5 Contrast-Specific Imaging Techniques: Methodological Point of View

Emilio Quaia and Alessandro Palumbo

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5.1 Introduction

Microbubble-based ultrasound (US) contrast agents consist of bubbles of gases, covered by a shell of different composition, with a diameter of approximately 2–6 μm that enhance the US signal (Albrecht et al. 2000) and persist exclusively in the blood stream. The nature of microbubble interaction with the insonating US beam depends on the scanning parameters, principally the acoustic power of insonation and the US frequency.

The basic underlying principle of all microbubble-based contrast agents is the high difference in the acoustic impedance between the gas in the microbubble and the surrounding blood in vivo, which makes the microbubble highly reflective as a simple backscatterer in the range of insonation power below 100 KPa. Increasing the acoustic insonation power, the microbubbles show an increasingly non-linear response and the reflected US signal contains harmonic and subharmonic frequencies that are multiples and fractions of the insonating frequency (de Jong et al. 1994a,b; Burns et al. 1996; Kirkhorn et al. 2001). These non-linear signals are produced since less energy is required to expand the microbubble than to compress it. At yet higher insonation acoustic power, microbubbles are destroyed by the acoustic field, producing a strong signal, similar to a burst, with wideband harmonic frequencies.

E. Quaia, MD, Assistant Professor of Radiology;
A. Palumbo, MD
Department of Radiology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste, 34149, Italy

Firstly, microbubbles have to be injected and this can be performed in two different ways, bolus or injection, according to the type of study the sonographer needs to perform. Secondly, microbubbles have to be correctly insonated and this can be performed by a low or high transmit power of insonation, according to the type of injected microbubble-based agent. Conventional grey-scale and colour Doppler US suffer as a result of limited sensitivity to harmonics signal and of colour signal saturation and blooming artefacts, respectively. Dedicated US contrast specific techniques were introduced to overcome these limitations and to selectively register the signal produced by microbubbles insonation. US contrast specific techniques are not of immediate application but a series of setting procedures have to be applied before and after microbubble injection. This chapter will describe the principal technical parameters which have to be correctly set to optimise microbubble insonation and harmonics registration.

5.2 Modes of Injection of Microbubble-Based Contrast Agents

Microbubble-based contrast agents may be injected intravenously as a bolus (2–4 ml/s) or as a slow infusion (0.2–1 ml/s). Intravenous bolus injection mode is usually performed manually and produces a transient increase in the blood backscattering. The echo-signal video-intensity exhibits a linear relation with the injected microbubble dose and the time-intensity curve (Fig. 5.1a) shows a first rapidly ascending tract followed by a progressive decay (Correas et al. 2000). The principal advantage is that the bolus injection mode is very easy to perform and is usually employed for all applications of microbubble-based agents, except for parenchymal or tumoral perfusion quantitation. The principal drawback of the bolus injection mode is artefact production,

especially with colour or power Doppler US, which are markedly evident at the peak of the time-intensity curve and which are reduced if dedicated US contrast-specific techniques are employed.

Intravenous slow infusion of microbubble-based contrast agents is usually performed by dedicated automatic injectors. The time-intensity curve (Fig. 5.1b) shows a progressive increase in echo-signal video-intensity, followed by a stationary plateau phase from 1 to 2 min from the beginning of microbubble injection and which lasts the duration of microbubble injection, expressing the equilibrium kinetic between microbubble injection and washout (Correas et al. 2000). The time of achievement of the stationary phase is determined by the half-life of microbubbles in the blood (about four-fold the half-life of microbubbles). The principal advantage is that the slow infusion mode may be applied in the quantitative analysis of parenchymal or tumoral perfusion since it guarantees the achievement of a stationary state in microbubble concentration. The principal drawback is that it is not easy to perform and that dedicated automatic injection equipment needs to be used.

5.3 Modes of Scanning

Exposure to the US wave determines that microbubbles contract and expand their diameter several-fold at their resonant frequency. At low acoustic power microbubbles produce an US signal with the same frequency as the sound that excited them. By increasing the acoustic power microbubble expansion and contraction are non-linear and generate sub- and higher harmonics of the applied frequency (Cosgrove 2001; Dayton et al. 1999). At further higher acoustic power of insonation the expansion/contraction eventually disrupts the microbubble shell resulting in the emission of a wideband frequencies signal.

