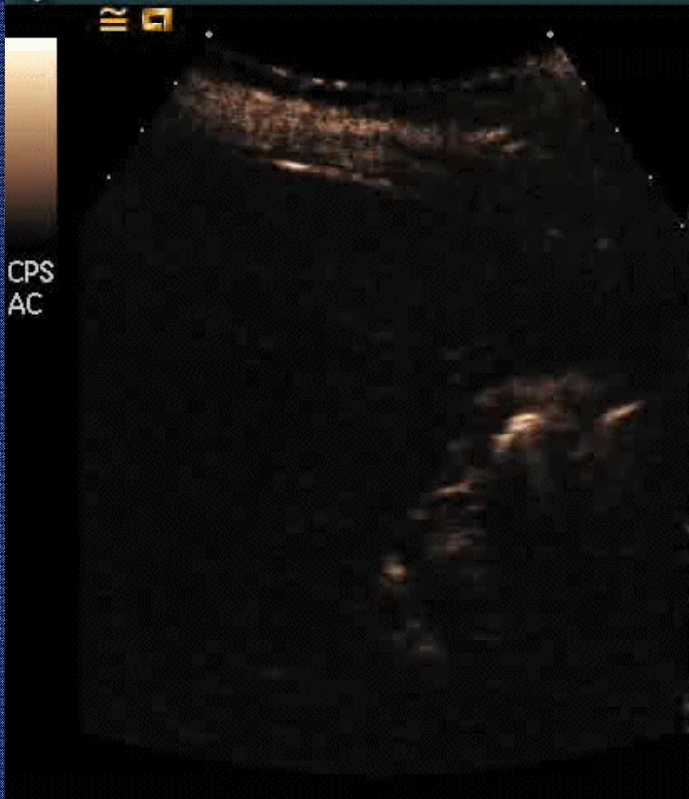
What do we need contrast agent for?

- “Boost” image quality
- Enhance diagnostic confidence
- Clinical applications
 - Estimation of myocardial perfusion
 - Detection and characterization of tumors
 - Amplification of Doppler signal

Exemples cliniques

Caractérisation des lésions focales hépatiques

Contraste Pulse Sequence (CPS)

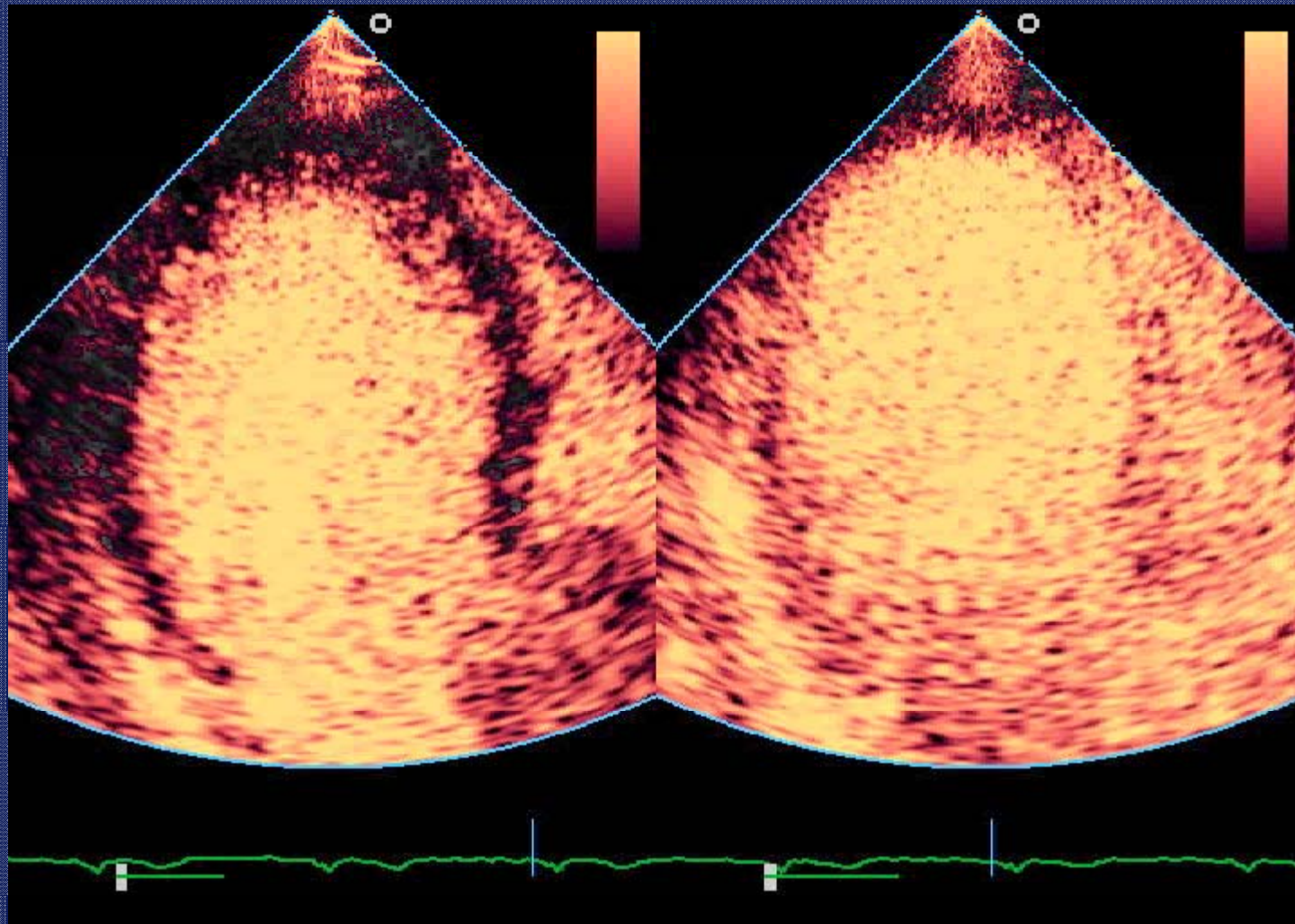


Tranquart, CHU Tours, France

- Chez tout patient avec une lésion hépatique de nature incertaine et particulièrement:
 - La découverte fortuite d'un nodule lors d'une échographie
 - La suspicion ou la découverte d'une lésion en cas d'hépatite chronique ou de cirrhose
 - La suspicion ou la découverte d'une lésion chez un patient porteur de cancer
 - L'absence de certitude diagnostique en TDM/IRM ou histol.

Exemples cliniques

Cardiologie: estimation de la perfusion myocardique



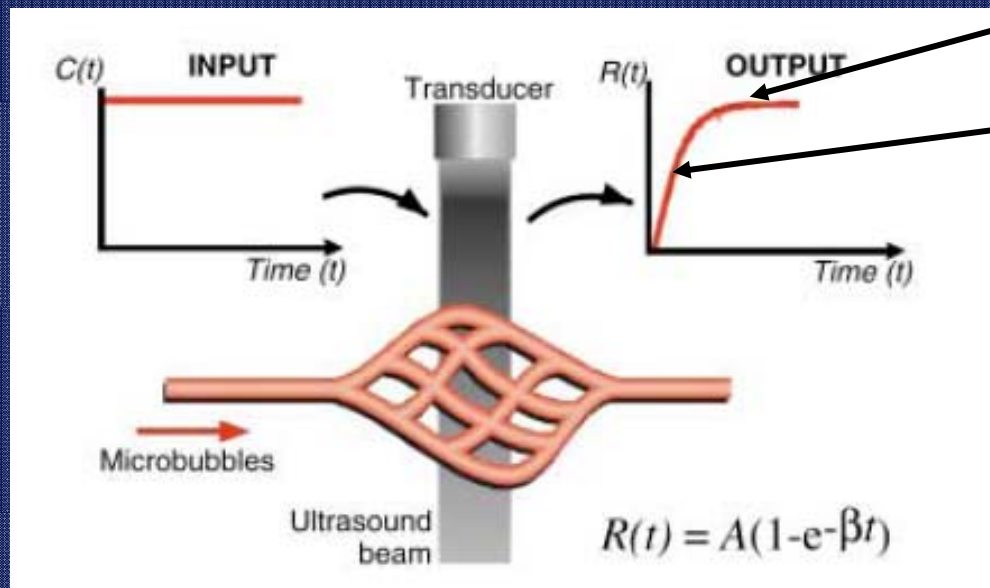
Courtesy: F. ten Cate, Thorax Center Rotterdam, NL

Exemples cliniques

Cardiologie: estimation de la perfusion myocardique

Destruction-reperfusion

- Destroying the vast majority of microbubbles and measuring their tissue replenishment in real time to assess blood flow velocity.
- Assessment of myocardial perfusion

