JACC Vol. 26, No. 1
July 1995:12–7

Myocardial Contrast Echo Effect: The Dilemma of Coronary Blood Flow and Volume

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Despite the useful information provided by myocardial contrast echocardiography, the meaning of myocardial contrast intensity remains elusive. This review is meant to define the contribution of physical and biologic factors in producing myocardial contrast and to elucidate the relative roles of coronary blood flow and intramyocardial blood volume in determining contrast effect. The main physical factors influencing the contrast echo effect include the properties of microbubbles as scattering elements (mainly their radius, compressibility, stability and concentration), electronic signal processing, instrument setting and contrast-induced signal attenuation. The effect of these factors can be limited by an appropriate experimental or clinical setup. Biologic factors are less easily controllable, and changes in coronary blood flow and alterations in myocardial blood volume appear to be the main determinants of myocardial contrast intensity. Moreover, these factors influence contrast intensity in opposite directions. Both the area under the time-intensity curve and the mean transit time of myocardial contrast are inversely related to coronary blood flow but directly related to myocardial vascularity and blood volume. Therefore, an increase in coronary flow not accompanied by an increase in myocardial vascularity and volume is accompanied by a decrease in the area under the curve and mean transit time of contrast. Conversely, an increase in coronary flow mediated by augmented myocardial vascularity and volume will produce an increase in the area under the curve and mean transit time. A better understanding of the physical and biologic determinants of contrast echo intensity will be fundamental in the clinical application of new agents and technologies.

(J Am Coll Cardiol 1995;26:12–7)

Opacification of the myocardium by intracoronary injection of an ultrasound contrast agent was first demonstrated in 1980 (1). Subsequently, the injection of a variety of contrast agents into the left atrium, left ventricle, aorta or coronary circulation during echocardiography has been shown to increase the intensity of myocardial ultrasound signals, a phenomenon referred to as the myocardial contrast echo effect. The spatial distribution of this effect within the ventricular walls and the change in the intensity of myocardial contrast over time constitute the basis for the study of myocardial perfusion by contrast echocardiography. The myocardial contrast echo effect appears to depend on a variety of factors, some of which are not yet completely understood. Thus, despite the useful information provided by myocardial contrast echocardiography (2–14) and the growing interest in this field, the meaning of regional myocardial contrast intensity remains elusive and potential clinical applications of this technique remain uncertain.

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Manuscript received July 14, 1994; revised manuscript received February 16, 1995, accepted February 27, 1995.

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Over the past few years several studies have been performed in our own and other laboratories with the aim of quantifying coronary blood flow by contrast echocardiography. These studies were performed in in vitro and experimental models of the coronary circulation, as well as in humans. Although shedding light on specific aspects of myocardial contrast, such studies have not provided a comprehensive understanding of this phenomenon. This review is meant to reevaluate these studies in an attempt to define the contribution of physical and biologic factors in producing myocardial contrast and to elucidate the relative role of coronary blood flow, intramyocardial blood volume or other factors in determining contrast effect.

Physical factors influencing the contrast echo effect. The major determinants of the intensity produced by a contrast agent are related to the properties of microbubbles as scattering elements, mainly including the radius, compressibility and stability of microbubbles (15,16). For a given intensity of the incident ultrasound beam, the amplitude of the backscattered signal increases exponentially with the radius of microbubbles. Signal amplitude also increases with the compressibility of microbubbles. For this reason, one cannot produce ultrasound contrast by administering solid, incompressible microspheres. Furthermore, gas microbubbles are unstable and disappear quickly in the fluid; for instance, a 10-μm air bubble disappears within 6 s in water. This decrease in microbubble size is due to the diffusion of gas in the medium and is favored by surface

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tension. Gas diffusion and microbubble collapse are responsible for the inability to opacify the left side of the heart by intravenous injection of hand-agitated contrast agents. To overcome this limitation, pharmacologic companies have used several approaches, including a reduction in the surface tension by a surfactant (17), microbubble protection by an albumin coat (18) and the utilization of a gas with a very low solubility in blood (19). The dose of contrast agent is another obvious determinant of contrast echo intensity. In fact, contrast intensity is influenced by the ratio between the dose injected and the distribution volume, which is contrast concentration.