Dedicated contrast specific US techniques may be employed by destructive or non-destructive mode according to the acoustic power. The acoustic power is variably related to the employed mechanical index

$$(\mathrm{MI}) = \frac{\mathrm{P}-}{\sqrt{\mathrm{f}}},$$

with the peak negative acoustic pressure [P–] expressed in MPa (Pascal; 1 Pa = 1 Newton/m^2), and the frequency [f] in MHz. Actually, the MI value, which is displayed on all approved US scanners, ranging from 0.06 to 1.3, was introduced for protection purposes, expressing the potential for mechanical effects during a diagnostic US examination. It can be considered a practical index to express the intensity of the acoustic field. Actually, the MI is an unreliable predictor of microbubbles destruction, since at the same MI value different values of acoustic powers of insonation were measured in different US equipment (Merritt et al. 2000). Of course, the higher the MI value, the higher the probability to produce microbubble destruction. In general, when the MI of the insonating beam is greater than 0.3 the microbubbles are increasingly destroyed, even though the threshold for microbubble destruction is

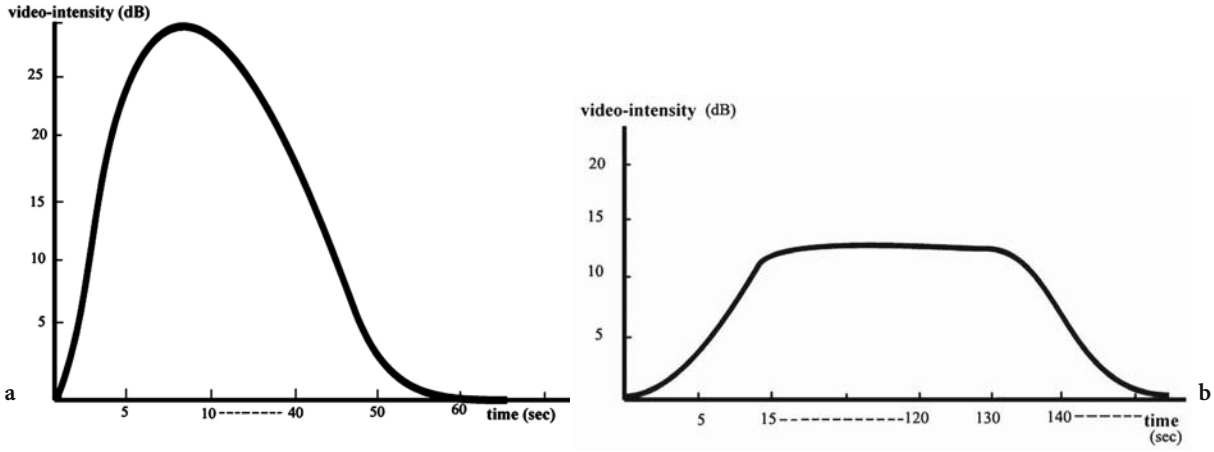


Fig. 5.1a,b. Bolus (**a**) versus infusion injection (**b**) profile of a microbubble-based contrast agent. After bolus injection (**a**), the microbubble concentration in the blood presents a rapid increase and a rapid decay. After slow continuous infusion (**b**), the microbubble blood concentration presents a progressive increase, a stationary state, which lasts according to the duration of microbubble injection, and a progressive decay when the microbubble infusion is stopped

variable and depends on many factors, such as the size and nature of the microbubble and the attenuation determined by the overlying tissues (Klibanov et al. 1998).

5.3.1 High Acoustic Power Insonation

The first mode, widely employed, made use of high-transmit acoustic power (Wo = peak negative pressure; 0.–2.5 MPa). Microbubble destruction produces the emission of a wideband frequency that includes both sub- and higher harmonics. Since MI value is limited, because of attenuation or safety regulations, the pulse length (K ~ 1/f) is the only parameter which can be further modified to increase the disruption efficiency (Frinking et al. 1998; Frinking 1999).

Microbubble destruction is a very fast process, taking place during a single or a few US pulses, during which a strong and highly non-linear signal is returned from microbubbles. This process is also called stimulated acoustic emission or transient scattering and may be considered as a sort of microbubble signature since it can be expressed exclusively by microbubbles. When colour Doppler is employed, microbubble destruction is displayed as a mosaic of randomly distributed pseudo-Doppler shifts that are independent of flow (Blomley et al. 1998).