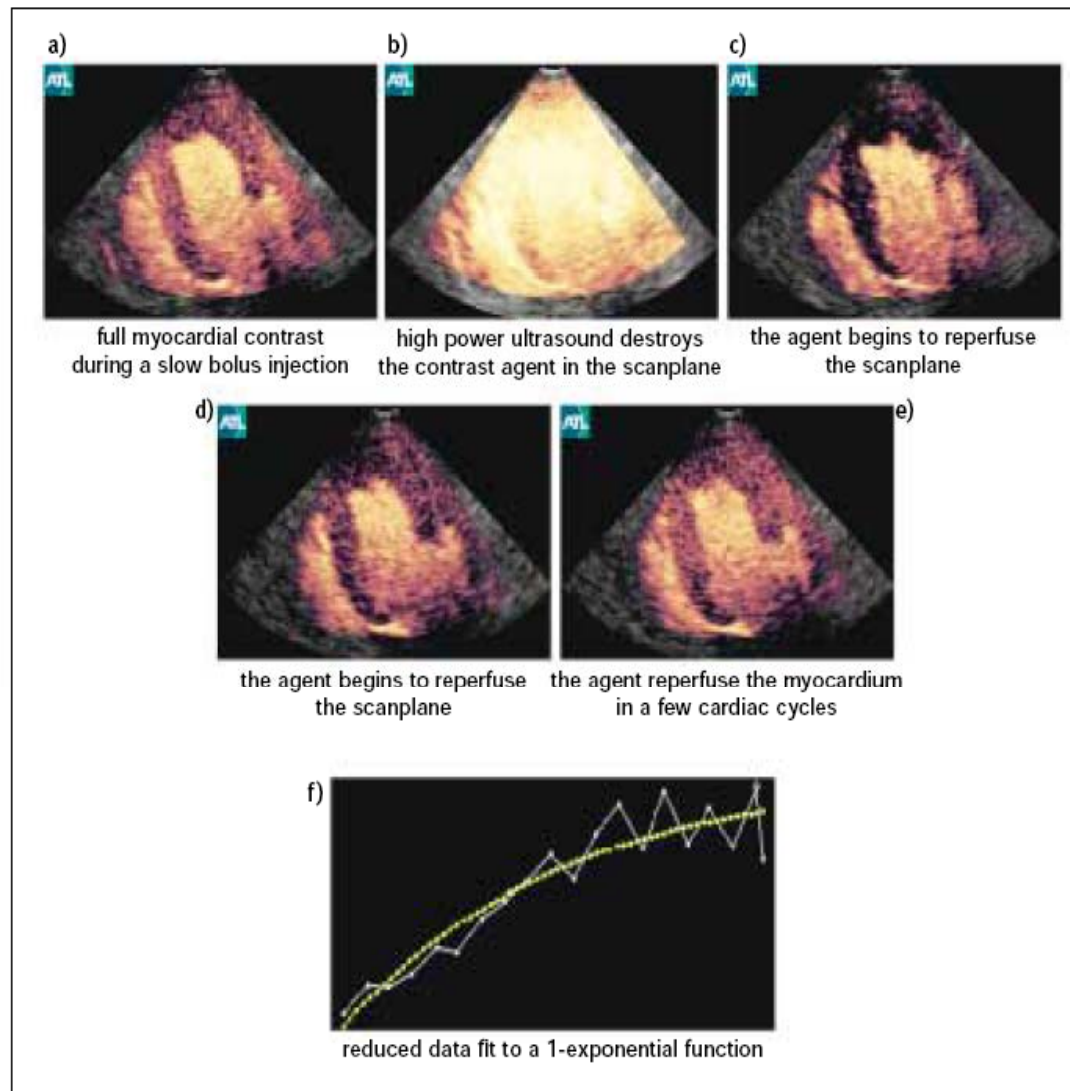


Total number of bubbles present in ROI (vascular volume) A

Rate at which the level is attained reflects the speed (mean velocity) β

$A \times \beta = \text{flow (perfusion) rate}$

Destruction-reperfusion



REAL TIME

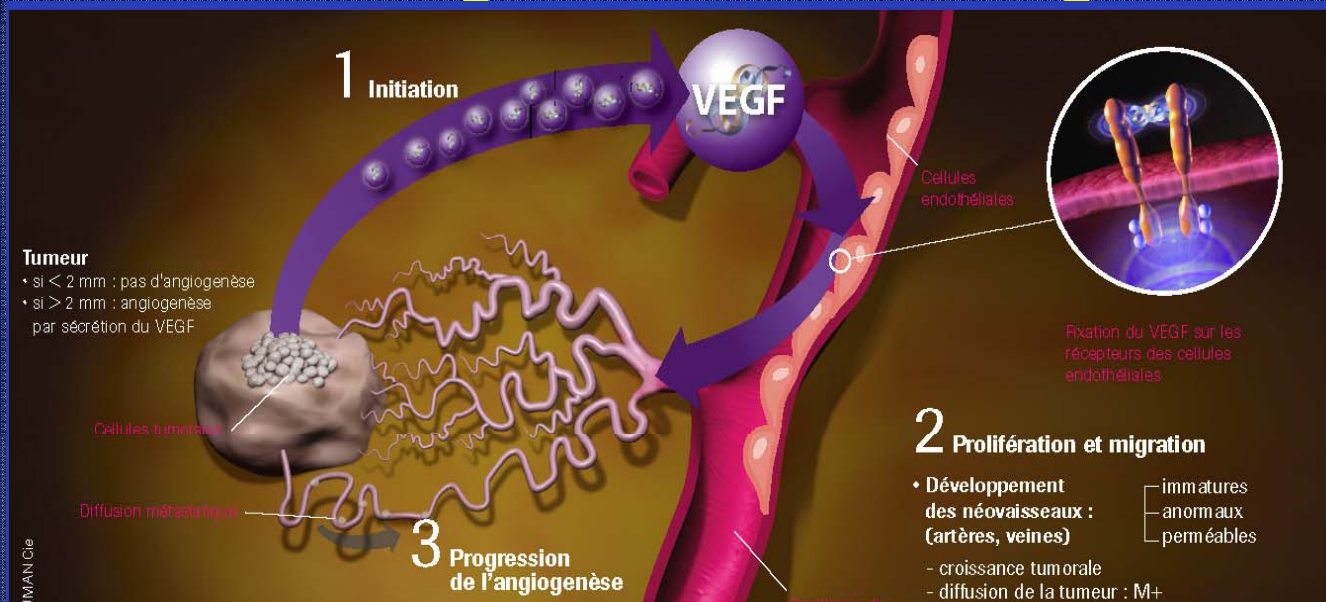
Fig. 13 Real-time myocardial contrast during a slow bolus injection at low MI using Power Pulse Inversion imaging (a). High power frames destroy all of the contrast agent in the scanplane (b). The agent begins to reperfuse the scanplane (c-d), and fully reperfuses the myocardium in a few cardiac cycles (e). Real-time data collection begins just after the high power frames. The data is reduced to include only end diastolic frames, and a monoexponential curve is fitted (f).

Agents de contraste US: Contre-indications

- Allergie à un composant
- Sonovue:
 - Insuffisance cardiaque sévère
 - Cardiopathie ischémique instable
 - Troubles du rythme sévères
- Par précaution: femme enceinte, allaitement, nourrisson et enfant

