Consensus Conference

Italian Society of Cardiovascular Echography (SIEC) Consensus Conference on the state of the art of contrast echocardiography

On behalf of the Consensus Conference Participants (see Appendix)

Key words:
Contrast media; Coronary artery disease; Costs; Echocardiography; Echo-Doppler; Management in cardiology; Myocardial infarction; Perfusion; Stress echocardiography; Ventricular function.

Part 1: Technical and methodological issues. **Contrast echocardiography is based on the use of gas microbubbles. The size, gas composition and shell structure of the microbubbles modify their stability, resistance to pressure and scattering behavior. A proposed classification of contrast agents is based on the modalities of production of microbubbles (galenic or industrial); the industrial agents are divided into three generations depending on their characteristics. Following venous administration, the industrial microbubbles behave as intravascular free-flowing tracers and this is fundamental for their use in perfusion studies. When insonated at a low acoustic pressure, microbubbles show a linear behavior and can be used for signal amplification. At intermediate acoustic pressures microbubbles resonate and produce a harmonic signal that is detectable by new scanners. Higher acoustic pressures cause microbubble disruption with emission of a transient acoustic signal. The available contrast agents behave differently in an ultrasound field.**

Part 2: Safety of contrast echocardiography. **Galenic contrast agents were tested in many studies for intracoronary and intravenous injection and no clinically relevant side effects were detected. The intravenous injection of industrial contrast agents is safe in all conditions, even in acute coronary syndromes. The interaction between ultrasound and microbubbles produces energy with potential effects on tissue for inertial cavitation and acoustic current production. These effects seem particularly interesting for the therapeutic applications of contrast echocardiography, but they do not appear to have clinically relevant effects.**

Part 3: Experimental studies. **Experimental studies in contrast echocardiography are designed to induce, in animal models, acute myocardial infarction and coronary artery stenosis and to evaluate the differences in blood flow. The risk area and infarct area are well visualized with serial contrast agent infusion. No-reflow after coronary occlusion is a well-known phenomenon and is detectable at contrast echocardiography. Different degrees of induced coronary stenosis cause differences in the regional flow rate. The results of contrast echocardiographic studies are comparable with those of other invasive flow measurements. Caution must be used to transfer the knowledge acquired from animal studies to the clinical arena, owing to both methodological and anatomical differences.**

Part 4: Enhancement of Doppler signal and coronary flow study. **The anterior descending coronary artery flow is detectable in almost all patients, and the posterior descending coronary artery in about 70%. The coronary flow reserve can be measured by injection of a vasodilator agent (dipyridamole or preferably adenosine) with a success rate of almost 100% for the anterior descending but only 50% for the posterior descending coronary artery. Data from transthoracic studies are comparable with those of Doppler flow wire. The fields of application presently include the evaluation of acute myocardial infarction, the short- and long-term results of percutaneous coronary interventions and coronary grafts, and the study of the microcirculation in several clinical conditions where the coronary flow reserve may be reduced, such as in syndrome X, hypertension, hypercholesterolemia or diabetes.**

Part 5: Endocardial border enhancement. **Opacification of the left ventricle is the main indication to contrast echocardiography that, in this setting, is principally used to improve endocardial border delineation. This allows accurate evaluation of left ventricular volumes and function, increasing the role of echocardiography for the quantitative study of the left ventricle. Other indications for left ventricular opacification are the identification of intraventricular thrombosis, non-compaction of the left ventricle and heart rupture. In this respect, industrial second-generation contrast agents are more useful. The most appropriate patients for contrast echocardiography are those with a poor or suboptimal acoustic window, in whom a predictable diagnostic and prognostic usefulness of the procedure is expected. If appropriately used, contrast echocardiography is a cost-effective technique, although lack of reimbursement presently limits its use.**

Part 6: Use of contrast agents during stress echocardiography. **Contrast agents during stress echocardiography may be used to improve the diagnostic accuracy of the test and to study myocardial perfusion. The diagnosis of ischemia in stress echo relies on the operator's visual assessment of changes in contractility during stress. Contrast agents must be considered an important tool that improve image quality especially in patients with an intermediate or poor acoustic window and their use has been reported to be cost-effective in the few studies designed to this end. The evaluation of myocardial perfusion during stress is certainly one of the most important goals of contrast echocardiography. Preliminary data are interesting but there is still a number of methodological problems that currently hamper clinical application.**

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Part 7: Myocardial perfusion. **Echocardiography has the potential of visualizing microbubbles in the microcirculation by detecting stimulated acoustic emission, produced by high-energy applied ultrasound, or by detecting the harmonic signal produced by resonance of the microbubbles in a low-energy ultrasound field. In the first case images are triggered at increasing end-systolic intervals (intermittent imaging), whereas in the second case entire cardiac cycles are analyzed (real-time imaging). Continuous infusion is the preferred method of maintaining a large and constant microbubble concentration inside the microcirculation. Analysis of the perfusion signal may be made in the qualitative, semi-quantitative or quantitative mode. Quantitative analysis is based on the construction of videointensity-time curves to study the refilling phase after complete microbubble destruction. There are not enough data in the literature showing the additional role of quantitative analysis for clinical purposes. Thus, at present, quantitative softwares should be considered as research tools. Conversely, there is a general consensus based on experimental and clinical studies on the use of myocardial contrast echo in patients with acute myocardial infarction by means of qualitative or semi-quantitative analysis. Important information on the infarct area extension, on the efficacy of reperfusion therapy, on the presence and extension of the no-reflow phenomenon and on the extent of residual tissue viability may be derived from the routine use of myocardial contrast echo. The reference technique still remains myocardial scintigraphy even though many theoretical problems are being discussed.**

Part 8: Implementing ultrasound contrast in the echocardiography laboratory. **Contrast echocardiography should be considered an extension of the existing echocardiographic examination. Standard laboratory equipment is sufficient to run a contrast echocardiography program. However, cultural and technological upgrading is mandatory to obtain good results in contrast echocardiography. Intravenous infusion is easier during stress echocardiography than during rest study, because the time and cost for the venous line are comprised. In this setting, the cost-effectiveness for the addition of contrast agent is optimal, but patient selection is a critical point. The economic issue (contrast agent and personnel costs, and time needed) of contrast echocardiography determines the fact that without adequate reimbursement there is no incentive to perform the procedure.**

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PART 1
TECHNICAL AND METHODOLOGICAL ISSUES

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The echographic contrast effect is generated by the presence of microscopic gas bubbles, known as microbubbles, which are contained in the ultrasound contrast agents. In this session we will briefly analyze some of the physical properties of microbubbles.

Contrast agent typologies and properties

Pharmacological research has allowed continued evolution of contrast agents. As shown in table I, the main determinants of the characteristics of a contrast agent are its size, shell structure, and gas composition of the microbubble[1-3].

Contrast agents may be galenic or industrially produced; the latter may be divided into first and second-generation contrast agents depending on the gas composition of the microbubbles. The proposed classification of contrast agents (Table II) includes a third generation of contrast agents, not yet available for clinical use, in which the targeted microbubbles are acti-

Table I. Properties that primarily influence microbubble behavior.

Effect of microbubble size
- Migration through the pulmonary filter and diffusion into the microcirculation of different organs
- Intensity of contrast effect, which is proportional to the power of microbubble radius
- Resonance when exposed to an ultrasound beam. The microbubbles of industrial contrast agents resonate at the frequencies utilized in diagnostic scanners
- Microbubble stability (according to Laplace's law)
Effect of shell structure
- Microbubble stability, limiting gas diffusion and increasing surface tension
- Resistance to external pressure
- Ability to resonate
Effect of gas composition
- Stability of microbubbles and their persistence in the circulation
- Resistance to external pressure
- Clinical tolerability and safety

Table II. Classification of ultrasound contrast agents.

