CONTRAST ECHOCARDIOGRAPHY

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AAN DE ERASMUS UNIVERSITEIT ROTTERDAM

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PROF. DR. J. SPERNA WEILAND

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DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP

WOENSDAG 14 APRIL 1982 DES NAMIDDAGS

TE 2:00 UUR

DOOR

RICHARD STUART MELTZER

GEBOREN TE NEW YORK CITY (USA)

PROMOTOR: PROF. P.G. HUGENHOLTZ

CO-REFERENTEN: PROF. DR. D. DURRER

PROF. DR. IR. N. BOM

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To Colette,

Michelle and Sara

To My Parents

CONTRAST ECHOCARDIOGRAPHY

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CHAPTER 1

INTRODUCTION AND THESIS OVERVIEW

My first interest in Contrast Echocardiography was stimulated by work presented by Anthony DeMaria at the American College of Cardiology meetings in March of 1978. This interest became intense after initial contacts with Glenn Tickner of Rasor Associates in Sunnyvale, California. Chapters 2,4, and 12 result from this enjoyable industrial-academic endeavor. I also helped to put Rasor Associates in touch with some of the other leading academic echocardiography research institutions: Dr. Bill Bommer in Davis, California (DeMaria's laboratory), and Dr.Evelyn Kinney in Dr. Feigenbaum's laboratory. My mentor and friend Dr. Richard Popp encouraged my interest in contrast echocardiography and in the more basic studies of the microbubbles of gas which are the ultrasonic "targets" that produce contrast. He first suggested to me the possibility of continuing this work at the Thoraxcenter after my cardiology fellowship was completed at Stanford in June of 1979. This is a unique institutionfor such research headed by Prof. Paul G. Hugenholtz, who had the foresight and vision in the late 1960's to commit a large amount of resources to the development of two-dimensional echocardiography by the Department of Experimental Echocardiography headed by Ir. N. Bom - now Prof. Ir. Dr. N. Bom. This department started the development of two-dimensional echocardiography in the late 1960's, and is unique also in that such a large ultrasound hardware and software engineering group are integrated organizationally within the department of cardiology in the medical school.

Special thanks are due to Dr. Jos Roelandt, my "Preceptor" according to the terms of the Clinician-Scientist Award I received from the American Heart Association in 1980. He is more than that, though: he is a teacher, role model, and above all, friend. Our close and continued interaction over the past two years, and Jos' unfailing support, made possible most of the work described in the following chapters.

I would also like to thank all my friends and colleagues at both Stanford and the Thoraxcenter who made this work possible, especially those in the animal laboratories (headed by Dr. Piet Verdouw at the Thoraxcenter) and clinical echocardiography laboratories. Most stimulating contacts have been maintained with engineers of Dr. Bom's group, especially Ir.Charles T. Lancée, and many at the Delft Engineering school, especially Ir. A. Chesters of the Division of Aerodynamics and Hydrodynamics. With a very personal and heavy sadness I acknowledge the help of Ir. Olchert Bastiaans, whose life was cut short by a tragic motor accident.

My profound gratitude goes to the American Heart Association, whose support has made my continuing work on Contrast Echocardiography possible.

This thesis is organized into four sections comprised of 13 chapters, including the introduction. Most have been published or are in press. A couple have been submitted for publication recently and are awaiting review.

The first section discusses several theoretical and methodological aspects of contrast echocardiography. It includes 2 articles which were compiled while I was at Stanford (chapters 2 and 4). I believe that our understanding of the basic aspects of contrast echocardiography has considerably progressed since the time when I was just getting interested in the topic and Dr. Popp told me that he believed that the source of ultrasound contrast effect was microbubbles but was not entirely convinced. Nevertheless, there is a great deal of work remaining to be done before we have an adequate knowledge of the basic dynamics and "physiology" of microbubbles in the circulation. This fundamental work may help to design better contrast agents and better methods of attaining transmission through the lungs, reproducible and quantifiable contrast injections, and just to let us know what the microbubble "targets" we image actually are, in terms of diameter spectrum and concentration. We are currently pursuing these research directions

Section II of the thesis deals with clinical applications of contrast echocardiography. Chapter 6 is a general review of the subject, and several specific aspects are discussed in chapters 7 through 10. Since the goal of my entire line of research on contrast echocardiography is clinical application to help patient diagnosis and care, this section is in many ways the "meat" of the thesis.

Section III discusses some new developments in the field of contrast echocardiography: videodensity curves from two-dimensional contrast echocardiographic recordings (chapter 11), and the use of precision microbubbles for transpulmonary transmission and myocardial perfusion imaging (chapter 12). Both of these techniques are in their early research stages, and much more work remains to be done before it can be determined if they will be clinically useful.

The last section is comprised only of chapter 13. "Future prospects and summary." In this chapter I hope to communicate to the reader my ideas about the possible development of the line of research into contrast echocardiography and microbubble dynamics as outlined in this thesis. Hopefully this will give the reader a glimpse of why an increasing number of physicians and ultrasound engineers are coming to consider the topic one of the most exciting in echocardiography - as the Dutch saying goes, "uiterst boeiend."

J Clin Ultrasound 8:121–127, April 1980

The Source of Ultrasound Contrast Effect

Richard S. Meltzer, M.D., E. Glenn Tickner, M.S., Thomas P. Sahines, B.A., and Richard L. Popp, M.D.

ABSTRACT: Evidence that microbubbles are the main sources of ultrasound contrast in injected solutions has been largely indirect. To investigate this directly, we examined freshly agitated indocyanine green, freshly agitated water, commercially prepared precision microbubbles (diameter 75 ± 25 μ) in gelatin, carbonated water, "degassed" indocyanine green solution, and "degassed" water in one or more of four different assay systems. Only fluids with microbubbles produced ultrasound contrast. Injected contrast material rose in a water bath at a rate that identified it as being caused by microbubbles. Indocyanine green and gelatin surface tensions were measured and found to be low (43 dynes/cm^2), thus explaining their tendency to stabilize the microbubbles that cause ultrasound contrast effect when injected and to hold foam after agitation. The force of hand injections (force similar to that used clinically through catheters and 19-gauge or 23-gauge needles) was below the force needed to cause cavitation or ultrasound contrast effect. Microbubble content could be quantified by the decrease in amplitude of the echo from a structure distant to the microbubbles. We conclude that the ultrasound contrast effect seen in peripherally injected fluids is caused by microbubbles present in the injectant. The contrast is not due to cavitation at needle tips, and it can be quantified over a limited range. Improved design for a peripheral contrast agent is suggested. **INDEXING WORDS:** Ultrasound · Contrast agents · Echocardiogaphy

In 1968 Gramiak and Shah *(1)* described an echocardiographic contrast effect caused by the injection of saline. Shortly thereafter, the Rochester group and others observed similar contrast effects associated with the injection of other liquids, including the patients' own blood *(2)*. Often the various descriptions of the effect referred to it as "a cloud of echoes." It is not surprising that these investigators speculated that the phenomenon might be due to the presence of tiny gas bubbles suspended in the liquid. Although various authors have suggested that the contrast is caused by microbubbles *(1–6)*, this hypothesis has not been proved. Some have suggested that particulate matter can cause ultrasound contrast *(7)*. It is the purpose of this report to provide some direct evidence on this subject, to demonstrate that microbubble content can be quantified sonically, and to show that the microbubbles used for peripheral contrast echocardiography are present in the injectant rather than being formed by cavitation during injection *(3–6)*.

METHODS

The echogenic properties of various candidate contrast agents were studied in four different assay systems. Three of these systems involved in vitro studies, and the fourth took place in vivo. Fluids selected for study included tap water allowed to stand overnight, warm tap water agitated in a syringe, indocyanine green solution (1.25 mg/ml) allowed to stand overnight, freshly mixed indocyanine green solution of the same strength, carbonated water, and commercially

From Rasor Associates, Inc., Sunnyvale, CA, and the Cardiology Division, Stanford University School of Medicine, Stanford, CA. Supported in part by Grant HL5866 from the National Heart, Lung, and Blood Institute, Bethesda, MD. Manuscript received July 5, 1979; revised manuscript accepted November 11, 1979. *For reprints contact* Richard L. Popp, M.D., Cardiology Division, Stanford University School of Medicine, Stanford, CA 94305.

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produced precision-size microbubbles* suspended in gelatin matrix *(8,9)*. Surface-tension measurements were carried out on indocyanine green and gelatin using the standard platinum-wire ring technique *(10)*.

To test whether or not microbubbles can be imaged sonically as contrast effect, very small ($10 \pm 5\mu$) precision microbubbles were released and imaged in a tank of degassed water, using a SmithKline Ekoline 20A sonograph† with an acoustically focused 2.25-MHz transducer. Additionally, hand and mechanical injections of degassed water were made through 19-gauge 7/8 inch and 23-gauge 3/4 inch needles submerged in the tank to determine if catheter-tip cavitation occurred. Observation for cavitation was made both visually (using bright side-lighting) and sonically (using the sonograph mentioned earlier).

Assay system 1 involved direct visual and microscopic inspection of the test fluids. Gross inspection was done with the fluid in a glass syringe. Microscopic examination was performed by placing a small quantity of the fluid on a glass slide.

Assay system 2 consisted of a heart-and-lung model capable of simulating human pulmonary artery pressure and flow. The 25-mm-diameter pulmonary artery was used for echo studies. Its latex walls provided suitable reflections for definition of the lumen. The test section was submerged in degassed water for this study, and the transducer was placed 2 cm above the artery. A standard transducer was fixed in a position below the surface of the water, aimed at the "pulmonary artery" through which the test solutions flowed. The sonograph mentioned earlier was used in this study. Echo contrast effect was recorded both on a strip-chart recorder in M-mode form and on Polaroid film from the A-mode output.

Assay system 3 consisted of a Silastic block 9 × 10 × 15 cm with a 1-cm-diameter tube molded into it running through its length. The block was submerged in a redwood tank 10 × 20 × 28 cm filled with degassed water. The redwood walls served to absorb ultrasound to prevent the multiple reverberations common to more reflective surfaces. A reservoir filled with tap water degassed by being left standing open to the air for several days was connected to the block through a variable-speed pump. A Y connector just proximal to the tank entrance allowed injection of test fluids into the flowing water. M-mode recording was carried out in the same manner as in the second assay system. Polaroid photographs were made of oscilloscope tracings of the preprocessed radio-frequency signal, rather than the A-mode display.

An anesthetized dog was used for assay system 4. The closed-chest animal was placed in the right lateral decubitus position, and his heart was imaged echographically from below the right precordium through a hole in a specially built cradle. The echo transducer was placed in a rigid holder that immobilized it and allowed the same position to be held steadily without image degradation. A real-time cross-sectional sonograph (Varian V3000‡) with a 2.25-MHz transducer was employed, from which a line was selected for an M-mode recording at the level of the aortic valve. The candidate contrast media were administered through a catheter placed at the root of the aorta.

RESULTS

Assay System 1

Assay system 1 involved direct observation. All test fluids were examined by eye and under a microscope. The following fluids exhibited bubbles or foam: freshly mixed indocyanine green solution, freshly shaken tap water, carbonated water, and the commercially prepared microbubbles in gelatin (Fig. 1). The 75-μ microbubbles were most stable in the gelatin preparation. Coalescence did not occur, so it was possible to know both the quantity and sizes of the bubbles. The microbubbles remaining in the fluid phase of the indocyanine green preparation were moderately stable, although low in numbers and with a wide spectrum of sizes. The bubbles were least stable in shaken water. Bubbles in carbonated water were also rapidly changing. They formed on the side of the syringe, they grew in size until large enough to leave the wall where they had formed, and then they rose to the upper surface, coalescing and growing during ascent. Warm tap water, when shaken, contained more small bubbles, and these were cleared more slowly than those in cold tap water. Tap water, D5W, saline, or indocyanine green allowed to stand overnight exposed to air contained no visually apparent microbubbles. Photomicrographic examination revealed no bubbles and no particulate matter in any of the four solutions at a magnification capable of detecting objects of 5 μ or larger. Surface-tension mea-

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†SmithKline Instruments, 880 West Maude Avenue, Sunnyvale, CA 94086.

‡Varian Associates, 611 Hansen Way, Palo Alto, CA 94303.

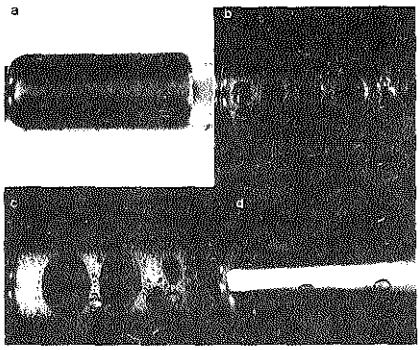

FIGURE 1. Photograph of syringes containing test fluids immediately after agitation. A: Indocyanine green. B: Water. C: Carbonated water. D: Precision microbubbles. This shows that wide spectra of sizes of gas bubbles are present in such liquids. All visible bubbles were removed from syringes A and B prior to injection. Continuous bubble formation occurred with the carbonated water in C.

surements showed that both indocyanine green solutions and liquid gelatin exhibited low surface-tension properties (43 dynes/cm², or 0.6 relative to water).

Microbubbles were formed at the needle tip with both mechanical and hand injections of degassed water into the degassed water tank. This is called "cavitation," and it is caused by forceful injection through a fixed narrowed orifice. Cavitation occurred because the exhaust pressure decreased (because of the Bernoulli effect§) sufficiently that water-vapor bubbles formed. This effect is not a Reynolds number effect, but rather, as shown by Bove and associates *(4)*, a Thoma cavitation number effect.** According to Bove and associates and later Ziskin and associates *(6)*, cavitation occurs whenever the Thoma cavitation number falls below a value of 0.35. When this occurs, microbubbles of water vapor are formed, and these bubbles are detected sonically as contrast effect. Microbubbles were made visible for our tests using a strong side light and a dark background. Cavitation occurred at a flow rate of 10 cc/sec through a 19-gauge 2.2-cm-long needle and at 3 cc/sec through a 23-gauge 1.9-cm-long needle. These corresponded to Thoma cavitation numbers of 0.27 and 0.16, respectively, and in both cases cavitation was expected because these values were less than the critical value. Reductions in flow rates resulting in higher cavitation numbers never caused observable cavitation, and greater flow rates always caused cavitation. These rates were at the upper limit of maximum hand injection using 10-cc and 20-cc plastic syringes. The force of injection necessary to cause cavitation was higher than that used clinically through peripheral "butterfly" needles when creating ultrasound contrast at our institution. On the basis of clinical experience, such force was also judged likely to cause peripheral vein rupture.

Cavitation in blood is just as likely as cavitation in water, because all the factors making up the Thoma number are nearly identical in the two cases. The key variable is the vapor pressure of blood, which is essentially the same as that of water. Hence, cavitation in blood can and does occur, depending on the needle or orifice size and the force of injection.

Precision bubbles ranging from 2 to 20 μ in diameter were imaged in a water tank by the M-mode ultrasound system as echo contrast. Identification of the bubbles as the sources of contrast was definite, because their spectrum of rate of rise in water corresponded to the calculated rate of rise of microbubbles, based on Stokes' law for frictional resistance *(11)*. No other particulate matter was seen microscopically in the microbubble preparation.

Assay System 2

Assay system 2 involved A-mode monitoring in a heart-and-lung model. Polaroid photographs of A-mode tracings during three injections into the heart-and-lung model are shown in Figure 2. There are prominent echoes from the anterior and posterior walls in parts A and B. Intraluminal echoes due to ultrasound contrast are seen in parts B and C. At the more rapid injection rate of the same calibrated microbubbles (part C), the posterior wall echo is obliterated.

All injections were performed with constant echocardiographic gain, reject and damping settings, transducer position, and model flow conditions; so the posterior wall echo amplitude decreased with an increase in contrast material. Hence, it was possible to use this signal amplitude as a quantitative measure of echo contrast. This signal decreased transiently during the more intense contrast, but it always returned to its control value after the contrast had cleared. A ratio of the experimental posterior wall echo

§$P + \rho V^2/2 =$ constant, where P, ρ, and V are the local stream pressure, density, and velocity, respectively.

**The Thoma cavitation number, Th, is defined as: $\mathrm{Th} = 2(P - P_v)/\rho V^2$ where ρ is the local catheter-tip pressure and P_v is the vapor pressure.

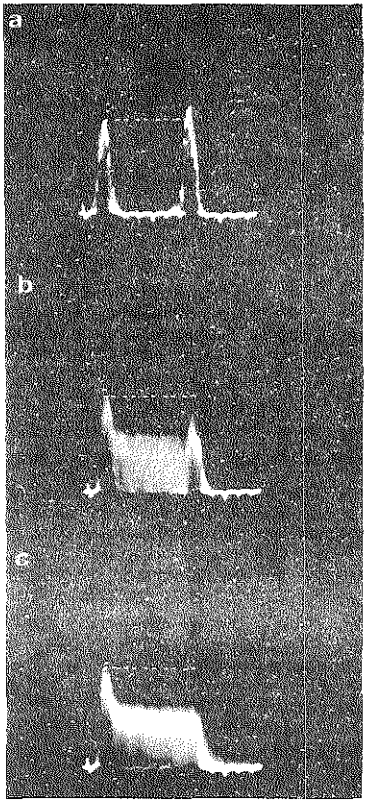

FIGURE 2. Polaroid photograph of A-mode tracings in assay system 2 (heart-and-lung model). A: Before test fluid injection; anterior wall to left, posterior wall to right. B: After slow injection of precision microbubbles. Note contrast within lumen and decreased posterior wall echo amplitude. C: With more rapid injection of precision microbubbles, the posterior wall echo amplitude decreases further.

amplitude to its control value was measured for each injection. No cavitation was observed with a constant injection rate of 17 cc/sec through a large catheter. Test fluids were divided into three groups based on their ability to decrease the posterior wall echo and on the intensity of their intraluminal echoes. The precision bubbles and carbonated water caused dense intraluminal echoes and nearly total disappearance of the posterior wall echo, and thus they were the most extreme ultrasound contrast agents. Neither indocyanine green nor freshly shaken water significantly decreased the amplitude of the posterior wall echo, but the intraluminal echoes from the indocyanine green were more intense than those from the agitated water. Water degassed by being left to stand exposed to air gave neither intraluminal contrast nor decrease in the posterior wall echo, and it was judged to have no ultrasound contrast effect.

Bubbles created in carbonated water and freshly shaken water or saline coalesce rapidly. Hence, test samples must be injected soon after preparation, and intraluminal flow rates must be sufficiently high to prevent coalescence.

Assay System 3

Assay system 3 involved an A-mode raw radio-frequency signal from a silastic tube in a redwood tank. An example of the preprocessed radio-frequency display is given in Figure 3. The echoes

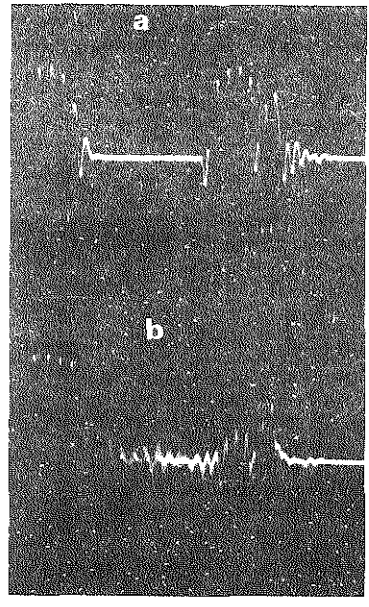

FIGURE 3. Preprocessed A-mode radio-frequency signal in assay system 3. A: Before contrast injection; the echoes from the tube's anterior wall are at left, and posterior wall is at right. B: Ten seconds after precision microbubble injection. Note intraluminal echoes (arrows) and decrease in size of posterior wall echo, as compared with A.

from the posterior wall decreased because of intraluminal bubbles. The mean of the largest three peak-to-peak cycle amplitudes (I) was computed for test injections of precision microbubbles at varying rates, and this was divided by the mean of the three largest control cycle amplitudes (I_o) measured immediately prior to injection, yielding a relative posterior wall amplitude I/I_o. This value is plotted on the ordinate of Figure 4, which shows the relationship between precision bubble density based on its infusion rate and the relative posterior wall echo amplitude. The solid line through the data is the calculated least-squares linear fit to this data forced to pass through 1 on the ordinate. Agitated saline and indocyanine green dye gave intraluminal contrast effect but did not decrease the amplitude of the posterior wall echo. The foam from the indocyanine green contained a spectrum of bubble sizes up to 1 mm and gave intraluminal contrast that entirely abolished the posterior wall echo. Indocyanine green and water allowed to stand exposed to air gave neither intraluminal contrast effect nor a decrease in the amplitude of the posterior wall echo.

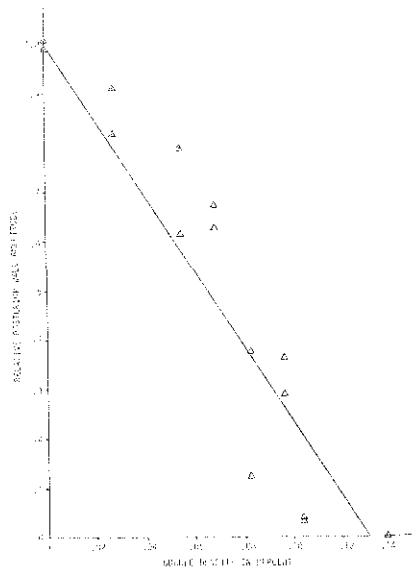

FIGURE 4. Plot of precision microbubble density (percentage of intraluminal volume) versus relative posterior wall echo amplitude. Each triangle represents one reading at the steady state of an infusion.

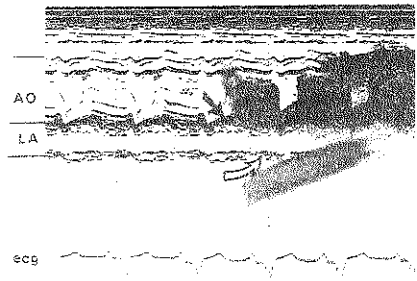

FIGURE 5. M-mode recording showing aortic root injection of uniform microbubbles in an anesthetized dog. Note the decrease in amplitude of the posterior aortic wall echo (solid arrow) and posterior left atrial echo (open arrow). LA: left atrium. AO: aorta.

Assay System 4

Assay system 4 involved echocardiographic monitoring of aortic root injections in an anesthetized dog. Aortic root infusions of precision microbubbles (75 ± 25 μ) at a rate of 2 cc/sec caused a decrease in the amplitude of the posterior aortic wall echo. An example of this is shown in Figure 5.

DISCUSSION

Three factors, (a) direct visualization of microbubbles, (b) correlation of microbubble content of a liquid with its ultrasound contrast effect, and (c) finding the rate of rise of the echoes in fluid to be the same as that of microbubbles, establish that microbubbles are the "targets" that cause ultrasound contrast effects in peripheral or central fluid injections in humans. Clinically, this effect is produced by agitation of the fluid to be used for contrast just prior to injection. Our direct examination of fluids before and after agitation led to the conclusion that one important quality for a good ultrasound contrast agent is good surfactant properties. Thus indocyanine green and the precision microbubbles in gelatin were able to keep microbubbles in solution for a long time because both were good surfactants. Surfactant properties keep bubbles from coalescing or rapidly dissolving because of high surface tension. Fluids with high surface tension, such as saline, are associated with high rates of coalescence and consequently large and potentially dangerous bubble sizes (Fig. 1).

Previous investigators were unsure whether

the microbubbles causing clinical contrast effects were initially in the injected fluid or were caused by catheter-tip cavitation *(2–4)* or were even caused by small amounts of gas trapped in the injecting apparatus and tubing *(5)*. Our water tank injections suggested that neither needle cavitation nor catheter-tip cavitation plays an important role. Barrera and associates *(5)* measured attenuation of sound by fluid as an index of gas content of a second fluid injected into the test system. They found that serial injections gave evidence of serial decreases in gas content unless the injection apparatus was exposed to gases between studies, and they concluded that "the origin of the contrast echocardiography echo-cloud appears to be microbubbles derived from small gas pockets trapped at junctions within the injection apparatus." In their study, vaporous cavitation occurred at high injection velocities, but "target life" was extremely short (<2 sec). This implies that attention to the configuration of the peripheral injection apparatus (stopcocks, tubing, etc.) is important, but our study focuses attention on the fluid inside the syringe. Gas trapped in the tubing gives inconsistent contrast effect and could confound attempts at quantitation of contrast for various purposes.

There are no widely available methods for quantifying the microbubble content of a given volume of fluid in vivo, although ultrasound has promising capabilities to do this *(12,13)*. We initially hoped that the A-mode amplitude of echoes within the lumen of the heart-lung model (assay system 2) would give us a rough idea of the microbubble content. This was not the case, for two reasons. Injections at low flow rates, with incomplete mixing of bubbles and water in the model's lumen, gave inhomogeneous echoes in the lumen. They tended to cluster near the upper wall, where the bubbles rose. When many bubbles were injected, all echoes were reflected from the upper dense bubble layer, and there were no echoes visible in the middle and posterior parts of the lumen, although bubbles were visually present there as well. We noted that the posterior wall echo seemed to give an amplitude that was inversely related to the intraluminal bubble density. We chose to look at the amplitude of the raw radio-frequency posterior wall signal, and we used a simple configuration (tube and water tank instead of heart-lung model) in assay system 3. Using this technique, we obtained a relationship between posterior wall echo amplitude and bubble density that varied roughly in a linear fashion.

Freshly agitated saline and indocyanine green dye gave intraluminal contrast effect insufficient to cause decreased amplitude of the subsequent echoes; so the quantitation of bubble content by this effect probably requires a density of microbubbles beyond that now available clinically.

Assay system 4 showed that the diminution of distant echoes because of microbubbles between them and the transducer is an effect that can occur in vivo. Further work may make quantification of microbubble content possible in vivo, in a manner similar to assay system 3. This is potentially important, because quantitative information of this nature might be useful for indicator-dilution cardiac output calculations. A preliminary communication using a simpler method of contrast quantification has indicated that cardiac output calculations using peripherally injected ultrasound contrast may be clinically useful *(14)*.

Our analysis does not imply that there can be no other causes of ultrasound contrast. The intriguing "spontaneous contrast" that has occasionally been reported *(15)*, and observed on several occasions in our echocardiography laboratory, may be caused by spontaneous cavitation or particulate material such as platelet aggregations.

In present clinical practice, most laboratories find that peripheral contrast injections do not consistently give the desired level of ultrasound contrast. Since the preceding analysis implies that this is due to lack of uniform microbubble content in the fluid reaching the heart, better contrast agents should have reliably high contents of microbubbles. Recommendations for microbubble use, however, must wait until they are proved safe. Air embolus is the most obvious potential problem if the bubble content of an injected fluid is increased. A current trend in some laboratories toward injection of visible bubbles for contrast effect should be discouraged.