Contrast echo intensity also varies with the electronic signal processing. The relation between contrast concentration and signal intensity (i.e., linear, logarithmic, sigma or other) largely depends on the type of processing (which varies with the different commercial scanners) and on the instrument setting selected by the operator (20,21). An increase in contrast echo intensity can also be obtained by increasing electronic signal amplification. However, signal amplification enhances both signal and noise levels, whereas an increment in contrast concentration only enhances signal intensity.

Furthermore, the intensity of contrast echo effect depends on the relation between microbubbles and ultrasound, which varies with contrast concentration. At low concentrations, the intensity of the backscattered signal increases with the concentration of the contrast agent; however, a plateau in signal intensity is reached at higher concentrations, and signal intensity may actually decrease at even higher concentrations (22,23). This phenomenon suggests that microbubbles behave like individual scatterers at low concentrations, whereas they form a kind of ultrasound shield, able to attenuate ultrasound energy, at higher concentrations. The investigators strive to prevent the plateau effect and contrast-induced attenuation by injecting appropriate amounts of contrast agent in each experimental and clinical situation. Finally, the intensity of contrast echo effect is affected by signal attenuation due to both cardiac and extracardiac tissues intervening between the probe and the target (24). Thus, myocardial contrast intensity is also regionally affected by differences in the amount of intervening myocardium (25,26). Although myocardial contrast is influenced by these physical factors, their effect can be limited by an appropriate experimental or clinical setup. Specifically, the type and dose of contrast agent, signal processing, instrument setting, signal amplification and the geometric imaging conditions can all be kept constant during data collection.

Biologic factors influencing myocardial contrast echo effect. Biologic variables also play a significant role when assessing myocardial perfusion by contrast echocardiography. Among these variables, coronary blood flow, intramyocardial blood volume and coronary blood pressure have been postulated to be the main determinants of contrast echo effect. In the initial attempt to quantify myocardial perfusion by contrast echocardiography, Ten Cate et al. (27) hypothesized that the myocardial contrast effect measured by intracoronary contrast injection would primarily reflect changes in coronary blood flow. In fact, the washout rate of myocardial contrast produced by hand-agitated meglumine diatrizoate appeared to be related to the rate of coronary blood flow. Subsequently, Feinstein et al. (28) hypothesized that myocardial contrast was determined by myocardial blood content, or volume, in addition to coronary blood flow. Finally, the washout rate of myocardial echo contrast agents was also shown to be influenced by coronary perfusion pressure; however, the relative weight of this variable appeared to be significantly lower than that of coronary blood flow (29).

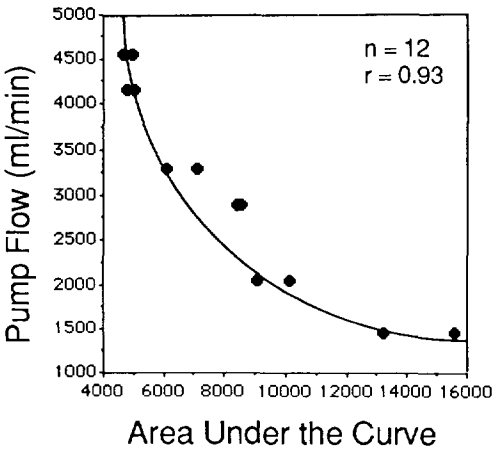

Figure 1. In vitro study. Close inverse relation between the area under the contrast time-intensity curve and experimental pump flow. Redrawn, with permission, from Figure 6 of Rovai et al. (30).

Variable flow rate and constant distribution volume: in vitro data. To evaluate the effect of variable flow rate on contrast echo intensity, we conducted an in vitro study in which variables other than flow volume could be controlled (30). A constant dose of contrast agent (SHU 454, Schering AG, Germany) was injected as a bolus in an in vitro circulatory model. Injections were performed at different flow rates in the absence of recirculation while the volume and pressure of the system were kept constant. Two-dimensional echocardiographic images of a short-axis view of the circuit were obtained at constant gain settings. The images were digitized, a region of interest was placed within the center of the circuit and mean video intensity was measured to generate time-intensity curves. Several variables were extracted from each curve, including peak intensity, area under the curve and mean transit time or washout half-time.