Production	Composition	Characteristics	Clinical use
Galenic	- Saline solution	- Non-homogeneous microbubble diameter	- Right heart cavity opacification
Manual shaking	- Emagel		
Sonication	- Radiological contrast agents	- Very limited microbubble stability and duration of contrast effect	- Patent foramen ovale
	- Human albumin		- Myocardial perfusion with intracoronary injection
	- Patient's blood	- Unable to cross the lung barrier	
Industrial			
I generation	- Atmospheric air	- Limited microbubble stability	- Doppler signal enhancement
	- Albumin capsule or surfactant	- Pressure sensitivity	- Improvement in endocardial border delineation
		- Limited persistence in vivo	
II generation	- Gases with high density and low diffusibility in blood	- Enhanced stability and resistance to pressure	- Myocardial perfusion with intravenous administration
	- Capsule	- Improved persistence in vivo	
III generation	- Ligands on microbubble shell	- Directed toward specific targets	- Detection of target lesions
	- Vehicle for medications or gene delivery	- Ultrasound-activated drug or gene	- Drug or gene delivery

vated by the ultrasound for diagnostic or therapeutic purposes[4].

In Italy, the available contrast agents are Levovist (Schering AG, Berlin, Germany), of the first generation, and SonoVue (Bracco International, Amsterdam, The Netherlands), of the second. Abroad, Optison (Amersham, Princeton, NJ, USA) and Definity (DuPont Pharmaceutical, Bristol-Myers Squibb, North Billerica, MA, USA), from the second generation, are available.

Microbubble rheology

The microbubbles of commercial contrast agents may move freely through the circulation. Following intravenous injection, the pulmonary filter retains only 1% of the microbubbles, as they are larger than the capillaries. From there, the microbubbles behave as intravascular free-flowing tracers[5] and have a rheology superimposable with that of red blood cells[6,7]. This is a fundamental premise for the utilization of echocardiographic contrast agents to study tissue perfusion.

The microbubble rheology varies depending on whether the same agents are injected intravenously (as appropriate) or intra-arterially[8-12].

Ultrasound beam energy

The effects of the ultrasound beam on microbubbles and tissues are strictly related to the energy of the beam[13], which is emitted by the combination scanner-transducer. Ultrasound energy may be measured by different parameters, as shown in table III.

The mechanical index, also known as the cavitation index, is a recently introduced parameter that supplies information on the energy of the ultrasound beam[14]. If a medium is exposed to high ultrasound energy, cavitation phenomena may occur leading to the formation of microbubbles, which oscillate and then implode. These microbubbles are generated during the negative phase of the acoustic wave, i.e. during the rarefaction phase. In addition to the medium's characteristics, the chances of initiating cavitation phenomena depend on the intensity of the negative acoustic phase and on its duration (which is inversely proportional to the ultrasound frequency). On a conceptual plan, the mechanical index is the ratio between the peak negative acoustic pressure and the central transducer frequency. The cavitation threshold is lowered if gas microbubbles are already present in the medium exposed to the ultrasound beam.

Table III. Parameters used to describe ultrasound beam energy.

Parameter	Definition	Characteristics
Acoustic pressure (Newton/m^2 or Pascal)	Compression and rarefaction grade of a medium exposed to ultrasound	- Maximum in the focal zone - Allows to measure forces acting on the medium crossed by ultrasound
Power (W = 1 J/s)	Capability of the whole ultrasound beam to transfer energy as it propagates	- Maximum in the focal zone - Related to the thermal ultrasound effect
Intensity (W/cm^2)	Ratio between ultrasound beam power and irradiated area	- Related to the thermal ultrasound effect

Microbubble behavior in the ultrasound beam

Depending on the ultrasound beam energy, three different microbubble behavior types may be schematically distinguished[1,2,15]. At a low acoustic energy (peak pressure < 100 kPa), the microbubble response to ultrasound is of a linear type and the intensity of the backscattered signal is proportional to the microbubble concentration, the intensity of the incident acoustic wave and the scattering cross-section of each element[2].

With higher acoustic energies (peak pressure between 100 kPa and 1 MPa), due to their resonance, the microbubble response is non-linear[16-19]. The resonance frequency of the microbubbles of commercial contrast agents is around 3 MHz, the same frequency as that of many diagnostic transducers. If the microbubbles are introduced into an ultrasound field of adequate acoustic energy, their oscillatory variations reach a limit at which their maximum expansion and maximum compression are not equivalent, thus leading to the production of harmonic waves. The latest generation scanners allow analysis of the signal produced by microbubble resonance, thus facilitating their detection for diagnostic purposes.

A further increase in acoustic energy (peak pressure > 1 MPa) leads to microbubble breakage by implosion. This transiently increments the backscattered signal (linked to microbubble rupture) which then decreases due to a reduction in microbubble concentration – a phenomenon known as transient acoustic emission[20,21].

Specifically, first-generation agents are fragile and do not produce a harmonic response to the ultrasound beam; they are used either as linear backscatter amplifiers (at low energy) or as flow tracers with the destructive method (at high energy). Second-generation agents characteristically give a non-linear, harmonic response, but may also present a linear response and transient acoustic emission.

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PART 2
SAFETY OF CONTRAST ECHOCARDIOGRAPHY

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The safety of both galenic and commercial contrast agents has been demonstrated in various clinical studies.

Gas embolism[1,2] is a potential side effect of galenic contrast agents, but has never been a major problem in a clinical context since no adverse events have been described following intracoronary injection[1].

A large number of cases have documented the good tolerability and scarce side effects, all classified as mild, of industrial contrast agents (Tables I and II)[3-14].

Levovist® is contraindicated in patients with galactosemia and must be used with caution, due to its osmolarity, in patients with severe heart failure. Optison® must not be administered to patients with known or suspected hypersensitivity to blood, hemoderivatives or albumin. SonoVue® is contraindicated in patients with known hypersensitivity to sulphur hexafluoride, right-to-left shunt, pulmonary arterial pressure > 90 mmHg, uncontrolled systemic hypertension, adult respiratory distress syndrome, assisted mechanical ventilation, and unstable neuropathies. SonoVue® has no known overdose effects, and in a phase I study in healthy volunteers it was used in dosages of up to 56 ml with no clinically significant effects.

Table I. Incidence of main adverse events during Optison infusion and in the subsequent 24 hours in 279 patients.

Adverse event	No. patients
Headache	15 (5.4%)
Nausea and vomiting	12 (4.3%)
Sensation of heat/flushes	10 (3.6%)
Dizziness	7 (2.5%)
Dysgeusia	5 (1.8%)
Chilling/fever	4 (1.4%)
Discomfort in injection site	3 (1.1%)
Dyspnea	3 (1.1%)
Weakness/asthenia	3 (1.1%)
Thoracic pain	3 (1.1%)
Flu symptoms	3 (1.1%)
Erythema	2 (0.7%)

Data supplied by Amersham Health.

Table II. Incidence of main adverse events during SonoVue infusion and in the subsequent 24 hours in 138 patients[14].

Adverse event	No. patients
Paresthesia	3 (2.2%)
Dysgeusia	3 (2.2%)
Headache	2 (1.4%)
Nausea	2 (1.4%)
Tiredness	1 (0.7%)
Pain at injection site	1 (0.7%)
Cutaneous reaction at injection site	1 (0.7%)
Pain	1 (0.7%)
Hyperglycemia	1 (0.7%)
Insomnia	1 (0.7%)
Nervousness	1 (0.7%)
Breathing alterations	1 (0.7%)

No studies have evaluated the safety of commercial contrast agents in case of direct intracoronary injection. As it is known that this infusion method influences microbubble kinesis, and as their rheology has not been studied in the absence of filtering by the pulmonary microcirculation, these agents should not be used for intracoronary injection.