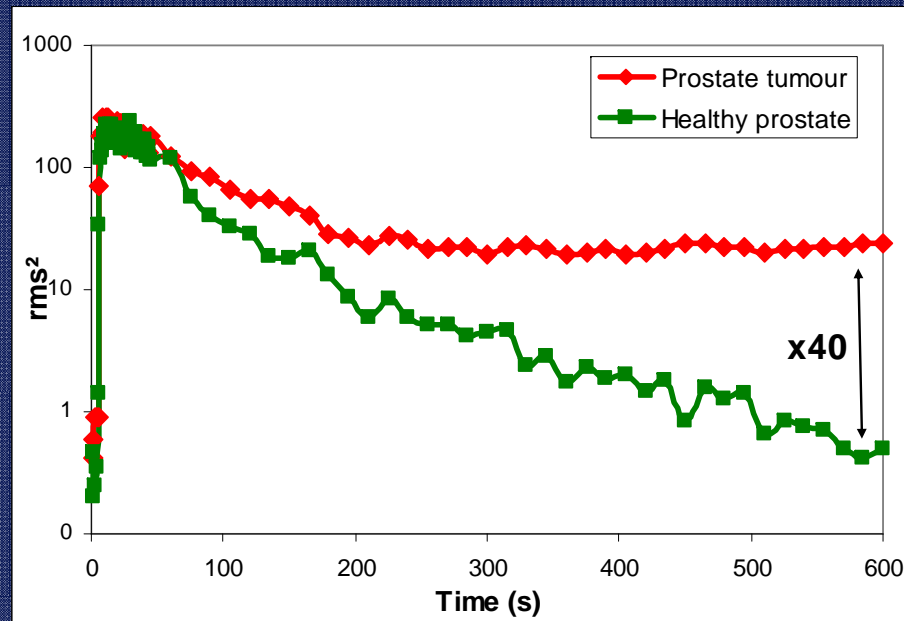
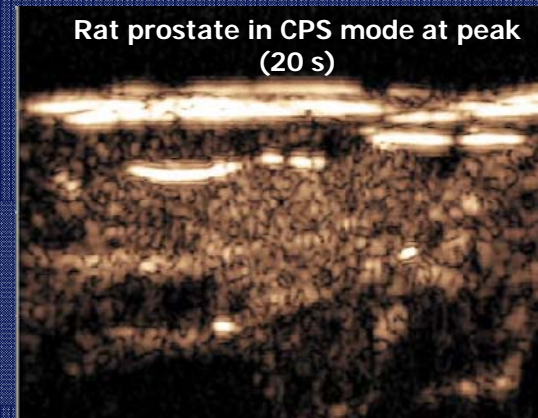
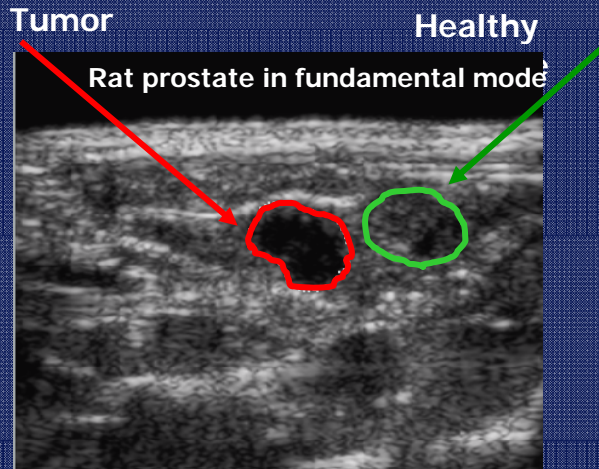
Ultrasound molecular contrast imaging

BR55: Targeted US contrast agent



- Angiogenesis is an important process involved in tumor growth: the angiogenic switch occurs when the tumour reaches 1-2 mm size. This is dependent on many stimulating factors such as VEGF.
- **Among the various markers of angiogenesis, Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)** is recognized as a major player. It is up-regulated on the vascular endothelium in tumors. It interacts with VEGF.
- BR55 is designed to target specifically VEGFR2, thanks to a specific lipopeptide.

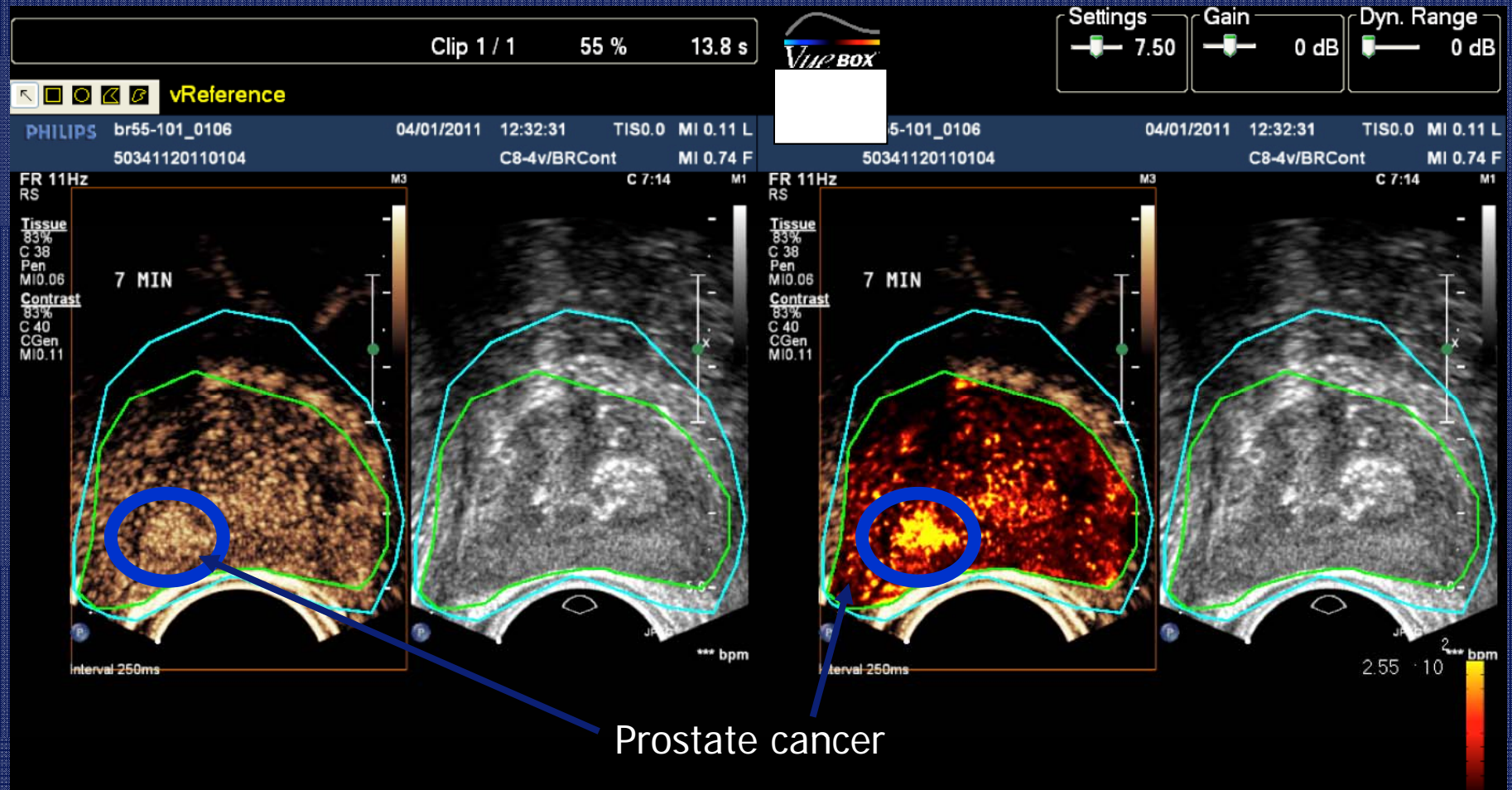
Molecular imaging of prostate cancer lesion in a rat Dunning model with BR55



BR55 can differentiate tumor from normal prostate based on angiogenesis

Tardy I, Pochon S, Theraulaz M, Emmel P, Passantino L, Tranquart F, and Schneider M, Investigative Radiology (2010), 45, 573