Our calculations suggest that less than 50 mm^3 of gas is injected when the precision microbubbles give striking contrast effect. Thus our work supports previous reports and suggests the injection of macrobubbles rather than microbubbles is unnecessary for clinically useful contrast effect. There has been uniform lack of adverse effects from uncontrolled injection of various fluids for ultrasound contrast effect in clinical reports.

ACKNOWLEDGMENTS

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J Clin Ultrasound 9:127–131, March 1981

Intravenous Carbon Dioxide as an Echocardiographic Contrast Agent

Richard S. Meltzer, MD, Patrick W. Serruys, MD,
Paul G. Hugenholtz, MD, and Jos Roelandt, MD

Abstract: Intravenous carbon dioxide (CO_2) was employed to cause echocardiographic contrast in 40 patients. One to 3 cc of medically pure CO_2 were agitated with 5 to 8 cc of 5% dextrose in water and rapidly injected into an upper extremity vein. Contrast was obtained in all patients. In 33 patients contrast density from 5% dextrose was compared with that from 5% dextrose-CO_2 injections. Six of these patients had no contrast on the initial 5% dextrose injection and definite contrast with the subsequent injection containing CO_2. Of the 33, 12 patients had initial contrast with 5% dextrose injections and greater contrast density when CO_2 was added; 15 showed no definite difference; and none had less contrast with intravenous CO_2-5% dextrose than with 5% dextrose alone. Intravenous CO_2-5% dextrose is a useful method of increasing contrast in those patients who fail to demonstrate echocardiographic contrast when routine techniques are employed. It is also safe, provided precautions emphasized in this paper are observed.
Indexing Words: Echocardiography · Ultrasound contrast · Carbon dioxide

Since Gramiak et al[1] first described ultrasonic contrast over a decade ago, contrast echocardiography has achieved widespread clinical application.[2-6] However, both the fluid employed and the injection techniques used vary widely among clinical echocardiography laboratories. As a result, a reliable and reproducible contrast effect is not always achieved. A 1975 textbook of echocardiography states: "Development of an ideal contrast agent is particularly important for the advancement of cardiac ultrasound . . . [it should] be administered noninvasively, be harmless and well tolerated, and produce a contrast effect that is consistent and reproducible. Development of such an ideal agent represents one of the important goals of echocardiographic research."[6]

Many echocardiography laboratories use indocyanine green solutions for their ultrasonic contrast studies. However, in our experience indocyanine green is expensive, must be freshly mixed, frequently causes stains, and cannot be used for many repeated studies.

Early echocardiographers thought that the microbubbles causing contrast came from catheter tip cavitation.[7] More recent work suggests that these microbubbles originate from gas present in the fluid or injection apparatus prior to injection.[8,9] Thus we felt that a safe method of increasing the gas-phase content of blood would probably increase its contrast content. Since intravenous carbon dioxide in small quantities is known to be safe, we decided to examine whether it could decrease the proportion of unsatisfactory echocardiographic contrast studies.

METHODS

The study population consisted of 40 patients undergoing contrast echocardiograms for routine clinical indications (N=15 patients) or as part of a research protocol attempting to assess tricuspid regurgitation (N=25). The study included all persons having contrast echocardiograms during a

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two-month period, with the exception of five persons suspected of having a right-to-left shunt.

Contrast injections were performed through 18- or 19-gauge catheters or butterfly needles introduced into a superficial upper extremity vein. All injections were performed forcefully by hand using a 10-cc plastic syringe attached to a three-way stopcock. The first one or two injections were 5 to 8 cc of 5% dextrose in water, and subsequent injections were 4 to 7 cc of 5% dextrose in water agitated with 1 to 3 cc of CO_2 immediately before injection. Only 100% (medically pure) CO_2 was used and a strict sterile technique employed. Three to ten (mean six) contrast injections were performed per study, generally employing several different transducer positions and echocardiographic views, and usually using both M-mode and two-dimensional equipment. An Organon Teknika EchocardioVisor 01* was used for M-mode studies, and an Organon Teknika EchocardioVisor 03 Fociscan linear array unit or a Toshiba SSH-10A phased array sector scanner† was used for the two-dimensional studies. On all studies receiver gain was set just under the threshold of intracavitary noise that may mask or mimic contrast.

Results were judged by subjectively comparing contrast density during the first injection with CO_2-5% dextrose to the density seen during the previous injection of 5% dextrose alone but with the same echocardiographic instrument and view. The two-dimensional echocardiographic view employed was most frequently the subcostal short axis view imaging the right atrium and inferior vena cava,[10] since these studies were combined with a research protocol to assess the utility of contrast echocardiography in this view for diagnosing tricuspid regurgitation. The apical four-chamber and parasternal long axis views were each used on several patients to compare contrast density. Density was rated during the echo study by the consensus of two of the authors (RSM and JM) who were present for all studies. Disagreements were resolved by later review of the studies.

RESULTS

Six of the 40 patients had no contrast from the initial 5% dextrose injection. All patients had ultrasonic contrast imaged in the right side of the heart as a result of the first peripheral injections with CO_2-5% dextrose which followed the initial 5% dextrose injection(s). Only two injections with CO_2-dextrose failed to yield contrast: These were the fifth and sixth injections with CO_2-5% dextrose in a subject whose intravenous line infiltrated, and subcutaneous crepitus could be palpated in the area of infiltration.

An average of six injections with CO_2-5% dextrose and 10 cc total CO_2 were administered per person. No one experienced any discomfort or any symptoms related to the contrast injections. There were no signs of new cardiorespiratory distress in any patient during the study.

Of the 40 patients, 33 had contrast studies where the initial injection of CO_2-5% dextrose employed the same view and ultrasonic apparatus as the 5% dextrose injection immediately preceding it. Of these, 15 had no definite change in contrast intensity. Twelve of the 33 had contrast on the initial 5% dextrose injection but definite increase in contrast intensity with CO_2-dextrose (Fig 1, 2). The six without echocardiographic contrast on the initial 5% dextrose injection all had contrast on the subsequent CO_2-5% dextrose study. We saw no instances in which the ultrasound intensity decreased from the 5% dextrose to the CO_2-5% dextrose.

DISCUSSION

During serial ultrasonic contrast injections, the contrast effect frequently seems to be influenced by prior injections. We believe this is due to the margination of microbubbles and perhaps macrobubbles of gas in the syringe and catheter along the course of an upper extremity vein after a contrast injection, and the "flushing" effect of a subsequent injection. Ultrasonic contrast can be induced by "milking" an upper extremity vein or elevating the arm long after a contrast injection. It is possible but unlikely that the contrast increase noted during the CO_2-5% dextrose injections relates to contrast introduced during the earlier 5% dextrose injections. We did not test this hypothesis for the following two reasons. First, we feel it is safer to begin contrast studies with 5% dextrose alone, to exclude major right-to-left shunts before CO_2 is used. Secondly, it would be difficult to do the study "blinded," since the physician can both see 1 to 3 cc of CO_2 in the syringe and hear it gurgle as it enters the vein during injection. Since our study was not blinded, we cannot entirely exclude bias as an explanation for our findings. However, a single observer (RSM) performed all the injections of both 5% dextrose and

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†Toshiba Medical Systems, 1154 Dominguez St, Carson, CA 90745.

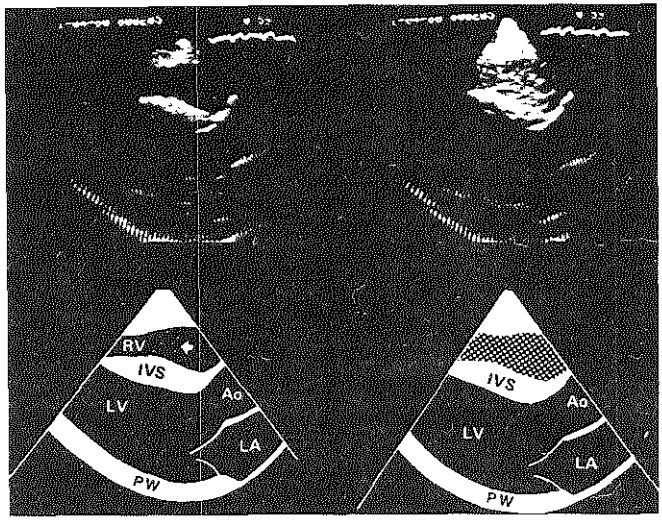

FIGURE 1. Upper panels: Polaroid photographs of stop-frame images from a two-dimensional echocardiographic study in a subject who had increased contrast density from the 5% dextrose injection (left) to the CO_2-5% dextrose injection (right). Parasternal long axis view. Lower panels: Diagrams of the photographs in the upper panels. Contrast in the right ventricle is indicated by arrow on the left and shaded area in the right-hand panel. RV: right ventricle. IVS: interventricular septum. LV: left ventricle. LA: left atrium. Ao: aorta. PW: posterior wall.

CO_2-5% dextrose and attempted to keep injection technique constant. We find it unlikely that the striking difference in contrast effect noted in most of the patients was due to bias alone.

Fifteen of our patients had no qualitative change in echo contrast from the initial 5% dextrose injection to the subsequent CO_2-5% dextrose injections. This is probably because sufficient microbubbles were delivered to the right heart with the initial injection to completely fill the right heart with contrast. Further microbubbles in this situation may cause an "overload" effect and actually decrease the intensity of displayed contrast (and all anatomic structures) distal to the strongly reflecting microbubble layer.[7]

Echocardiographic contrast cannot at present be quantified, though some experimental approaches have been suggested that may lead to this goal in the future.[8,11,12] The grading system in this study therefore had to be qualitative. This corresponds with the clinical state of the art in contrast echocardiology. Occasionally there is a need for qualitatively more intense contrast in a patient, but as yet quantification is not in routine clinical use.

The safety of intravenous CO_2 had been established in the radiologic literature for diagnosing pericardial effusions, largely before the echocardiographic era.[13-18] Considerably larger volumes of CO_2 were injected (50 to 100 cc) than those necessary to create echocardiographic contrast. Emphasis on left lateral decubitus position and exclusion of patients with intracardiac shunts is found in several of these articles. Fortunately, most echocardiographic studies are performed in various degrees of left lateral decubitus position. Recently a large series of patients received 200 cc of intravenous CO_2 without detrimental effects.[17] Blood chemistry does not change significantly with 1-cc CO_2/kg body weight, and experimental animals even tolerate 7.5 cc/kg of CO_2 rapidly injected into the left ventricle or carotid artery with minimal cardiorespiratory effects.[13] The same dose of air intravenously is fatal in most animals.

We feel that the smaller doses of CO_2 employed to attain echocardiographic contrast in our patients are safe. Since data on intravenous CO_2 in patients with right-to-left shunts do not exist, we would be cautious in its use in patients known to have shunts. Reale et al have recently reported on injections of 0.5 to 1 cc of CO_2 in the pulmonary

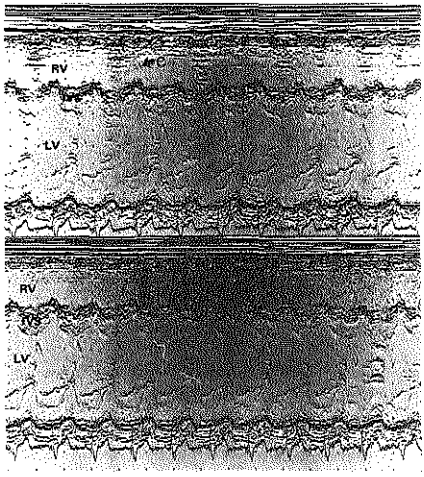

FIGURE 2. M-mode echocardiograms recorded from a patient who was judged to have definite increase in right ventricular contrast density from the 5% dextrose injection (upper panel) to the following injection of 2 cc of CO_2 in 5 cc of dextrose (lower panel). Injection technique and instrument settings were held constant. C: contrast. LV: left ventricle. IVS: interventricular septum. RV: right ventricle.

wedge position in humans. These injections yielded left heart echo contrast with no adverse effects observed.[19]

As pointed out above, a reliable method to achieve echo contrast would be desirable. In clinical practice, echocardiographic contrast techniques vary widely: Some laboratories use indocyanine green, others insist on small needles and specific stopcock arrangements, and some even tolerate the injection of small amounts of air. Part of this variability is due to a lack of theoretic understanding of the source of ultrasound contrast. We are convinced that the source is microbubbles present in the injecting fluid and apparatus rather than needle tip cavitation.[8] Although elaborate right-angle stopcocks may cause turbulence and break up larger bubbles into microbubbles, small needles probably hinder the rapid flush effect necessary to deliver contrast to the central circulation and thus cause loss of microbubble content due to margination. Indocyanine green increases contrast content because it is a surfactant and stabilizes microbubbles.[8] However, as mentioned, it is relatively expensive, must be used the same day it is prepared, contains a small amount of iodine which may cause allergic reactions or interfere with thyroid function tests, and frequently causes stains. Intravenous ether, carbonated water, and peroxide are other agents that cause echo contrast in small quantities,[20] but their safety and practicality have not been evaluated in large groups of patients. There remains in clinical echocardiographic practice a small portion of patients in whom adequate contrast is difficult to obtain. Frequently these are patients with only distal veins available. Three of the six in our study whose initial injections failed to cause contrast had butterfly needles inserted in small hand veins. These may be the patients in whom CO_2 contrast enhancement is most advantageous. Of course it is possible that in some patients even CO_2 will fail to yield contrast, although we have not yet encountered such a patient.

CONCLUSION

We feel that a few cc's of intravenous medically pure CO_2 is safe in persons with no right-to-left shunt. This procedure frequently increases echocardiographic contrast density and may be useful clinically in some patients. With further experience, CO_2 might also provide a basis for quantitative contrast echocardiology, which is technically feasible and may yield important information in the future.[7,10,11]

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CLINICAL NOTE

WHY DO THE LUNGS CLEAR ULTRASONIC CONTRAST?*

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Abstract—Peripherally injected ultrasonic contrast is removed by the lungs. The source of this contrast effect is microbubbles in the injected fluid. We studied bubble dynamics to attempt to explain their removal by the lungs. Commercially prepared precision microbubbles of 5–10 μm could be imaged using standard *M*-mode echocardiographic equipment. Thus, absence of contrast in left atrial echocardiogram after peripheral contrast injections implies that bubbles of this size are absent, though they are small enough to traverse the pulmonary capillary "sieve". Calculations show that a bubble of diameter small enough to get through these capillaries (mean size 8 μm) will totally dissolve due to surface tension effects, in a time shorter than the pulmonary capillary to left atrial circulation time.

Key words: Echocardiography, Ultrasonic contrast, Microbubbles.

Echocardiographic contrast was first reported during indocyanine green injection in the catheterization laboratory (Gramiak, 1969). Although many empiric observations have been made since then (Feigenbaum *et al.*, 1970; Hagemeijer, 1977), theoretic understanding of ultrasound contrast has moved slowly. The following is an attempt to explain a well-known echocardiologic observation—the disappearance of ultrasound contrast from blood during passage through the lungs. Prior investigations suggest that the source of ultrasonic contrast in peripherally injected solutions is microbubbles (Kremkau *et al.*, 1970; Barrera *et al.*, 1978). Data from our laboratory confirm this, and suggest that the microbubbles in shaken saline and indocyanine green are of a wide spectrum of sizes (Meltzer *et al.*, 1979). If such bubbles are much larger than the pulmonary capillary diameter of about 8 μm (Weibel, 1963; Weibel, 1962), they will be held up by the pulmonary capillary "sieve". This is the explanation usually given for their disappearance. Those that are originally smaller that 10 μm, that are fractured into fragments of this size, or that have their gas partly resorbed and "shrink" until they are smaller than 10 μm in diameter should be able to traverse the capillaries and emerge into the pulmonary veins. We wished to learn why such small bubbles were not detectable in the left heart by ultrasound. We thought that either these small bubbles were present but not detectable by standard echocardiographic techniques, or that they somehow disappeared from the circulation by a mechanism separate from the capillary sieve action that should remove bubbles larger than 10 μm.

METHODS

To ascertain whether microbubbles with a nominal diameter of 10 μm can be imaged by commercially available echocardiographic equipment, the following test was performed. Pure nitrogen microbubbles were created in a supersaturated solution of 42 DE corn syrup diluted with distilled water 4 : 1. This liquid had a measured viscosity of 1000 cp at 20°C. A surfactant, Tween 80, was added to this solution in the amount of 2% by volume. This surfactant served two useful purposes: first, it decreased coalescence of the newly created microbubbles; and second, it reduced the pressure within the bubble caused by surface tension and thereby decreased its dissolving rate. The degree of supersaturation of the syrup was adequate to stabilize microbubbles long enough to transport them via a large syringe. Hence, the microbubbles were delivered to the experimental set-up at the same diameters as created. These microbubbles were measured with a microscope and found to be 10 ± 5 μm in diameter.

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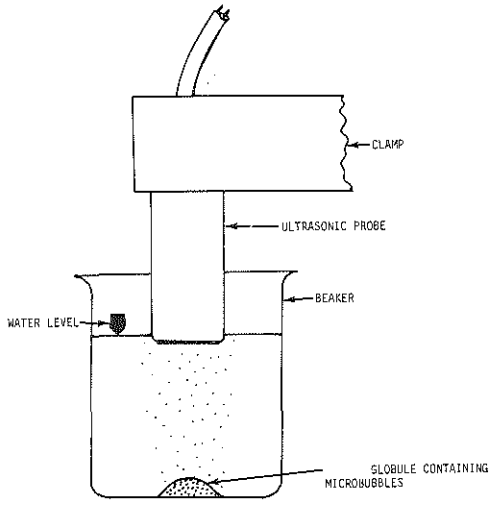

Fig. 1. Schematic showing experimental set-up for bubble rise test.

The experimental set-up, shown schematically in Fig. 1, consisted of a large beaker filled with water degassed by prolonged standing exposure to air. A 2.25 MHz acoustically focused transducer was placed just under the surface of the water aiming downward. A SKI Ekoline 20A *M*-mode ultrasonograph was used to record echoes.

Lack of signals recorded from the beaker prior to the injection of any material assured us the beaker was free of invisible microbubbles or other echo-producing materials. Then a mass (1 ml) of the syrup containing approx. 100,000 microbubbles was injected, with the syringe and a long needle, onto the bottom of the beaker. The dense syrup lay on the bottom and slowly began to dissolve. Also, the entrapped microbubbles rose slowly in the viscous syrup. The larger bubbles reached the drop interface first and rose in water. The purpose for using the viscous liquid was to permit this slow release of nitrogen bubbles and to grade somewhat the size. Visual identification of microbubbles rising from the viscous mass at the bottom of the beaker was performed using a bright sidelight in a darkened room. The bubbles did not begin to dissolve until they left the supersaturated mass and reached the unsaturated water, and then dissolved as they rose in the water.

RESULTS

Single microbubble (or family of microububble) trajectories could be recognized on the *M*-mode echocardiographic recording (Fig. 2). Because of the nature of the bubble release from the viscous globule, fairly uniform sized bubbles are released at any given time. Hence, one measures the slope of an entire family to obtain their size by computation based upon Stokes' law for frictional resistance (Happle and Brenner, 1965). The rate of rise of the slowest of these was 0.023 mm/sec corresponding to a bubble size of 6.5 μm; the fastest was 3.6 mm/sec, representing a few bubbles of 80 μm probably formed by coalescence of the smaller bubbles or air introduced during the procedure of placing the syrup-containing microbubbles at the bottom of the beaker. The ultrasonic trajectories correspond with the visual size of bubbles in the beaker seen using the bright side-light. Prolonged recording of some small bubbles (Fig. 2) apparently was due to a capsule of syrup slowing the dissolution of the bubbles, nevertheless the bubble size can be calculated from the slope measured for a single echo tracing.

BUBBLE DISSOLUTION CALCULATIONS

Studies of bubble dissolution dynamics have appeared in the literature over the years

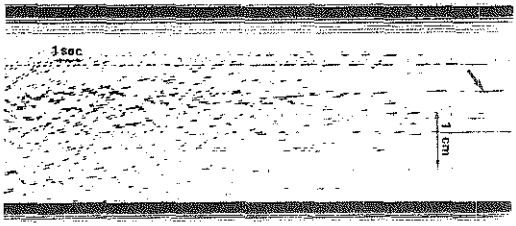

Fig. 2. *M*-mode echocardiographic strip chart recording of microbubbles rising in a beaker of degassed water. The slope of the bubbles shown by the arrow is 0.023 mm/sec, corresponding to a calculated size of 6.5 μm. Note the more rapid rate of rise of larger bubbles or groups of bubbles earlier (to the left in this panel) near the label "1 sec".

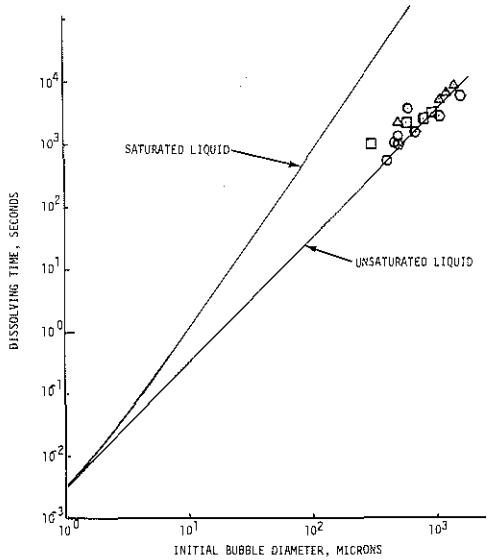

Fig. 3. Log-log plot showing relationship between initial bubble diameter and time to total dissolution. Calculated based on theory presented by Epstein and Plesset (1950), assuming a bubble of nitrogen in degassed whole blood but not correcting for flow effects. Data by Yang *et al.* (1971) for unsaturated liquids given by symbols (○, oxygen bubbles in human blood; □, oxygen bubbles in canine blood; △, nitrogen bubbles in human blood plasma; and ⊙ oxygen bubbles in human blood plasma).

(Epstein, 1950; Ward, 1975). Epstein and Plesset (1950) examined gas bubbles dissolving in liquid solutions, and others have extended this work to account for chemical reactions, bubble/liquid motion and bubble gas composition. Bubbles will shrink and disappear by diffusion in unsaturated solutions, and bubbles will also shrink in saturated solutions because of surface tension effects. The very small bubbles necessary to traverse the capillaries would have a high internal pressure due to the high surface tension effect that goes along with the small size. Gas inside the bubble would rapidly diffuse down its concentration gradient into the surrounding fluid, decreasing the bubble size and increasing the surface tension. This would accelerate the process, causing rapid total dissolution for this population of very small microbubbles. The time for total dissolution, taking into account the effects of surface tension, is presented in Fig. 3 for both saturated and unsaturated solutions. An 8 μm bubble will completely dissolve in between 190 and 550 msec depending upon the degree of saturation of the surrounding fluids. Data from Yang *et al.* (1971) indicates that nitrogen bubbles in blood plasma dissolve as if in an unsaturated solution. Thus the expected time of complete dissolution will be close to 190 msec. All other effects, such as wiping away the diffusion boundary layer, can decrease this time dramatically (Yang *et al.*, 1971). Hence, this figure should be considered conservative.

In man, blood transit time from the pulmonary capillaries to the left atrium is two seconds or more (Hamilton, 1963). Hence, if bubbles smaller than 8 μm dissolve completely in less than 190 msec, they cannot appear in the left atrium.

DISCUSSION

We were not surprised to find that microbubbles small enough to pass through the pulmonary capillary sieve can be imaged with currently available echocardiographic equipment, since we know that we could image 38 and 140 μm microbubbles from prior experience (Carroll *et al.*, 1980). We observed a spectrum of rates of rise and bubble size, the same phenomenon as seen when bubbles

rise in carbonated water after a bottle has been opened. As seen in Fig. 2, some slopes of rise correspond to bubble sizes below the pulmonary capillary diameter, and thus if these bubbles were present on the left side of the heart they should be imaged during routine echocardiographic examinations. A possible exception to this thesis is that our *in vitro* model does not correspond to *in vivo* conditions, and perhaps echoes of low intensity might be so scattered and attenuated by body tissues that they could not be seen. We consider this unlikely, however, since slightly larger microbubbles (75 μm) gave a qualitatively similar contrast effect both *in vivo* and *in vitro* in our laboratory (Meltzer *et al.*, 1980).

The large difference in acoustic impedence between the liquid blood and gas-containing bubble produces relatively high intensity echoes. The desire to resolve neighboring bubbles as separate echoes or resolve both surfaces of a single bubble could be a problem with low resolution systems, but we are only concerned here with the presence or absence of echoes. The echo amplitudes from these microbubbles are well within the range detectable by our equipment.

Relatively large bubbles may be fractured in the right heart and will continuously shrink because of diffusion as mentioned above. The disappearance time calculated here explains why microbubbles larger than about 5 μm are not present in the left atrial and left ventricular blood after peripheral venous injections, in the absence of right-to-left shunts or abnormal pulmonary arteriovenous connections that could provide rapid transport to the left heart (Lewis *et al.*, 1978). We conclude that the reason ultrasonic contrast is removed by capillary networks is that microbubbles larger than the capillary size are held up by the "sieve" action of the network, and those that become small enough to get through the capillaries dissolve very rapidly. The detection in the left heart of microbubbles, in injected indocyanine green dye, due to unusually rapid flow through a pulmonary fistula is interesting (Lewis *et al.*, 1978). This dye lowers surface tension and "stabilizes" or changes the dissolution characteristics of microbubbles (Meltzer *et al.*, 1980). The size of the microbubbles traversing a pulmonary fistula to enter the left heart has not been measured. Perhaps use of surfactants, or inhalation of specially constituted gas mixture after peripheral microbubble injection, could enable microbubbles to survive long enough after transport through the lungs to be consistently imaged on the left side of the heart.

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TRANSMISSION OF ULTRASONIC CONTRAST THROUGH THE LUNGS

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Abstract—The pulmonary capillary bed normally removes echocardiographic contrast from the circulation, so contrast injected peripherally or on the right side of the heart is not seen on the left side of the heart in the absence of intracardiac or intrapulmonary shunts. Based on recent advances in the theoretic understanding of microbubble physiology, we propose several theoretic methods for causing the transmission of ultrasonic contrast through the lungs to enable opacification of the left side of the heart. Three of these methods are tested: (1) injection of ether, an organic compound which may pass the pulmonary capillaries in the liquid phase and cavitate in the pulmonary veins to yield left heart echo contrast, (2) injection of hydrogen peroxide, a substance which chemically decomposes on the left side of the heart to yield gaseous oxygen that can be imaged as echo contrast, and (3) injections of 5% dextrose in the pulmonary wedge position. The first two methods were tested in anesthetized pigs, and the third method in humans and anesthetized rabbits. All methods could cause transmission of echocardiographic contrast through the lungs. There were no adverse reactions in the human subjects. Pulmonary wedge injections in rabbits were associated with one large and three small myocardial infarctions out of 7 animals sacrificed 24 hr later. We conclude that transmission of echocardiographic contrast through a capillary bed is feasible though potentially dangerous.