Safety of contrast agents in acute coronary syndromes

To our knowledge, no collateral effects have ever been documented in the various studies on myocardial infarction. Infusion methods are identical to those approved for endocardial border delineation in both basal conditions and during stress echocardiography. The only difference in the test execution protocol is the use of software to detect the signal from microvessels, present in echo-equipment of the latest generation. Myocardial perfusion study requires a higher contrast agent dosage than is used for endocardial border study, but dosages tested in safety studies have never been overcome. Thus, although no controlled studies have ever been performed in this setting, contrast agents may be deemed to be safe for the study of the endocardial border and perfusion even in patients with acute coronary syndromes.

Potential local side effects

The interaction between ultrasound and microbubbles produces energy with potential effects on tissue. Two mechanisms of local interaction are described here below: inertial cavitation and acoustic current production.

Inertial cavitation refers to all the phenomena of formation, growth and collapse of the gas cavities within a fluid as a result of ultrasound exposure[15,16]. This releases high energy levels in a very small volume, with a temperature increase of up to thousands of degrees Kelvin in the center of the collapsed zone, generating free radicals and emitting electromagnetic radiation (sonoluminescence)[17-20]. Potential tissue damage has been reported in a study on red blood cells *in vitro* and animal cells *in vivo*[21-25]. In a clinical environment, attenuation from the tissues between the heart and transducer leads to a reduction of 0.3 dB/cm/MHz in the energy reaching the transducer's focal point. The mechanical index reported on the echo-equipment monitor takes and indicates the energy present at the transducer's focal point. As most of the myocardium lies outside the focal area, it receives a lower amount of ultrasonic energy. With the contrast agent concentrations, sound energy (< 7 W/cm^2), wave length and mechanical index used in clinical settings, the probability of important biological effects on the human heart (which is notably

larger and heavier than that of experimental animal models) is negligible[20].

Miller et al.[26] recorded in a study using an electron microscope the effects on the cell membranes surrounding oscillating microbubbles in an ultrasound field. They found an increase in membrane permeability, an effect which could be used for local drug delivery. Hilgenfeldt and Lohse[27] and Marmottant et al.[28] clarified that this increased cell membrane permeability is due to an increase in tangential stress, which deforms the cells and stretches them to the point of rupture, caused by acoustic currents secondary to the microbubble oscillation. These effects seem particularly interesting for the therapeutic applications of contrast echocardiography, but they do not seem to have clinically relevant effects.

Conclusions on the safety of contrast agents

The available data allow us to consider contrast agents for echocardiography safe and with a low risk profile:
- the contrast agents in use in Italy are hemodynamically and electrocardiographically inert;
- use for direct intracoronary injection is not permitted;
- no serious adverse events have been recorded;
- a low incidence of clinically irrelevant adverse events has been reported;
- it is unlikely that they may provoke local tissue damage in a clinical environment;
- use in acute coronary syndromes is safe.

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Part 3
Experimental studies

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Experimental studies provide fundamental data on the clinical use of contrast agents. Research on laboratory animals is concentrated on two experimental models: the evaluation of myocardial blood flow in the presence of coronary stenosis and acute myocardial infarction.

Evaluation of myocardial blood flow in the presence of coronary stenosis

Data from various experimental models demonstrate that the method has an interesting potential in the study of chronic coronary artery disease. The flow measured with contrast echocardiography relative to the different degrees of coronary stenoses correlates with invasive Doppler flowmeter and microsphere data[1-8].

Acute infarction study

The model utilized is that of prolonged coronary occlusion, with reopening of the vessel at variable time intervals. The experimental model demonstrated that contrast microbubbles are able to accurately distinguish the non-perfused (risk area) from the perfused area, and produced observations on the different aspects of the pathophysiology of acute myocardial infarction[9-26]:
- the risk area is well delineated as the area without contrast after coronary occlusion;
- during coronary occlusion, late opacification of the risk area may indicate the presence of a collateral coronary circulation able to partially compensate for the absence of flow;
- the videodensitometric signal intensity is dependent on the microbubble concentration and thus is an indicator of microvessel density;
- serial studies allow evaluation of the dynamic phenomenon of microcirculatory stunning;
- the no-reflow phenomenon occurs in around 30% of reperfusion cases;
- study of the occlusion over time allows good definition of the extent of the infarct area.

One of the most interesting aspects is the study of no-reflow, a condition of absence of perfusion in the risk area in spite of the restoration of a normal flow in the infarct-related artery. The responsible mechanism has not been unequivocally identified[27-29]. Contrast echocardiography, differently from angiographic techniques, has shown potential in the study of this phenomenon, highlighting some peculiarities:
1) there is a possibility that the reperfused area after recanalization is overestimated, due to the reactive hyperemia occurring after coronary artery recanalization. For this reason, an accurate no-reflow estimation should be performed 12-24 hours after the infarction[22,30];
2) although experimental data are not in agreement[31-33], it has been observed that, during reperfusion, damage may occur at the level of the myocardial and endothelial cells, probably caused by an increase in endothelin levels[34-36]. The use of contrast echocardiography permitted documentation of the improvement in the post-ischemic microvascular reflow after treatment with an endothelin antagonist[37].

The potential of contrast echocardiography in the identification of collaterals is known[38] and recent studies have demonstrated its importance in predicting the extent of the infarct area[13]. The evaluation of collaterals is important, not only in the acute phase, but also in chronic ischemic conditions, to evaluate the natural development of the collateral network or the phenomenon of neoangiogenesis after the administration of angiogenic substances[39,40].

Study of myocardial viability. The premise for the use of contrast echocardiography in the study of myocardial viability relates to the demonstration of microvascular integrity, a prerequisite for myocyte viability. Data deriving from experimental studies are sparse and should be considered as preliminary[41].

Concluding considerations on experimental studies

Experimental studies are a fundamental step in the understanding of the pathophysiological mechanisms and the study of the potential clinical applications of contrast echocardiography. Transfer of knowledge acquired from animal studies to the clinical arena, however, must be performed with caution for the following reasons:
- in animals with an opened chest, high-quality images are obtained, while transthoracic imaging in humans may be suboptimal due to attenuation phenomena from the chest wall and lungs, and the presence of a worse signal to noise ratio;
- animals examined during contrast echocardiographic studies are healthy before the determination of coronary stenosis, while humans undergoing such studies may be affected by various degrees of ischemic diseases;
- in animals, a single coronary stenosis is created, while humans may present with multivessel disease and/or endothelial dysfunction;
- the reperfusion pathophysiology in animals always occurs with the same mechanism, while in humans the mechanism is not always easily identifiable;

- in animals, the area of the produced coronary stenosis is compared with a healthy coronary area. This is not always possible in humans;
- reperfusion quantification using refilling curves may be complex in humans due to the presence of artifacts.

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PART 4
ENHANCEMENT OF DOPPLER SIGNAL AND CORONARY FLOW STUDY

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Doppler enhancement

Several studies have tested the efficacy of contrast agents in improving the Doppler signal[1-4] in tricuspid and mitral regurgitation, aortic transvalvular flow and pulmonary venous flow[4-7]. However, interest in this type of application has considerably dropped year by year, above all following the technological improvements in echocardiographic equipment.