Proof of concept: human studies

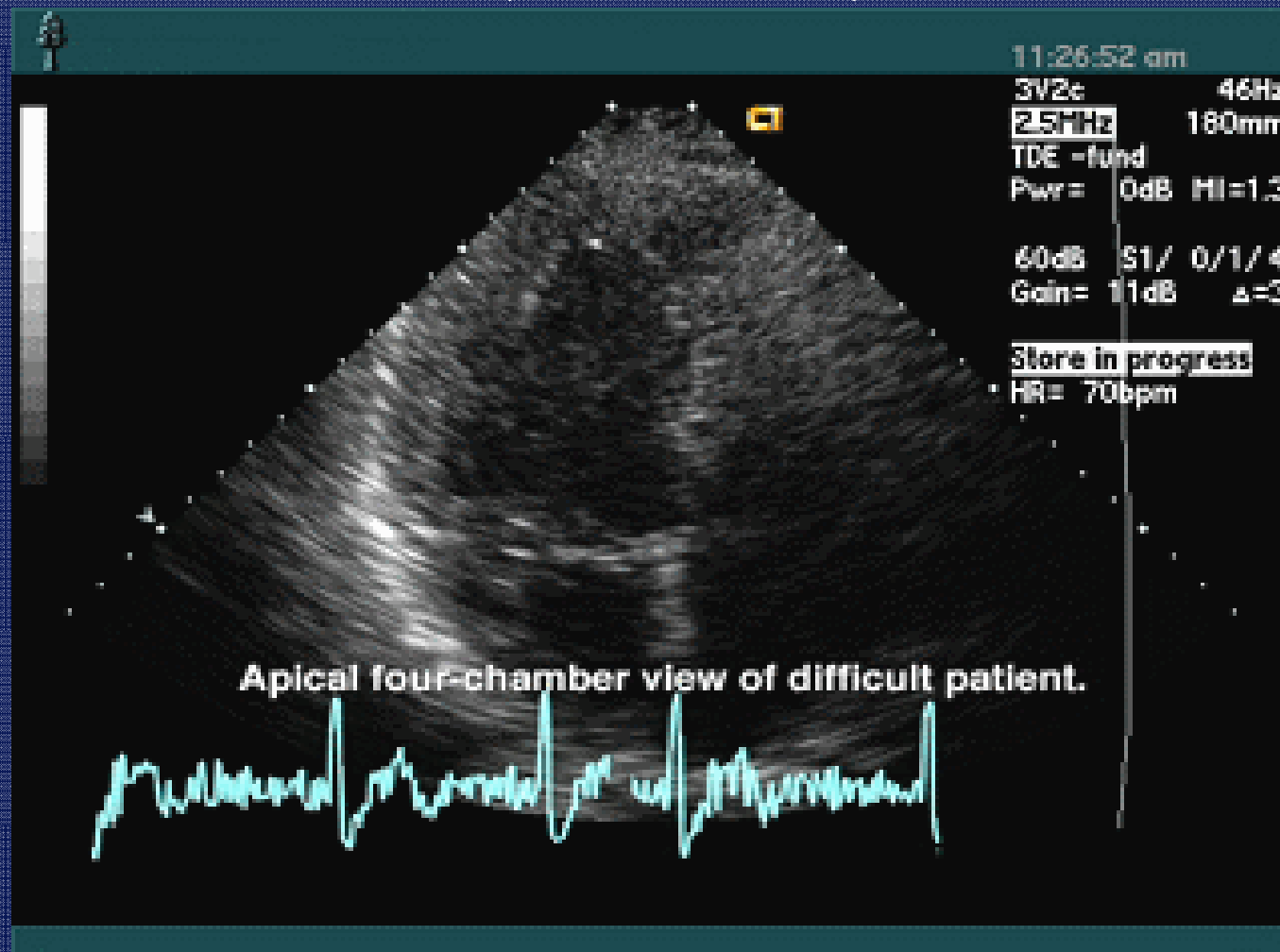


Immunostaining demonstrates moderate VEGFR2 expression in that PCa lesion

BR55 is able to bind to VEGFR2 in humans and is safe and well-tolerated

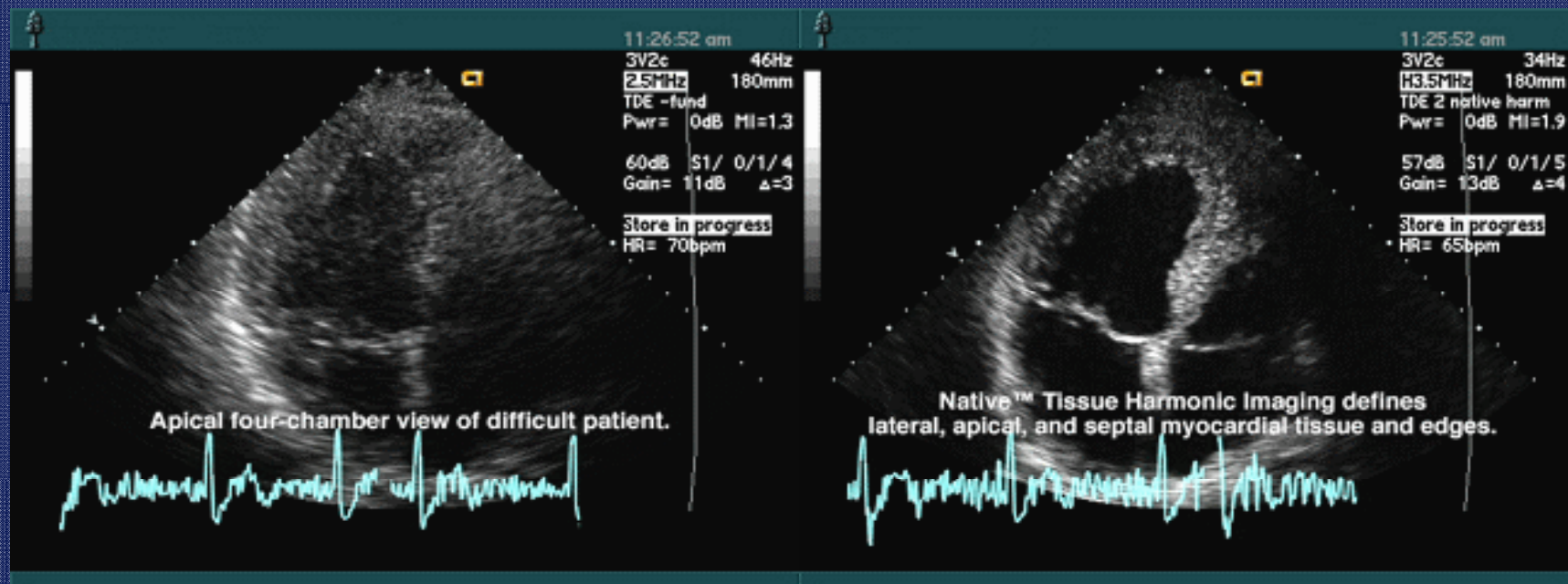
Imagerie harmonique tissulaire

Conventional B-mode image (AP4CH)

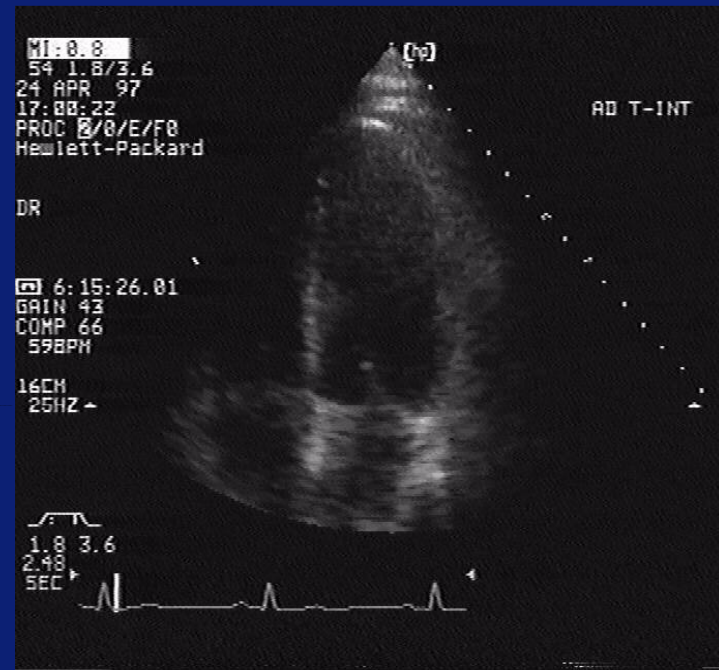
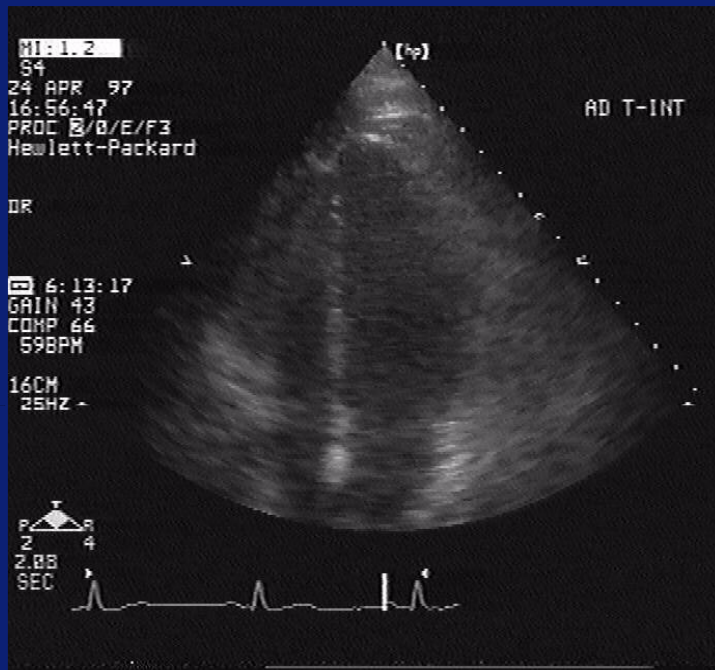