In agreement with the Stewart-Hamilton principle (31), the area under the contrast time-intensity curve was inversely related to actual flow rate (Fig. 1). In fact, flow calculated according to the equation $F = K/AUC$, where F is flow rate, K is a constant of the system (including a constant injected dose) and AUC is the area under the curve, provided a close correlation (correlation coefficient $r = 0.93$) with actual pump flow. Time-related variables were also in close agreement with tracer theory, and pump flow, calculated according to the equation $F = K/\bar{t}$, where K is a constant of the system (including a constant distribution volume) and $\bar{t}$ is mean

transit time, yielded a close correlation (r = 0.95) with actual flow. Thus, consistent with the mathematical model proposed by Feinstein et al. (28), if the dose of contrast agent, distribution volume and gain setting controls are constant, and if contrast microbubbles do not interfere with the microcirculation, both the area under the curve and the mean contrast transit time are inversely related to actual flow rate.

Variable coronary blood flow: experimental data. To evaluate the effects of variable coronary blood flow in vivo on myocardial contrast echo effect, a constant dose of contrast agent (sonicated iopamidol, Bracco S.p.A., Italy) was injected as a bolus into a cannulated coronary artery in dogs (29). The coronary artery was perfused with blood drawn from the femoral artery and delivered by a roller pump. To minimize changes in intramyocardial blood volume, which may accompany changes in coronary tone, adenosine was continuously infused into the cannulated coronary artery to achieve maximal vasodilation. The efficacy of the adenosine infusion in abolishing coronary autoregulation was documented by the lack of hyperemic response after brief periods of coronary occlusion. Thus, echo contrast injections were performed at variable coronary flow rates and, presumably, with minimal changes in coronary blood volume. Two-dimensional echocardiographic images of the left ventricular short-axis view were obtained while gain setting controls were kept constant. Echocardiographic images were digitized and myocardial time-intensity curves were generated. For each curve, the area under the curve and myocardial washout rate were measured. Attention was not paid to the time of myocardial contrast appearance because its short duration limits the reproducibility and accuracy of the measurements (32).

Coronary transit times of sonicated iopamidol appeared to be longer than expected from coronary physiology, suggesting that this agent does not behave as an intravascular "free flowing" tracer. However, as in the in vitro model, the area under myocardial time-intensity curve (AUC) was inversely related to coronary blood flow (F), as described by the equation F = K/AUC (Fig. 2). Time-related variables were also in agreement with tracer theory; thus myocardial washout rate was inversely related to coronary blood flow (r = 0.87). These findings were similar to those of a study by Kaul et al. (33) in which the left circumflex coronary artery of dogs was perfused with carotid artery blood, sonicated meglumine was injected into the coronary cannula at variable flow rates, obtained by changes in perfusion pressure, and myocardial time-intensity curves were fitted by a gamma-variate function. The width of the curves obtained by Kaul et al. showed a good inverse correlation with transmural blood flow, even though adenosine was not infused. The same investigators confirmed these results in a more recent study (34) in which the mean myocardial transit rate of air-filled albumin microbubbles (Albunex, MBI) appeared to be very similar to that of radiolabeled red blood cells. Thus, in the pump-perfused coronary circulation, coronary blood flow can be quantified by myocardial contrast echocardiography according to indicator-dilution theory, despite the use of contrast agents (29,33) that do not fulfill the characteristics of a free flowing tracer and the presence or absence of autoregulation.

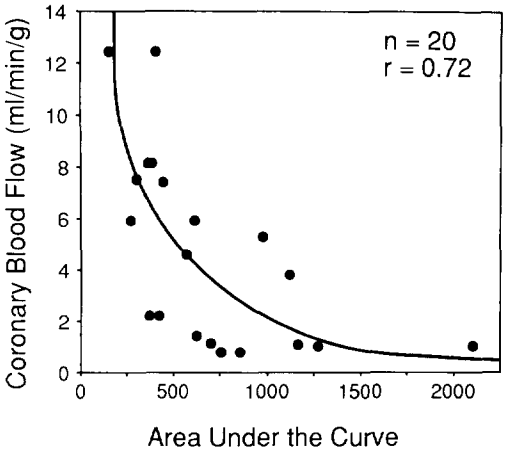

Figure 2. Experimental study. Inverse relation between the area under myocardial time-intensity curve and coronary blood flow in the pump-perfused experimental animal preparation.