The use of a shaken saline solution for the study of left-to-right shunts had been completely abandoned after the introduction and technical refinement of color Doppler. Currently, the main indication in this area is the study of patent foramen ovale during transesophageal echocardiography, with injection of a manually shaken saline solution[8]. However, since the resolution of transesophageal echocardiography is ≤ 1 mm, a patent foramen ovale should be always detected without the help of a contrast agent.

A possible field of application of ultrasound contrast agents is the study of the Doppler signal from the left anterior descending coronary artery[9] (Table I) in the minority of patients (< 5%) in whom the "native" flow is difficult to record[10-13]. However, all studies were performed using first-generation industrial contrast agents, which produce several artifacts in the Doppler spectral curve, and which may only in part be prevented by adjusting the equipment settings.

Table I. Pros and cons of the use of contrast agents in the study of coronary flow.

Pros
Increase in examination feasibility
Faster operator learning curve
Detection of low flow in small caliber vessels
Cons
Additional costs
Introduction of Doppler noise and other artifacts
Increase in test procedure complexity due to the necessity of a double infusion pump

As with other Doppler applications, the use of contrast agents for the study of the coronary flow has progressively decreased because of the improvement in echocardiographic settings and individual technique, and because of the use of higher frequency transducers[14-18]. Therefore, the latest studies are aimed at the selected use of contrast agents, limited to cases where the registration of coronary flow in basal conditions is impossible[13]. The possibility of a more extensive use of contrast agents is predicted in the study of the posterior descending arterial flow, due to anatomical reasons, a vessel which is difficult to visualize[14].

Coronary flow visualization and study of the coronary flow reserve

Resting coronary flow. The left anterior descending coronary artery flow may be studied at the middle-distal tract in almost all patients[12,14,19-21].

The visualization of long tracts of the vessel is difficult but, on the basis of the resting flow acceleration, may yield information on the presence of coronary plaques. However, quantification of the stenosis is not yet possible.

With high-frequency transducers (≥ 7.0 MHz) perforating branches of the anterior descending artery may also be visualized. The presence of flow in these vessels seems to be an accurate predictor of the recovery of post-recanalization function in acute myocardial infarction[22].

The posterior descending artery is visible in around 50-70% of cases[17,18]. The vessel position seems less favorable for flow visualization, in part because its distance from the thoracic surface does not allow the use of high-frequency transducers.

The possibility of extending the study of the coronary flow to the right coronary artery seems fundamental if coronary flow reserve (CFR) studies are to be complete. However, this is an objective which to date has not yet been reached.

Study of coronary flow reserve. CFR is measured by recording the flow in basal conditions and after vasodilation induced with adenosine or dipyridamole[23], and is calculated as the ratio of the hyperemic and resting peak diastolic flow velocities.

These drugs act in two ways:
• endothelium-independent mechanism, provoking vasodilation of the coronary microvessels with a diameter < 170 μm, which accounts for 75% of the total coronary resistance;
• endothelium-dependent flow mechanism, which dilates coronary arteries with a diameter > 170 μm, responsible for the remaining 25% of the total coronary resistance.

High doses of adenosine and dipyridamole may induce a similar vasodilation[24] and can be used effectively (Table II), but adenosine is a more reliable, safe and versatile drug. On the other hand, dipyridamole may be used to evaluate the coronary flow and myocardial contractility in the same examination[25].

The reference method for the study of CFR is with no doubt intracoronary Doppler (Doppler flow-wire). Various studies have compared the two methods and the results indicated that the data calculated with transthoracic echocardiography are reliable[12,19,26-28].

Clinical applications. *Evaluation of the entity of coronary stenosis.* Values of CFR > 2.5 are considered indicative of the absence of a flow-limiting coronary stenosis. Values < 2 indicate the presence of a flow-limiting coronary stenosis. There is a gray zone of intermediate CFR, ranging from 2 to 2.5, where the correlation with angiography is less strong. A CFR ≤ 1 suggests the presence of a severe coronary artery stenosis[20,29].

Table II. Drugs used in the study of the coronary flow reserve.

In favor of adenosine
Speed of action
Speed of elimination
No need for an antidote
Greater safety (rapid interruption of examinations when side effects occur)
Shorter examination
Better patient compliance
In favor of dipyridamole
Cheaper product
Possibility of simultaneous evaluation of myocardial contractility

Follow-up of percutaneous coronary interventions. The most commonly used clinical application of CFR with transthoracic echocardiography is currently the follow-up of percutaneous coronary interventions[30]. Serial measurements are potentially useful in the early identification of restenosis[31-33], as a reduction in CFR compared to a post-procedural reference value, may identify the development of a subclinical restenosis[34].

It is known that other provocative tests of ischemia are not accurate in predicting restenosis over time, and symptoms are often atypical and non-specific. The definitive role of transthoracic coronary Doppler will be highlighted by the results from multicenter studies currently in progress.

Study of the microcirculation. Possible areas for the study of the microcirculation by means of echocardiographic evaluation of CFR are:
• the evaluation of the functional integrity of the microcirculation after primary angioplasty[35]. The vasodilatory response in the infarcted area is directly proportional to the extent of viable myocardium[36] and CFR after primary angioplasty could thus predict the functional recovery of the infarcted myocardium[24,37];
• the study of patients with chest pain and normal coronary arteries[15,34]. An altered CFR may confirm the cardiac origin of the chest pain and may conversely rule out false positives from ECG stress tests[38];
• the study of patients with disease potentially affecting the microcirculatory function, such as diabetes[39], hypertension[40-45], hypercholesterolemia[31] and other metabolic[46] or endocrine[47] disorders.

Study of arterial grafts. The Doppler curve of the grafted mammary artery changes from a "native" triphasic pattern, with a dominant systolic and a reduced dias-

tolic component, to a biphasic pattern, with a reduction in the systolic and an increase in the diastolic component[47-50]. In order to obtain adequate information on graft function, CFR should be measured by dipyridamole or adenosine, following the same guidelines proposed for coronary artery study[51].

Conclusions

The study of CFR is feasible in the left anterior descending coronary artery and requires mastering of an unusual examination method.

The calculation of CFR is not burdened by any methodological difficulties, and is a highly sensitive pathophysiological index in the evaluation of coronary stenosis, and therefore in the clinical and therapeutic management of patients with coronary artery disease.

This non-invasive method allows one to perform serial measurements in subjects undergoing revascularization procedures in the area of the anterior and posterior descending arteries or, in the context of other cardiac diseases, to evaluate over time the efficacy of pharmacological therapies aimed at improving the coronary flow[52,53].

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PART 5
ENDOCARDIAL BORDER ENHANCEMENT

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The main clinical indication for industrial contrast agents is the opacification of the left ventricular cavi-

ty[1]. In particular, contrast agents are used to enhance the definition of the endocardial borders and improve evaluation of left ventricular volume, geometry and function in patients with a reduced acoustic window. In fact, it is estimated that, even when using tissue harmonic imaging, endocardial borders are still inadequately visualized in about 5-15% of routine echocardiograms[2-4].

Other indications for intravenously injected contrast agents are the detection of endoventricular thrombosis[5-7], non-compaction of the left ventricle and heart rupture[8].

Contrast echocardiography for endocardial border delineation

Only second-generation contrast agents may be clinically used for this indication (Table I). Compared to first-generation agents[9-12], in fact, they have shown a higher increase in the percent improvement of endocardial borders[13]. This advantage is also seen in patients with global left ventricular dysfunction[14-16]. By the use of second-generation contrast agents, 75% of non-diagnostic echocardiograms may now be evaluated, and in 50% of cases it is possible to respond to the primary diagnostic question[17].