High acoustic power mode has to be employed with air-filled microbubbles, such as Levovist (SH U508A, Schering, Berlin, Germany) or Sonavist (SH U563A, Schering AG, Berlin, Germany), which present low harmonic behaviour (Blomley et al. 1998, 1999; Quaia et al. 2002). For this reason, the only way to produce harmonics is to destroy these types of microbubbles. High acoustic power mode is less suitable for new generation perfluorocarbon or sulphur hexafluoride-filled microbubbles which present an effective harmonic response even if insonated at low acoustic power. Anyway, some of the new generation microbubble-based agents, such as Sonazoid (NC100100, Amersham Health, Oslo, Norway), a perfluorocarbon-filled contrast agent, may be effectively insonated even at high acoustic power (Forsberg et al. 2002).

High acoustic power mode may be employed continuously or intermittently (Quaia et al. 2003). In continuous scanning, the frame rate has to be registered at the lowest level, with a lower time resolution, to minimise microbubble destruction, while the echo-signal persistence has to be switched-off to visualise fresh undestroyed microbubbles in each new frame. Continuous insonation is usually applied to detect focal liver lesions in the liver or in the spleen since it allows the complete evaluation of the parenchyma. The focal zone has to be positioned at 10–12 cm from the abdominal surface to produce homogeneous contrast enhancement during insonation throughout the liver parenchyma.

In intermittent high acoustic power insonation different trains of between four and six high acoustic power US pulses are sent during the different parenchymal phases (arterial, portal and late phases in the liver or spleen; early and late corticomedullary phase in the kidney). The intermittent insonation is usually applied to characterise focal tumour in the liver, spleen or kidney, since it allows the tumour insonation during the different parenchymal phases.

The two principal advantages of high acoustic power mode over low acoustic power mode are the intense signals produced by microbubble insonation and the possibility to visualise the deep areas of the insonated parenchyma without signal attenuation from the superficial levels. Conversely, high acoustic power mode has four principal drawbacks. First, the destructive nature of this mode means that real-time scanning may be performed one single time and the largest amount of microbubbles are destroyed after the first sweep. For this reason, there is no possibility to assess the parenchymas with different acoustic windows at the same time. Second, liver scan has to be rapid and uniform to produce homogeneous microbubble rupture on liver parenchyma. In fact, the scanning irregularities, determined by a less than uniform free-hand sweep, or patient movements, during the emission of the two out phases US pulses, may produce artefacts (Cosgrove 2001; Forsberg et al. 1994) simulating focal liver lesions. Third, at high acoustic power insonation the suppression of stationary tissue background is imperfect due to the harmonic signals produced by native tissues which present non-linear behaviour as microbubbles at high acoustic power, with a consequent production of significant tissue background on which bubble signal is superimposed.

5.3.2 Low Acoustic Power Insonation

The introduction of perfluorocarbon and sulphur hexafluoride-filled microbubbles, with effective harmonic properties, has made it possible to perform continuous low acoustic power insonation (Wo = peak negative pressure 100–600 KPa; MI below 0.2)

