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● *Safety of Ultrasound Contrast Agents*

RECOMMENDATIONS ON THE SAFE USE OF ULTRASOUND CONTRAST AGENTS[1]

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Clinical applications and safety concerns

Clinical users should balance the expected clinical benefit from ultrasound contrast agents against the possibility of associated bioeffects.

Caution should be exercised in the use of microbubble ultrasound in tissues where damage to microvasculature could be dangerous. Some areas of concern include the brain, the eye, the fetus and the neonate.

Clinical users of contrast echocardiography should be alert to the possibility of cardiac rhythm disturbances. Electrocardiograms should be monitored during these procedures.

Idiosyncratic allergy-like or hypersensitivity reactions are rare but recognized untoward side effects with currently approved agents. Health care professionals are advised to carefully follow the instructions of the package inserts of ultrasound contrast agents. Health care professionals should be alerted to the possibility of rare adverse side effects whenever ultrasound contrast agents are administered to patients, and should be prepared to appropriately treat them should any occur.

The mechanical index (MI) is a useful but imperfect guide for safety and no absolute threshold can be defined. Bioeffects have been observed in small animals in ultrasound contrast agent studies with MI as low as 0.4; the clinical implications are yet to be determined.

Strategies that reduce the likelihood of bioeffects include:

i. Scanning at lower MI
ii. Scanning at higher frequencies
iii. Reducing total acoustic exposure time
iv. Reducing contrast agent dose
v. Adjusting the timing of cardiac triggering (end-systole being, in general, the most vulnerable phase for triggering ventricular arrhythmias).

The use of contrast agents in a diagnostic ultrasound study should be avoided 24 hr before lithotripsy procedures.

The clinical significance of microvascular damage and cardiac rhythm effects requires further investigation.

Training

Proper training of new investigators in the clinical use of ultrasound contrast agents is of the utmost importance. Practitioners need to be competent in the administration of contrast agents, familiar with any contraindications and be able to deal with any possible adverse effect, within the medical and legal framework of their country.

Epidemiology

Properly designed epidemiologic studies should be undertaken to establish long-term safety of ultrasound contrast agents.

Mechanisms for the interaction of ultrasound

Research should be continued into *in vitro* bioeffects, *in vivo* bioeffects and mechanisms of interaction between diagnostic ultrasound and contrast agents. Much remains to be learned about the dynamics of the various kinds of ultrasound contrast agents in ultrasound fields and about biologic effects that may occur when the ultrasound contrast agents are used clinically.

In vitro bioeffects

Acoustic cavitation-induced biologic effects have been revealed *in vitro* from diagnostic ultrasound exposures in the presence of contrast agents. *In vitro* experimental results should be considered relevant for safety

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evaluations because contrast agents introduce gas bodies into the *in vivo* environment.

In vivo bioeffects

Where feasible and consistent with adequate diagnostic imaging quality, clinicians should use higher frequencies of insonation, lower exposure levels and lower contrast agent doses to minimize the occurrence of reported *in vivo* effects such as damage to microvasculature and altered cardiac rhythm.

Exposure from diagnostic ultrasound equipment relating to cavitation risk

Clinical users should monitor thermal and mechanical indices and keep them as low as is consistent with clinical needs.

Output display indices should be documented as a part of the permanent record of the examination and manufacturers should facilitate this process.

Verification of the accuracy of the displayed MI should be undertaken, particularly when new hardware or software is introduced.

The adequacy of the mechanical index as a guide to the likelihood of rupture of contrast micro-bubbles should be examined. A new index specific for this purpose may be appropriate.

Manufacturers should set the default (switch-on) MI to less than 0.4, except for high MI modes.

Manufacturers should provide unambiguous on-screen display of centre frequency (acoustic working frequency). For scientific purposes, it would be helpful to make available the value of the peak negative acoustic pressure to explore alternative means to assess clinical bioeffects responses in particular circumstances.