Fundamental

THI



Exemples cliniques



4 chamber view

Génération de fréquences harmoniques

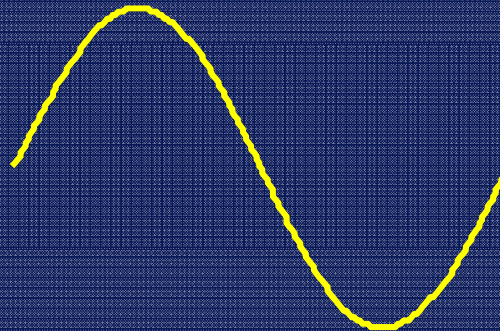
⇒ Non linéarité:

- Apparition des effets d'acoustique non linéaire
- Création de composantes fréquentielles absentes dans le faisceau émis

→ Harmonique tissulaire (native) → propagation

Origine physique de la distorsion de l'onde

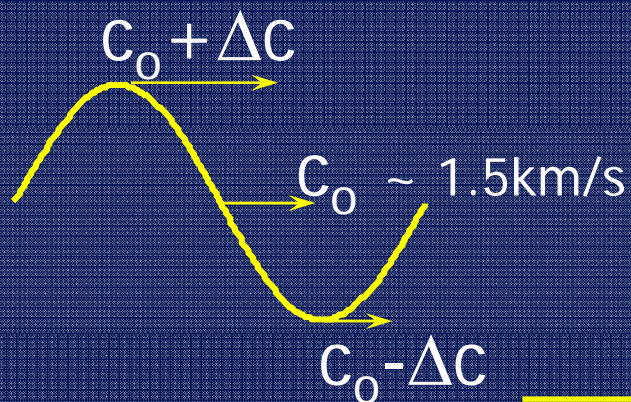
Pression positive \Rightarrow Tissu comprimé (forte densité) \Rightarrow Vitesse



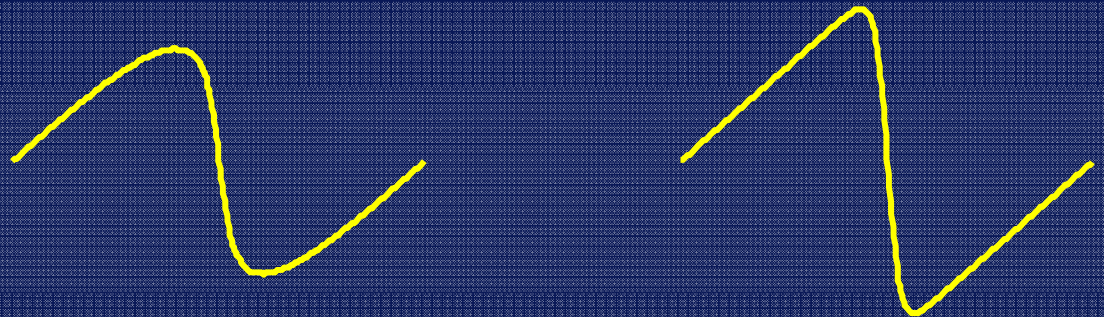
Pression négative \Rightarrow Expansion du tissu (faible densité) \Rightarrow Vitesse



Accumulation de la distorsion

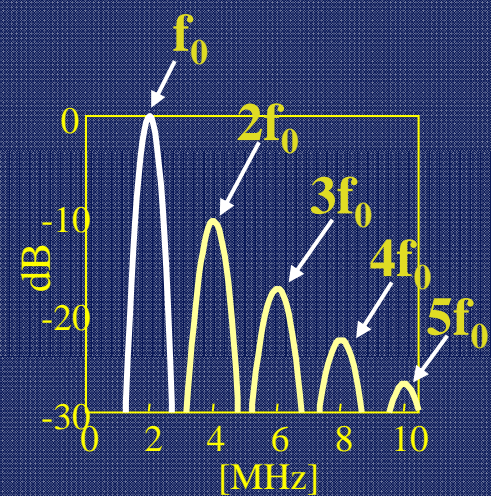
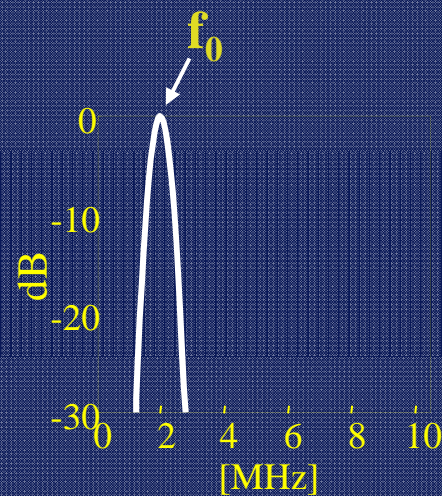
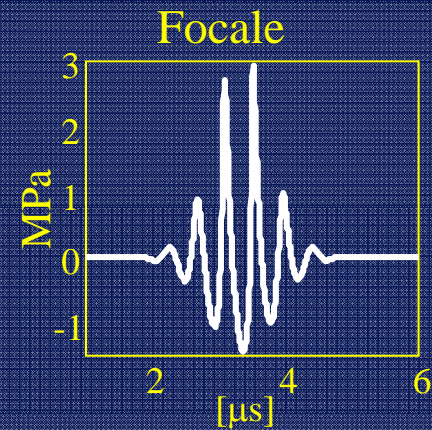
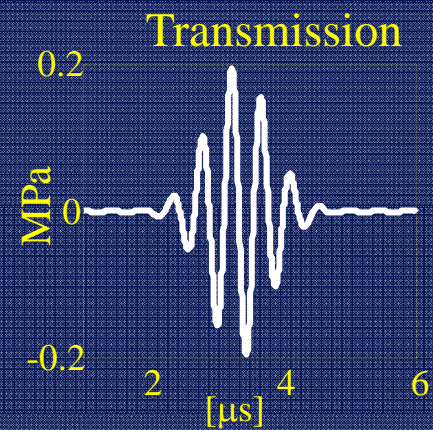


direction de propagation



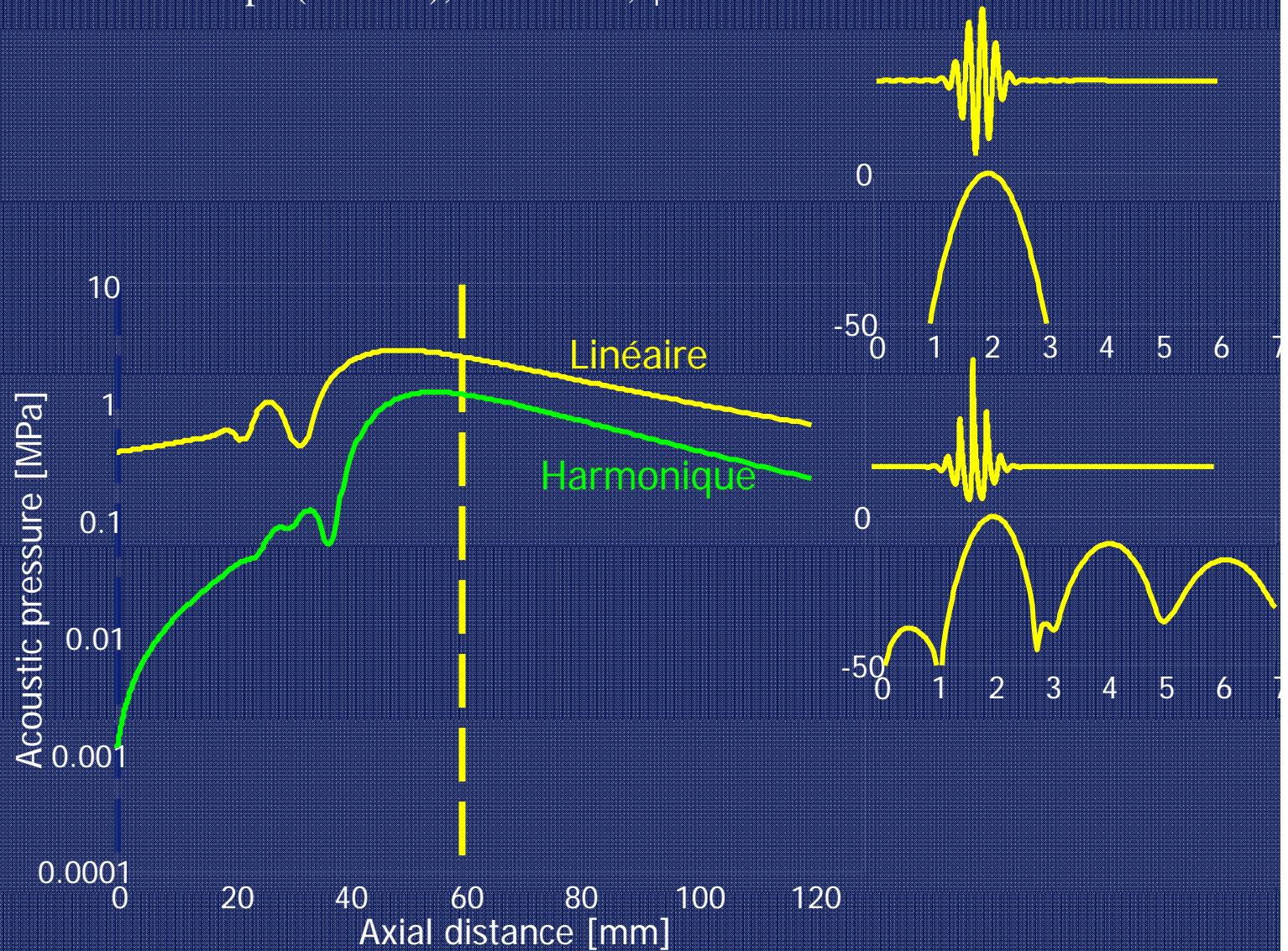
Génération des fréquences harmoniques

Propagation non linéaire (native)