Data from the literature show that the use of contrast agents increases both the accuracy and reproducibility of the echocardiographic examination[11,18-21]. In particular, injection of contrast agents improves the ability to identify and evaluate changes in the regional left ventricular wall motion, especially at the level of the anterior and lateral walls.

Contrast echocardiography and automated endocardial border recognition

One of the most promising research fields in contrast echocardiography is the automated recognition of the endocardial borders for rapid and accurate evaluation of left ventricular volume, global systolic performance, and regional wall motion. Actually, the increased definition of the endocardial borders obtainable with current contrast agents has the potential of making computerized algorithms for border extraction working accurately, which is not possible at present using fundamental imaging[22-25].

Power Doppler images have favorable characteristics for automated border extraction, despite reduced spatial resolution and anatomical details compared to standard gray-scale echocardiography[26-30]. The critical point is the differentiation of myocardial wall from ventricular cavity. In this respect, pulse-inversion, power-modulation and phase-inversion techniques are very promising. The high sensitivity of weak echoes generated by low contrast agent concentrations associated with low-energy ultrasound imaging facilitates a uniform opacification of the left ventricular cavity without significant attenuation: this significantly improves visualization of the intramyocardial contrast[31].

Table I. Impact of contrast medium on the echocardiographic examination.

Influence on information content
- About 70% of non-diagnostic examinations become diagnostic
- Clinical questions relative to the quantitative evaluation of left ventricular function may be answered in about 50% of cases
- Best results are obtained when 2 to 6 adjacent myocardial segments are not adequately visualized at standard echocardiography

Influence on reproducibility
- Compared to reference methods, the accuracy of volume calculation is improved
- Inter- and intraobserver variability is reduced
- The ability to identify regional wall motion alterations is improved

Examination reimbursement

Despite the advantages of contrast echocardiography for the evaluation of left ventricular function in technically difficult patients and/or in difficult environmental conditions, such as in the intensive care or emergency units, this technique is still underutilized in Italian laboratories. The same seems to hold true in the United States[32,33], while in Great Britain contrast echocardiography seems to be more utilized[34]. The main reasons for a reduced use of contrast agents are the need for specific training and the non-reimbursable cost[32,35]. A survey conducted among regional delegates of the Italian Society of Cardiovascular Echography showed that contrast echocardiography currently is only reimbursed in Friuli Venezia Giulia (Ä 83 specifically). The cost-efficacy of the method, however, has been demonstrated[36,37]. A study of Yong et al.[20] on patients admitted to the intensive care unit, for example, showed that the use of contrast agents allowed avoidance of transesophageal echocardiography for the evaluation of left ventricular systolic function in technically difficult patients, saving $423 for every 1% increase in accuracy per 100 patients.

Conclusions

Standard echocardiography is a highly feasible technique. In this respect, contrast echocardiography offers little margin of improvement. Conversely, in patients with suboptimal image quality, opacification of the left ventricle by intravenous injection of industrial contrast agents significantly increases the informative content of the echocardiographic examination, improving the accuracy and reproducibility of quantitative

evaluation of volumes and ejection fraction. Power Doppler echocardiography seems to be the most effective ultrasound technique for the accurate differentiation between the ventricular cavity and myocardial wall[38] and is also the most promising approach for the application of automated border extraction algorithms.

Because of the high cost of current contrast agents, the use of contrast echocardiography for ventricular opacification should be restricted to patients where the cost-effectiveness ratio is acceptable. These patients are identified by the presence of at least two of the following characteristics:
- lack of visualization of the endocardial borders of 2-6 adjacent segments in the apical views;
- inappropriate visualization of the ventricular myocardium for the evaluation of regional wall motion;
- predictable diagnostic and prognostic usefulness of the procedure.

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Part 6
Use of contrast agents during stress echocardiography

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The use of contrast agents during stress echocardiography has two main objectives:
- to improve endocardial border detection and thus facilitate recognition of wall motion abnormalities during pharmacological stress or physical exercise;
- to obtain information on perfusion as well as function during stress.

Improvement of diagnostic accuracy

Interpretation of stress echocardiography is notoriously qualitative and based on the operator's subjective assessment. Accurate visualization of every ventricular wall is thus a fundamental prerequisite to guarantee good reproducibility and a high diagnostic accuracy.

Harmonic imaging has considerably improved image quality, providing undoubted benefits to stress echocardiography[1,2]. In particular, a limited number of patients are considered inadequate to undergo stress echocardiography because of poor image quality; thus, the feasibility of stress echocardiography with harmonic imaging can currently be considered very high. However, the increasing number of patients eligible for stress echocardiography results in a significant number of patients with an echocardiographic window which may be defined as intermediate.

Visualization of the endocardial border further improves after the infusion of a contrast medium both at rest and during stress echo[3-8]. In patients with poor image quality, the contrast medium reduces interobserver variability and increases diagnostic accuracy[9]. This results in an improvement in the cost/benefit ratio in the context of the diagnostic procedure for patients with coronary artery disease[6,10-14].

Border definition is only one of the interpretative parameters of stress echocardiography and should always be associated with the evaluation of systolic thickening. In the past, this was unfeasible in a significant proportion of patients, especially at peak stress, due to the physical properties of contrast agents and limited ultrasound equipment settings. Currently available software suitable for the real-time study of myocardial perfusion may also be used during stress echo, considerably improving the signal from the myocardium. In this way, both the endocardial border and left ventricular wall are enhanced through cavity and myocardial opacification.

Evaluation of myocardial perfusion

The possibility of obtaining information on both function and perfusion during stress is an attractive issue pursued by echocardiography. When considering that during the ischemic cascade, changes in contractility are preceded by perfusion abnormalities, the usefulness of perfusion study during ischemic challenge can easily be appreciated. Until recently, only scintigraphic methods were able to supply perfusion information during physical exercise or pharmacological tests. For this reason, studies evaluating perfusion with contrast agents during stress echo have considered nuclear methods as the reference methods. There are a number of comparative preliminary studies showing satisfactory agreement between the two methods[15-21] especially in the area of the left anterior descending coronary artery.

Vasodilators such as adenosine and dipyridamole were used at first, especially in comparative studies with scintigraphy, due to the presence of validated diagnostic protocols in nuclear medicine[16,17], while dobutamine use is more recent[22,23] and is currently limited to the experimental field. Thus, to date there are insufficient data to establish which is the best stressor in conjunction with contrast echocardiography to highlight the presence of perfusion abnormalities during stress (Table I).

Conclusions

Contrast agents require optimal settings of the echocardiographic equipment to allow real-time analysis and improved visualization of the wall thickness (Table II).

Even taking into account the increased feasibility of stress echo due to the introduction of harmonic imaging, contrast agents may be used during stress echocardiography not only in patients with poor but also in those with intermediate acoustic windows. This is due to the fact that the accuracy of stress echocardiography increases with improvement in the echocardiographic image quality and thus any tool which improves image quality must be considered useful.

The added cost is related only to the use of the contrast medium, given that, in pharmacological stress echo, the infusion line is already prepared. Preliminary cost-benefit studies suggest an advantage in contrast medium use, although this must be confirmed in larger studies.

Myocardial perfusion evaluation during stress echocardiography is an interesting study area, but it does not currently have any specific clinical applications.

Table I. Type of stressors available for the evaluation of myocardial perfusion during stress echocardiography.

Physical exercise
Advantages
Increased oxygen consumption
Limitations
Tachypnea and tachycardia
Post-test image acquisition
Dipyridamole and adenosine
Advantages
Low increase in respiration and heart rates
Stressors used with other imaging techniques
Limitations
Lower sensitivity (without atropine)
Few data on stress echocardiography with adenosine
Dobutamine
Advantages
Additional information on contractile reserve
Limitations
Tachypnea and tachycardia
Perfusion data more difficult to obtain

Table II. Requirements for the use of contrast agents in stress echocardiography to improve diagnostic accuracy.