Key words: Echocardiography, Ultrasound contrast, Ether, Hydrogen peroxide.

INTRODUCTION

Echocardiographic contrast was first reported during injections of indocyanine green in left sided heart cavities (Gramiak and Shah, 1968). Since then numerous studies have commented on the use of echocardiographic contrast on the left side of the heart, but in the absence of right to left shunts all have necessitated cardiac catheterization and direct intracardiac injection to create left heart echocardiographic contrast (LHEC) (Gramiak *et al.*, 1969; Feigenbaum *et al.*, 1970; Sahn *et al.*, 1974; Kerber *et al.*, 1974).

Noninvasive or minimally invasive creation of LHEC would be helpful in left sided structure identification, left to right shunt detection, and perhaps in the detection of mitral and/or aortic regurgitation and proximal coronary artery narrowing. It might also have use in noncardiac arterial ultrasonography.

Lack of theoretic understanding of the nature of ultrasound contrast and the physiology of its removal by the lung has precluded efforts to create LHEC without performing left heart catheterization. Our recent experimental (Meltzer *et al.*, 1980a; Meltzer *et al.*, 1980b) and clinical (Meltzer *et al.*, 1980c) work in this field has enabled us to form several concepts about methods that might cause contrast to pass the pulmonary capillary bed and yield LHEC. This communication reports on animal experiments during which three of these methods were tested, comments on our clinical experience with pulmonary wedge injections and discusses the relevance of these findings in relation to the ultimate goal of noninvasive LHEC creation.

THEORETIC BACKGROUND

Recent studies suggest that microbubbles of gas injected with liquid solutions are the source of ultrasonic contrast (Meltzer *et al.*, 1980b; Barrera *et al.*, 1978). The high contrast is due to the extremely large difference in acoustic impedance between gas and liquids, much larger than occuring between various non-air containing biologic tissues. In the absence of pulmonary arteriovenous shunting, the lungs like any capillary bed remove ultrasonic contrast. This is because gas bubbles considerably larger than the pulmonary

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capillary diameter of approx. 8 μ are stopped by the "sieve" action of the capillaries. On the other hand, due to surface tension, bubbles small enough to pass the capillary bed have an internal pressure significantly higher than the ambient pressure in the pulmonary veins. Gas inside the microbubbles therefore dissolves down its concentration gradient into the surrounding fluid. Consequently the bubble becomes smaller, internal pressure larger, and the process continues in an accelerating manner until the microbubble of gas is totally absorbed. We calculate that the duration of this process is shorter than the pulmonary capillary to the left heart circulation time, and this is the reason that the lungs remove peripheral injected ultrasonic contrast (Meltzer *et al.*, 1980a).

"Spontaneous" ultrasonic contrast has been noted in patients with mitral valve prostheses (Schuchman *et al.*, 1975; Preis *et al.*, 1980). Though this has been attributed to fibrin or particulate matter (Schuchman *et al.*, 1975) or to oxygen released due to hemolysis (Preis *et al.*, 1980), we believe that it occurs mainly in patients with local areas of pressure below the combined vapor pressure of blood and partial pressures of all dissolved gasses, due to the Bernouilli principle in jets of regurgitant blood in the low pressure left atrium. The foreign body provided by an artificial valve may act as a source of nuclei to allow cavitation to take place with a lesser degree of supersaturation than needed with an intact endocardium.

These considerations allow proposal of the following mechanisms for the creation of LHEC:

(1) A liquid could be administered intravenously which would pass through the lungs in liquid state and boil on the left side of the heart.

(2) A liquid or combination of substances could be administered intravenously which would pass the lungs and undergo a chemical reaction on the left side of the heart, yielding a gas.

(3) Bubbles of gas might be forced through the capillary bed by the increased pressure that could be applied locally by an injection through a catheter in the pulmonary wedge position.

(4) A "super" surfactant might stabilize microbubbles small enough to pass the pulmonary capillaries until they reach the left heart.

(5) A more solid coat might protect a "mini-microbubble" from dissolving but still be small enough to allow transcapillary transmission (Bommer *et al.*, 1980).

(6) A gas might be inhaled which, due to its composition and airway pressure, could sufficiently alter the partial pressures of gases in the pulmonary capillaries so intravenously injected microbubbles would grow instead of decay.

(7) High energy ultrasound could be focussed in the left atrium or ventricle until cavitation occurs.

(8) The concept of "rectified diffusion" might be used to enable lower, nontoxic energies of ultrasound to cause growth rather than decay of small microbubbles which can pass the pulmonary capillary bed (Higashizumi *et al.*, 1979; Plessett and Prosperetti, 1977).

(9) An ultrasonic contrast medium in the liquid phase might be developed, allowing transcapillary transmission as a liquid, without the difficulties faced by gas bubbles.

(10) A combination of any of the above methods.

In the following set of experiments we tested the efficacy of the first three methods. Since we were already aware of the occasional efficacy of wedge injections in causing LHEC (Meltzer *et al.*, 1980c; Bommer *et al.*, 1978; Reale *et al.*, 1980), we decided to examine potential toxicity of this technique.

METHODS

Method 1: *physical cavitation—ether*

Ten pigs were anesthetized with barbiturates and placed on a respirator. Surface ECG and intra-arterial pressure were monitored continuously. In each pig the thorax was opened by a median sternotomy and a Krautkramer–Branson 3.5 MHz ultrasonic transducer was sutured directly onto the left ventricular epicardium and used to search for LHEC. Rapid hand injections were made in the right heart or proximal pulmonary artery via Swan–Ganz balloon catheter. Two control injections of 5–8 cm^3 normal saline were monitored by *M*-mode tracings to insure that no resting intracardiac or pulmonary arteriovenous shunts existed. Each pig had one or more of the following amounts of diethyl ether—0.5, 1, 1.5, 2 or 3 cm^3—followed by a 3-cm^3 "flush" of normal saline (Table 1). Following each injection the left ventricular

Table 1. Ether injections

Pig no.	Injected volume (cc)	Contrast with 5cc saline	Contrast with ether
1	0,5	-	-
	1,0		+
2	1,0	+	
3	0,5	-	-
	1,0		-
4	0,5	-	-
	1,0		-
	1,5		+
5	1,0	-	+
6	2,0	-	+
7	1,5	-	+
	2,0		+
8	1,0	-	-
	2,0		-
9	1,0	-	+
10	1,0	+	

+: left heart contrast obtained

-: no left heart contrast seen

echocardiogram, ECG and arterial pressure were recorded for 30–60 sec and monitored visually on the oscilloscope for several minutes further. Subsequent injections were not made until ECG and pressure returned to baseline.

Method 2: *chemical reaction—hydrogen peroxide*

Twelve pigs were anesthetized with barbiturates and placed on a respirator, with an ultrasonic transducer sutured to the left ventridular epicardium as in method 1. Control injections of normal saline were monitored by *M*-mode tracings to insure that no cardiac or pulmonary shunting existed. Right heart injections of 0.3–5 cm^3 of hydrogen peroxide followed by a 3-cm^3 normal saline "flush" were then performed. The volumes and concentrations employed in each pig are listed in Table 2. Sometimes more than 1 injection was performed with the same volume and concentration.

Method 3 (*animal studies*): *pulmonary wedge injections*

Seven adult rabbits were anesthetized with fluanison 0.5 mg/kg. Number 6 French Swan–Ganz catheters were advanced to the wedge position under fluoroscopic and pressure control. They were inflated with 0.5–0.75 cm^3 air and 3–10 repeated injections of 3–5 cm^3 normal saline were performed. In most injections the small amount of air normally trapped in the 3-way stopcock was not assiduously excluded as is our practice in clinical injections. The animals were sacrificed 1 day later. The lungs, heart and kidneys were examined grossly and by light microscopy.

Method 3 (*human studies*): *pulmonary wedge injections*

During routine cardiac catheterization in patients, pulmonary wedge injections were performed either through a 7 French Cournand ($n = 9$), a 7 French Swan–Ganz catheter in the wedge position but without an inflated balloon ($n = 3$), or both catheters ($n = 5$). LHEC was monitored by two-dimensional echocardiography. Ten patients had X-ray angiograms performed during a hand injection of a new nonionic radiographic contrast agent-Amipaque®, Nyegaard & Co., Oslo, Norway (Enge *et al.*, 1977) in the same

Table 2. H_2O_2 injections

Pig no.	H_2O_2 concentration	H_2O_2 volume (cc)	Contrast with saline	Contrast with H_2O_2
1	30%	0,2	-	+
		0,3		+
		0,5		+
2	30%	0,2	-	+
		0,3		+
3	30%	0,2	-	-
		0,3		-
4	2,5%	5	-	+
5	1,5%	5	-	+
6	30%	0,5	-	+
7			+	
8	15%	1,5	-	+
9	0,75%	2		-
	1,5%	2	-	+
	3,0%	2		+
10	1,5%	2	-	+
11	1,5%	1,5	-	-
		3		-
12			+	

+: left heart contrast obtained
-: no left heart contrast seen

wedge position as used for the dextrose injections attempting to achieve LHEC.

RESULTS

Method 1: *physical cavitation—ether*

Two of the 10 pigs had LHEC after initial right heart saline injections, and were excluded from further analysis due to the presumed presence of cardiac or pulmonary shunts. Six of the remaining eight animals had LHEC after ether injections (Fig. 1). Since these volumes of intravascular ether are frequently toxic in pigs, we always saw hypotension and occasionally asystole in the pigs after 2 or 3 cm^3 of ether.

Method 2: *chemical reaction—hydrogen peroxide*

Two of the 12 pigs had initial LHEC after right heart saline injections, and were excluded from further analysis due to presumed cardiac or pulmonary shunting. Eight of the remaining 10 pigs had LHEC after hydrogen peroxide injections (Fig. 2).

In one pig (number 9) a threshold effect for LHEC could be demonstrated, such that all injections of H_2O_2 with a concentration at or above 1.5% yielded LHEC and those below did not. This was repeatable for 8 injections crossing the threshold concentration 4 times.

Method 3 (*animal studies*): *autopsies of rabbits subjected to pulmonary wedge injections*

One rabbit died during the night between the experimental protocol and the day of scheduled sacrifice. At its autopsy, edematous lungs, renal tubular necrosis, and a large myocardial infarction were found. The other 6 rabbits survived to sacrifice and were apparently healthy at the time of sacrifice, 24 hr after the experimental protocol. Three of these 6 rabbits had small myocardial infarctions at autopsy. None of them had renal

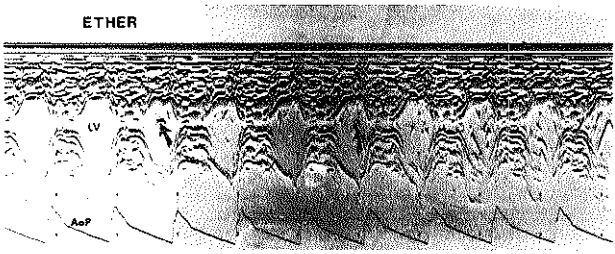

Fig. 1. *M*-mode echocardiogram recorded from an anesthetized pig with the transducer sutured directly onto the left ventricular free wall epicardium. An injection of ether into the right heart causes contrast (arrows) in the left ventricle (LV). AoP: aortic pressure.

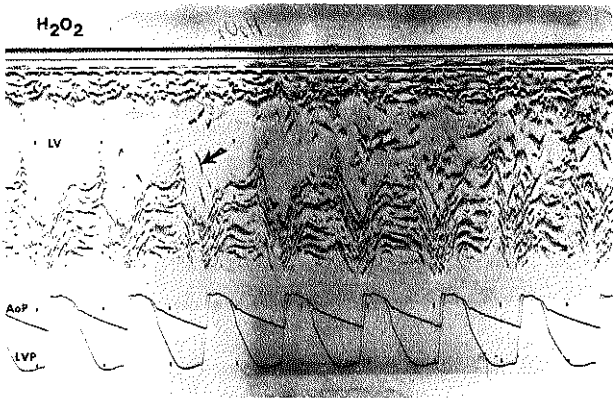

Fig. 2. *M*-mode echocardiogram recorded from an anesthetized pig with the transducer sutured directly onto the left ventircular free wall epicardium. An injection of hydrogen peroxide into the right heart causes contrast (arrows) in the left ventricle (LV). AoP: aortic pressure, LVP: left ventricular pressure.

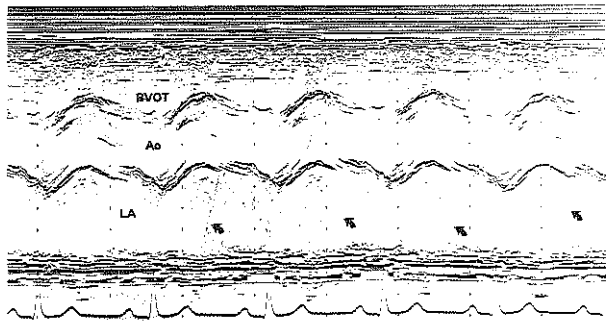

Fig. 3. *M*-mode echocardiogram in a human subject after injection of 10 cm^3 of 5% dextrose solution through a catheter in the pulmonary wedge position. Note the appearance of fine contrast in the left atrium (arrows). Ao: aorta, LA: left atrium, RVOT: right ventricular outflow tract. Reproduced with permission from the *British Heart Journal*.

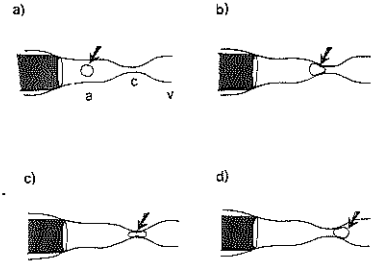

Fig. 4. Diagrammatic representation of proposed mechanism by which microbubbles of gas larger than the pulmonary capillary diameter may pass through the lungs to yield LHEC. (a) A bubble of gas (arrow) injected through a catheter (shaded) in the wedge position enters a pulmonary arteriole (a). (b) Due to the hydrodynamic driving force applied to the local pulmonary circulation due to an injection directly in the wedge position, the bubble is deformed and forced into a pulmonary capillary (c). (c) The bubble elongates and may even fill a capillary entirely with air. (d) The bubble emerges on the venous side (v) of the pulmonary capillary bed.

lesions or pulmonary injury that could be attributed to the wedge injections.

Method 3 (human): pulmonary wedge injections

No subject has symptoms or worsening of cardiopulmonary status in relation to wedge injections. Eleven of the 15 patients with wedge injections through Cournand catheters achieved LHEC, whereas only 1 of 8 subjects with injections through Swan–Ganz catheters achieved LHEC. An example of a positive study is shown in Fig. 3. LHEC was only attained in the patients where no retrograde flow of X-ray contrast agent around the catheter was noted during wedge injection of the nonionic radiographic contrast agent.

DISCUSSION

As predicted from the physiologic understanding of microbubbles described earlier, both ether and hydrogen peroxide can pass the pulmonary capillaries in liquid from and yield a gas phase, thus ultrasonic contrast, on the left side of the heart. Though small amounts of each of these substances can be administered in humans, we feel that each is probably too toxic to administer safely intravenously in amounts necessary to obtain LHEC. However, a group from Wuhan, China, has reported the use of IV hydrogen peroxide in animals and humans (Wang *et al.*, 1979a, 1979b). They claim acceptable toxicity. They also note that LHEC was not seen in the absence of intracardiac shunts.

Our studies do not exclude opening of intrapulmonary arteriovenous shunts as a mechanism for transpulmonary transmission of contrast. However, we are unaware of animal studies suggesting that ether, peroxide or wedge injections open such anatomic channels.

Potential toxicity of transpulmonary transmission of ultrasonic contrast is of concern in the light of our autopsy findings in rabbits after wedge injections. We think that the unexpected and serious toxicity (1 large fatal infarction and three small myocardial infarctions out of seven rabbits) relates to our technique of not carefully excluding small amounts of air from the syringe and 3-way stopcock. Due to this tolerance of small amounts of air, the amount of injected air in relation to body weight was many times that used in human contrast studies, either in routine peripheral injections or our wedge injection protocol. We assume that the high prevalence of rabbit myocardial infarctions was due to coronary air embolism. Two mechanisms may explain this phenomenon. First it is possible that most rabbits had significant pulmonary arteriovenous shunts. Though pigs and dogs under anesthesia have a prevalence of these shunts that is about 10% (unpublished observations), we doubt that this occured in most rabbits. The second possibility is diagrammed in Fig. 4. Whereas normally large bubbles of air are retained by the "sieve" action of the pulmonary capillaries (Meltzer *et al.*, 1980a), the increased driving hydrodynamic pressure applied to the capillary bed during a wedge injection may allow deformation of a bubble into a "dumbbell" shape and intact passage through the capillary bed. The hypothesis that high proximal pressures are needed to obtain LHEC after wedge injections is supported by the observation that in humans LHEC only occurs when the catheter is wedged firmly enough to prevent "blowout" and retrograde X-ray contrast flow during the wedge injections.

Though this study suggests caution in designing a clinical method for noninvasive LHEC creation, the long experience with ultrasonic contrast injected into the left heart with catheters implies that the presence of microbubbles in sufficient concentration to cause LHEC need not cause an unacceptable toxicity. Nontoxic, noninvasive LHEC creation remains thus a valid research goal and we are optimistic that a better understanding of microbubble physiology—the factors affecting bubble growth and decay—will permit successful attainment of this goal.

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CHAPTER 6

CONTRAST ECHOCARDIOGRAPHY

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MS 80-21

SUMMARY

During the 1970's, contrast echocardiography was used clinically to aid 1) structure identification, 2) shunt detection or exclusion, 3) the diagnosis of complex congenital heart disease, and 4) evaluation of valvular insufficiency. Systematic analysis of contrast timing and M-mode as well as two-dimensional echocardiographic patterns can extend these applications. New developments in microbubble technology and videodensiometric processing of two-dimensional echo-contrast images may lead to important advances in the 1980's. These include the ability to attain contrast in the left heart after peripheral venous injections, the ability to better characterize and quantify intra-cardiac shunts and flows, and possibly a capability for measuring intracardiac pressures or myocardial perfusion.

INTRODUCTION

Ultrasound contrast was first introduced a little more than a decade ago (1,2) and has come into widespread clinical use during the p 7).In this communication we propose to comment on methodology and contrast agents, to review the current status of contrast echocardiography in clinical practice, and to point out some promising areas for future research. Contrast echocardiography is an exciting and rapidly developing field, and we entirely agree with Harvey Feigenbaum's assessment that " the full potential of this technique has not yet been realized" (8).

* Clinician-Scientist Awardee of the American Heart Association

Methods, Microbubbles, and Contrast Agents

Considerable variation exists in clinical practice in the methods used to create ultrasonic contrast. This is partly due to uncertainly about the source of the contrast effect. In Gramiak's original communications he identified the source of contrast effect as microbubbles (1,2) but held that these microbubbles came mainly from cavitation at catheter tips (9). With this thought, though not understanding the nature of cavitation (10), many clinicians devised elaborate methods which they believed increased the like-lihood of cavitation. Thus a folklore has developed about these methods, such as the necessity of using right-angle stopcocks, large (or small) syringes, small (or large) needles, hefty cardiology fellows for the strongest injection possible, etc. In the last few years there is experimental evidence that the source of contrast is microbubbles of air present in the syringe and injection apparatus before injection, rather than cavitation occurring during injection (11,12) though this still remains controversial (13). If correct, this understanding would lead us to downplay the importance of certain methods - such as right-angle stopcocks and different syringe sizes. It would emphasize the importance of methods that would increase the microbubble content of the injectate - such as agitation immediately prior to exclusion of air from the syringe (14) and a short delay from hook-up to injection. Contrast agents that stabilize microbubbles due to their surfactant properties, such as gelatin, indocyanine green (11) or blood, improve the yield of satisfactory contrast studies. Rapid injection in a large antecubital vein is also important, though not because it causes cavitation. Rather, it flushes the bolus of microbubble-containing blood to the heart with less chance of "margination" and resorption of gas bubbles than occurs with more hesitant and more distal injections. Evidence for margination is the frequently seen phenomenon of contrast appearance in the heart minutes after injection but associated temporally with upper extremity vein "milking", arm or head motion, or deep inspiration.

Contrast agents that have been investigated experimentally for their ultrasonic contrast effect include distilled water, normal saline, 5% dextrose solution, isopropyl alcohol, milk, blood, decholin, Diodrast, Renografin-60, Renografin-70, indocyanine green, carbonated water, carbon dioxide (CO_2), diethyl ether, precision microbubbles in gelatin and hydrogen peroxide (11,15,16). Though some of these are too toxic for clinical use, others have been used at some time for clinical ultrasound studies (17,18). Preliminary work has been reported on a non-gaseous ultrasonic contrast agent in the form of collagen (19) or gelatin (20) microspheres.

We prefer 5% dextrose solutions for clinical use in our patients, since it is inexpensive and readily available. We add one or two cc of CO_2 in the occasional patient with difficult-to-achieve contrast. We do not use CO_2 if a shunt is suspected since its safety has not been established in that setting. In neonates, where volume considerations may be important, the patient's own blood - a good surfactant - is probably the contrast agent of choice.

An important current limitation in contrast echocardiographic methodology is the variability of results. It is impossibile to reliably and reproducibly attain similar contrast effects on successive injections, despite similar injection technique. In this regards research on precision stabilized microbubbles in gelatin is promising (11,21). A reproducible contrast agent will probably be necessary in the future if the quantitative contrast techniques described later in this review are to be successful.

Systematic Analysis

It is not in generally realized how much physiologic information is potentially available from systemic analysis of contrast echocardiograms. For example, there has been very little attention to the slope of contrast trajectories on M-mode echocardiographic tracings, though these represent the component of the blood velocity moving in the direction of the sound beam. This is very similar information to that obtained by pulsed Doppler echocardiography, a technique which has awakened widespread interest (Table I).

TABLE I: M-MODE CONTRAST ECHO VERSUS DOPPLER ECHO

Similarities:

- Both look at the component of blood velocity along the echo beam direction (towards or away from transducer)

- The same transducer may be used for both studies

Advantages of M-mode Contrast Echocardiography

- Samples many depths simultaneously (only multigate or continuous wave Doppler instruments do this)

- Not limited by distance from target or maximum velocity that can be detected

- Uses less expensive, more generally available equipment (only M-mode instrument and intravenous line needed)

- May have higher signal-to-noise ratio

Advantages of Doppler Echocardiography

- Entirely non-invasive

- Can visualize left heart structures in absence of shunt

A recent article, suggests that since the main pulmonary artery is usually nearly parallel with the sound beam, slopes of contrast trajectories on M-mode recordings have a reasonable correlation with invasively measured pulmonary blood velocities in humans (23). In other situations where the echo beam is not parallel with the blood flow velocity, the direction rather than absolute value or magnitude of the slope may be important: appearance of contrast in the inferior vena cava with a positive slope when the transducer is aimed superiorly is due to retrograde flow in the inferior vena cava; antegrade flow then yields a negative slope (away from the transducer).

Further, the timing of appearance, clearance, and cyclic alterations of contrast may yield important information about cardiac physiology: left heart contrast appearing within a few cycles after right heart opacification implies an intracardiac shunt, but consistent delay of more than 6-8 cardiac cycles suggests intrapulmonary shunting (24). Cyclic pulmonary artery opacification in diastole after peripheral venous contrast injection suggests transposition of the great arteries with blood reaching the pulmonary artery through a patent ductus arteriosus (25). The timing of appearance of contrast in the left heart after peripheral injection in patients with ventricular septal defects may help in the evaluation of right ventricular hemodynamics (26). The cyclic difference of left ventricular and right ventricular opacification in a patient with an atrial septal defect is shown in figure 1.

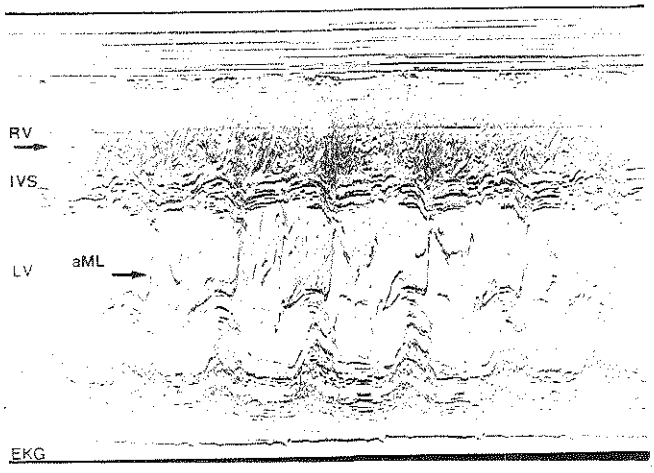

Figure 1: M-mode contrast echocardiogram in a patient with a secundum atrial septal defect. Contrast initially appears in the right ventricle (RV) during diastole and on the following cardiac cycle it appears in the left atrium, passes the anterior mitral leaflet (aML) and appears in the left ventricle (LV). Note that the contrast intensity increases in the right ventricle during inspiration (vertical arrows), while the amount of contrast passing the mitral valve decreases. Reproduced with permission from Hart Bulletin 11: 164, 1980.

During inspiration, there is relatively more intense right ventricular and less intense left ventricular contrast, and this effect is reversed during expiration. Patterns such as these must be sought for, perhaps on multiple injections in different views to piece together complementary bits of information. A few proposed contrast patterns in various right heart conditions are illustrated in figure 2 (27-29). These are consistent with our experience (30), but the sensitivity and specificity of these patterns has not been adequately investigated.

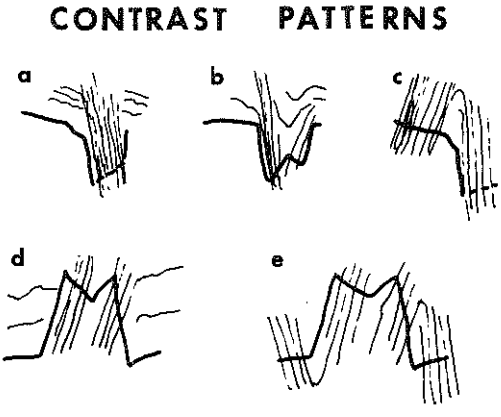

Figure 2: Some proposed M-mode contrast patterns in various right heart conditions (diagrammatic). a) Normal - there is antegrade flow and thus contrast with negative slope - motion away from the transducer - in the right ventricular outflow tract (RVOT) and proximal pulmonary artery throughout systole. b) Pulmonary hypertension. The anterograde blood flow in the RVOT occurs mainly in early systole, and retrograde flow may be seen in late systole, especially in patients with mid-systolic closure of the pulmonic valve (PV). c) In pulmonic insufficiency retrograde flow - contrast with positive slope - is seen. crossing the PV in diastole. d) Normal tricuspid valve, with antegrade flow during diastole and no retrograde flow - negative slope - during systole. e) Tricuspid regurgitation, with retrograde flow - negative slope - occurring durmg systole.