Profile axial du champs acoustique

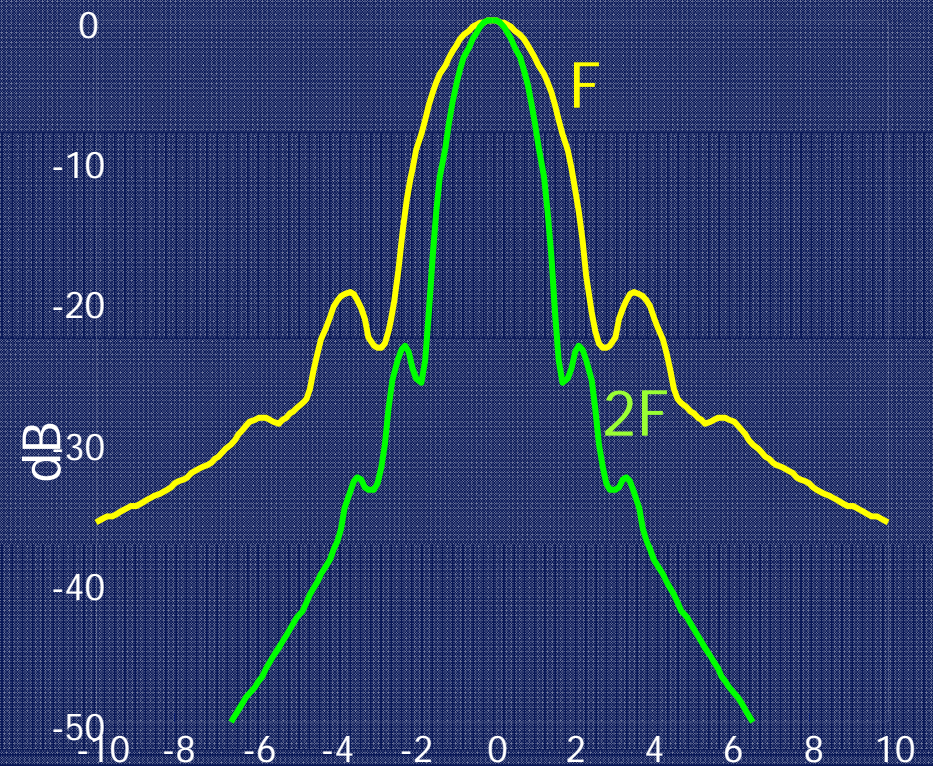
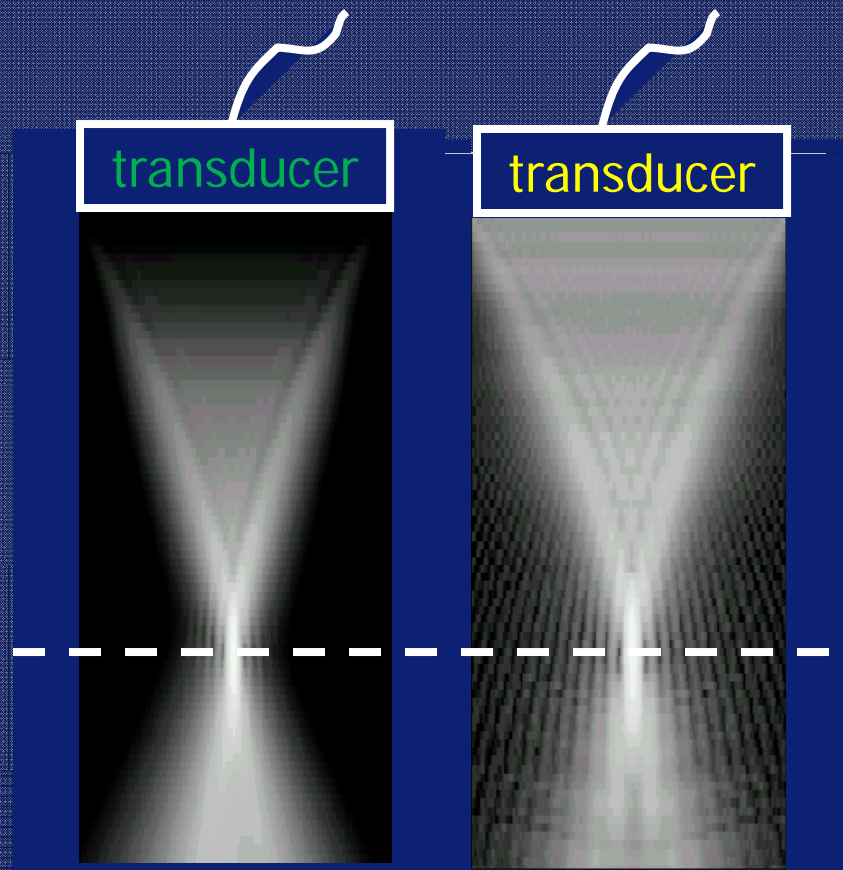
500 Kpa (IM=0.3), 2.25 MHz, $\phi=12$ mm



Profile latéral du champs acoustique

500 Kpa (IM=0.3), 2.25 MHz, $\phi=12$ mm

Beam profile at the focus



Lateral Position (mm)