Real-time evaluation
Possibility of identifying the endocardial border even at high frequencies
Myocardial wall visualization to improve systolic thickening evaluation
Preferential use in patients with suboptimal acoustic windows

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PART 7
MYOCARDIAL PERFUSION

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Two imaging modalities, intermittent and real-time imaging, are currently used to detect the presence of microbubbles in the myocardium. At sufficiently high acoustic pressures, ultrasound destroys microbubbles (stimulated acoustic emission) producing a strong signal that may be easily detected using the intermittent imaging modality, whereas at low acoustic pressures microbubbles resonate producing a weak harmonic signal that may be detected using real-time imaging[1-8] (Table I).

Table I. Technical issues for an adequate myocardial opacification.

Intermittent imaging
- A microbubble concentration sufficiently high to produce an intense breaking signal
- Intermittent imaging with ultrasound impulse emission at increasing trigger intervals sufficiently long to guarantee that the contrast medium refills the beam
- Equipment able to detect the microbubble breakage signal by Doppler power

Real-time imaging
- Contrast agents able to resonate at low acoustic pressures
- A microbubble concentration sufficiently high to guarantee a return signal intense enough to be analyzed
- System for detecting non-linear signals produced by microbubble resonance

Imaging modalities

Intermittent imaging. To obtain a reliable myocardial opacification by destructive methods, contrast agents with a thin shell and a low persistence gas should be used. The reduced solubility and high molecular weights of the gases used for second-generation contrast agents makes it harder to differentiate them from tissue when a microbubble destruction imaging technique is used.

It is relatively easy to detect myocardial perfusion using this technique since a strong signal is produced by bubble destruction; however, it is relatively hard to maintain the same scan plane during intermittent imaging and this limits the routine use of this method.

Real-time imaging. The "flash" method is currently used to assess the replenishment curves. After a few frames (5 to 9) using the highest possible mechanical index, all the bubbles are destroyed. Switching at a low mechanical index (0.09 to 0.15), a signal produced by bubble resonation may be followed until complete refilling is reached. For this imaging modality, only second-generation contrast agents may be used.

Commercially available echocardiographic instruments use various systems to detect microbubble resonance[5,9,10] (Table II). All of these have the aim of identifying the distorted low intensity signal produced by microbubbles (non-linear response), which is completely masked by the tissue components in traditional settings.

Table II. Softwares to detect microbubble resonance.

Application	Function principles
Pulse inversion	Emission of two consecutive ultrasound pulses in phase opposition
Power pulse inversion	As pulse inversion using a Doppler power signal
Single pulse cancellation	Two-dimensional analysis of the different phases of adjacent ultrasound sectors
Power modulation	Use of two consecutive ultrasound pulses with differing amplitudes
Contrast pulse sequence	Analysis of the linear and non-linear response components of microbubbles with exclusion of the components deriving from tissue

With this technique, there is no need to use trigger-type imaging and microbubbles are not destroyed, thus allowing continuous detection of the signal within the myocardium. For these reasons, the technique has been defined "real-time perfusion imaging"[11-18].

Using a low-energy technique, higher doses of contrast media have to be used to enhance the weak signal detected within the myocardium, however, it is easier to maintain the same scan plane during contrast injection. Myocardial perfusion and contraction may simultaneously be assessed, thus reducing artifacts and pitfalls.

Intermittent versus real-time imaging. The relative advantages and limits of the two methods for microbubble signal detection (stimulated acoustic emission and detection of a non-linear signal) are summarized in table III. Only one comparative study has been published on the two different imaging modalities and similar results were obtained[19].

Although more consistent literature data are needed, there is general agreement on the greater benefits offered by real-time imaging.

Infusion method. Both bolus injection and continuous contrast agent infusion throughout a pump are used (Table IV). It currently seems advisable to use continuous infusion, limiting the use of bolus injection to the evaluation of the area at risk in acute settings[20-22]. The infusion speed cannot be currently standardized due to the variability of the contrast packages available in the various echocardiographic instrument sets and to patient to patient differences in the acoustic window, but it should be regulated in each individual laboratory to optimize the relationship between the perfusion signal and the attenuation provoked by high concentrations of microbubbles in the left ventricle.

Myocardial perfusion: evaluation methods

Myocardial perfusion may be evaluated with qualitative, semi-quantitative or quantitative methods (Table V).

Qualitative and semi-quantitative methods. Myocardial perfusion may be qualitatively graded as normal,

Table III. Advantages and limits of different imaging modalities to assess myocardial perfusion.

For	Against
Trigger	
More clinical data	Non-uniform bubble destruction within the ultrasound field
Strong signal easy to detect at ultrasound	Increasing trigger intervals needed for quantification
Used in experimental models to validate quantification methods	Possible scan plane changes during prolonged trigger intervals
Usable with first- and second-generation contrast media	
Currently widespread use	
Real-time	
Possible to maintain a well-centered image in the ultrasound field	Less widespread use
Easier to use with a larger potential diffusion	Less clinical data
Simultaneous evaluation of flow and contractile function	Software not yet optimized

Table IV. Advantages and limits of different contrast agent infusion modalities for myocardial perfusion.

Bolus	Continuous infusion
Rapid plateaus but frequently with attenuation	Prolonged diagnostic threshold
Brief diagnostic threshold	Constant input function for microcirculation replenishment (mandatory for quantification)
Not useful for quantification	Microbubble concentration strictly dependent on infusion speed
	Need of dedicated infusion pumps (high-infusion speed, self-stabilizing)

Table V. Different methods for myocardial perfusion analysis.

	Method	Characteristics
Qualitative	Presence or absence of microbubble signal	Useful in the acute phase All or nothing response Ischemia severity not assessable
Semi-quantitative	0 to 3 score for each segment based on myocardial contrast enhancement CSI calculation	Variability in the interpretation of the intermediate score CSI damage extension index CSI prognostic index
Quantitative	Video intensity/time curves reconstructed with dedicated softwares	Intracoronary injection: wash-in/wash-out curve Intravenous injection: refilling curves

CSI = contrast score index.

abnormal or non-homogeneous. A semi-quantitative contrast score is generally used: 0, no enhancement; 1, patchy enhancement; 2, homogeneous enhancement. A contrast score index may be calculated by dividing the sum of the contrast scores for each segment by the number of segments analyzed. For viability purposes, a perfusion score index in the risk area may be derived by dividing the summed perfusion scores in the risk area by the number of dysfunctional segments.

Semi-quantitative methods are currently used to study acute myocardial infarction. The diagnostic and prognostic roles of a preserved myocardial opacification and/or of perfusion defect within the dysfunctional area have been well established in several clinical studies[22-32]. Controversial data have been reported as for the prognostic role of patchy perfusion. For the better delineation of non-homogeneous perfusion within the infarct zone, future quantitative studies are needed.

Quantitative methods. The extent of a perfusion defect may be calculated as the sum of the endocardial border length of the perfusion defect divided by the total endocardial length. The ratio between the relative perfusion defect size before and after different reperfusion strategies should be considered as a valid quantitative instrument to assess the extension of the reflow area in reperfused acute myocardial infarction[33-37]. A useful threshold value (50%) may be extrapolated for prognostic purposes.