The type of information obtained by contrast echocardiography is fundamentally different for M-mode, two-dimensional and Doppler studies. M-mode display is best suited to analysis of timing and slopes of individual contrast trajectories. Two-dimensional display provides the spatial orientation to best define other flow characteristics, such as shunts, vortices, filling or emptying patterns, myocardial perfusion, etc. Two-dimensional echocardiography is not well suited for the study of contrast velocity, which is best measured on M-mode tracings and perhaps in Doppler studies. Doppler contrast echocardiography has only been reported in preliminary work to date (31).

CLINICAL APPLICATIONS (Table II)

1. Structure identification

Structure identification was the first reported use of contrast echocardiography (1,2) and the ability to perform central or peripheral contrast injections has been an important aid to the correct interpretation of structure on both M-mode and two-dimensional echocardiography (32-34). Specific structures where contrast echocardiography has aided identification or interpretation include the aortic root (1), left ventricle (32), left main coronary artery (35), the coronary sinus (36), the common pulmonary venous return (37), the inter-atrial baffle after Mustard's operation for transposition of the great arteries (38), and the pericardial space during pericardiocentesis (39). Since these require special catheter injections, echocardiography has no advantage over conventional roentgenologic techniques, except in the rare case where there is a contraindication to ionizing radiation such as early pregnancy (40), or to angiographic contrast agents, such as allergy, renal disease or fluid overload. However, peripheral venous injections may be used to provide better identification of structures on the right side of the heart by echocardiography. This technique is helpful to correctly delineate the right side of the interventricular septum, an important clinical problem where M-mode echocardiograms may be misleading (41-43) (figure 3). In normals, differentiation between the superior vena cava, pulmonary artery and aorta is aided by peripheral contrast injections using the suprasternal transducer position. In transposition of the great arteries, suprasternal notch contrast echocardiography can be used to help identify the great vessels and aid diagnosis (25).

TABLE II: CLINICAL APPLICATIONS OF CONTRAST ECHOCARDIOGRAPHY

1. Structure identification and validation
   a. Peripheral injection - right heart structures
   b. Central injection via catheters - left heart structures

2. Shunt detection or exclusion
   a. Atrial septal defect, patent foramen ovale
   b. Ventricular septal defect
   c. Intrapulmonary shunt

3. Complex congenital heart disease

4. Valvular insufficiency
   a. Aortic and mitral insufficiency - aortic root or left ventricular injection necessary
   b. Tricuspid insufficiency
   c. Pulmonic insufficiency

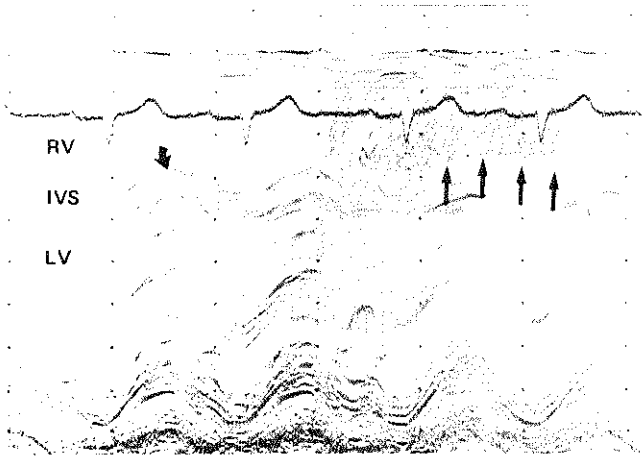

Figure 3: M-mode echocardiogram during peripheral contrast injection, showing incorrect apparent position of the endocardium on the right side of the interventricular septum (IVS) - curved arrow - and correct position of endocardium outlined by contrast - straight arrows.

2. Shunt detection (or exclusion)

Normally the microbubbles that are the source of echocardiographic contrast are entirely removed from the circulating bloodstream by a capillary bed (44). Thus the appearance of contrast in the left heart after peripheral venous injection is evidence for a right-to-left shunt. The timing and pattern of contrast appearance in the left heart are related to the level of the shunt and the relative pressures in the various cardiac chambers. Shunts as small as 5% can be detected by contrast echocardiography (45). Shunts with pulmonary hypertension and Eisenmenger physiology are reliably diagnosed by peripheral contrast injections: in our series all contrast studies showed shunts in patients with ventricular septal defects and a peak right ventricular pressure half or more of systemic pressure (46). In the absence of pulmonary hypertension, however, ventricular septal defects (VSD's) often fail to show right-to-left shunting after peripheral venous injections (26). Occasionally a negative contrast effect of unopacified blood from the left ventricle can be noted in the right ventricle, but this sign is neither sensitive nor specific in our hands. Thus, peripheral contrast echocardiography cannot be used to rule out the presence of a VSD, and is only useful if appearance of contrast on the left side of the heart is observed. Shunts can occasionally be demonstrated during respiratory maneuvers or arrhythmias, such as ventricular premature contractions (47), even when they are not imaged at rest (figure 4).

The situation for atrial septal defects (ASD's) is somewhat different from that for VSD's. This is due to the fact that even in ASD's uncomplicated by pulmonary hypertension, there is usually a small degree of right-to-left shunt present in early systole (48). Thus, left sided appearance of contrast after peripheral contrast echocardiography is a fairly sensitive test for the presence of an ASD (46, 49-55) (figure 1, page 5). In our laboratory sensitivity of contrast echocardiography for ASD diagnosis is 88%, and specificity 100%: this is superior to oximetry or nuclear medicine techniques. We find the "negative contrast effect" of unopacified blood entering the right atrium to be neither sensitive nor specific, though others have found this sign useful (55). It is difficult to differentiate the normal "negative contrast" effect due to unopacified inferior vena cava and coronary sinus blood entering the right atrium from negative contrast due to an ASD. It is important not to call a test negative unless adequate right atrial contrast has been obtained on multiple injections from several different transducer positions, and

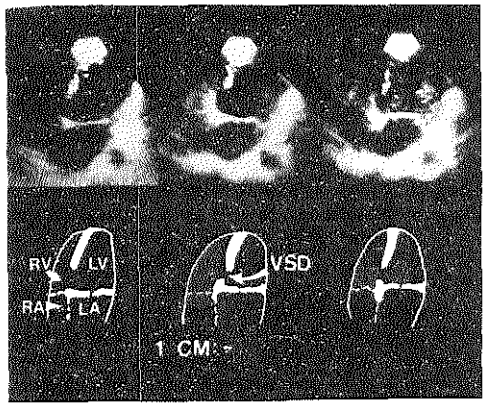

Figure 4: Apical four-chamber views from preoperative two-dimensional echocardiogram showing dropout of interventricular septal echoes in the region of a ventricular septal defect (VSD). Left panels: pre-injection. Middle panels: after peripheral 5% dextrose injection contrast opacifies the right atrium (RA) and ventricle (RV) (shading on lower middle diagram). Right panels: with a premature beat, the contrast crosses the VSD and is present in the left ventricle (LV). Further abbreviations: LA - left atrium.

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a Valsava maneuver should always be performed during several contrast injections before the echocardiographer can be assured that the study is indeed negative. In fact, contrast echocardiography during a Valsava maneuver is probably "overly sensitive" to the presence of an ASD, since it may allow patent foramen ovale to be diagnosed (56,57). Contrast echocardiography also aids in the diagnosis of partial anomalous pulmonary venous return, a condition associated with ASD's (58).

Postoperative shunts may occasionally be seen in the early (59) or late (60) period after operative closure of an ASD. Though this may imply an unsuccessful operation, such is not always the case: a small number of patients have persistent postoperative shunts despite successful operative closure of their ASD. The mechanism for this is at present unclear.

Recent reports indicate that pulmonary wedge injections can cause left heart echocardiographic contrast (61-63), and that this may be used to diagnose left-to-right shunts. This procedure is potentially hazardous however (64), and is certainly experimental at present, having only been reported in humans in 2 small series by Reale et al and our own laboratory. Potential hazards include local pulmonary vascular complications (65) as well as the theoretic possibility of systemic air embolism.

3. Complex Congenital Heart Disease

ASD's and VSD's, which are often parts of more complex malformations, are discussed above. Contrast echocardiography has been an important advance to the pediatric cardiologist, especially in the care of critically ill newborn infants with cardiac and pulmonary disease (66). In these patients information on intracardiac flow patterns and relations is frequently of vital importance. Using the parasternal and suprasternal transducer positions, it is possible to ascertain the number and position of the great vessels and their ventricular connections (25). Specific or suggestive contrast echocardiographic patterns have been described in atrioventricular canal defects (67), univentricular hearts (68), tricuspid atresia (69), overriding tricuspid valve and double-inlet left ventricle (5,70). Systematic use of the ability to evaluate flow using contrast techniques is playing an increasingly important role in pediatric cardiology. For example, the largest pediatric cardiology center in England (Newcastle-upon-Tyne) sends a cardiologist and M-mode echocardiographic instrument on its mobile intensive care unit to transport critically ill newborns back to Newcastle. The diagnosis can usually be made on the basis of clinical and contrast echocardiographic findings, allowing optimal scheduling of emergency catheterization and/or surgery upon arrival.

4. Valvular insufficiency

Demonstration of left sided valvular insufficiency requires cardiac catheterization. Kerber et al showed that echocardiographic monitoring of left ventricular or aortic root injections could detect mitral or aortic regurgitation, respectively with high sensitivity and specificity and none of the toxicity associated with angiographic dye injections (71). Since it requires left heart catheterization, though

this technique is rarely used.

Contrast echocardiography is more useful in detecting right sided valvular insufficiency than left sided lesions. Recent work shows that contrast may be observed to appear in the inferior vena cava coincident with the "v" pulsation on the right atrial pressure tracing, after upper extremity injection, in patients with tricuspid insufficiency (72-74) (figure 5).

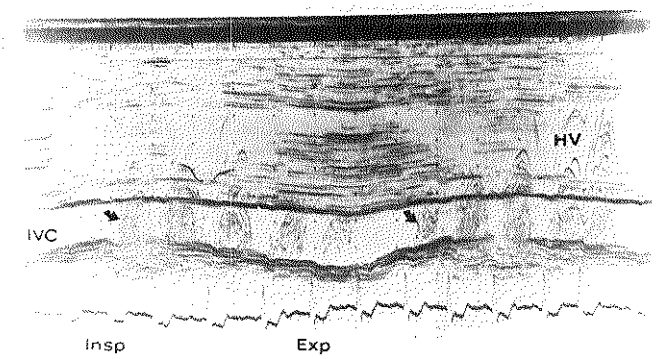

Figure 5: Inferior vena cava (IVC) echogram in a patient with tricuspid regurgitation. After injection of 5% dextrose solution in an upper extremity vein, contrast can be seen entering the IVC and hepatic vein (HV) and flowing retrograde in late systole, then reversing slope and flowing antegrade in early diastole. This effect of "v-wave synchronous" contrast is more pronounced during inspiration (insp) than expiration (exp).

The inferior vena cava can be imaged in nearly all patients studied, since there are no "window problems" of overlying lung or bone (75). Analysis of the timing of the contrast bolus appearance in the inferior vena cava allows the echocardiographer to diagnose tricuspid insufficiency with a fair degree of certainty - 90% sensitivity and 100% specificity to date in our laboratory. M-mode echocardiography is superior to two-dimensional techniques for this application, though inexperienced examiners will find it easier to locate the inferior vena cava with two-dimensional techniques. It is important to realize that many normals will have contrast appearing in the inferior vena cava after peripheral venous injection due to deep inspiration or Valsava maneuver, but this will always be

coincident with "a" wave. Some of the causes of false positive and false negative diagnosis of tricuspid insufficiency by contrast echocardiography are listed in table III.

TABLE III: TRICUSPID INSUFFICIENCY: CAUSES OF FALSE POSITIVE AND FALSE NEGATIVE TESTS
(IVC echo during contrast injections in arm)

False positive	False negative
a-wave synchronous pattern of IVC contrast appearance	insufficient central contrast
pattern of IVC contrast appearance random in cardiac cycle; not v-wave synchronous	failure to correctly identify IVC (?aorta)
deep inspiration; Valsalva maneuver, cough	failure to make repeated injections
arrhythmia (e.g., VPC) leading to IVC contrast	failure to use M-mode and exclusive reliance on 2D echo
M-mode transducer position too superior, near right atrium	M-mode transducer position too inferior

(for further details, see reference 73)

Since no technique to diagnose tricuspid insufficiency is really ideal (76), peripheral contrast studies are a significant advance. However, they do not provide quantitative information at present. Another interesting and related technique is Doppler echocardiography, which has also been reported accurate in diagnosing tricuspid regurgitation. Since microbubbles are also strong contrast agents in Doppler echocardiography (31), it is possible that contrast Doppler studies might be useful in tricuspid insufficiency.

M-mode contrast echocardiographic patterns (figure 2, page 6) have been described in tricuspid and pulmonary insufficiency (27-29).

Videodensitometric techniques are being tested to obtain indicator-dilution type curves from the appearance and disappearance of contrast in two-dimensional echocardiographic studies. These may be useful in the quantitation of cardiac output (21,77,78), intracardiac shunts (22), and ejection fraction (79).

A unique property of echocardiographic contrast is that the motion of individual contrast particles can be followed and analyzed, in so far as they remain in the echo beam. This fact has been insufficiently utilized, though some authors are now beginning to study flow patterns in the heart, (vortices, turbulence, etc.), or quantifying one vector of the blood velocity by determining slopes of contrast trajectories on M-mode tracings.

Transmission of echocardiographic contrast through the lungs after peripheral venous injection has been achieved in experimental animals (61,80). If safely achieved in humans, this would enhance our ability to image left heart structures, and might particularly aid proximal coronary artery visualization.

Intra-coronary injections of a new microbubble contrast agent* have been reported to allow visualization of myocardial perfusion in experimental animals by two-dimensional echocardiography (80,81). An example of such a study is shown in figure 6.

Another exciting possibility is that intracardiac pressure measurement may become available using resonant frequency analysis of precision microbubbles (82-84). Precision microbubbles may also be used in the future to provide a contrast agent with a more reliable, reproducible and quantifiable contrast effect. Possibly non-gaseous contrast agents such as aggregated collagen or gelatin spheres may be employed (19,20). Better understanding of the phenomenon of "spontaneous contrast" on the left (85-87) or right (88,89) side of the heart is needed: this might shed light on whether cavitation is ever present in human circulation. Ultrasonic studies on microbubbles may provide a method of removing small bubbles from heart-lung machines by a method known as "rectified diffusion" (90). Contrast techniques have been used to study experimental (91) and human (92) decompression, and there is room for more work in this direction.

* produced by Ultra Med., Inc. of Sunnyvale, California

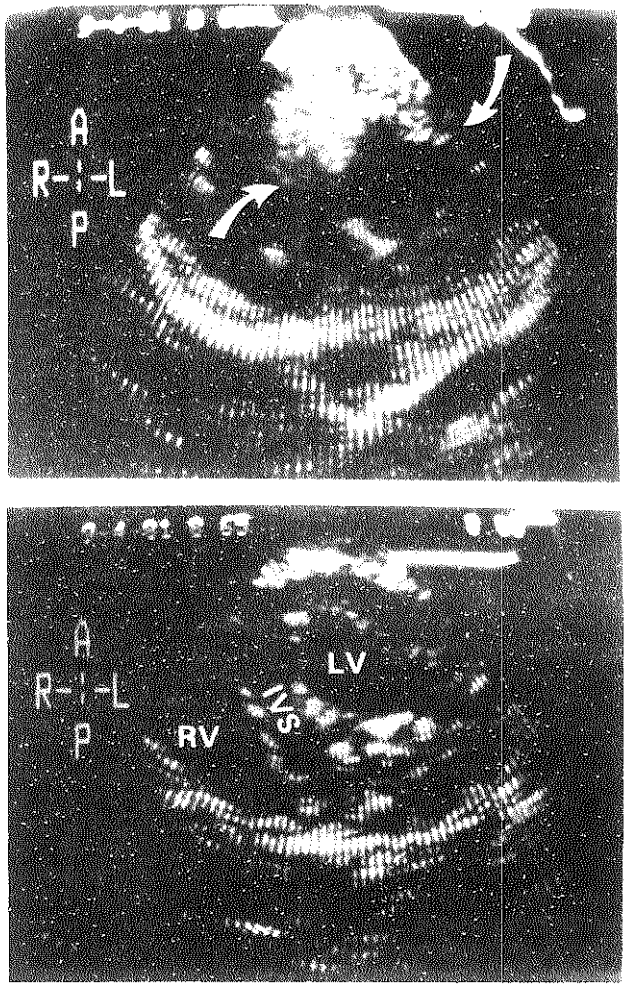

Figure 6: Stop-frame photographs from the two-dimensional echocardiogram of an open-chested pig. Short axis view. Upper panel: control. Lower panel: several seconds after injection of contrast into the left anterior descending (LAD) coronary artery. Note contrast in the myocardium in the area of LAD perfusion (between the 2 arrows). Abbrevations: LV - left ventricle, RV - right ventricle, IVS - interventricular septum, A - anterior, P- posterior, R - right, L - left.

Microbubbles are very strong contrast agents for Doppler ultrasonic studies. Their use in this field, one of the most rapidly expanding areas in echocardiography, has just begun.

CONCLUSION

Contrast echocardiography was first noticed serendipitously by Joyner and described by Gramiak in the late 1960's. In the decade of the 1970's contrast was used for structure identification during the rapid development of echocardiography and for many clinical studies. Systematic analysis of contrast echocardiograms and the introduction of new precision microbubble contrast agents will be increasingly important in the 1980's, and indeed this field may provide the new "sonic boom" area in echocardiography. Interested readers are referred to our more extensive treatment of the topic in book form (93).

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CONTRAST ECHOCARDIOGRAPHIC SHUNTS MAY PERSIST AFTER ATRIAL SEPTAL DEFECT REPAIR

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SUMMARY

We performed contrast echocardiography on 19 subjects who were asymptomatic in the postoperative period after surgical repair of atrial septal defects. Eighteen of these subjects had adequate right heart echocardiographic contrast to assess the presence or absence of right-to-left shunting. Multiple M-mode and two-dimensional echocardiographic views were studied during several contrast injections with and without Valsalva maneuver. Six patients had postoperative shunts and twelve patients had no postoperative shunts. The age of the six patients with post-operative shunts was 26 ± 10 years (mean ± 1 SD) and that of the twelve patients without postoperative shunts was 39 ± 14 years. The postoperative shunt group had 4/6 males and 3/6 patch repairs compared to 2/12 males and 1/12 patch repairs in the no shunt group. There were no definite differences between the two groups in the following variables: type of ASD (primum vs. secundum), preoperative shunt size, preoperative peak right ventricular pressure, preoperative New York Heart Association Classification, pre- or postoperative right ventricular or left ventricular dimensions, aortic and left atrial dimensions. Four of the six patients with postoperative contrast echo shunting underwent cardiac catheterization, showing no significant step-up in oxygen saturation in three, and a significant shunt in one patient who had patch dehiscence at re-operation. We conclude that right-to-left shunts as demonstrated by contrast echocardiography are common in the late postoperative period after atrial septal defect repair. They need not indicate unsuccessful repair or hemodynamically important residual shunts.

INTRODUCTION

Contrast echocardiography (CE) is a sensitive method for the detection of atrial septal defects (ASD's). A small right-to-left shunt is always present in patients with uncomplicated ASD's. Even in the absence of oxymetric evidence, these shunts are frequently demonstrated by CE (1-7). Being non-invasive, simple and safe when properly performed, CE is an attractive and practical method for the study of patients with known or suspected ASD's.

Persistent shunts have been demonstrated by CE during the first three to five days after surgical correction of ASD's (8). It is also known that M-mode echocardiographic abnormalities indicating right ventricular volume overload do not always resolve after ASD closure (9-13). Recently we studied two asymptomatic patients who demonstrated residual right-to-left shunting by CE long after operative closure of their ASD's (the first patient was referred to us because of clinical findings suggesting the presence of residual ASD, and the second patient underwent CE study as part of an unrelated research protocol). We were unsure whether this shunting implied an unsuccessful operative result, and thus decided to prospectively explore the prevalence of residual shunting in the late post-operative period after ASD closure.

PATIENTS

The study consisted of 19 patients who had undergone surgical repair of an ASD. Patients 1 and 2 were the index cases. Seventeen patients were studied prospectively. Since an adequate CE study could not be obtained in one subject, he was excluded from further analysis. Of the remaining 18 patients, 6 were male and 12 were female (table I). Their ages ranged from 17 to 58 years (mean 34). All patients had ASD's diagnosed at preoperative cardiac catheterization and confirmed at surgery. Two patients had an ASD of the primum type and 16 had an ostium secundum ASD. Two patients had associated anomalous pulmonary venous drainage and one of these had persistence of a left superior vena cava draining into the coronary sinus. No other congenital abnormalities were present. One patient had single vessel coronary disease. Preoperative shunt size was 3.5 $\pm$ 1.6 (pulmonary to systemic flow ratio).

The peak right ventricular systolic pressure ranged from 20 to 50 mmHg. Twelve patients were in New York Heart Association Class I and 6 were in Class II. The defect was closed with a primary suture in 13 patients and patch graft in 5 patients (table I).

The time between ASD repair and CE was more than one year in 8 patients, between one month to one year in 9 patients and one patient was studied 5 days postoperatively.

Table I: CLINICAL AND HEMODYNAMIC DATA

Patient Number	Age/Sex	Type of ASD	Preop. NHYA Class	Peak RVSP (mmHG)	Preop. Aortic sat.(%)	Type of repair	OP-CE Time
1	23F	II	I	25	97	pr	11 y
2	25M	I	I	32	98	patch	2 mo
3	43M	II	II	49	98	pr + CABG	1 1/2 y
4	17M	II	I	28	95	patch	7 y
5	31F	II+ PAPVD+ LSVC	I	35	97	patch	1 1/4 y
6	17M	II	I	28	98	pr	1 1/4 y
7	31F	II	I	30	97	pr	4 mo
8	29F	II	I	24	97	pr	5 d
9	48F	I	II	20	96	patch	5 mo
10	47F	II	I	30	98	pr	4 mo
11	21F	II	I	39	97	pr	1 mo
12	48F	II	I	32	96	pr	2 3/4 y
13	54M	II	II	33	97	pr	10 mo
14	22F	II+ PAPVD	I	47	98	pr	11 mo
15	42F	II	I	28	96	pr	4 y
16	48F	II	II	39	95	pr	1 mo
17	16M	II	I	50	99	pr	8 y
18	58F	II	II	40	95	pr	11 mo

Abbreviations: Type of ASD I: primum, II: secundum, NYHA: New York Heart Association classification, RVSP: right ventricular systolic pressure, Sat.: saturation, OP-CE Time; interval between ASD closure and postoperative contrast echo study, F: female, M: male, pr: primary suture, CABG: coronary artery bypass surgery, PAPVD: partial anomalous pulmonary venous drainage, LSVC: left superior vena cava, y: years, mo: months, d: days.

METHODS

M-mode echocardiograms were obtained with an EchocardioVisor SE (Organon Teknika) and recorded on light sensitive paper with a Honeywell LS6 recorder. Two-dimensional echocardiograms were made with a Toshiba SSH-10A phased array sector scanner or Organon Teknika EchocardioVisor 03 linear array instrument. Images were recorded on videotape for subsequent analysis. Stop frame images were obtained by Polaroid photography.

All CE exmaninations were performed with the patient in the left lateral decubitus position. Echocardiographic contrast was produced by a forceful hand injection of 5 to 10 ml of 5% dextrose in water solution through a 16 or 18 gauge Teflon venous cannula placed in an antecubital vein. At least 10 injections were performed in each patient.

During recording of M-mode echocardiograms, CE was performed in two sound beam directions: (1) right ventricular outflow tract - aortic - left atrial level and (2) mitral valve level. The projections employed for CE with two-dimensional echocardiography were the (1) parasternal long axis view, (2) parasternal short axis view at the level of aortic valve, (3) apical four chamber view, (4) apical long axis view and if possible the (5) subcostal short axis and (6) right parasternal views (14). Attention was focused on the interatrial septum in each view (except the parasternal long axis view).

In 14 patients CE was also performed during Valsalva maneuver to increase the amount of right-to-left shunting. This maneuver was done by blowing with an open glottis in a mouthpiece connected to a mercury manometer and holding the pressure above 30 mmHg for about 10 seconds. Careful patient instruction was necessary to prevent the patient from taking a deep breath on release, obscuring the echocardiogram just at the moment when shunting is likely to be present during the CE study.

The preoperative M-mode tracings were available in 14 patients, and analyzed in the same manner as the postoperative tracings (see below).

DATA ANALYSIS

Each M-mode and two-dimensional study was assessed for the presence of right-to-left shunting. Two-dimensional studies were also assessed for the presence of left-to-right shunting (on the basis of negative contrast effect). Right-to-left shunting was considered present when contrast echoes appeared in one or more of the following areas: left atrium, mitral orifice, left ventricular outflow tract or aorta. To avoid false positive interpretation as a result of overload effects, care was taken to use gain settings just under the threshold for intracavitary noise. Recordings were considered adequate for analysis if the right-sided heart chambers were densely opacified with contrast echoes (Figures 1,2). Interpretations were done by two independent observers. M-mode echocardiographic measurements of the right ventricle at end-diastolic (RVED), left ventricle at end-diastolic (LVED), aorta at end-diastole (Ao) and maximal left atrial dimension (LA), were made using previously discribed methods (16). The interventricular septal

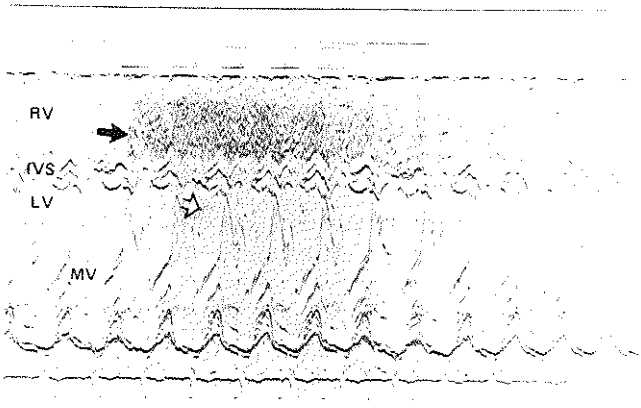

Figure 1: Postoperative M-mode contrast echocardiogram from patient 4 at the mitral valve (MV) level. Peripheral venous injection of 5% dextrose solution performed before the start of this tracing. Note presence of contrast in the right ventricle (RV) (closed arrow) and left ventricle (LV) (open arrow), indicating an intracardiac shunt. IVS - interventricular septum.