Rest versus hyperemic blood flow: clinical data. In contrast to these animal models, in the clinical setting myocardial contrast will mainly be applied to compare baseline with hyperemic perfusion. In an attempt to assess coronary blood flow reserve and regional myocardial blood flow distribution, Cheirif et al. (8), Keller et al. (9) and Agati et al. (10) injected ultrasound contrast medium into the left coronary artery of patients with single-vessel coronary artery disease. Injections were performed both before and after coronary vasodilation with papaverine or dipyridamole. Compared with the baseline value, the area under the curve was increased for the normally perfused bed during coronary hyperemia, whereas it was decreased for the myocardium perfused by the stenotic vessel. These data reflect a redistribution of blood flow between the normal and the stenotic vascular bed, with a higher fraction of the contrast dose entering the normal bed during coronary hyperemia. Also, the changes in myocardial video intensity observed in these studies could be favored by microvascular recruitment in the normal bed, as opposed to vascular collapse downstream from the stenosis (caused by the decrease in perfusion pressure).

Reisner et al. (35) also utilized myocardial contrast echo to assess coronary blood flow reserve. These investigators injected a constant dose of sonicated human albumin into the left main coronary artery of patients with either normal coronary angiograms or stenoses of the left anterior descending coronary artery. Injections were performed both before and after intracoronary administration of papaverine. Relative to baseline, the area under the curve increased by 100% during coronary hyperemia in patients with normal coronary arteries, increased slightly in patients with myocardium perfused by arteries with mild coronary lesions and decreased in patients with myocardium perfused by arteries with severe coronary stenoses. The decrease in the area under the curve observed after papaverine in the myocardium dependent on severely

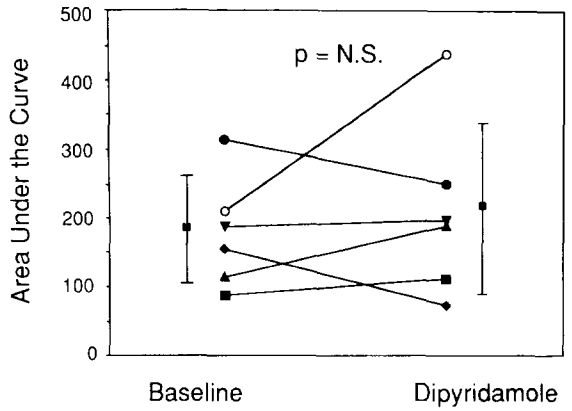

Figure 3. Clinical study. Changes in the area under the myocardial time-intensity curve observed after dipyridamole in patients with normal coronary arteries. Redrawn, with permission, from Figure 8 of Rovai et al. (30).

stenotic vessels can be explained by the mechanisms just discussed. However, the increase in the area under the curve and the prolongation in myocardial transit time observed in patients with normal coronary arteries cannot be explained by a repartitioning of the dose; rather, the finding suggests a huge recruitment of coronary microcirculation (with additional contrast microbubble targets) and intramyocardial blood volume expansion.

Results similar to those of Reisner et al. were contemporaneously obtained in our laboratories (30). To evaluate the effects of coronary hyperemia on myocardial contrast intensity, sonicated iopamidol was injected as a bolus into the normal left coronary artery of six patients both before and after intravenous dipyridamole infusion. In contrast to the in vitro and experimental data, coronary hyperemia resulted not in a reduction in the area under the curve but in values not significantly different from baseline (Fig. 3). Furthermore, the washout rate of myocardial echo contrast medium was not higher during hyperemia than under baseline conditions. As in the study of Reisner et al., these results can be attributed to an increased density of the coronary microcirculation during hyperemia.

The only apparent exception to the previously cited studies is represented by the report of Porter et al. (36). To determine coronary blood flow reserve in humans, sonicated albumin was injected into the left coronary artery of patients without angiographically significant coronary artery disease. A weak but significant inverse correlation was found between the area under the myocardial time-intensity curve and Doppler-measured coronary flow; that is, the area under the curve decreased with coronary hyperemia. However, all the patients studied by Porter et al. were recipients of an orthotopic heart transplant. Thus, even though epicardial coronary arteries were angiographically normal, microvascular damage, with inability to recruit new microvascular units, cannot be ruled out. Further, these investigators injected the same ultrasound contrast agent into the coronary arteries of patients with coronary artery disease, and they also found a significant increase in the area under the curve when intracoronary papaverine was administered after successful coronary angioplasty (37).