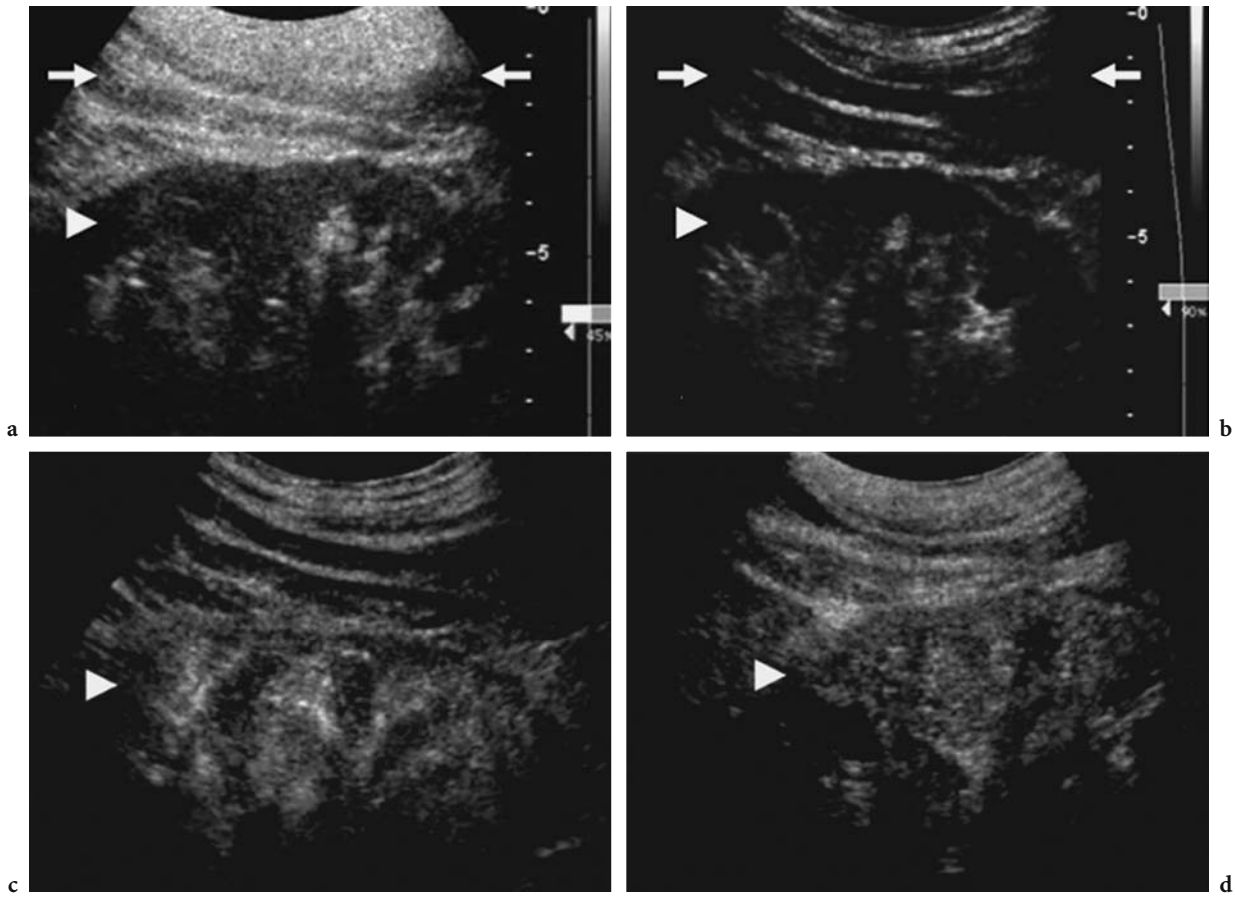


Fig. 5.2a–d. Kidney insonation (*arrowhead*). **a** Before microbubble injection, excessive signal gain is evident in the superficial planes (*arrows*). **b** Correct signal gain before microbubble injection. The signal gain is correctly set in the superficial planes (*arrows*) and appears uniform throughout the scanned parenchyma. The same signal gain is maintained after microbubble injection (**c,d**) providing the effective visualisation of contrast enhancement in renal parenchyma

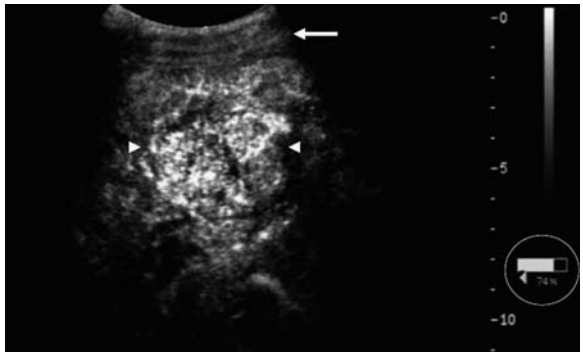
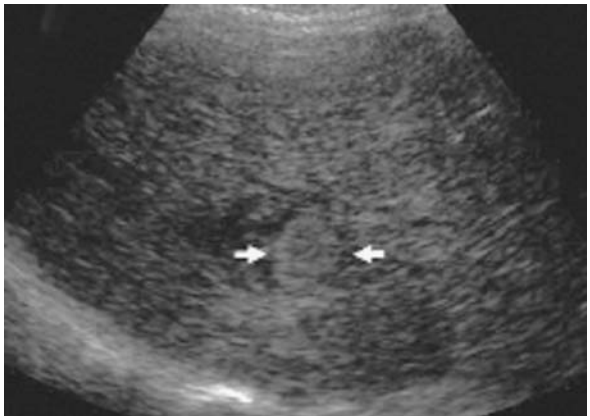