Using quantitative software, an off-line analysis of the refilling curves may be obtained. After flash in real-time imaging, or increasing pulse intervals using intermittent imaging, myocardial videointensity progressively increases with time until the myocardial blood volume within the entire ultrasound beam is filled and reaches a plateau. At this stage, videointensity reflects the myocardial blood volume. At this point, the signal detected within the myocardium is a corollary of the blood volume of the myocardial capillaries. The rate of change of videointensity from baseline to the plateau represents the microbubble velocity. For each segment, plots of the signal intensity vs the time or pulsing intervals may be constructed and fit an exponential function $y = A \times (1\text{-}e^{-\beta t})$ where A is the plateau or videointensity peak and β is the rate constant that determines the rate of increase of videointensity. A is a measure of the myocardial blood volume, β is a measure of the microbubble velocity and the product $A \times \beta$ is a measure of the myocardial blood flow.

The calculation of these parameters has been widely validated in experimental studies[11,13,38-43]; in particular, preliminary data showed that the microcirculatory flow reserve during hyperemic stimulation may be calculated[12,44,45].

Using intermittent imaging, only systolic frames are stored; similarly, there is a general consensus on the analysis, even in real-time imaging, of selected consecutive systolic frames to improve the quality of quantitative assessment.

Despite a solid theoretical and experimental basis there are not enough data in the literature showing the additional role of quantitative analysis for clinical purposes. Thus, at present, quantitative softwares should be considered as research tools.

Clinical applications

Acute myocardial infarction. Myocardial contrast echocardiography (MCE) has been widely employed in patients with acute myocardial infarction. Both intracoronary and intravenous contrast agent injection have been used.

Intracoronary myocardial contrast echocardiography. Several MCE studies showed that about one fourth to one third of acute myocardial infarction patients treated with primary angioplasty have an inadequate tissue perfusion (no-low-reflow phenomenon) despite angiographically successful coronary recanalization. The clinical impact of the "no-reflow phenomenon" has been largely demonstrated by several intracoronary MCE studies showing that patients with microvascular dysfunction soon after infarct-related artery reopening may

exhibit no significant contractile reserve or functional recovery at follow-up. The infarct size in experimental animal models is slightly underestimated due to the hyperemic response immediately after recanalization. The greatest changes in the injured microvasculature occur within one day of infarct-related artery reopening whereas the extent of microvascular damage is relatively stable on the second hospital day. Thus, the best timing to perform contrast studies should be 1 day after the achievement of a sustained coronary reflow. Whereas there is consensus, based on experimental and clinical studies, on the use of the MCE extent of the no-reflow area after reperfusion as a good predictor of irreversible left ventricular dysfunction at follow-up, the available data on the changes in microvascular perfusion in the convalescent phases after acute myocardial infarction are conflicting. Different studies indicate that ischemic microvascular damage may be reversible or progressive after coronary reflow confirming the presence of "microvascular stunning". The degree of perfusion and functional improvement varies among patients; however, the extent of MCE reflow at 1 week after acute myocardial infarction is highly predictive of left ventricular functional recovery up to 6 months after acute myocardial infarction. Thus, in patients surviving acute myocardial infarction, the predischarge MCE analysis of the extension of residual perfusion within the infarct zone is a simple and useful method to better distinguish still viable from necrotic myocardial regions[24,25,27,29,33,34,36,46-69].

Intravenous myocardial contrast echocardiography. Several intravenous MCE studies have been recently published further confirming previous intracoronary MCE data.

In brief, the results obtained at intravenous MCE in the setting of acute myocardial infarction may be summarized as follows:

• there is a close correlation between intravenous and intracoronary MCE in detecting the no-reflow phenomenon[67];

• there is a close correlation between a preserved microvascular perfusion after acute myocardial infarction and the coronary flow reserve using intracoronary Doppler flow-wire[37];

• microcirculatory perfusion may improve 24 hours after acute myocardial infarction, confirming that microvascular damage after reperfusion may be a dynamic phenomenon[70];

• there is a close correlation between the predischarge contrast defect extent and the contractile function recovery over time[37,71-73];

• the contrast defect extent is an independent predictor of left ventricular remodeling[74].

Thus, intravenous MCE assessment of microvascular dysfunction plays a crucial role in the phases of acute myocardial infarction:

• during infarct-related artery occlusion, to evaluate the extent of the area at risk;

• after infarct-related artery reopening, to evaluate the efficacy of reperfusion. Preliminary studies showed that intravenous MCE may be particularly helpful in the assessment of the efficacy of different recanalization strategies[75]; further clinical studies are needed to demonstrate the role of this technique in the assessment of distal microembolization;

• on day 1 after reperfusion, to evaluate the residual area at risk;

• at predischarge, to assess the final microvascular damage.

Myocardial viability. Several studies support the hypothesis that either the contractile reserve as assessed by dobutamine stress echocardiography or the possibility of myocardial dysfunction to recover are strictly dependent on the maintenance of microvascular integrity.

In patients with myocardial infarction, myocyte loss is accompanied by a loss of microvasculature; thus, the MCE detection of a perfusion defect may be evidence of lack of tissue viability. A recent elegant study[76], designed with the aim of assessing, in patients with postischemic left ventricular dysfunction, the histological correlates of MCE-derived quantitative parameters, confirms this hypothesis showing that the peak contrast effect (A), an index of the myocardial blood volume, correlates with the microvascular density and capillary area and inversely with the collagen content and thus helps to differentiate hibernating from necrotic tissue.

For these reasons, MCE seems to be one of the most effective techniques for the assessment of tissue viability.

Quick confirmation of the extent of microvascular integrity in acute myocardial infarction patients and of successful reperfusion has important implications for patient management. The presence of a preserved microvascular flow in the acute postinfarction period is associated with a lower rate of fibrous scar formation and with less ventricular remodeling. Moreover, there is a close relation between the extent of microvascular perfusion soon after acute myocardial infarction and the relative risk of major cardiac events. Controlling for infarct size did not eliminate the power of microvascular obstruction in predicting the occurrence of adverse postinfarction events.

Comparison with other imaging techniques. The relationship between the residual perfusion and inotropic reserve of dysfunctional myocardium has been investigated. The proportion of segments showing a positive dobutamine stress echo response is significantly lower than that with a normal ^{201}thallium uptake or a preserved MCE perfusion. The rate of agreement between dobutamine stress echocardiography and perfusion techniques is low. It was hypothesized that the cellular mechanisms responsible for a positive response to dobutamine stimulation require a higher degree of myocyte functional integrity than those responsible for perfusion imaging. However, the prevalence of postoperative functional im-

provement in single-photon emission computed tomography-MCE-viable patients is low, resulting in a lesser specificity and positive predictive value as compared to dobutamine stress echocardiography. On the contrary, in all dyssynergic segments graded as viable at dobutamine stress echo and improving after revascularization, a residual perfusion was detected. On the other hand, in the absence of residual perfusion, contractile recovery at follow-up has never been observed, despite a positive response to dobutamine stress echo. Finally, in some severely dysfunctional but viable segments, the contractile reserve may be exhausted if the residual stenosis is subcritical. However, the functionality of these segments may improve after revascularization, when graded as viable at MCE[77-79]. Furthermore, recent MCE studies have suggested a beneficial role of microvascular integrity in postinfarction left ventricular remodeling, independent of the effective functional recovery. Further studies are needed to evaluate the long-term impact of different extents of dysfunctional areas with preserved microvascular integrity on ventricular remodeling and cardiac death.