Given the foregoing data obtained in humans, several concepts seemed of importance. At the level of coronary microcirculation, an increase in coronary blood flow can be obtained by three different mechanisms alone or in combination: 1) an increase in blood flow velocity in each perfused microvascular unit, 2) increased arteriolar dilation of microvascular units already perfused at baseline, and 3) recruitment of new microvascular units. Some of these events can blunt the changes in myocardial contrast echo effect expected during coronary hyperemia. Specifically, the recruitment phenomenon—related to the number of perfused vessels per unit volume—is likely to increase myocardial contrast echo intensity, thus counterbalancing the decrease in the area under the curve expected during coronary hyperemia. In addition, both coronary dilation and recruitment expand intramyocardial blood volume, which prolongs the transit time of the tracer, thus blunting the reduction in mean transit time expected with an increased rate of coronary blood flow. As a further complication, the contrast echo agents utilized did not always comply with the strict requirements for a suitable tracer (15,38), as suggested by the consistently longer than expected myocardial transit time.

Rest versus hyperemic blood flow: experimental data. With these considerations in mind, a study was planned in dogs, using a contrast agent (Albunex, Nycomed AS, Olso, Norway) that was described as an intravascular free-flowing tracer for the study of myocardial perfusion (39). To evaluate the effects of coronary hyperemia on myocardial contrast echo effect, this agent was injected into the cannulated left circumflex artery of dogs under baseline conditions and during dipyridamole-induced coronary hyperemia. After dipyridamole, coronary blood flow increased by three times or more. However, once again, coronary hyperemia resulted not in a reduction in the area under the curve but in values not significantly different from baseline (Fig. 4), and myocardial mean contrast transit time showed a weak inverse correlation with coronary blood flow (40). These results conform with those of a recent study by Desir et al. (41). These investigators injected sonicated human albumin into the aortic root of dogs at baseline, after the creation of a coronary stenosis and at peak dipyridamole-induced hyperemia; they found a slight increase in the area under the myocardial time-intensity curve during coronary hyperemia. The ratio of the area under the curve in the normal and stenotic territories showed a good correlation with the corresponding ratio of coronary flow, as previously shown by Keller et al. (9).

Conclusions and perspectives. Left ventricular myocardium can be readily opacified by the introduction of ultrasound contrast agents into the coronary circulation. Several studies have demonstrated that failure to opacify a myocardial region identifies a vascular bed in which no perfusion is present. Thus, it is not surprising that physicians have intuitively believed that

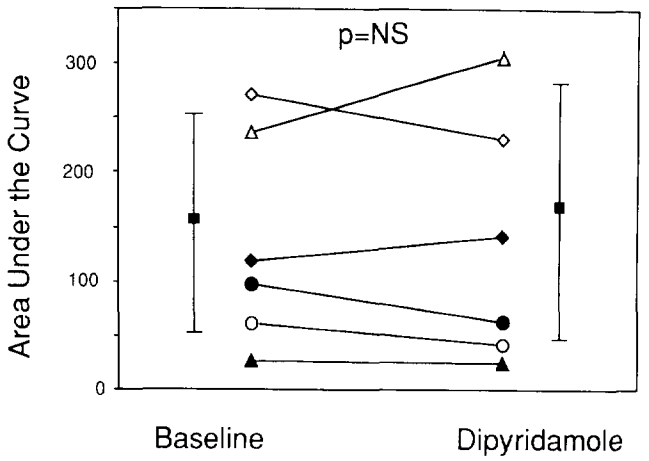

Figure 4. Experimental study. Dipyridamole-induced changes in the area under the myocardial time-intensity curve in the animal preparation.