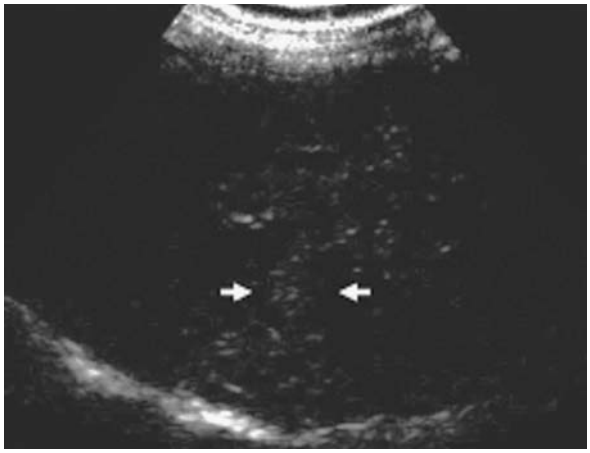
Fig. 5.3. The correct focal zone position (*circle*) at low acoustic power insonation. The focal zone has to be positioned below the focal liver lesion (*arrowheads*) to be characterised. The signal gain in the superficial planes (*arrow*) is correctly registered

which is the most employed scanning mode nowadays after microbubble administration (Albrecht et al. 2003; Correas et al. 2003; Nicolau et al. 2003; Hohmann et al. 2004; Quaia et al. 2004).

Before microbubble-based agent injection, the background signal from stationary tissues has to be uniformly set at the lowest level, from the superficial (Figs. 5.2 and 5.3) to the deeper scanning levels (Fig. 5.4). The focal zone has to be positioned (Fig. 5.3) below the parenchymal region to be assessed, the echo-signal persistence should be turned off to reduce artefacts, while the frame rate should be registered at the lowest level to minimise microbubble destruction (which does occur, even though at a much lower level than with high acoustic power insonation).



a



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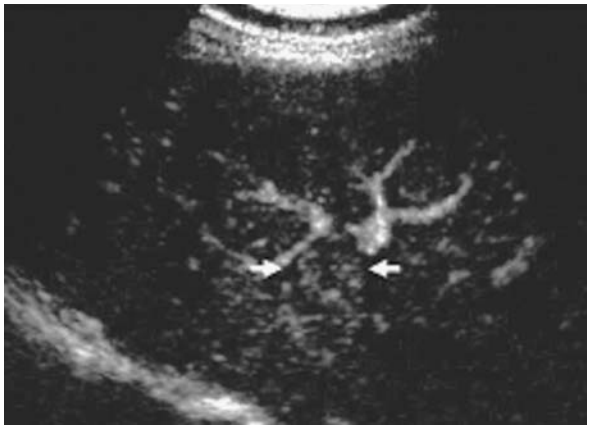

c

Fig. 5.4a–c. The correct signal gain before microbubble injection in the liver by using low acoustic power insonation. **a** A focal liver lesions (*arrows*) is identified in the liver at baseline conventional greyscale US. **b** Before microbubble injection, the acoustic power and the echo-signal gain have to be registered at the lowest level to suppress the background signal from stationary tissues and to make the signal intensity in the different scanning phases uniform. **c** After microbubble injection, diffuse increase in the echo-signal intensity, due to parenchymal contrast enhancement, is visualised

The two principal advantages of low over high power mode is, firstly, to minimise microbubble rupture allowing the continuous real-time evaluation of contrast enhancement and, secondly, to allow the effective suppression of the stationary tissue background and the selective registration of harmonic signals produced by microbubbles with improved contrast-to-noise-ratio. The only limitation of low power mode is the lower reliability in assessing the deep parenchymal regions, since harmonics present a lower intensity than with high power mode. However, this limitation has been almost completely resolved in state of the art US equipment and by multi-pulse contrast specific techniques which present an increased sensitivity to microbubble harmonic signals.

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