(IVS) motion on M-mode echocardiogram was classified as normal, intermediate, or paradoxical. Left-to-right shunting was diagnosed by the presence of a negative contrast effect along the right margin of the interatrial septum.

Clinical (age, sex, preoperative shunt size, preoperative peak right ventricular systolic pressure, preoperative New York Heart Association functional class, type of ASD, patch or suture closure) and echocardiographic (RVED, LVED, Ao, LA, type of IVS motion) data for the patients with postoperative shunts were compared to those of the patients without postoperative shunts using Student's unpaired t-tests or the chi-square test. Pre- and postoperative changes in echocardiographic measurements were compared using the paired Student's t-test.

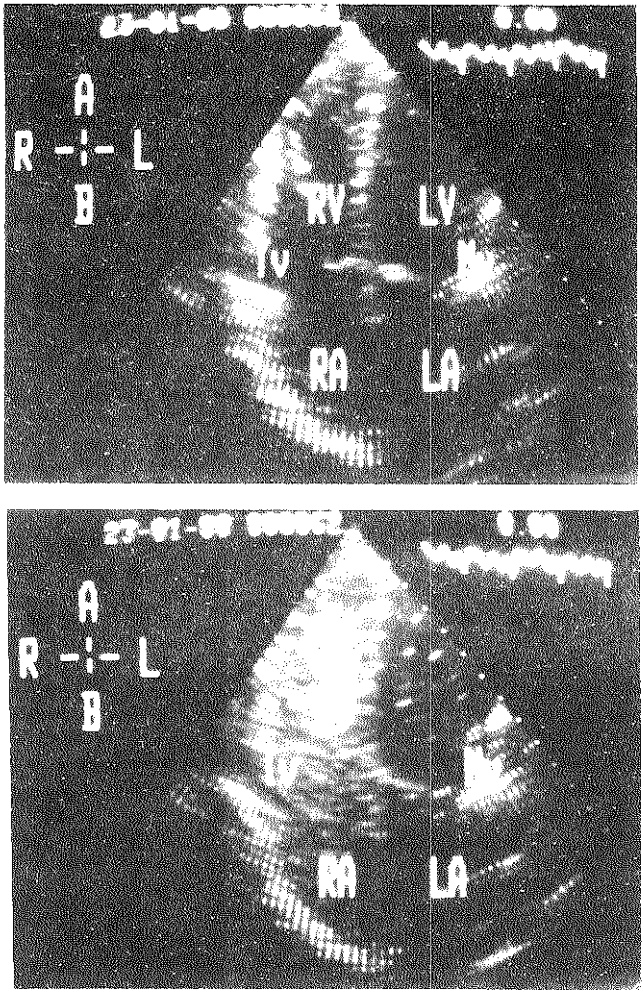

Figure 2: Stop-frame Polaroid photograph from the two-dimensional contrast echocardiographic study of patient 2. Upper panel: just before contrast injection. Lower panel: 10 seconds later. Note dense contrast in the right atrium (RA) and right ventricle (RV), and less dense contrast in the left ventricle, again indicating intracardiac shunt. AP: apical: BA: basal; R: right; L: left; LA: left atrium; LV: left ventricle.

RESULTS

Presence of shunts

Six of the 18 patients had right-to-left shunts postoperatively (patients 1 to 6). These included the two index patients and 4 of the prospectively studied 16 patients with adequate CE. Examples of studies with residual shunts are shown in Figures 1 and 2. Two-dimensional echocardiography was not performed in patient 1, in whom the right-to-left shunt was demonstrated by M-mode echocardiography alone. Patient 3 had no detectable shunt during resting M-mode and two-dimensional CE,but showed repeated right-to-left shunting during the strain phase of the Valsalva maneuver. Right-to-left shunting was demonstrated in patients 2, 4, 5 and 6 on both M-mode and two-dimensional CE without Valsalva. Twelve patients had no residual shunting by either M-mode or two-dimensional CE dispite Valsalva maneuvers during several of the contrast injections.

Three subjects (patients 1, 2 and 4) had no oxymetric evidence of a residual postoperative shunt by heart catheterization shortly after right-to-left shunts were demonstrated on their CE. One further subject (patient 5) had a large step-up in right-sided oxygen saturations. This patient became symptomatic again shortly after her positive postoperative contrast echo study. At re-operation the interatrial patch was loose.

Right-to-left shunts were detected by two-dimensional CE in the apical four chamber view (5 patients), parasternal long axis view (4 patients), and parasternal short axis view (3 patients) of the 5 patients showing right-to-left shunt on two-dimensional CE. Two of the 5 patients with positive CE in the apical four chamber view had echo discontinuity of the interatrial septum. In one of these the discontinuity was also seen in the parasteral short axis view at the level of aortic cusps. Right-to-left shunting was detected in the other 3 patients in the absence of an echocardiographic discontinuity in the interatrial septum. Three of the 12 patients without demonstrable shunt had echocardiographic discontinuity of their interatrial septum in the apical four chamber view. In none of the 18 patients studied was a definite negative contrast effect seen in the right atrium.

Clinical differences between patients with and without shunts: (Table I)

The six patients with residual shunts (patient 1 to 6) did not differ from the 12 patients without shunts (patients 7 to 18) in the following parameters: type of ASD (5 secuncum, 1 primum vs. 11 secundum, 1 primum), preoperative shunt size (Qp/Qs)= (2.8 ± 1.0 vs. 3.8 ± 1.8, mean $\pm$ 1 SD), preoperative peak right ventricular systolic

pressure (33 ± 9 vs. 34 ± 8 mmHg), preoperative New York Heart Association Classification (5 Class I, 1 Class II vs. 8 Class I, 4 Class II), age (26 ± 10 years old vs. 39 ± 14 years old), sex (4/6 males vs. 2/12 males), or proportion of the patients with patch as opposed to primary suture closure (3/6 vs. 1/12). Though these differences did not reach statistical significance, it is possible that some tendencies were masked by the small number of patients. All patients were asymptomatic after surgery and all except patient 5 (see above) remained so.

The time between ASD repair and CE study was 44 ± 52 months (mean ± 1 SD) in patients with postoperative shunts and 19 ± 28 months in patients without shunts. In 5 of the 6 patients with shunts CE was performed more than one year after surgery as compared to 3 of 12 patients without shunts.

Echocardiographic differences between patients with and without shunt: (Table II)

There was no difference between patients with and without postoperative shunts in the following preoperative echocardiographic parameters: right ventricular dimension (44 ± 22 mm vs. 46 ± 10 mm), left ventricular end-diastolic dimension (43 ± 5 mm vs. 38 ± 15 mm), left atrial dimension (35 ± 7 mm vs. 39 ± 8 mm), aortic root diameter (29 ± 1 mm vs. 30 ± 7 mm), and prevalence of abnormal (paradoxical or intermediate) interventricular septal motion (3/4 vs. 9/10).

There was also no difference between the patients with and without shunt in the following postoperative echocardiographic parameters: right ventricular dimension (24 ± 12 mm vs. 29 ± 8 mm), left ventricular end-diastolic dimension (48 ± 6 mm vs. 44 ± 5 mm), left atrial dimension (35 ± 4 mm vs. 37 ± 7 mm), aortic root diameter (31 ± 4 mm vs. 30 ± 5 mm), abnormal interventricular septal motion (4/6 vs. 8/12), discontinuity of the interatrial septum by two-dimensional echocardiography (2/5 vs. 3/12).

No echocardiographic finding could differentiate a primary suture closure of the defect from a patch closure. One patient (case 8) whose ASD was repaired with a primary suture closure had a highly reflective and thickned midportion of the interatrial septum. None of the remaining 11 patients without echo discontinuity in the interatrial septum or the 5 patients with such discontinuity present showed any abnormal echoes or thicknening of the septum (Table II).

Comparison between preoperative and postoperative M-mode echocardiographic findings

Four of the six patients with residual postoperative shunting and ten of the twelve patients without postoperative shunting had preoperative M-mode tracings available for analysis.

Table II: ECHOCARDIOGRAPHIC FINDINGS

Patient Number	PREOPERATIVE						POSTOPERATIVE							
	RV (mm)	LVED (mm)	Ao (mm)	LA (mm)	IVS	CE	RV (mm)	LVED (mm)	Ao (mm)	LA (mm)	IVS	CE	CE+V	IAS
1	ND						45	40	25	33	P	+	ND	ND
2	30	38	28	34	P	+	22	48	30	32	P	+	ND	ED
3	55	45	28	48	P	-	32	50	35	41	N	-	+	C
4	ND						20	44	33	33	I	+	+	ED
5	70	50	30	48	P	ND	10	57	27	31	P	+	+	C
6	22	40	28	28	N	-	17	51	34	40	N	+	ND	C
7	48	38	24	44	P	+	32	45	28	38	I	-	_	ED
8	42	42	23	32	P	+	37	45	21	28	N	-	ND	C,IE
9	40	38	28	38	P	+	23	40	30	40	P	-	_	ED
10	45	30	35	28	P	+	41	34	34	40	I	-	_	C
11	48	40	28	32	P	ND	21	46	30	30	I	-	_	C
12	25	52	32	45	N	ND	21	50	28	48	N	-	_	C
13	65	50	40	50	P	ND	38	49	37	43	I	-	_	C
14	40	40	30	30	P	ND	24	40	28	28	N	-	_	ED
15	53	41	40	45	P	ND	36	50	39	41	N	-	_	C
16	ND						40	50	32	43	I	-	_	C
17	ND						25	46	29	28	I	-	_	C
18	50	50	28	45	P	ND	20	38	27	31	I	-	-	C

Abbreviations: RV: right ventricle, LVED: left ventricular end-diastolic dimension, Ao: aortic root diameter, LA: left atrial dimension, IVS: interventricular septal motion, CE: contrast echocardiography, V: Valsalva, IAS: interatrial septal appearance on 2D echo, ND: not done, P: paradoxical, I: intermediate, N: normal, ED: echodiscontinuity, C: continuous, IE: increased echoes from area of IAS on 2D echo, +: right-to-left shunt seen, -: no right-to-left shunt seen.

The only echocardiographic parameter which showed a statistically significant difference before and after surgery was the right ventricular dimension (Table II). In all patients with preoperative echocardiograms available for comparison, the right ventricular dimension decreased after surgery (figure 3). It was 45 ± 14 mm (mean $\pm$ SD) postoperatively ($p < 0.001$). The decrease in right ventricular dimension was similar in patients with or without postoperative shunts (Table II, figure 3).

The right ventricular dimension failed to decrease entirely to normal in two patients with postoperative shunt detected by CE. One of these (case 1) was a patient whose postoperative catheterization revealed no oxymetric evidence of shunting, and the other patient showed contrast shunting only during Valsalva maneuver. On the other hand, six of the twelve patients without CE evidence of shunting still had right

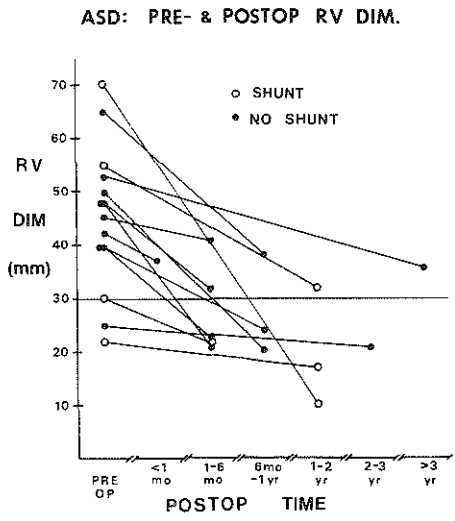

Figure 3: Right ventricular dimension (RVD) is displayed on the ordinate (in mm) preopertively (left column) and postoperatively (on right). Solid lines connect the preoperative and postoperative studies of each individual patient. Open circles indicate the patients with residual postoperative shunting by contrast echo. Closed circles indicate the patients without residual shunting. Note that there is no definite correlation between RVD and the interval between operation and postoperative echo (x-axis). Line through 30 mm represents upper limit of normal.

ventricular dilatation. There was no significant correlation between age at operation and right ventricular dimension on the postoperative M-mode echocardiogram.

DISCUSSION

Contrast echocardiography for ASD detection

Contrast echocardiography is a sensitive and specific technique for the detection of right-to-left intracardiac shunts (1-7, 17). Various series report sensitivity in detecting ASD's at 75 to 100%, even in the absence of demonstrable arterial desaturation (3, 5-7,17). Technique variation with respect to the cross-sectional views employed,

performance of Valsalva maneuver, and insistence on adequate right heart opacification before judging a study to be negative probably explain the different reported sensitivities. The sensitivity of CE has been reported to be higher than oximetry (6, 17). This is not particularly surprising, since oximetry is known to lack sensitivity and small shunts with a pulmonary systemic flow ratio of less than 2:1 are not consistently detected by oximetry (18).

Though uncomplicated ASD's have predominantly left-to-right shunts, detailed studies have consistently shown small amounts of right-to-left shunting as well (19-21). This is the reason for the sensitivity of peripheral CE in detecting uncomplicated ASD's. Since Valsalva maneuver increases the proportion of right-to-left shunting (5,22) it should increase the sensitivity of CE in patients with ASD's. It is possible that a Valsalva maneuver may cause a "false positive" right-to-left shunt in a patient with a patent foramen ovale. We have seen one such case (unpublished data) and Kronik et al have recently reported that 3 of 5 patients with patent foramen ovale and normal right sided pressure had right-to-left shunt on peripheral CE (22). There is a report of two cases with paradoxical embolism where ascorbate dye dilution curves showed an interatrial shunt only upon Valsalva maneuver (23). Thus CE may be "overly sensitive" to interatrial communications -i.e., it may pick up clinically insignificant shunts as well as more major shunts, especially during Valsalva maneuver. We suspect that the transient right-to-left pressure gradient seen in early systole in patients with uncomplicated ASD's may partly persist after operation in some patients, and even may be present in some normals, though mean left atrial pressure is higher than right atrial pressure.

Clinical and echocardiographic studies after surgical ASD repair

Studies of patients who have undergone recatheterization after surgical closure of ASD's suggest that residual defects may be found in as many as 36% of the cases (24, 25). Fortunately, in most of these the shunt size is small (Qp/Qs is less than 1.5/1). These residual postoperative defects may be unsuspected clinically because auscultatory findings may decrease or disappear, heart size may decrease, and the electrocardiographic manifestations of right ventricular overload may normalize (26).

Postoperative M-mode echocardiographic studies may also be misleading, since a sizable number of patients have persistence of right ventricular dilatation and abnormal interventricular septal motion despite no demonstrable shunt at postoperative catheterization (13, 24).

Valdes-Cruz et al (8) studied 26 patients with complex congenital heart disease by CE through central venous and left atrial lines in the first 3-5 days after surgical closure of atrial

or ventricular septal defects. Using CE they found that residual left-to-right and right-to-left shunts were common. They concluded that "positive studies in the first day after surgery may represent either temporary flow through the newly implanted patch or shunting across a true residual defect". They suggested that persistent shunting beyond the early postoperative period would imply a true residual defect. However, none of their patients had only isolated ASD's and late follow-up studies are not reported. Therefore the significance of persistent postoperative shunting in an uncomplicated group of patients remained to be determined.

Significance of shunt detection by CE in the late postoperative period

Of course, a postoperative right-to-left shunt by CE may indicate an unsuccessful operative result, as was the case in patient 5. However, an important finding of this study answers the question posed by our 2 index cases: that a positive postop CE study need not imply an unsuccessful operative result. In fact, this finding is not uncommon.

Of interest is a possible trend toward younger age (26 $\pm$ 10 vs. 39 $\pm$ 14 years old) and higher proportion undergoing patch closure 3/6 vs. 1/12) in the postoperative shunt group. The younger age is not due to this group being symptomatic earlier on the basis of larger shunts, since they were generally asymptomatic and did not have larger preoperative pulmonary: systemic flow ratios compared to the patients without postoperative CE shunts. It is possible that late postoperative CE shunting is facilitated by patch closures via the following mechanism: incompletely endotheliazed patches or small folds of tissue around the sutures may allow contrast shunting in the absence of a clinically significant shunt. The data in the present series are too limited, though, to further elucidate the mechanism.

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Diagnosis of Tricuspid Regurgitation by Contrast Echocardiography

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SUMMARY **Sixty-two subjects underwent M-mode and two-dimensional echocardiographic studies that included imaging of the inferior vena cava (IVC) during upper extremity contrast injections. Group 1 consisted of 10 patients with clinical tricuspid regurgitation (TR). Group 2 consisted of 40 patients without definite clinical signs of TR but with conditions known to be commonly associated with TR (e.g., mitral valve disease, pulmonary hypertension, former tricuspid valve surgery). Group 3 consisted of 12 normal subjects. The IVC could be imaged by two-dimensional echocardiography followed by M-mode in all subjects. M-mode IVC measurements in the absence of contrast were not sufficient to reliably separate TR patients from non-TR patients. IVC contrast was imaged, frequently during deep inspiration, in all 10 group 1 patients, 36 of 40 group 2 patients and three of 12 group 3 normal subjects. Three patterns of contrast appearance in the IVC were observed: "v-wave synchronous" patterns in all but two patients with TR and "a-wave synchronous" or "random" patterns in patients without TR. The presence of TR was independently assessed during angiography or surgery in 26 patients. There were two false-negative echo studies, as judged by intraoperative palpation of a thrill on the right atrium. There were no false-positive v-wave synchronous studies. M-mode echocardiography was superior to two-dimensional echocardiography in detection of the appearance of contrast in the IVC and ease of pattern interpretation. Recognition of false-positive (a-wave synchronous or random) and false-negative patterns (insufficient central contrast, excessively inferior transducer position) improves the diagnostic accuracy of contrast IVC echocardiography, which is a sensitive and specific method for diagnosing TR.**

LIEPPE et al.[1] recently suggested that two-dimensional echocardiography is a sensitive and specific means for diagnosing tricuspid regurgitation (TR). They used ultrasound contrast from an antecubital vein injection of saline or indocyanine green, and monitored the inferior vena cava (IVC) for appearance of contrast from the subcostal transducer position. We noted appearance of contrast in the IVC with this technique in several patients without TR, and undertook a study to examine the sensitivity and specificity of contrast echocardiography for the diagnosis of TR. We also examined the relative usefulness of M-mode and two-dimensional echocardiography in diagnosing TR.

Methods

Patients

Sixty-two patients underwent M-mode and two-dimensional echocardiography with peripheral contrast injections. Each patient was examined by a cardiologist, with particular attention to the jugular venous pulse, the presence or absence of a murmur consistent with TR, hepatic pulsations and peripheral edema. Patients were divided in three groups with respect to the clinical assessment of the presence or likelihood of TR.

Group 1 included 10 patients with a definite clinical diagnosis of TR, based on a prominent jugular systolic pulsation, a holosystolic murmur that increased with respiration (Carvalho's sign), and a pulsating liver on palpation. Three of these patients had right ventricular angiograms and two underwent cardiac surgery; TR was present in all five. Group 2 included 40 patients who did not have clinical TR but had cardiac disorders frequently associated with TR, such as rheumatic mitral stenosis, pulmonary hypertension, and status post tricuspid valve repair or replacement for TR. Most of these patients had atrial fibrillation and systolic murmurs of nontricuspid origin, rendering clinical assessment of the tricuspid valve difficult. Twenty-one of these patients had operations or right ventricular angiograms: 10 had no TR and 11 had TR. Group 3 included 12 subjects who were normal by history, physical examination and M-mode and two-dimensional echocardiograms.

Angiographic and Operative Diagnosis of Tricuspid Regurgitation

The presence of TR was diagnosed from right ventricular angiograms if contrast appeared in the right atrium in the absence of premature complexes. Intra-

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operative diagnosis of TR was made if a thrill was present upon right atrial palpation before cannulation for cardiopulmonary bypass.

Echocardiographic Methods

Patients were studied in the supine position with slightly flexed knees and hips to allow better relaxation of the abdominal musculature when the subcostal transducer position was used. The IVC was visualized in the sagittal plane by means of two-dimensional echocardiography during the initial three to five contrast injections, with M-mode IVC imaging during later injections. Two-dimensional contrast echocardiograms were also recorded from the left sternal border and apical transducer positions with the patient in the partial left lateral decubitus position.[2, 3] M-mode echocardiograms were obtained with an EchocardioVisor SE (Organon Teknika) interfaced to a Honeywell LS6 strip-chart recorder. Two-dimensional echocardiograms were recorded with an EchocardioVisor 03 (Organon Teknika) multielement, linear-array scanner or a Toshiba SSH-10A phased-array sector scanner and stored on videotape for subsequent analysis. Gain, reject and damping settings on both instruments were adjusted to display the IVC cavity just at the threshold where noise is seen. Microbubbles, the source of contrast effect,[4] are strong reflectors and can usually be differentiated from noise by their characteristic motion patterns.

Echocardiographic contrast was obtained by rapidly injecting 5–8 ml of 5% dextrose in water (D5W) into an upper extremity vein through a three-way stopcock and a #18- or #19-gauge butterfly needle or plastic catheter. To ensure adequate contrast, 1–3 ml of medically pure (100%) carbon dioxide (CO_2) were added to 4–6 ml of D5W to create an improved ultrasonic contrast agent.[5] This was done for three to 10 injections after the initial one or two injections of D5W alone in the first 49 patients studied. The mixture was prepared and agitated just before each injection to increase the contrast content of the venous blood. When connecting and agitating the mixture of CO_2 and D5W in the syringe, we were careful to hold the syringe so the CO_2 could never mix with room air. Subcostal IVC imaging during contrast injection was performed during quiet respiration, deep inspiration and Valsalva maneuver in each patient.

IVC dimensions were calculated using the leading-edge method from the mean of three measurements at (1) the onset of QRS on the simultaneously recorded ECG, (2) the minimal diameter in early systole before the onset of the "v" wave, and (3) the maximal diameter during the "v" wave (fig. 1). With this method, the minimal diameter after the "a" wave and the peak "v" wave maximal diameter are measured. The percentage of systolic pulsation was calculated using the formula ([maximal dimension − minimal dimension]/minimal dimension) × 100. Two groups were compared with respect to differences in IVC measurement: a definite TR group and a non-TR group. The TR group included 21 patients — all 10 in group 1 with clinical TR, plus 11 additional group 2 patients with an angiographic or intraoperative diagnosis of TR. The non-TR group of 22 subjects in-

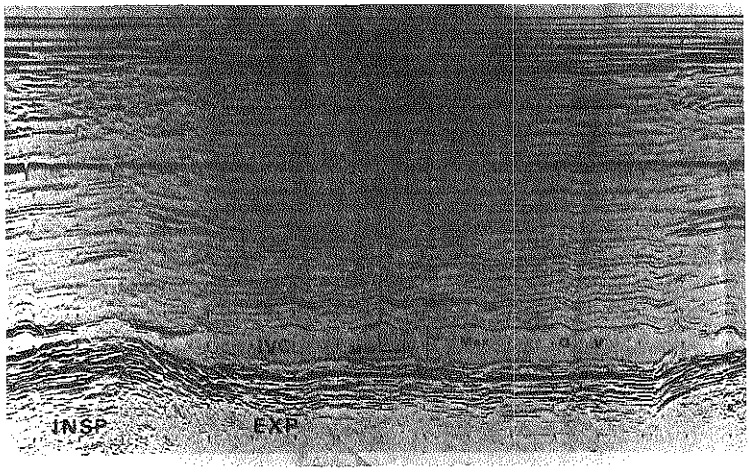

FIGURE 1. *Normal M-mode inferior vena cava (IVC) echocardiogram showing how measurements were made. IVC dimensions were measured at the onset of the QRS, minimal systolic dimension before onset of the "v" pulsation (Min) and maximal dimension during the "v" pulsation (Max). INSP = inspiration; EXP = expiration; a = "a" pulsation; v = "v" pulsation.*

TABLE 1. *Inferior Vena Cava Dimensions*

Group	D-QRS	D-min	D-max	% systolic pulsation
TR	23 ± 4	23 ± 4	24 ± 4	3 ± 6
	n = 21	n = 21	n = 21	n = 21
Non-TR	18 ± 3	16 ± 5	18 ± 4	12 ± 13
	n = 10	n = 16	n = 20	n = 20
p	< 0.001	< 0.001	< 0.001	< 0.02

Measurements are given as mean ± SD.

Abbreviations: D-QRS = IVC diameter at QRS onset (in mm); D-min = IVC minimal diameter in early systole before onset of "v" wave; D-max = IVC dimension at maximal "v" wave; n = number of subjects with tracing of sufficient quality to perform measurement; *p* = *p* value of unpaired *t* tests between the groups listed.

cluded the 12 normal subjects in group 3, nine group 2 patients with negative intraoperative palpation for TR and one group 2 patient with a negative right ventricular angiogram.

Results

IVC size and Pulsation

The IVC was adequately visualized by both M-mode and two-dimensional echocardiography in all patients. Patients with TR had a larger IVC dimension than those without TR (table 1). This was statistically significant for measurements made at QRS onset at the minimal dimension before the "v" wave, or at the maximal dimension during the "v" wave. However, there was considerable overlap between the groups, so IVC dimension alone cannot differentiate between patients with and those without TR. Patients with IVC dimension at QRS onset, or maximum "v" pulsation, of greater than 24 mm all had TR, and none of those with dimensions less than 16 mm had TR. However, most patients in this study had IVC dimensions of 16–24 mm. The percentage of systolic pulsation was higher in the non-TR group, but the large overlap precluded using this test to predict the presence of TR in individual patients.

Patterns of IVC Contrast Appearance

No side effects from contrast injections were noted. Contrast was detected in the IVC on M-mode examination in all patients in group 1, 36 of 40 patients in group 2 and three of 10 normal subjects in group 3. Different patterns of IVC contrast appearance were noted. Figure 2 is an example of the echo pattern in patients with TR. The appearance of contrast in middle and late systole is indicated by upward-slanting lines. The lines slant upward because the contrast is moving inferiorly and approaches the superiorly aimed transducer. The contrast then reverses direction and returns toward the heart during diastole, producing downward-sloping lines. This is the most common pattern seen in TR. The timing of the appearance of contrast in the IVC is neither predominantly systolic nor predominantly diastolic, but coincides with the "v" wave of the right atrial pressure tracing or the jugular venous pulse. Therefore, this pattern was termed "v-wave synchronous." An example of a two-dimensional echocardiogram from a patient with TR is shown in figure 3.

A false-positive pattern is shown in figure 4. Contrast appears in the IVC during the "a" wave of the jugular venous pulse tracing and is thus due to atrial contraction rather than TR. A more subtle false-positive pattern is shown in figure 5, in a patient with no palpable TR at operation. In this pattern, appearance of contrast is influenced by respiration but has no clear relation to the cardiac cycle, and was therefore designated the "random" pattern.