The diagnostic agreement between dobutamine stress echo and MCE is higher than that reported in radionuclide studies. This result could be related to the higher specificity of MCE as compared to ^{201}thallium scintigraphy in predicting reversible dysfunction. Three factors may contribute to the observed discordance between these two perfusion techniques:

• direct assessment of myocardial perfusion cannot be achieved by radionuclides since these tracers simply provide estimates of the relative differences in tracer distribution in different areas. Conversely, MCE provides an estimation of the relative myocardial opacification within a segment, independently of the perfusion in the other segments;

• at MCE both microvascular perfusion and regional wall motion may be simultaneously evaluated; thus, false contrast defects are reduced;

• microbubbles behave as a pure flow tracer whereas ^{201}thallium behaves as a metabolic tracer.

Finally, only few comparative studies with positron emission tomography and magnetic resonance imaging were published; thus, at present it is impossible to derive any significant information[57,80-84]. Several studies compared MCE perfusion and myocardial blush and TIMI frame count as assessed at coronary angiography: both angio parameters were found to be less effective than contrast echocardiography[71]. Unless new data are presented, it does not currently seem worthwhile to proceed with further comparative studies with myocardial blush or TIMI frame count.

Conclusions

In the field of acute myocardial infarction, perfusion studies with contrast echocardiography seem to have great potential, especially in the evaluation of the effects of reperfusion therapy. There is general consensus on the use of MCE to assess the results of reperfusion therapy and to obtain prognostic information. However, the additional value of contrast echocardiography has not yet been validated in large clinical trials, although some multicenter studies are currently in progress. More extensive use of this technique is particularly indicated in acute myocardial infarction patients with suspected failed reperfusion. In this subgroup of high-risk patients, MCE may be particularly helpful in indicating more aggressive strategies.

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PART 8
IMPLEMENTING ULTRASOUND CONTRAST IN THE ECHOCARDIOGRAPHY LABORATORY

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Incorporating the use of ultrasound contrast agents into the routine echo-lab procedures requires a significant reorganization of the laboratory in terms of culture, resources, staff and materials. As performing a contrast echocardiogram involves the administration of a pharmaceutical agent, the decision on whether to perform it must be taken by a physician alone or in consultation with the sonographer and/or registered nurse, in those laboratories where such staff are skilled in the acquisition of echocardiographic images. In any case, the performance of contrast studies requires a team approach and the cooperation of several health workers (just as for stress or transesophageal echocardiographic studies) and the reorganization of the laboratory[1]. The physician has the responsibility of coordinating the group in such a way as to optimize results, avoid artifacts, and reduce waste of contrast media, whose cost is not negligible. It is thus essential that the group coordinator understands the effects of contrast media in echocardiographic imaging, their dosages, administration methods and contraindications, and has sufficient experience to set the machine and optimize image acquisition. In fact, the quality of contrast images depends both on the quality and quantity of contrast agent infusion and on the appropriate settings of the echo machine[2].

Impact on laboratory resources

Ultrasound contrast should be considered an extension of the existing echocardiographic examination. For this reason, the laboratory design and equipment should be standard, and meet the requirements on laboratory accreditation of the Italian Society of Cardiovascular Echography[3]. A hazardous waste container, in accordance with the universal precautions and hazardous waste guidelines[4], where supplies used to access veins and to infuse ultrasound contrast agents (gloves, needles, syringes, cotton) can be discarded should be added to the standard equipment. The examination bed should be positioned to allow access to the patient's arm and vein and inject the contrast agent.

When the standard practice is to image the patient from the left side, placement of the vein access (needle size ≥ 20G) in the right arm is preferable. For right-handed scanners that position the echocardiographic system to the right of the patient, the left arm may be preferable for intravenous insertion and contrast agent injection. Of course, in some patients vein access will be limited to the arm opposite to the preferred one.

Apart from supply availability, staff experience and knowledge requirements and the incorporation of ultrasound contrast into routine practice may also represent a considerable source of increased expenditure for the laboratory. It is in fact estimated that around 20% of routine echocardiographic studies are of non-optimal quality and about 30% of echo stress studies are non-diagnostic due to suboptimal image quality[5]. Since around 50% of echocardiographic studies are per-

formed to evaluate the left ventricular function, and even though a single vial of contrast medium may be used to study more than one patient, the annual cost increase for the laboratory will certainly be significant (Table I). This cost should however be cushioned, taking into consideration that these patients would otherwise have to undergo other imaging modalities (transesophageal, radionuclide angiography, or magnetic resonance) to assess their left ventricular function. Yong et al.[6] have demonstrated how the performance of contrast echocardiography in patients with a suboptimal echocardiographic window leads to a transesophageal echocardiogram saving 3% for regional wall motion evaluation and 17% for global left ventricular systolic function evaluation. It may be assumed that for methods such as ventriculography with radionuclides or magnetic resonance the savings will be even greater.

Echocontrastographic examination significantly prolongs the duration of the routine echocardiographic examination. In our experience, the need to explain to patients the indication for the examination, obtain their written consent, access a peripheral vein, and prepare the contrast medium and physiological agent prolong the routine echocardiographic examination by 20 ± 7 min.

The economic impact and time commitment are much less when contrast agents are used during stress echocardiography. This is generally an examination which is performed to select patients for coronary angiography and possible revascularization. For this reason, the economic impact of injection of a contrast medium improving the accuracy of the evaluation of regional kinesis on the complete diagnostic-therapeutic protocol is relative. Finally, patients undergoing stress echocardiography already have an intravenous line and consent for the addition of the contrast medium to the examination may be contextual to that for stress echocardiography.

The economic issue, time consumption, and personnel upgrading requirements to run a program of contrast echocardiography determine the fact that without adequate reimbursement there is no incentive to perform this procedure. A survey we performed among regional delegates of the Italian Society of Cardiovascular Echography demonstrated that, at present, in only one Italian region (Friuli Venezia Giulia) is cardiac contrast echo reimbursed.

Table I. Cost analysis of incorporating ultrasound contrast into echocardiography laboratory routine practice. Example of costs for staff and supplies.

Item	Cost
Direct cardiologist's time (hours): 0.20	€7,1*
Direct sonographer's/nurse's time (hours): 0.20	€2,9*
Direct support staff time (hours): 0.12	€1,6
Ultrasound contrast agent (1/3 vial per patient)	€22
Direct procedure supplies (gloves, tourniquet, 1 10 ml syringe, 1 10 ml saline vial, 1 19G needle, 1 20G angiocatheter, injection cap and/or extension tubing, 3-way stopcock, sharps and waste containers)	€7,65
Direct patient supplies (tape, 2×2, alcohol pads, etc.)	€0,35
Support supplies (pens, billing and report forms)	€0,10
Equipment cost/depreciation	Not available
Total directs costs	€41,70

* calculated by using an average salary for registered nurses and diagnostic cardiac sonographer from the 2002 National Salary Contract for Health Operators.

Patient selection

The procedure costs and its organizational impact on the laboratory limit its application to specific patient categories. The quality of non-enhanced endocardial visualization images (with or without the harmonic imaging, according to the local technological facilities) and the expected impact on patient management should be the key parameters on which the decision to complete a standard echocardiographic examination by adding an injection of a contrast agent is made. The currently recognized technical indications are:

- enhancement of left ventricular endocardial border delineation;
- improvement in Doppler signal;
- intracardiac/intrapulmonary shunt diagnoses.

Some American echocardiography laboratories have specified written criteria to define the cases in which there are indications to complete the echocardiographic examination with injection of a contrast agent. In general, there is agreement to administer a contrast agent to improve the visualization of the endocardial border in examinations where the main clinical requirement is the evaluation of the left ventricular function and it is not possible to evaluate ≥ 2 segments out of 6 (using a 16-segment left ventricular segmentation model) in the apical sections[7].

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Appendix

Consensus Conference Participants

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