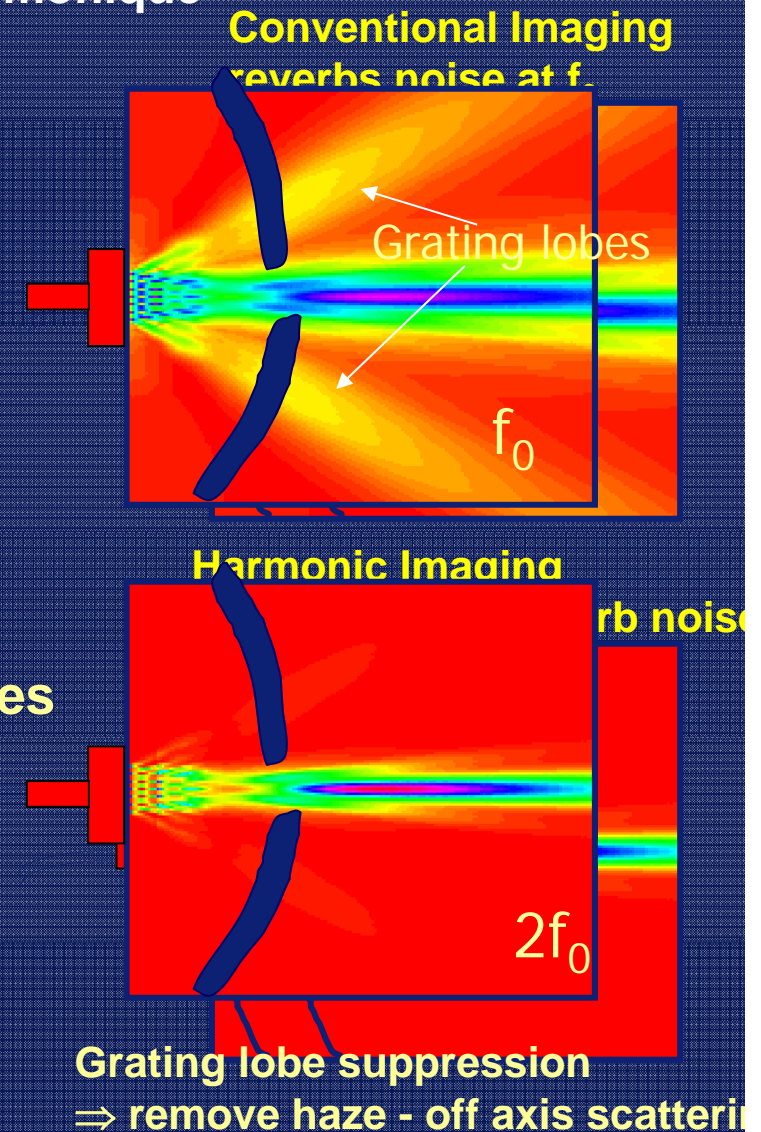
Intérêt des fréquences harmoniques

➔ Amélioration de la qualité d'image en mode harmonique

➔ Patients « techniquement » difficiles

No reverberation

Meilleure suppression des lobes secondaires
⇒ Elimination des artéfacts hors axe



Intérêt de l'imagerie harmonique

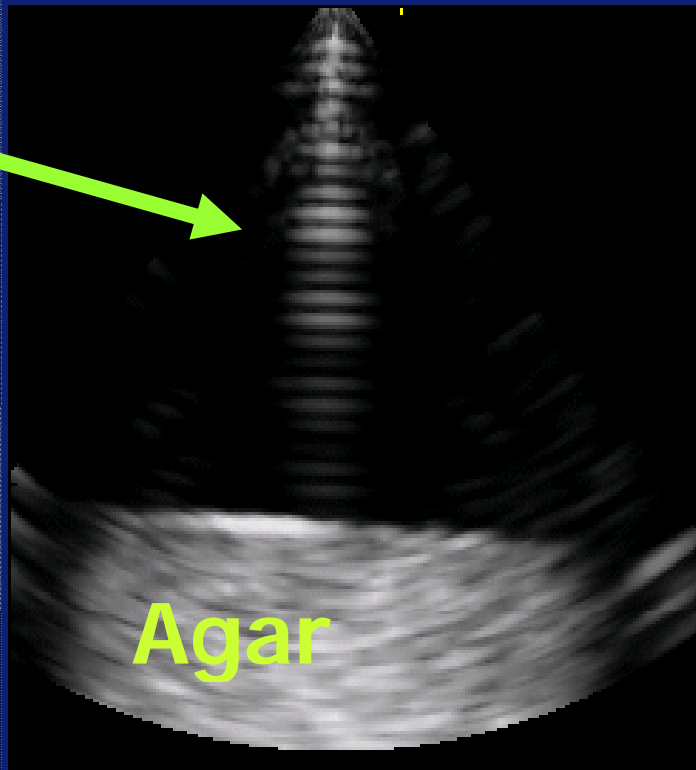
En cardiologie, plus de 40% des patients sont "techniquement difficiles en raison de: obésité, pathologies pulmonaires, ...