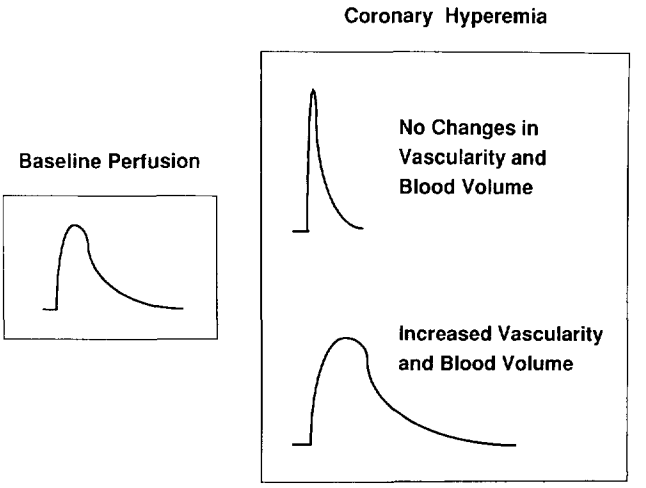

Figure 5. Schematic diagram of the effects of changes in coronary blood flow and volume on the myocardial time-intensity curve. An increase in coronary blood flow—not accompanied by an increase in myocardial vascularity and volume—is accompanied by a decrease in both the area under the curve and the mean contrast transit time (**right upper panel**). Conversely, an increase in coronary flow mediated by augmented myocardial vascularity and volume produces an increase in both the area under the curve and the mean transit time (**right lower panel**).

the magnitude and time course of contrast intensity are a function of coronary blood flow. Unfortunately, several variables determine contrast intensity, which presents a challenge to the application of myocardial contrast echocardiography in the assessment of myocardial perfusion.

The determinants of myocardial contrast echo effect include both physical and biologic factors. The former can be kept constant during data collection; biologic factors are less easily controllable. Among biologic factors, changes in coronary blood flow and alterations in intramyocardial vascularity and blood volume appear to be the main determinants of myocardial contrast intensity. Moreover, these factors influence contrast intensity in opposite directions. Both the area under the curve and the mean myocardial contrast transit time are inversely related to coronary blood flow but directly related to myocardial vascularity and blood volume. Accordingly, an increase in coronary blood flow—not accompanied by an increase in myocardial vascularity and volume—is accompanied by a decrease in both the area under the curve and the mean contrast transit time (Fig. 5, right upper panel). Conversely, an increase in coronary flow mediated by augmented myocardial vascularity and volume will produce an increase in both the area under the curve and the mean transit time (Fig. 5, right lower panel). The rate of blood flow and myocardial vascularity and blood volume are not independent entities and generally exhibit parallel changes. Thus, coronary hyperemia is usually accompanied by vascular recruitment and intramyocardial blood volume expansion; and coronary hypoperfusion could be followed by a functional occlusion of some microvascular units and a reduction in intramyocardial blood volume.

In light of these findings, changes in myocardial contrast intensity cannot currently be related to alterations in coronary blood flow without knowledge of the underlying physiologic conditions. However, these considerations do not apply to the model of acute coronary occlusion where coronary blood flow, myocardial vascularity and intramyocardial blood content all similarly tend to zero downstream from the occlusion. In such a model myocardial contrast echocardiography can provide useful information regarding the extent of the area at risk (42), the presence of collateral channels (3–6), the presence of viable myocardium (6,7) and the efficacy of reperfusion (2). In patients with coronary stenoses myocardial perfusion should be assessed under maximal coronary dilation. In this condition a heterogeneity of myocardial perfusion occurs between regions with and without stenoses. This flow disparity should be studied mainly in the hyperemic images by comparing the different myocardial walls (9,41), instead of comparing baseline with hyperemic conditions. At present this information can be obtained only after intracoronary contrast injection. However, it is clear that ultrasound contrast agents that can opacify the myocardium after a venous injection will soon become available (19). The new aspect of these agents also relates to the kinetics of their microbubbles. For years both investigators and pharmaceutical companies have striven to produce ultrasound contrast agents similar to intravascular tracers that can flow freely in the microcirculation (15,38). Conversely, these new agents tend to persist in the coronary circulation, behaving like deposit tracers. It is tempting to speculate that coronary blood flow with these tracers should be assessed according to Sapirstein's partition principle (43), i.e., by comparing contrast intensities of different ventricular walls, as suggested in a recent study by Skyba et al. (44). Finally, a significant effort is being made by electronic companies to produce new scanners able to record and store the echocardiographic images in a digital form and to give access to the unprocessed ultrasound data (45). A better understanding of the physical and biologic determinants of contrast echo intensity will be fundamental in the clinical application of these new agents and technologies.

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