Distribution of Echo Patterns (table 2)

All 10 patients in group 1 with clinical TR had a v-wave synchronous pattern of echocardiographic con-

TABLE 2. *M-mode Inferior Vena Cava Echo Patterns*

Group	V-wave synchronous	A-wave synchronous	Random	No contrast
1 (n = 10)	10	0	0	0
2 (n = 40)	20	9	7	4
3 (n = 12)	0	3	0	9

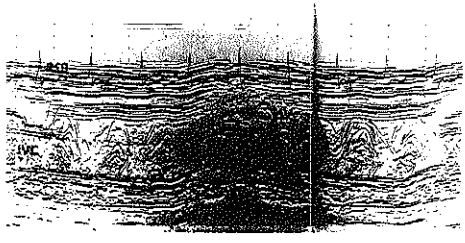

FIGURE 2. *M-mode contrast inferior vena cava echocardiogram showing a v-wave synchronous pattern typical for tricuspid regurgitation. Note the increased contrast effect due to inspiration in the middle of the figure. All of the contrast in the hepatic vein (HV) and most of the contrast in the IVC has an upward slope during the early part of systole, indicating retrograde flow coming toward a superiorly directed transducer, and a negative slope as the contrast returns towards the heart during the latter part of the v-wave, in early diastole.*

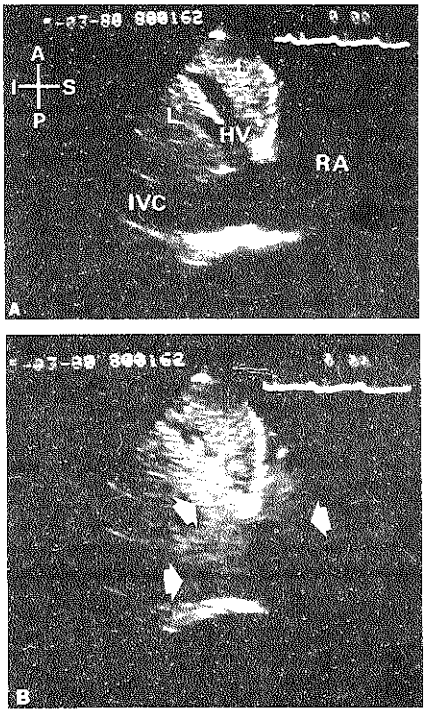

FIGURE 3. *Stop-frame photographs from a subcostal two-dimensional echocardiographic study of the inferior vena cava (IVC) and right atrium (RA) before (A) and immediately after (B) upper extremity injection of 5% dextrose in water. The IVC and hepatic vein (HV) fill with contrast (arrows) in this patient with tricuspid regurgitation later proved by intraoperative right atrial palpation. L = liver; A = anterior; P = posterior; I = inferior; S = superior.*

trast appearance in the IVC (fig. 2). Five of the 10 patients had right ventricular angiograms or intraoperative right atrial palpation in close temporal proximity to their echocardiographic study and TR could be confirmed by these independent means in all five. Two of the 12 normal subjects in group 3 had IVC echocardiographic contrast on their M-mode study but not on the two-dimensional IVC echocardiogram and another group 3 patient had it on both. In all three, contrast appeared at end-inspiration only. None of the group 3 subjects had contrast in the IVC during normal quiet respiration.

Of the 40 patients in group 2, 20 had v-wave synchronous IVC echo patterns suggesting TR. Several of these were seen only near the end of inspiration; none of the patients with isolated late-inspiratory v-wave synchronous patterns had operation or right ventricular angiography to verify the presence or absence of TR. Ten group 2 patients had a-wave synchronous IVC contrast patterns, indicating the absence of TR. Seven group 2 patients had a random pattern of echo appearance. All of these studies showed strong inspiratory variation in IVC contrast. The last four group 2 patients had no IVC contrast.

Confirmation of Echo Patterns

Twenty-six of the study subjects had either right ventricular angiograms or right atrial palpation at operation to verify the presence of TR. Sixteen of the studies were positive for TR, and 14 of these 16 patients had v-wave synchronous IVC contrast during normal respiration. The last two had no IVC contrast appearance even though a thrill was detected during intraoperative right atrial palpation. These were the only two false-negative echo studies. Of the 10 patients with normal tricuspid function at angiography or operation, five had a random appearance of contrast unrelated to "a" or "v" waves, and four showed contrast during the "a" wave only. These four were the only patients in sinus rhythm; the others were in atrial fibrillation. One patient with a negative operative diagnosis of TR had no contrast appearance in his IVC during contrast echocardiography.

M-mode vs Two-dimensional Echocardiography

Thirteen of the study subjects had no IVC contrast by either M-mode or two-dimensional echocardiography despite deep inspiration and the Valsalva maneuver. Thirty-eight had the same contrast pattern diagnosed both by M-mode and two-dimensional echocardiography (27 v-wave synchronous, eight a-wave synchronous and three random patterns). Within this group, timing analysis was considerably simpler from M-mode recordings, which allowed measurement of contrast appearance, and simplified comparison of the ECG, echo and respiratory events. Timing analysis of two-dimensional echoes involved review of videotapes and repeated slow-motion analysis, with tedious loading and unloading of tapes onto the video head for forward and reverse tape motion.

Eleven patients had IVC contrast on their M-mode studies but no definite contrast on their two-dimensional studies. Their M-mode patterns were as follows: four a-wave synchronous, four random and three v-wave synchronous. Only two of these patients, neither of whom had TR, had operative or angiographic study of the tricuspid valve; one had an M-mode a-wave synchronous pattern and the other had a random pattern. Two further normal subjects had small amounts of a-wave synchronous contrast appearance on M-mode but none on two-dimensional echocardiography.

Assessment for a "back-and-forth" pattern of contrast flow across the tricuspid valve on two-dimensional studies was difficult because of the normal slight retrograde motion of contrast in the right

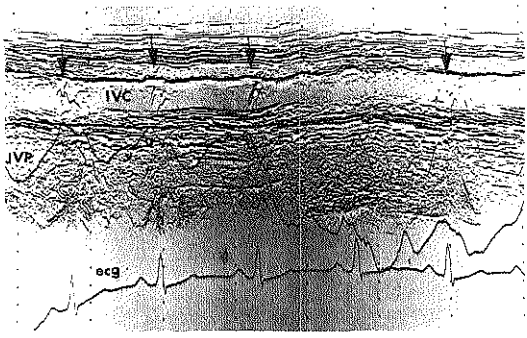

FIGURE 4. *M-mode contrast inferior vena cava (IVC) echocardiogram showing an a-wave synchronous pattern in a patient with pulmonic stenosis and no tricuspid pathology. The jugular venous pulse tracing (JVP) shows a large respiratory variation but always a prominent "a" wave and x' descent, making significant tricuspid regurgitation unlikely. Contrast appears in the IVC (arrows) during the late part of the JVP "a" pulsation, suggesting retrograde flow due to forceful atrial contraction. a = "a" pulsation; v = "v" pulsation.*

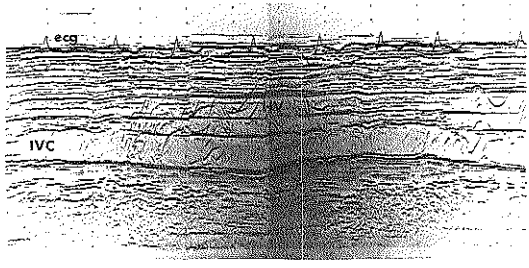

FIGURE 5. *M-mode contrast inferior vena cava (IVC) echocardiogram showing a "random" pattern of contrast appearance in the IVC and hepatic vein (HV), with retrograde flow (upward-sloping contrast lines) occurring with no fixed relation to the cardiac cycle. This is the most common false-positive pattern of contrast appearance in patients with atrial fibrillation.*

ventricle at the time of closing of the tricuspid valve. Only a minority of patients with v-wave synchronous IVC contrast patterns had definite "back-and-forth" motion as assessed subjectively by two observers in the echo lab at the time of the study.

Discussion

Diagnostic Tests for TR

TR may be an obvious diagnosis clinically. In patients with prominent jugular "v" waves, a positive Carvalho sign and a pulsatile liver, further studies are not needed to establish the diagnosis. However, in adults, TR is usually associated with disease of the left side of the heart and pulmonary hypertension, and most patients with TR are in atrial fibrillation.[6, 7] In the absence of sinus rhythm, the jugular venous pulse is less useful in diagnosing TR, and clinical diagnosis is further obscured because many patients with TR also have systolic murmurs of aortic or mitral valve origin. Thus, an accurate diagnostic test for TR would be useful. Right ventricular angiography is not an ideal test because it is invasive and false-positive studies may be caused by catheter interference with normal tricuspid valve mechanics. Unfortunately, there is no accepted "gold standard" for the diagnosis of TR.[8, 9] Even intraoperative right atrial palpation may be subject to false negatives due to insufficiently widespread palpation, and false-positive palpation of a thrill in the right atrium can result from intraoperative manipulation of the heart with resulting distortion and incompetence of the tricuspid valve. Perhaps one of the two false-negative echo contrast studies in our series was in fact a false-positive palpation due to a transmitted thrill caused by a flail mitral valve leaflet in a patient with a thrill that was also palpated on the thoracic wall. Because the palpated thrill was fairly localized and superior on the right atrium, another possibility is that the regurgitant tricuspid jet was superiorly directed, thereby explaining the failure to visualize contrast in the IVC. However, because there is no better standard than angiocardiography or intraoperative palpation against which to judge the proposed echo contrast technique, it is prudent to consider this case as a false-negative echocardiographic study.

Echocardiographic Diagnosis of TR

A major shortcoming of echocardiography is the less-than-100% success rate in acquiring diagnostic information. Subcostal imaging of the IVC, however, is not hampered by the usual echocardiographic "window" difficulties. In fact, all 62 patients in the current series had successful two-dimensional and M-mode imaging of the IVC. M-mode imaging without initial

two-dimensional study should have a very high success rate after the examiner has gained some experience in IVC echocardiography, though this hypothesis was not tested in the present study.

It would be desirable if IVC echocardiography could separate patients with TR from normal subjects on the basis of an entirely noninvasive variable, such as IVC dimension or systolic pulsation. We could not do this in the present study, because there was overlap in IVC dimension between the two groups, and frequently patients in both the TR and non-TR groups had no detectable pulsations. IVC dimensions greater thn 24 mm (measured at onset of QRS or peak "v" pulsation) were only seen in patients with TR, and dimensions less than 16 mm were seen only in patients without TR. Most of the patients in this study had IVC dimensions between these values. Contrast echocardiography, a minimally invasive test, appears to offer a sensitive and specific method for diagnosing TR, according to our series and other reports.

Doppler echocardiography may offer an entirely noninvasive echocardiographic method for diagnosing TR.[11] Because the microbubbles that cause ultrasonic contrast are easily detected with Doppler techniques,[12] contrast Doppler echocardiography can be considered. Quantification of TR may become possible with improved Doppler or contrast techniques, though it is not possible by the method used in this study.

Improving the Diagnostic Accuracy of Contrast IVC Echocardiography in TR

The various patterns of IVC contrast appearance must be clearly recognized to exclude a-wave synchronous and random studies and thereby improve the specificity of echocardiography in diagnosing TR. Only v-wave synchronous patterns should suggest the diagnosis of TR. Many normal subjects have a-wave synchronous IVC contrast appearance on deep inspiration.

M-mode tracings are superior to two-dimensional echocardiographic video recordings for analysis of the timing of IVC contrast appearance. M-mode was also more sensitive in detecting the appearance of contrast in the IVC. Thus, M-mode rather than two-dimensional echocardiography should be used routinely when searching for TR with IVC contrast echocardiography, except perhaps in patients in whom locating the IVC by M-mode is difficult. In this situation, the improved spatial orientation of two-dimensional echocardiography may facilitate correct IVC localization. Two-dimensional and M-mode echocardiography, however, are complementary techniques and usually can be performed with the same instrument.

A two-dimensional echocardiographic sign that has been proposed for TR, "back-and-forth" motion of contrast across the tricuspid valve, was too subjective in the current study. Because a slight retrograde motion of contrast near the tricuspid valve as it closes is normal, this sign depends on detection of excessive retrograde motion. We found that two-dimensional echocardiography is insufficiently sensitive and specific to reliably separate patients with TR from those without TR on the basis of this sign.

Clearer analysis of the timing of the appearance of contrast in the IVC may be aided by calling the "true-positive" patterns v-wave synchronous and "false-positive" patterns a-wave synchronous or random. These have advantages over the alternative proposal of "presystolic" and "systolic"[10, 13] because much of the IVC "a" wave comes during electrical systole, and the "v" wave is late systolic and early diastolic (fig. 1).

On two-dimensional echocardiography, the cloud of contrast moving retrogradely with the "v" wave was occasionally limited to a small area immediately adjacent to the right atrium. A possible cause of false-negative studies, therefore, would be excessive inferior angulation of the echo transducer, visualizing the IVC more than 1–2 cm inferior to the right atrium. This is more likely to occur by M-mode than two-dimensional echocardiography. One clue to excessive inferior angulation of the echo transducer is appearance of contrast with a negative slope. If contrast is imaged with a v-wave synchronous pattern, TR can be diagnosed regardless of contrast slope. However, a negative study with only a few "lines" of negatively sloped contrast suggests that the transducer may have been directed too inferiorly.

Medically pure (100%) CO_2 has been used as a roentgenologic i.v. contrast agent in diagnosing pericardial effusion before echocardiography was available. It is safe[14, 15] and we have seen no side effects after small amounts of i.v. CO_2 (1–2 ml per injection, in 5 ml D5W) to obtain echo contrast in over 40 patients.[5] Medically pure CO_2 is commercially marketed and should be distinguished from the less pure CO_2 sold in metal cylinders for use in powering various pneumatic devices. CO_2 is useful for adequate echo contrast delivery to the right atrium. In this way the echocardiographer is certain that lack of IVC contrast is due to lack of retrograde flow in the IVC rather than to inability to detect this flow. If contrast is seen in the IVC with D5W, CO_2 is probably unnecessary, as patients with a-wave synchronous, v-wave synchronous or random patterns after D5W alone have always had the same pattern after CO_2 and D5W. However, we have seen several cases in which an initial injection with D5W failed to yield IVC contrast and subsequent injections with CO_2 and D5W gave IVC contrast. Particularly when antecubital veins are difficult to enter and a smaller hand vein is used, contrast delivery to the central circulation may be insufficient with routine injection techniques. If contrast is not readily apparent in the IVC after an injection, the right side of the heart must be checked from the parasternal or apical transducer position to verify whether contrast has been obtained in adequate density. We suggest that no study be considered negative for TR until the echocardiographer is convinced that adequate central contrast has been achieved. This should reduce the number of false-negative studies and thereby improve the diagnostic sensitivity of contrast IVC echocardiology.

Perhaps CO_2 can cause false-positive diagnosis of TR, although this is doubtful. Because IVC contrast after upper extremity injection must reflect retrograde flow in the IVC, its presence combined with v-wave synchronous timing is unlikely when TR is absent. We have seen no false-positive v-wave synchronous studies. A false-positive diagnosis of TR caused by excessive contrast from CO_2 is less likely than a false-negative diagnosis due to inadequate contrast during routine contrast injections.

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PULMONARY WEDGE INJECTIONS YIELDING LEFT-SIDED ECHOCARDIOGRAPHIC CONTRAST

BY

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Pulmonary wedge injections yielding left-sided echocardiographic contrast*

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SUMMARY Ultrasound contrast on the left side of the heart without the need for left heart catheterisation was achieved by hand injections of 8 to 10 ml 5 per cent dextrose solution through a catheter in the pulmonary wedge position. Injections were performed in 18 patients undergoing routine cardiac catheterisation and M-mode or two-dimensional echocardiography was used. An adequate wedge position was attained in 17 of the 18 patients. Nine had injections through Cournand catheters, three through Swan-Ganz catheters, and five through both. In 11 of these 17 patients left atrial or left ventricular echocardiographic contrast was seen immediately after wedge injection. Two patients showed diminished or absent contrast on later injections from the same position. Better results were obtained with the Cournand catheter (11/15 positive) than with the Swan-Ganz (1/8 positive) catheter. Pulmonary artery injections proximal to the wedge position did not cause left-sided contrast. No complications were observed. The safety of this method remains to be determined.

In the late 1960s, Gramiak and Shah[1] noted that indocyanine green and other solutions caused intracardiac ultrasonic contrast. They speculated that the source of this contrast was microbubbles of air. Since then, further work has more definitely identified the ultrasonic contrast targets to be microbubbles of air introduced during injection.[2 3] Peripheral contrast echocardiology has become an important diagnostic technique.[4–6] Normally, contrast injected peripherally or in the right side of the heart is entirely removed by the lungs, so contrast appearing on the left side of the heart implies an intracardiac right-to-left shunt or an intrapulmonary arteriovenous shunt. In the absence of these anatomical abnormalities, there has been no method of creating left-sided ultrasonic contrast without direct injection, requiring left heart catheterisation.[7]

Several years ago we unsuccessfully attempted to produce contrast in the left side of the heart using Swan-Ganz balloon catheters in the wedge position in six patients (unpublished data). The balloons were inflated during these wedge injections. Recently, Bommer *et al.*[8] from Davis noted that forceful injections in the wedge position in dogs caused ultrasonic contrast on the left side of the heart. We undertook the present study to retest the hypothesis that pulmonary wedge injections may yield left-sided echocardiographic contrast in humans without known pulmonary or intracardiac shunts. Success in attaining left-sided contrast might allow more sensitive diagnosis of left-to-right shunts and better imaging of left-sided cardiac structures by echocardiography, thereby reducing the need in some cases for left heart catheterisation and radiological contrast angiograms.

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Patients and methods

Eighteen patients undergoing right and left heart catheterisation for routine clinical indications were studied. There were eight men and 10 women. Their ages ranged from 20 to 67 years (mean 44 years). The diagnoses are listed in the Table.

Number 7 French Cournand or Swan-Ganz catheters were introduced via a right antecubital cutdown and advanced to the wedge position. This was attained without balloon inflation in any of the patients in whom Swan-Ganz catheters were used. Confirmation of wedge position was obtained by

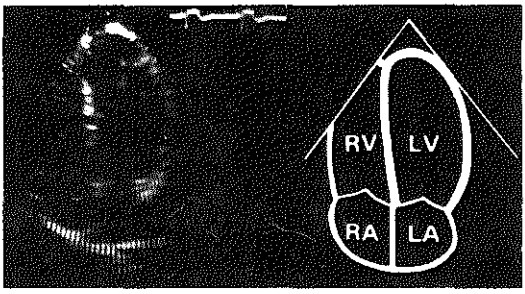

Fig. 1 Left—*stop-frame photograph from the two-dimensional echocardiogram of a subject immediately before wedge injection. Apical four chamber view.* Right—*diagram of left-hand panel. Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.*

fluoroscopy and pressure tracings. Three to seven rapid hand injections of eight to 10 ml 5 per cent dextrose solution were given during normal quiet respiration.

Echocardiographic imaging of the left heart during each injection was performed with the patient in either the supine or slight left lateral decubitus position. An Organon Teknika Echocardiovisor 01 M-mode instrument or a Toshiba SSH-10A phased array two-dimensional ultrasonograph was used.

The symptoms experienced by the patient during injection and subsequent stay in the catheterisation laboratory were carefully monitored, along with electrocardiogram and haemodynamic state. Most of the first 10 patients had post-catheterisation chest films, or lung scans in the anterolateral and left lateral positions between 12 and 36 hours after catheterisation.

Results

An adequate wedge position was attained in 17 of the 18 patients. In the patient in whom the wedge position could not be obtained (Table, case 4), right pulmonary artery injections failed to yield left heart echocardiographic contrast. In 11 of the 17 patients echocardiographic contrast was seen in the left heart immediately after wedge injection. Still frames from a two-dimensional echocardiogram before and immediately after wedge injection in one of these patients are shown in Fig. 1 and 2. Contrast is seen in the left ventricular cavity. Fig. 3 shows an M-mode study at the aorta-left atrial level from another subject, with appearance of contrast in the left atrium after wedge injection.

No patient developed symptoms, deteriorated clinically, or showed any haemodynamic or electrocardiographic changes after the wedge injections.

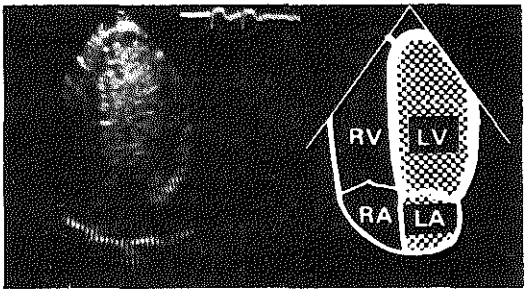

Fig. 2 Left—*stop-frame photograph from the two-dimensional echocardiogram of the subject in Fig. 1, immediately after wedge injection. Apical four chamber view.* Right—*diagram of left-hand panel. Note contrast* (shaded area) *filling the left atrium and left ventricle. Abbreviations as in Fig. 1.*

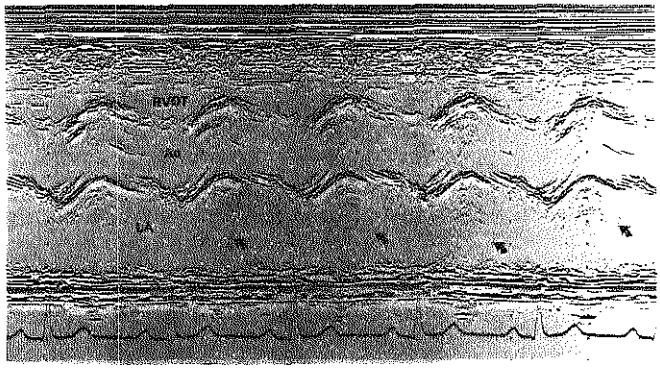

Fig. 3 *M-mode tracing of a subject in the catheterisation laboratory immediately after wedge injection. Note the appearance of fine contrast in the left atrium* (arrows). *Abbreviations: Ao, aorta; LA, left atrium; RVOT, right ventricular outflow tract.*

Chest films were taken between six and 24 hours after catheterisation in five of the first 10 patients studied and were compared with the pre-catheterisation films. None showed new lesions. Lung scans were also negative in the seven patients of the initial first 10 in whom they were performed.

All 17 patients in whom the wedge position was attained had repeated injections. Six persistently showed no left-sided contrast, and two others showed a definite decrease in the amount of left-sided contrast on later compared to earlier injections. In these patients the catheter position was held constant. The other nine patients showed positive findings for three or more injections.

Table *Patient data and outcome of wedge injections*

Case no.	*Age/sex*		*Diagnosis*	*PA pressure systolic/diastolic, mean*	*Mean wedge pressure*	*O_2 saturation (%)*		*Contrast results*	
						Arterial	*Venous*	*Cournand*	*Swan-Ganz*
1	54	M	AS/AR	32/16, 23	13	98	73	-	ND
2	44	M	CAD	×	6	98	-	-	ND
3	37	M	CAD	×	13	96	-	+	ND
4	20	F	ASD	30/16, 19	-	97	MV 62, PA 93	-	ND
5	21	F	Coarct	19/12, 15	7	97	80	-	-
6	48	F	Subvalv AS	21/8, 13	6	96	80	-	ND
7	59	F	CAD	×	×	97	-	+	ND
8	42	M	CAD, MR	19/7, 13	5	98	80	-	ND
9	67	F	AS/AR, MR	32/12, 20	14	95	73	+	ND
10	44	F	CAD	×	15	96	-	+	ND
11	33	F	AR/MR	×	15	-	-	+	ND
12	48	M	CAD	29/15, 21	14	96	75	ND	-
13	51	M	AS/AR	54/22, 34	15	96	70	ND	-
14	50	M	CAD	23/6, 13	7	96	84	ND	-
15	37	F	MS	×	14	×	-	-	-
16	49	F	MS/MR	48/20, 35	31	95	77	-	-
17	31	M	CAD	27/15, 20	15	96	77	+	-
18	58	F	MS/MR	83/33, 54	27	93	67	-, +	+

All pressures are in mmHg.
Abbreviations: AS, aortic stenosis; AR, aortic regurgitation; CAD, coronary artery disease; ASD, atrial septal defect; Subvalv, subvalvular; MR, mitral regurgitation; MS, mitral stenosis; MV, mixed venous; PA, pulmonary artery; ND, injection not done with this catheter. ×, information not obtained or not available; +, left-sided contrast attained; -, no left-sided contrast seen.

Eleven positive studies were obtainable using a Cournand catheter (Table). Injections in an initial position were negative in one patient (case 18) through a Cournand catheter, but became positive after its position was changed. Only one of the eight studies performed with a Swan-Ganz catheter was positive (case 18). Three patients had negative studies with both catheters (cases 5, 15, 16). Except for the patient in whom wedge position could not be obtained (case 4), who had an atropic septal defect, none of the 18 patients had intracardiac shunts. No right-sided contrast was seen after either wedge injections or pulmonary artery injections.

We had the subjective impression that the left-sided contrast was finer than that seen in the right heart after peripheral injections. This finding can be noted in Fig. 3.

Discussion

The results of this study show that in the majority of subjects rapid hand injections in the wedge position cause echocardiographic contrast on the left side of the heart. This could be of help in excluding a left-to-right shunt when performing a right-sided catheterisation as a quick and simple alternative to a saturation run. Its sensitivity needs to be determined, but the high success rate of peripheral venous contrast echocardiography in imaging right-to-left shunts suggests that left-to-right shunts might be very sensitively detected. The high success rate of echocardiographic detection of left-to-right shunting after intracardiac injections leads to the same conclusion.

While it seems likely that the pulmonary capillary "sieve" effect is overcome by rapid wedge injections the exact mechanism by which wedge injections transmit microbubbles through the pulmonary capillary bed is uncertain. Perhaps capillaries are dilated by the force of injection, or, alternatively, the short transit time permits microbubbles which are small enough to pass through pulmonary capillaries and which normally rapidly dissolve because of surface tension effects, to survive long enough to reach the left side of the heart. The "fineness" of the echocardiographic contrast observed in our patients suggests that passage through the pulmonary capillaries alters the microbubble content of the blood but this is a subjective observation and very dependent on individual control settings.

There was no obvious factor apart from the use of the Cournand catheter which strongly correlated with the successful achievement of contrast. Age, sex, diagnosis, pulmonary artery or pulmonary wedge pressure, and arterial and venous oxygen saturations were similar in the groups with successful and unsuccessful studies. Catheter position may be important, for in one patient (case 18) previously negative left-sided contrast was followed by a positive study after catheter repositioning. Injection technique, too, may influence results, especially in regard to the force of injection and the possibility of the inclusion of tiny amounts of air with each bolus.