**Ideal Patient
for
Harmonic Imaging**

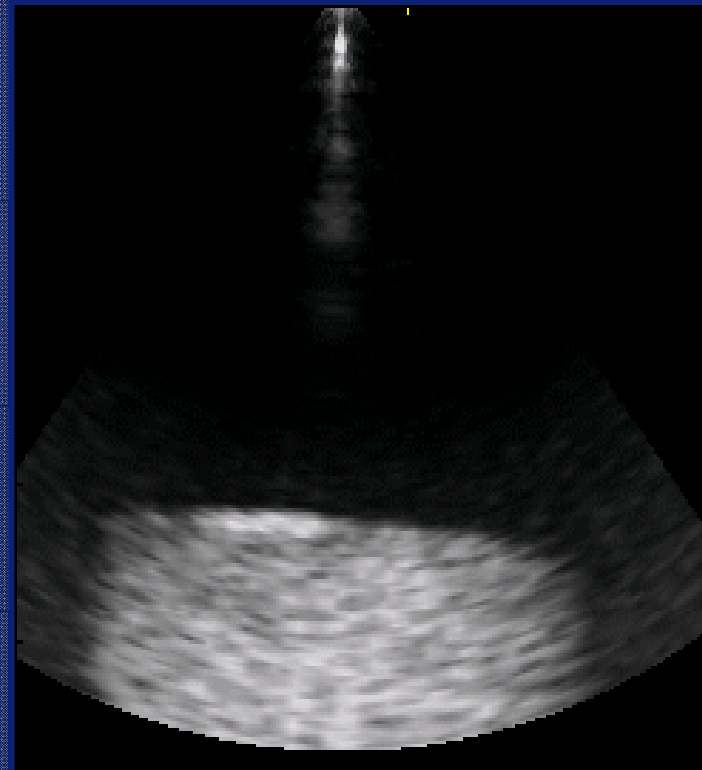


In vitro data

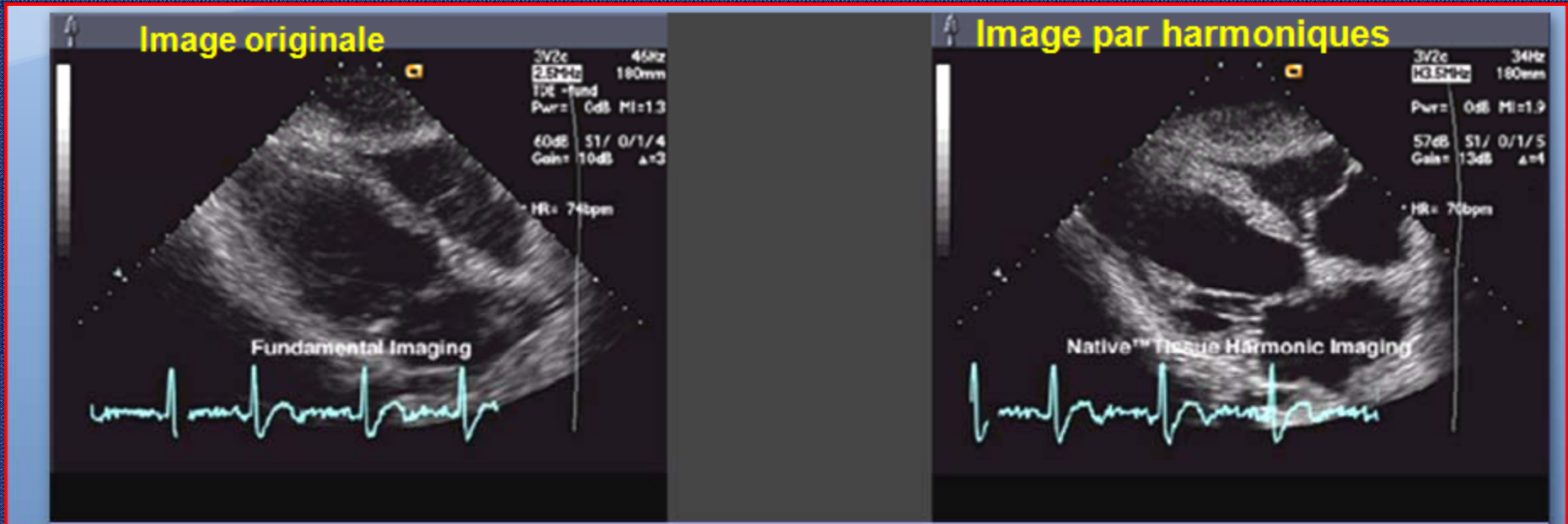
Fundamental 3.3 MHz



Harmonic 1.7 MHz

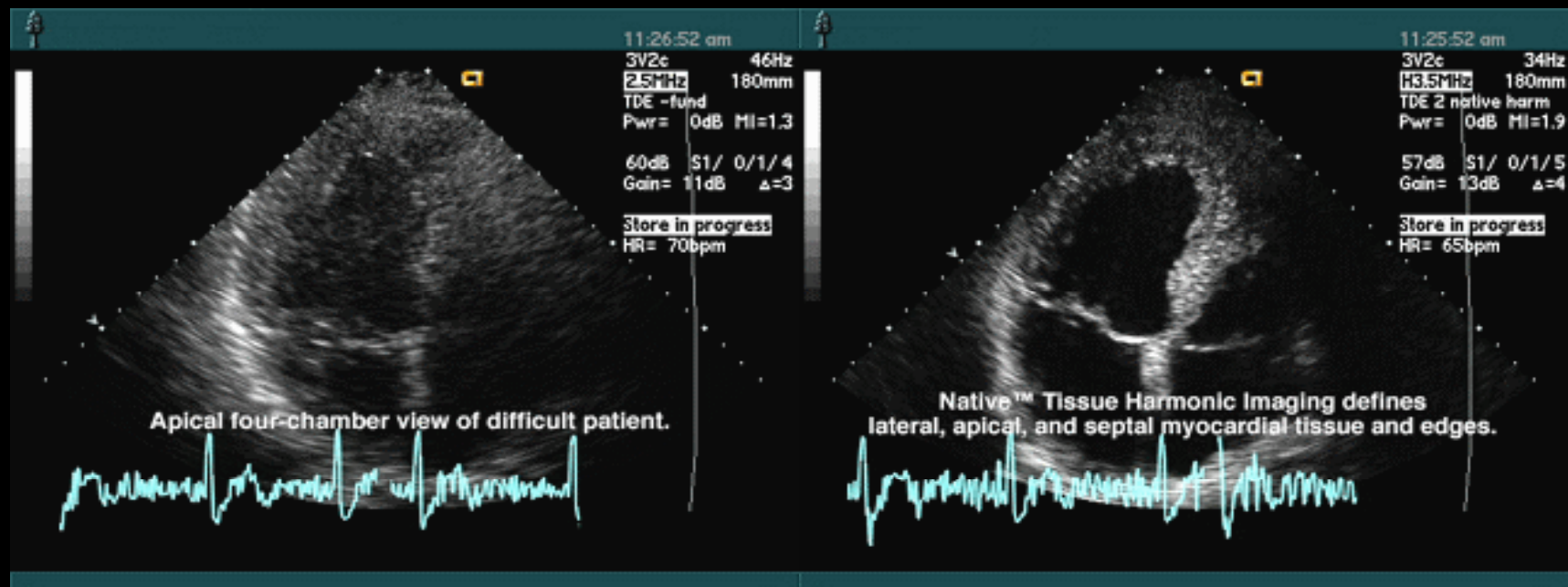


Exemples cliniques



Fundamental

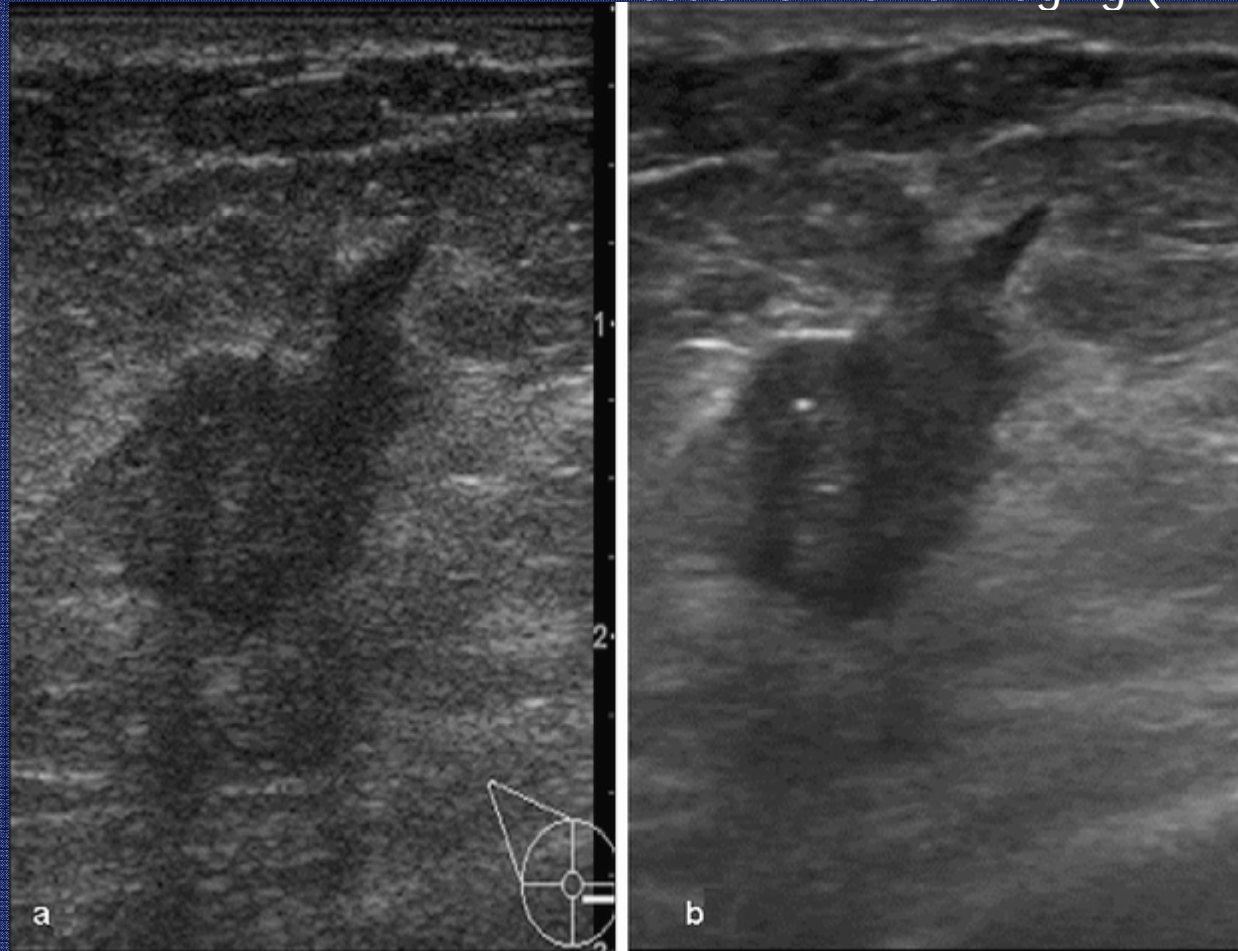
THI



Exemples cliniques

Fundamental B mode

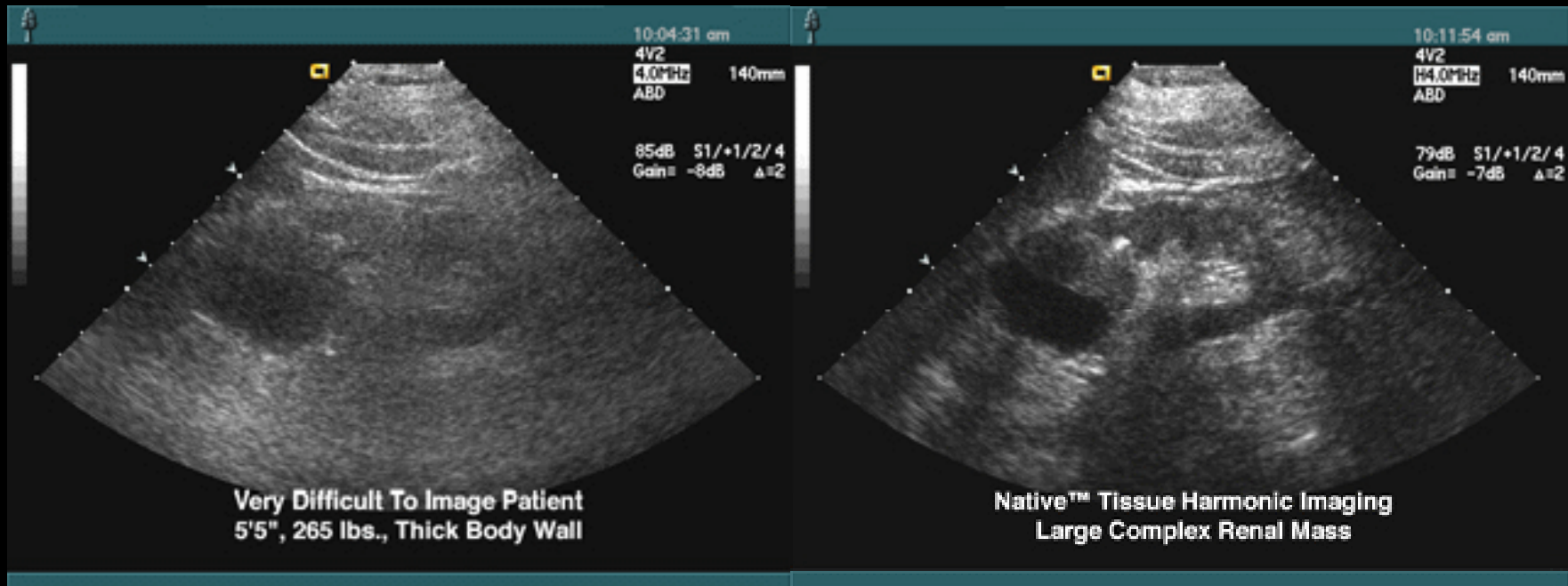
Tissue harmonic imaging (THI)



Effect on visibility of calcifications and delineation of tumour margin

Fundamental

THI





2:07:06 pm

8C4

H8.0MHz

75dB S1/+1/1/4

Gain= -6dB $\Delta=2$