The technique has not yet been shown to be totally safe, but there are reasons to expect that with care serious complications are unlikely to occur. Firstly, the flushing of catheters in the wedge position in an attempt to improve wedge tracings is a not uncommon occurrence, and, secondly, microbubbles are probably routinely introduced during left-sided injections and flushing during catheterisation, as judged by echocardiography—indeed, echocardiographic contrast was first noted in this way.[1] There is no demonstrable harm attributable to these injections, and it is likely that the smaller microbubbles that pass the pulmonary capillary "sieve" are even less harmful. However, it is important to be aware of the potential hazards from wedge injections: these are (1) lung damage from too forceful an injection (excessive pressure in a pulmonary artery branch from a Swan-Ganz catheter balloon may cause pulmonary artery rupture[6]); (2) prolonged wedging, which may cause pulmonary infarction[10]; and (3) gas embolisation to the coronary, cerebral, or systemic circulations. Thus, a meticulous technique, particularly in excluding obvious air from the wedge injections, as in left-sided intracardiac injections, is mandatory. Until the safety of this technique has been more firmly established, therefore, it must be considered an experimental procedure.

The authors wish to thank Willem Gorissen for technical assistance.

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26. CONTRAST ECHOCARDIOGRAPHY OF THE LEFT VENTRICLE

J. ROELANDT, R.S. MELTZER, and P.W. SERRUYS

1. INTRODUCTION

Rapid injection of biologically compatible solutions produces a "cloud of echoes" in the blood which is otherwise echo free. The source of this echocardiographic contrast is microbubbles of air introduced during injection [1, 2].

Left ventricular catheter injections have been employed to identify left side structures from M-mode echocardiograms [3, 4] and to validate cardiac views imaged by two-dimensional echocardiography [5, 6]. The method has also been found to be accurate and sensitive for the demonstration of small, intracardiac, left-to-right shunts and of minimal degrees of aortic and mitral valve regurgitation [7, 8, 9].

Injection of echo contrast material into the left ventricle, however, requires cardiac catheterization, making it an invasive procedure. This probably explains why left ventricular contrast echocardiography has not gained widespread clinical application.

Recently the possibility of transmitting echo contrast material across the capillary bed of the lungs to the left heart with pulmonary wedge injections [10, 11, 12] or with peripheral venous injections using experimental contrast agents [13, 16] has been demonstrated. These possibilities show great promise and may stimulate an increasing interest in ultrasonic left heart opacification. This chapter aims to review some methodological and clinical aspects of left ventricular contrast echocardiography. Most of this area is still investigational.

2. METHODOLOGIC ASPECTS OF LEFT VENTRICULAR CONTRAST ECHOCARDIOGRAPHY

At present, echocardiographic contrast studies of the left ventricle are performed in the catheterization laboratory. M-mode or two-dimensional techniques can be employed, each having its specific advantages and limitations for clinical problem-solving and research.

Rijsterborgh H. ed: Echocardiology. p 219-232.

2.1. Two-dimensional echocardiographic views employed

Our experience with left ventricular echo contrast has been mainly with two-dimensional echocardiography, using a dynamically focussed linear-array instrument (Fociscan, Organon Teknika) or a phased-array sector-scanner (Toshiba SSH-10A). The long-axis and short-axis views from the parasternal transducer position as well as the four-chamber and long-axis views from apical transducer position are routinely recorded [6, 14]. The apical views are especially useful for quantitative left ventricular studies, since the entire left ventricle from apex to base can often be recorded.

2.2. Left ventricular injection of echocardiographic contrast material

The rapid injection through a catheter of any biologically compatible fluid into the left ventricle causes echocardiographic contrast. We routinely use a manual flush of 5 to 10 ml of 5% dextrose in water.

Indocyanine green dye may yield a better contrast effect because of its surfactant properties, which keep the microbubbles of air, resulting from the vigorous shaking during preparation, stabilized in the solution [2]. One milliliter of indocyanine green solution (5 mg/ml for adults) is injected into the catheter and manually flushed with 5 to 10 ml of physiologic saline or 5% dextrose [7]. We have never observed any adverse patient reaction to direct left ventricular injections during echocardiographic contrast studies [15].

2.3. Pulmonary wedge injection of echocardiographic contrast material

Bommer et al. [10] reported in 1979 that catheter injections in the pulmonary wedge position in dogs cause echocardiographic contrast on the left side of the heart. Reale et al. [11] studied 43 patients with acquired or congenital heart disease and injected different echo-producing substances (indocyanine green dye, saline and carbon dioxide) via a balloon-tipped catheter in the pulmonary wedge position. Echocardiographic contrast was seen in the left ventricle in all patients studied. No complications or side effects were observed. We have studied 41 patients, using a Cournand 7F catheter alone in 27, a Swan-Ganz 7F catheter alone in 3 and both catheters in 11, for pulmonary wedge injections. Left ventricular echocardiographic contrast was seen in 3 out of 14 patients with the Swan-Ganz catheter and in 30 out of 38 patients when the Cournand catheter was used (Figure 1). We found that injection pressure proximal to the catheter had to be more than 40 kPa (300 mmHg) in order to obtain left side echocardiographic contrast.

Angiocardiographic studies with injections of Amipaque® further demon-

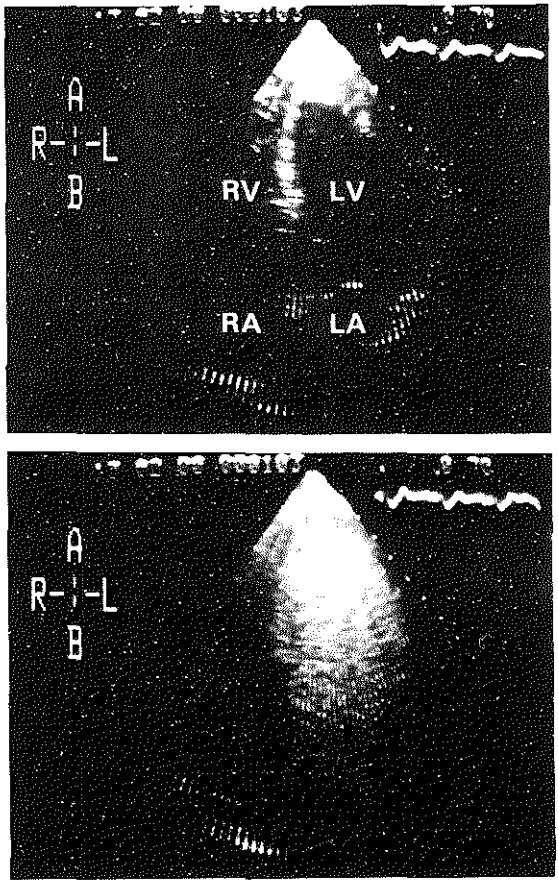

Figure 1. Stop-frame, apical four-chamber views obtained from a patient with a normal left ventricle immediately before (upper panel) and after pulmonary wedge injection of echocardiographic contrast (lower panel). The echo contrast fills both the left atrium (LA) and left ventricle (LV), of which the cavity contour becomes clearly delineated.
A = apical; B = basal; L = left; R = right; RA = right atrium and RV = right ventricle.

strated that a complete occlusive wedge position of the catheter must be achieved. The latter finding probably explains the higher success rate with a Cournand catheter: its higher stiffness allows more complete occlusion. It is conceivable that the pressure applied during occlusive injections may allow deformation of the air bubbles into a "dumbbell" shape resulting in their intact passage, rather than being retained by the "sieve" action of the capillary bed [16]. Apart from coughing, none of our patients had symptoms or worsening of their cardiopulmonary status related to the pulmonary wedge injections. Nonetheless, the method must still be considered as an experimental procedure until its safety has been finally established [12, 16].

2.4. Transmission of peripherally injected contrast through the lungs

Microbubbles of gas larger than the capillary diameter (approximately 8 microns) are stopped by the "sieve" action of the pulmonary capillary bed. On the other hand, microbubbles small enough to pass the pulmonary capillaries have an internal pressure which is significantly higher than the ambient blood pressure. Gas inside the microbubble therefore dissolves down its concentration gradient into the surrounding blood. The duration of this process is shorter than the pulmonary transit time and explains why the commonly employed contrast materials for peripheral venous injection are removed from the circulation before they reach the left side cavities [17].

We have created left side echocardiographic contrast in pigs by the injection of diethyl ether and hydrogen peroxide in the right heart or proximal pulmonary artery. Our studies demonstrated, however, that these agents are potentially dangerous [16]. Recently, transmission of echocardiographic contrast through the pulmonary capillary bed following peripheral venous injection has been demonstrated in dogs by Bommer et al. [10] using 2 to 10 micron diameter microbubbles. Human application must await toxicity studies.

Opacification of the left ventricle following peripheral venous injection is thus a valid research goal. A better understanding of physical characteristics and physiological behaviour of microbubbles will probably permit successful attainment of this goal in the not too distant future.

3. CLINICAL APPLICATIONS OF LEFT VENTRICULAR CONTRAST ECHOCARDIOGRAPHY

3.1. Demonstration of valvular insufficiency

Systolic regurgitation of echo contrast material to the left atrium after left ventricular injection is indicative of mitral regurgitation. The method is

sensitive and minimal amounts of regurgitation are readily detected [9, 18]. In moderate to severe degrees of mitral incompetence, the clearance time of the echo contrast from both the left atrium and left ventricle is considerably prolonged. Normally, echo contrast material remains from 4 to 10 cycles in the left ventricle and from 4 to 6 cycles in the left atrium. Uchiyama et al. [19] were able to determine the site of regurgitation in two patients with mitral valve prolapse syndrome using the echo contrast technique. Aortic regurgitation is demonstrated with a high degree of sensitivity by injecting echo contrast material in the aortic root and detecting its appearance in the left ventricle during diastole. The clearance time of the echo contrast from the left ventricle is much prolonged (15 to 50 cycles). In some instances, the regurgitant pattern of echo contrast may be observed as a "shower of echoes" hitting the anterior mitral valve or interventricular septum. Clearance time cannot be used to quantify mitral or aortic regurgitation reliably. It may serve, however, to confirm or exclude its presence in patients in whom roentgenographic contrast studies are contraindicated due to pregnancy [20] or angiographic dye allergy.

3.2. Demonstration of left-to-right shunts

Echo contrast flow patterns after left ventricular injection are helpful in identifying ventricular septal defects with left-to-right shunting and are at least as sensitive as indicator-dilution studies. Appearance of the echo contrast in the right ventricle or right ventricular outflow tract may be simultaneous with injection or be delayed by one cycle. The appearance time is dependent upon the timing of injection during the cardiac cycle and the position of the catheter in the left ventricle. A left-to-right shunt as small as 5 % of the pulmonary flow may be detected [8]. We have experience with two patients in whom a ventricular septal defect was missed by oximetry and diagnosed by left ventricular contrast echocardiography (Figure 2). The method is useful for the demonstration of a left ventricular to right atrial shunt and the localization of small defects in the trabecular septum using the apical four-chamber view. Recently, Reale et al. [11] have demonstrated the possibility of using pulmonary wedge injections (see paragraph 2.3) for direct visualization of a left-to-right shunt at atrial or ventricular level, thus obviating left heart catheterization. They rightly concluded that the method could be used as a simple screening procedure during right heart catheterization to avoid invasion of the left heart in some patients. The toxicity of pulmonary wedge injections and the sensitivity of this approach as compared to oximetry and indicator dilution techniques need further evaluation.

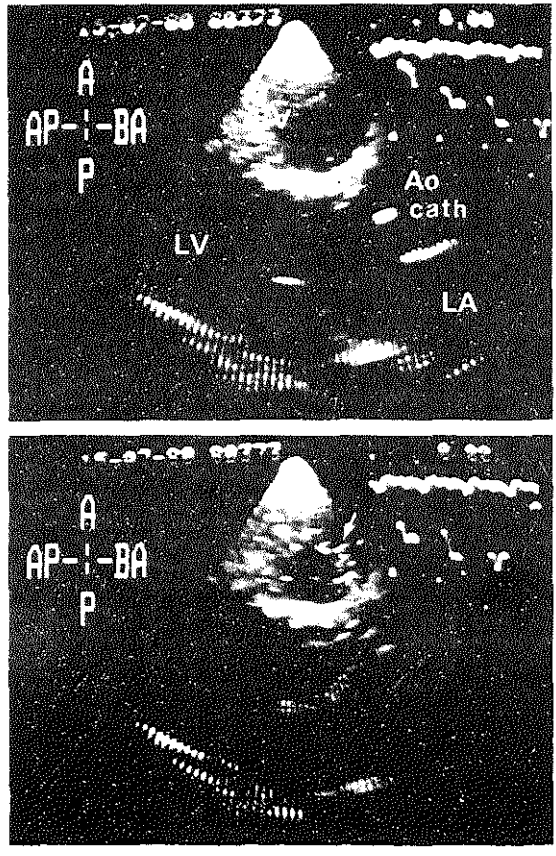

Figure 2. Parasternal long-axis views of a patient with a small ventricular septal defect before (upper panel) and after (lower panel) catheter injection of echo contrast in the left ventricular outflow tract. Echoes appear in the right ventricular outflow tract (arrow) proving the existence of a small left-to-right shunt.

A = anterior; AP = apical; BA = basal; P = posterior; Ao = aorta; cath = catheter; LA = left atrium; LV = left ventricle; RV = right ventricle.

3.3. Delineation of the left ventricular cavity

Feigenbaum et al. [4] utilized left ventricular injections of indocyanine green dye to identify the endocardium from other echoes within its cavity. Even when using newer equipment, non-structural echoes often obscure the endocardial boundaries and make proper delineation of the left ventricular cavity difficult or even impossible [21]. It is conceivable that opacification of the left ventricular cavity with echocardiographic contrast would improve border recognition. An illustrative case of a patient with clinical features of restrictive (obliterative) cardiomyopathy is shown in Figure 3. The size and shape of the left ventricle could not be appreciated from the routine echocardiographic study because the apical area was obliterated by non-structural echoes (Figure 3, upper panel). After opacification with echocardiographic contrast via a pulmonary wedge injection, a bilocular deformity of its shape was demonstrated (Figure 3, lower panel).

It would seem likely that improved cavity delineation by echocardiographic contrast would increase the accuracy of left ventricular volume determination from two-dimensional images. We therefore made recordings of the left ventricle in four views (parasternal long-axis view and short-axis view, at mitral level; apical four-chamber view and long-axis view) before and during left ventricular injections of 5% dextrose in water in 13 patients (Figures 1 and 4). Long axis length and surface area within the endocardial contours were measured from stop-frame images, independently, from recordings with and without contrast, using a lightpen system and a digital computer. The measurements were repeated by the same investigator one month later. Long axis length was 71.5 ± 14.0 mm without and 70.8 ± 12.0 mm with contrast (mean ± 1 SD). This difference was not statistically significant. For the surface area, the measurement with contrast was 1.5 cm^2 larger than without contrast and this was significant ($P > 0.001$). Thus, the use of echo contrast did not affect measurement of the long axis length but did increase the value for surface area. To our surprise, measurements on contrast images showed a higher intra-observer variability. In another series of 18 patients we compared left ventricular volumes determined by angiocardiography with these measured from two-dimensional echocardiographic views (apical four-chamber view and apical long-axis view) before and after injections of echocardiographic contrast. The use of contrast did not improve the correlation between echocardiographic and angiocardiographic volumes. Our studies, although preliminary, indicate that contrast echocardiography does not improve the accuracy of quantitation of the left ventricle from echocardiographic stop-frame images.

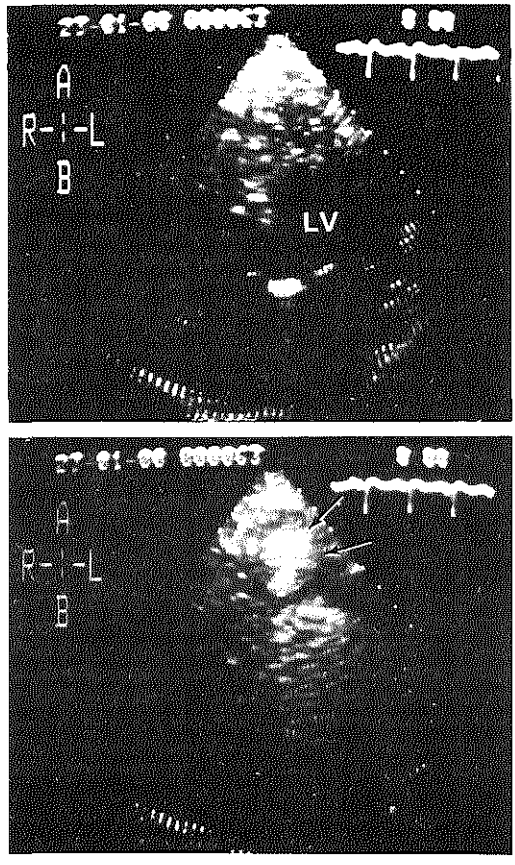

Figure 3. Apical four-chamber views of a patient with Loeffler's eosinophilia. Before opacification, the contour of the left ventricle cannot be appreciated because of non-structural echoes filling its cavity, mainly in the apical area (upper panel). After a pulmonary wedge injection of echo contrast, a bilocular shape of the left ventricular cavity is demonstrated (lower panel).
A = apical; B = basal; R = right; L = left; LV = left ventricle.

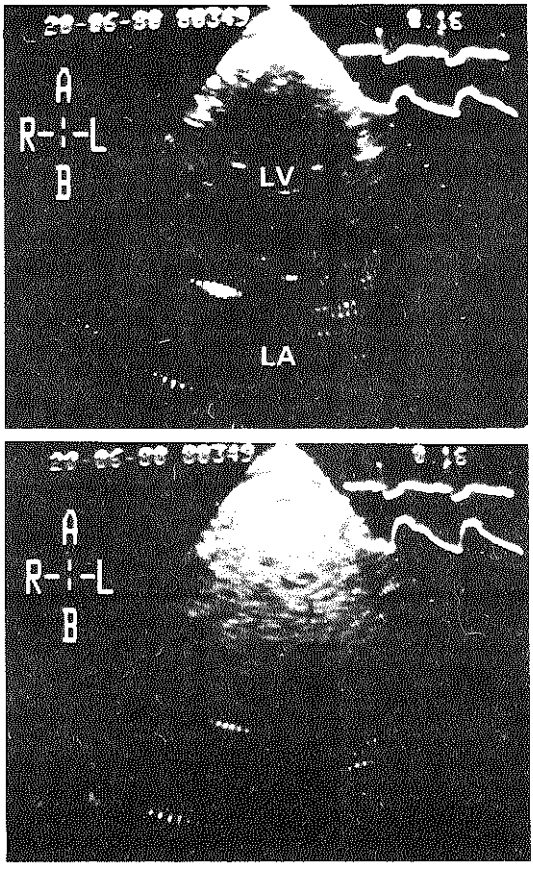

Figure 4. Stop-frame images of apical four-chamber views obtained from a patient with a dilated left ventricle before (upper panel) and after (lower panel) catheter injection of echo contrast in the left ventricle (LV). The left atrium remains echo free, which excludes mitral insufficiency. Border recognition is not facilitated after its opacification.
A = apical; B = basal; L = left; R = right; LA = left atrium.

3.4. Study of blood flow patterns

The non-contrast blood flowing from the left atrium into the left ventricle after its opacification with echo contrast allows us to observe transmitral blood flow. The negative contrast shadow delineates the functional mitral valve orifice. This is demonstrated in Figure 5, obtained from a patient with mitral valve stenosis. The anatomical dimension of the valve is visualized during the baseline study in the parasternal long-axis view (Figure 5, upper panel). The functional dimension is visualized by the echo-free blood entering the left ventricle after its opacification and appears smaller in the same cross-section (Figure 5, middle panel). Intracavitary flow patterns produced by a mitral valve prosthesis can be followed after pulmonary wedge injections. Occasionally one may observe a vortex of echo contrast circulating within an ischaemic aneurysm in patients with coronary artery disease (Figure 6). Left ventricular contrast echocardiography thus allows a new type of study on local flow, turbulence and stasis, which promises to become more useful in the future if transpulmonary echo contrast transmission becomes available.

3.5. Densitometric dilution curves of echocardiographic contrast

Bommer et al. [22] described in 1978 a method of obtaining dilution curves of echocardiographic contrast by videodensitometry. They focused an analog photometer upon the screen of the videomonitor over the middle of the right ventricular cavity during two-dimensional echocardiographic contrast studies. The dilution curves were reproducible on multiple echocardiographic contrast injections to an accuracy of 15%. The time course of decay made it possible to separate patients with normal from those with low cardiac output and/or tricuspid regurgitation. Echo-contrast indicator dilution curves of the left ventricle were subsequently performed in dogs using injections of 10 ml of a 1:100,000 concentration by volume of 30 micron diameter microballoons. Good correlations with cardiac output measurements were found [23]. We have used an image-processing computer to analyze video recordings of contrast injections in order to follow the decay of density after left ventricular and pulmonary wedge injections in 17 patients. A meaningful calculation of the area under the curve could not be made because of limitations due to video "overload" immediately after injection. In consequence, contrary to the studies by DeMaria et al. [23], it seems that cardiac output measurements cannot be estimated reliably using routine contrast dilution techniques. The decay phase was found to be exponential and has characteristics of indicator-dilution curves, as predicted theoretically. Preliminary data indicate that R-wave gating may allow estimation of ejection fraction [24].

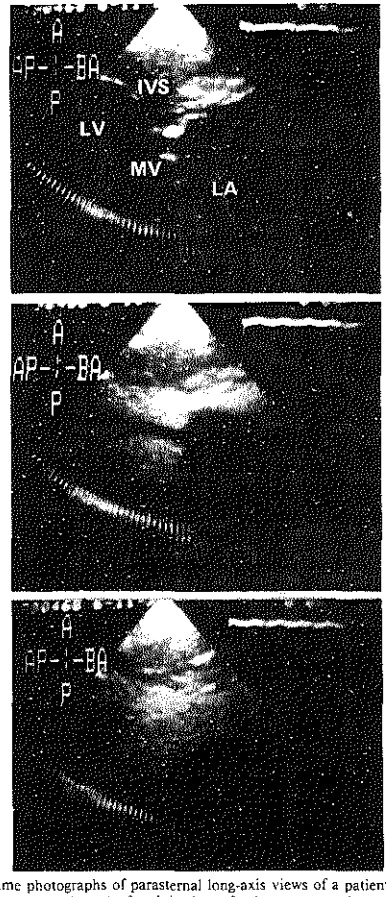

Figure 5. Stop-frame photographs of parasternal long-axis views of a patient with mitral valve stenosis before (upper panel) and after injection of echo contrast via a catheter in the left ventricle. The middle panel shows a frame recorded during diastole. The negative shadow caused by the non contrast blood flowing from the left atrium into the ventricle visualizes the transmitral blood flow pattern. During systole (lower panel), the echo contrast does not pass into the left atrium, excluding mitral incompetence.

A = anterior; AP = apical; BA = basal; P = posterior; IVS = interventricular septum; LA = left atrium; LV = left ventricle; MV = mitral valve.

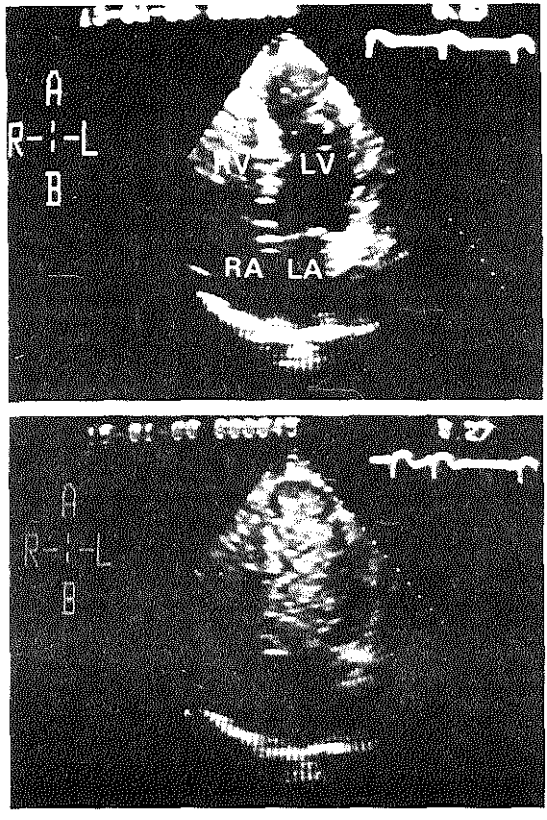

Figure 6. Apical four-chamber views before (upper panel) and after (lower panel) left ventricular opacification by echo contrast via a pulmonary wedge injection in a patient with an apical aneurysm. Wash-out of echo contrast from within the aneurysm was delayed.

A = apical; B = basal; L = left; R = right; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Hagler et al. [25] used computer-based videodensitometric techniques to analyze video recordings of left ventricular contrast echocardiograms to quantitate left-to-right shunts. Time-density histograms were generated from the right and left ventricular cavities after injection of echo contrast in the left ventricle in 7 patients with a ventricular septal defect. Their results indicate the possibility of quantitating shunts with these techniques.

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CHAPTER 11

VIDEODENSITOMETRIC PROCESSING OF CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHIC DATA

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SUMMARY

We developed a computer program to analyze videodensity changes due to contrast appearance within a given operator-designated rectangle using two-dimensional echocardiograms previously recorded on videotape. Videodensity curves have been obtained from two-dimensional echocardiographic recordings in 14 patients after a total of 32 injections of 5% dextrose solution into the left ventricle during cardiac catheterization.

The resulting videodensity versus time curves have some of the characteristics of indicator dilution curves. The decay phase of these curves is largely mono-exponential. Potential clinical applications of this technique in measurement of ejection fraction, cardiac output and shunt quantification are discussed, as well as some potential limitations.

INTRODUCTION

Since 1978, the group from Davis, California has presented several abstracts describing methods for obtaining curves with properties similar to indicator-dilution curves by using videodensitometric analysis of videotaped two-dimensional echocardiographic studies recorded during peripheral contrast injections (1-4). Investigators from the Mayo Clinic have presented preliminary data on videodensitometric studies for the quantitation of left-to-right shunts during left heart echocardiographic contrast injections (5).

In this report we examine the possibility and discuss some of the advantages and disadvantages of using videodensity data for obtaining "indicator-dilution curves."

PATIENTS AND METHODS

Videotaped two-dimensional echocardiographic studies of contrast injections recorded in the catheteriz ation laboratory during two prior research protocols were used for analysis (6,7). Twelve patients had hand injections of 10 ml of 5% dextrose in water directly into the left

ventricle (6) and 5 patients had hand injections of 5% dextrose in water into the pulmonary wedge position. All patients were studied during catheterization for routine clinical indications. The two-dimensional echocardiograms and contrast injections added only 5 to 15 minutes to the total duration of the procedure. There were no adverse effects. All patients having pulmonary wedge injections and 9 of the 12 patients with direct left ventricular injections were judged during review of the videotapes to have sufficient contrast density in the left ventricle to allow videodensitometric analysis.

Echocardiographic analysis

Echocardiograms were recorded in the supine or shallow left lateral decubitus position. All studies were performed in the apical four-chamber view (8). A Toshiba SSH-10A phased array sector scanner was employed, and studies were recorded on videotape for subsequent analysis.

The hardware configuration for data analysis is diagrammed in figure 1. A videorecorder capable of display in real time, slow-motion, or stop-frame modes is connected to a PDP-11 minicomputer. The operator can interact with the system by means of s Summagraphics digitizing tablet and light pen system. After viewing and reviewing the recording of an echo contrast injection, the operator can tantatively designate a rectangular area for analysis (figures 2 and 3). He then views the entire study, from the initial contrast appearance to its complete disappearance, to verify that the boundaries of the selected area remain entirely within the ventricular cavity where contrast dynamics are to be assessed. If the cavity wall (usually at end-systole) or other anatomic structures (such as a valve) enter the area during the cardiac cycle the boundaries of the rectangle are re-adjusted so the structure remains outside the tentative test area. When this process is completed the study is rewound to a point just prior to contrast appearance and the videodensity program is started. It calculates the total videodensity of all pixels within the designated test area for each subsequent frame chosen by the operator. The program allows an operator to obtain videodensity measurements for each frame, every other frame, or every "n"th frame, etc.

RESULTS

Videodensity curves could be obtained in all cases where prior real-time viewing revealed a cavity size about 2x2 cm or greater and "moderate" to "intense" contrast. An example of such a curve is given in figure 4.

To test whether the latter part of these curves was a mono-exponential decay as would be expected from one-compartment indicator-dilution theory (9), we plotted log videodensity versus time. Figure 5

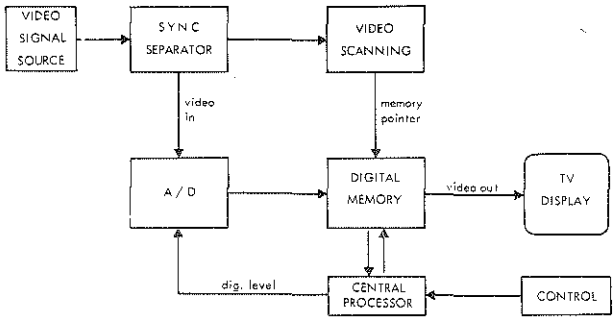

Figure 1: Hardware configuration for data analysis. The video synch signal is obtained from a video signal source (usually videotape) and the image is entered into a digital memory after analog/digital (A/D) conversion. The operator can interact (CONTROL) with the central processor (in this case a PDP 11 minicomputer) and the resulting superimposed original video image and alphanumeric information are displayed on the monitoring TV screen.

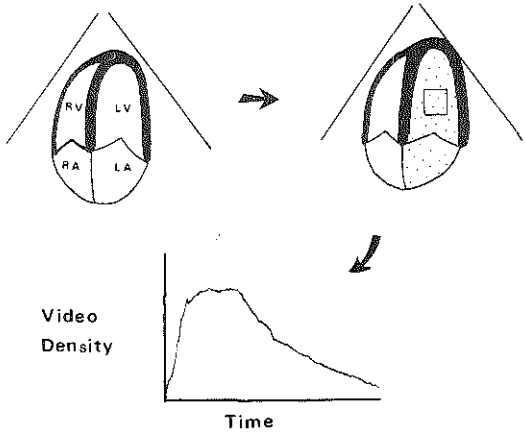

Figure 2: Principle of videodensity analysis. Upper panels: Two-dimensional echocardiographic data is videotaped during a contrast injection, depicted here by stippling in the left atrium (LA) and left ventricle (LV) after LV or pulmonary wedge injection. Upper right: After review, the operator designates a rectangular area for anlaysis. Lower panel: The program output is in the form of total videodensity within the designated rectangle versus time.

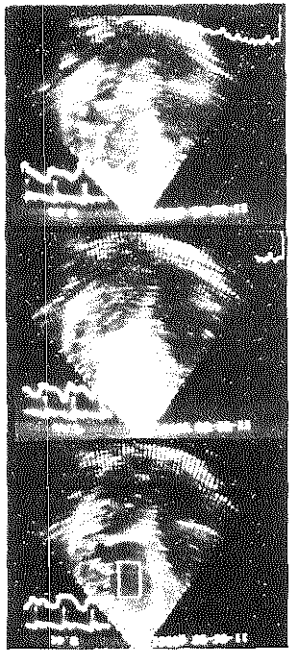

Figure 3: Upper panel: a rectangular sample area has been designated within the left ventricle. Apical four-chamber view. This frame is immediately prior to contrast opacification after a catheter left ventricular injection. Middle panel: the outline of the sample area is seen faintly during maximal contrast intensity. Note simultaneous display of cumulated videodensity at lower left of panel. Lower panel: The left ventricular contrast has nearly been cleared at the end of the injection.

presents the resulting plot for the curve illustrated in figure 4. In this patient the decay phase has a log videodensity closely correlated with time (correlation coefficient r=0.98), which implies that the decay fits a mono-exponential model, as predicted. Small cyclic deviations from linearity may be expected due to the incoming contrast free blood during each diastole, unless the videodensity readings are performed only once per cycle, from a frame at the same point in each cardiac cycle.

Of the 32 injections in 14 patients, 15 injections in 10 patients had correlation coefficients between log videodensity during decay and time that were greater than or equal to 0.95. The slope of this semilog decay plot should be one of the most important parameters obtainable from this technique: it is the time constant of contrast disappearance. We therefore undertook to examine a single good quality injection to

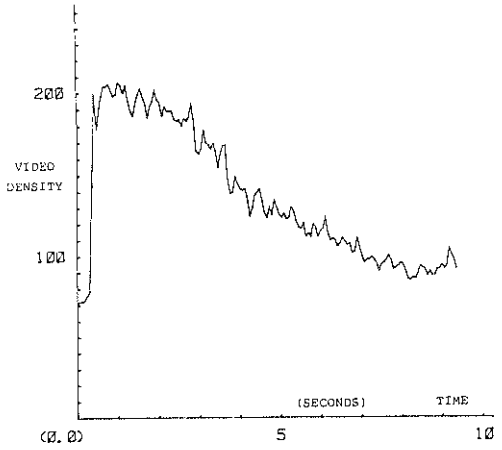

Figure 4: Sample videodensity versus time curve obtained from left ventricular injection. Videodensity in arbitraty units.

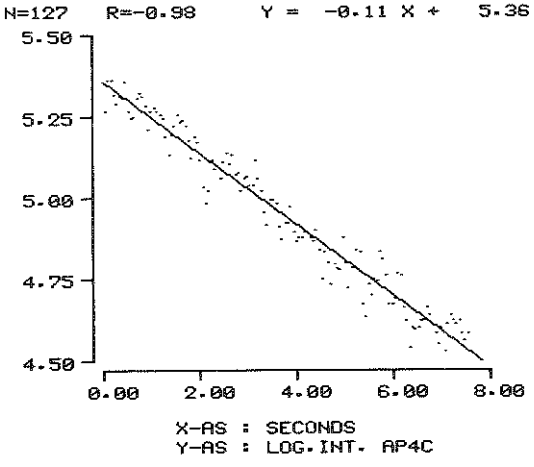

Figure 5: Log videodensity (on ordinate) versus time curve for the decay phase of the videodensity-versus-time curve shown in figure 4.

determine for what duration its decay needed to be sampled to obtain reliable information about this slope. We arbitrarily defined a "reliable" slope as that obtained from at least 5 separate videodensity determinations during decay, yielding a semilog correlation coefficient of greater than or equal to 0.95. Figure 6 is the result. On the abscissa is the duration of the segment randomly chosen during the decay decay phase and then analyzed for videodensity every fifth frame. On the ordinate is the linear correlation coefficient obtained in the resulting log videodensity versus time plot. The shape of this curve is to be expected: a wider range (longer time of sampling, on the abscissa) yields a better correlation coefficient. The important result is that when performing videodensity analysis every fifth frame, about 5 seconds of decay need to be entered to yield the best correlation coefficient. In this specific injection, longer analysis is unnecessary.

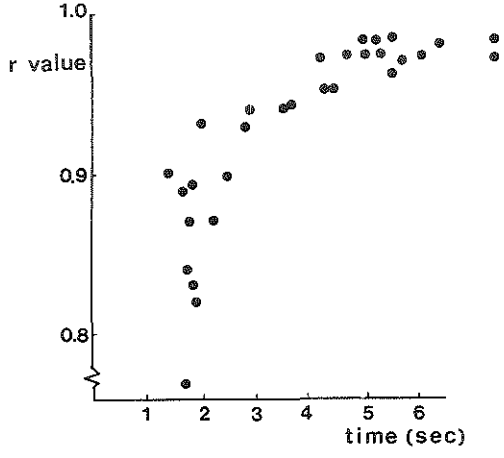

Figure 6: Correlation coefficient (between log videodensity and time) versus the duration of the decay phase measured for different arbitrarily chosen time durations (abscissa) during the decay of a single curve. For this curve, it would seem unnecessary to measure more than 5 seconds of decay.

DISCUSSION

Videodensity techniques for indicator-dilution analysis

The most important finding in this study is that videodensity versus time curves can indeed be obtained from most left ventricular injections in the majority of patients, and that these seem to have the qualitative shape we expect of a one-compartment indicator-dilution curve, as well as the quantitative characteristic of a mono-exponential decay. The set of contrast injections we used (LV or wedge) has two known advantages for this type of analysis: a rapid and complete delivery of the injected bolus into the chamber to be studied (by direct catheter injection) and a relatively large cross-sectional surface area on two-dimensional echocardiography (the LV in the apical 4-chamber view). Whether a similar success rate can be obtained with peripheral venous injection and right ventricular imaging is uncertain.

Advantages

An advantage of right-sided videodensity analysis is that it is minimally invasive, needing only an intravenous injection and the same two-dimensional echocardiographic equipment and videorecorder available in many or most cardiology divisions. Rudimentary curves can even be ovtained in real time using an inexpensive photoelectric cell. Theoretically, videodensity curves may be used to quantify right and left ventricular ejection fractions, intracardiac shunts, and cardiac output (if no "overload" occurs - see below).

Limitations

Echocardiographic contrast injections are not reproducible: the microbubble size and concentration reaching the central circulation and resulting ultrasonic contrast effect vary widely, even on consecutive injections with apparently identical tecyhnique. This problem may be partly surmountable if precision microbubbles are used as the contrast agent (3,4,10). However, it is possible that even precision microbubbles injected peripherally will result in very variable cardiac videointensity curves. Some patients have rapid delivery of a peripherally injected bolus into the right heart, and others have an intermmitent delivery over many minutes, with oscillations of contrast intensity in the absence of new injections, frequently caused by arm or head motion or deep inspiration.

Compared to the dynamic range of ultrasonic signals returning to the transducer, the gray-scale capabilities of the cathode ray tube display offer a very restricted range. This is further complicated by signal degradation during the videoprocessing and recording in most commercially available systems. The initial system designed to process

two-dimensional echocardiographic recordings to yield videodensity curves was reported in 1978. It used a hand-held photoelectric cell applied directly to the cathode ray tube screen (1). Theoretically, more information can be obtained by direct analysis aof the pre-processed signal of the returning echoes, eliminating the need for an intermediary video step with its attendant loss of information.

There are 2 different types of "overload" effects that may limit the peak density observed during a contrast injection. Above a certain intracardiac microbubble density so much ultrasonic energy is reflected that too little energy remains in the distal sound beam, and more distant structures are only weakly imaged, or may entirely disappear. Aside from this ultrasonic overload, video-display overload may occur since the gray-scale display range of video equipment is considerably more limited than the range of reflected ultrasonic energies that can be detected at the transducer. Thus, the upper ranges of intensity (bright echoes) are all displayed as a single maximal intensity on the video screen. Overload may have occured during the maximum intensity of our contrast injections. If so, this would preclude obtaining useful information from calculating the area under these curves: the maximum videodensity during "overload" underestimates the concentration of microbubbles in the sample volume. Whether "overload" occurs after many or most peripheral or central injections has not yet been determined, so the clinical importance of this effect has not been established.

CONCLUSIONS

Videodensity versus time curves can be obtained from two-dimensional echocardiographic recordings during left ventricular injections in most patients. In the absence of valvular regurgitation or shunts, these ususlly have a mono-exponential decay, as judged by a straight line when log videodensity is plotted against time. These curves may permit quantitation of cardiac output, ejection fraction and intracardiac shunts, though they have important theoretic and practical limitations.

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NEW ECHOCARDIOGRAPHIC CONTRAST AGENTS : TRANSMISSION THROUGH THE LUNGS AND MYOCARDIAL PERFUSION IMAGING

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SUMMARY

A new ultrasonic contrast agent, consisting of saccharide particles with microbubbles of air, was tested in 21 open chested pigs. Seventeen had injections of the new agent into the internal jugular vein during epicardial two-dimensional echocardiography, and nine of these had echocardiographic contrast in the left heart. Thus, this new right heart contrast agent is capable of passing the lungs to yield contrast in the left heart after peripheral venous injection.

Eight of nine pigs receiving the new agent in the left anterior descending coronary artery had observable contrast in the myocardium in the area of distribution of this artery. This is the first echocardiographic method to permit direct visualization of myocardial perfusion, and can be performed in real time and in vivo.

INTRODUCTION

Prior work has led us to believe the reason capillary beds remove ultrasonic contrast from the bloodstream is that bubbles larger than the capillary diameter are physically stopped by the "sieve action" of the capillaries, and that bubbles small enough to pass through the capillaries dissolve rapidly due to surface tension effects (1,2). Since the source of ultrasonic contrast is microbubbles of gas (3), a detailed knowledge of microbubble kinetics should allow a contrast agent to be designed that is capable of transmission through a capillary bed (4). Transmission through the lungs after a peripheral venous injection would yield left heart echocardiographic contrast. This would be potentially useful in structure identification in the left heart (perhaps enhancing echocardiographic diagnostic accuracy in proximal coronary artery disease), diagnosing left-to-right shunts, for studies of left heart blood flow patterns, and perhaps for peripheral arterial sonographic studies. Furthermore, the ability to image contrast in the myocardium might permit the study of myocardial perfusion.

Microbubbles designed as echocardiographic contrast agents for the right heart have recently become available*. Independent testing of this material has already been reported (5,6). We wish to present our experience with this material in 21 anesthetized, open chested pigs.

* (Ultra Med, Inc., Sunnyvale, California).

MATERIALS AND METHODS

Minimicrobubbles

Microbubbles are small gas bubbles whose diameter is less than 300 microns. "Minimicrobubbles" are the size range of microbubbles which are small enough to traverse the capillary beds, generally considered to be 8 to 10 microns (7). Consequently minimicrobubbles are defined as bubbles whose diameters lies below 10 microns.

The saccharide microbubble agents used in this study were of two specific size groups. Each group contained a spectrum of particle and microbubble sizes. Agent A was designed for peripheral injection for obtaining right heart contrast and has a particle size ranging from less than 1 micron to 200 microns. The microbubbles associated with this agent also exhibit a sizeable spectrum and are less than 20 microns in diameter, with a mean diameter of 10 microns. One cc of agent A yields several million microbubbles, most of which are in the minimicrobubble range. The total gas content of one cc of agent A is approximately 0.004 cc.

Agent B was developed for direct left heart and coronary injection and has a saccharide particle size range from 1 to 165 microns. These particles are quite soluble in blood, and dissolve withinn a few minutes. As with agent A, the bubbles in agent B have a spectrum of diameters less than 20 microns and a mean of 10 microns.

A varying volume (see tables 1 and 2) of each contrast agent was injected into each animal. Each injection was followed by a 5cc flush of normal saline.

Experimental Protocol

Twenty-one pigs (mean weight 25 kg) were anesthetized with pentobarbital, placed supine, and connected to a respirator. ECG and aortic pressures were continuously monitored. The thorax was opened by a midline sternotomy and the heart exposed. An internal jugular catheter was introduced for venous injections. A 19 gauge needle attached to a short plastic catheter was placed in the left anterior descending (LAD) coronary artery, distal to the first septal perforating artery, just prior to intracoronary injections.

Initial injections of physiologic saline were performed through the internal jugular catheter during echocardiographic recording in 16 of the 17 animals tested for transpulmonary transmission of microbubbles. These were performed in order to exclude animals with intracardiac or intrapulmonary right-to-left shunting. Subsequent injections of minimicrobubble suspensions followed by a 5 cc saline flush were performed (Table 1).

Studies of myocardial perfusion were performed in 8 of the 21 pigs. They were also preceded by a control injecton of saline during two-dimensional echocardiographic recording. Each injection of 5 cc of saline was performed by hand via the LAD catheter, followed by a 5 cc saline flush (Table 2).

Echocardiographic methods

A Toshiba SSH-10A phased array sector scanner with a 2.25 Megahertz transducer was used to image the heart using either direct epicardial application of the transducer or a 2-3 cm "standoff" created by placing a piece of fresh porcine muscle between the heart and the transducer. For studies of transmission through the lungs after peripheral injection, an "epicardial 4-chamber" view was employed (Figure 1). For studies of myocardial perfusion, an "epicardial short axis" view was used (Figure 2). These views are comparable to the human apical 4-chamber and parasternal short axis views, respectively (8).

The attainment of contrast in the right heart, left heart, and myocardium was judged subjectively (yes-no) by 3 observers (RSM, HWJV, NKV). Intra-observer variability was tested by repeat review of videotapes by 1 observer (RSM) 6 months after originally viewing them.

RESULTS

No adverse effect on blood pressure or heart rate or rhythm were observed after either saline or new contrast agent injections.

All 3 observers agreed on the subjective presence of contrast in 97% of injections. The other 3% were resolved by consensus upon repeat review of the videotape recorded during the injection. Intra-observer agreement was 99% for the 1 observer tested.

Transmission through lungs after peripheral venous injecton (Table 1)

Intravenous injection of saline and both contrast agents A and B always yielded dense right heart contrast opacification.

None of the sixteen pigs had resting intracardiac or intrapulmonary shunts during initial saline injections: all had right heart contrast and absence of left heart contrast. Seven of the 13 pigs receiving agent A had left heart contrast after a delay of more than 3 beats, indicating transpulmonary transmission rather than intracardiac shunting. Four of the 10 pigs receiving agent B had left heart contrast after a similar delay. An example of a study with left heart contrast is given in figure 3.

Myocardial perfusion (Table 2)

All animals developed anteroapical wall motion abnormalities within seconds after insertion of the LAD needle distal to the first septal perforating branch. These wall motion abnormalities were evident on visual inspection of the beating heart in the open-chested preparation as well as by two-dimensional echocardiography. This was because the needle was occlusive.

Two of the 8 pigs had myocardial contrast after control injections of saline in the LAD; the other 6 had none. All 4 pigs receiving agent A and 7 of the 8 receiving agent B had myocardial contrast. In all cases the extent of the myocardial contrast was similar to the extent of wall motion abnormalities, with contrast starting or ending within 1 cm of the boundary of abnormal wall motion. An example of a study showing myocardial contrast is presented in figure 4.

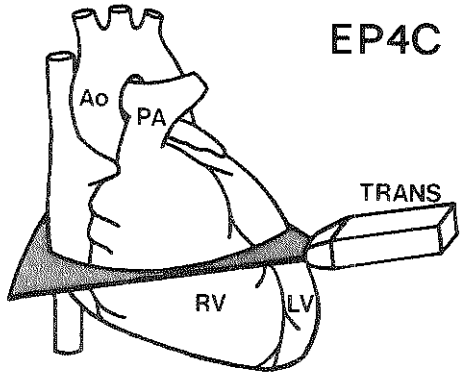

Figure 1: Diagram of epicardial four-chamber (EP4C) plane of imaging through the heart. Abbreviations - Ao: Aorta; PA: pulmonary artery; RV: right ventricle; LV: left ventricle; TRANS: transducer.

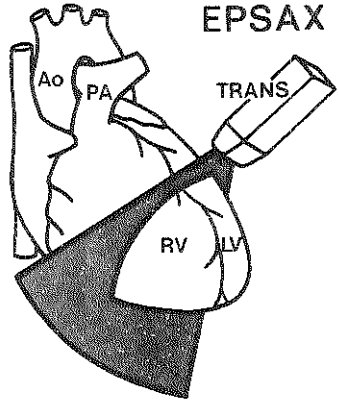

Figure 2: Diagram of epicardial short axis (EPSAX) plane of imaging through the heart. Abbreviations as in Figure 1.

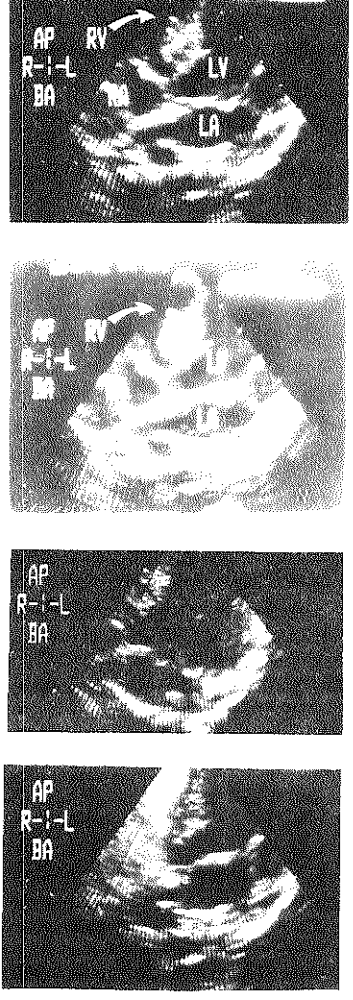

Figure 3: Stop-frame Polaroid photographs from the two-dimensional echocardiographic study of pig 14. EP4C plane of imaging as diagrammed in Figure 1. Upper panel: before injection. Middle panel: 2 heart beats later, after contrast opacification of the right heart. Lower panel: The transducer has been angled slightly towards the left after initial verification of right heart contrast. 15 beats after injection. Note contrast in the left heart. Abbreviations: AP: apical; BA: basal; R: right; L: left; RV: right ventricle; RA: right atriam; LV: left ventricle; LA: left atrium.

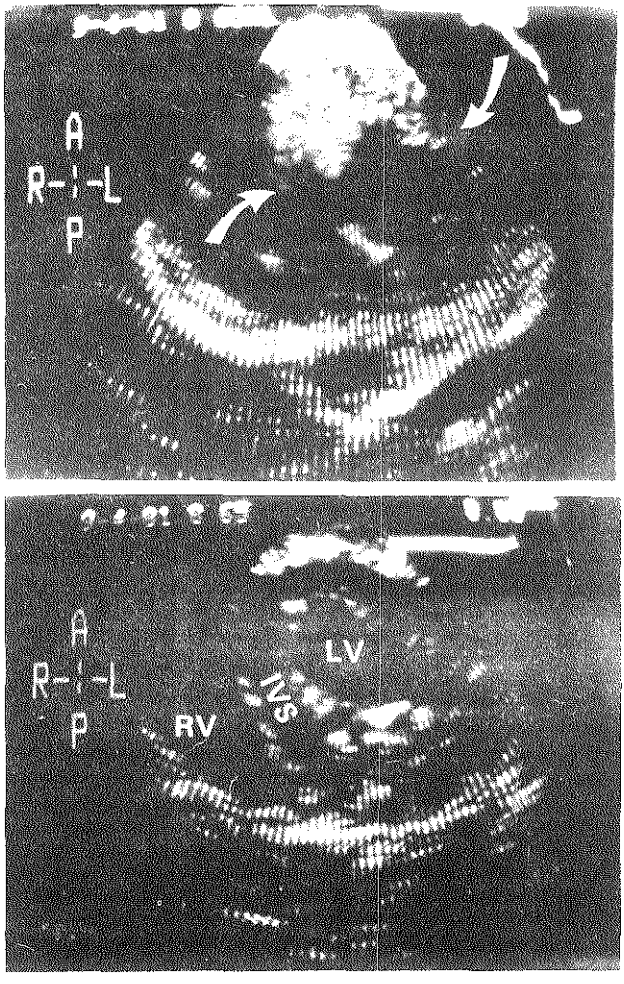

Figure 4: Stop-frame Polaroid photographs from the two-dimensional echocardiographic study of pig 8. EPSAX plane of imaging as diagrammed in figure 2. Upper panel: before injection of contrast agent into left anterior descending (LAD) coronary artery. Lower panel: Several seconds later, with contrast in the area of LAD distribution, from 9:00 to 2:00 along the left ventricular circumference (arrows). Abbreviations: A: anterior; P: posterior; Further abbreviations as in Figure 3.

TABLE 1: TRANSPULMONARY CONTRAST IN PIGS

PIG NR.	PERIPHERALLY INJECTED SUBSTANCE	RV	LV
1	5cc NS	+	-
	1cc A	+	+
2	5cc NS	+	-
	1cc A	+	+
4	5cc NS	+	-
	1cc A	+	+
5	5cc NS	+	-
	0.5cc A	+	-
6	5cc NS	+	-
	1cc A	+	-
	0.25cc B	+	-
7	5cc NS	+	-
	0.25cc A	+	-
	0.25cc B	+	-
8	0.25cc A	+	+
9	5cc NS	+	-
	0.5cc A	+	-
12	5cc NS	+	-
	0.25cc B	+	-
13	5cc NS	+	-
	0.25cc B	+	-
14	5cc NS	+	-
	0.5cc A	+	+
	0.5cc B	+	+
15	5cc NS	+	-
	2cc A	+	+
	2cc B	+	+

(Continued on the following page)

(Table 1, continued)

PIG. NO.	PERIPHERALLY INJECTED SUBSTANCE	RV	LV
16	5cc NS	+	-
	1cc A	+	-
	2cc B	+	+
18	5cc NS	+	-
	3cc A	+	+
19	5cc NS	+	-
	2cc A	+	-
	3cc B	+	+
20	5cc NS	+	-
	3cc B	+	-
21	5cc NS	+	-
	3cc B	+	-

ABBREVATIONS:
NS = Normal saline (0,9% NaCl in water)
RV = Right ventricle
LV = Left ventricle
A = Contrast agent A
B = Contrast agent B
\- = No contrast observed
\+ = Contrast observed

TABLE 2: MYOCARDIAL PERFUSION IN PIGS

PIG NO.	INJECTED SUBSTANCE IN LAD	ATTAINMENT OF MYOCARDIAL CONTRAST
4	5cc NS	-
	0.5cc B	+
5	0.5cc A	+
	0.5cc B	+
6	5cc NS	-
	0.5cc A	+
	0.5cc B	+
7	5cc NS	-
	0.5cc A	+
8	5cc NS	-
	0.5cc B	+
10	5cc NS	+
	0.5cc B	+
11	5cc NS	-
	0.5cc A	+
	0.5cc B	+
18	5cc NS	+
	0.5cc B	+
21	5cc NS	-
	0.5cc B	-

(Abbreviations as in Table 1)

DISCUSSION

Transmission of echocardiographic contrast through the lungs

Potential uses of transpulmonary transmission of precision microbubbles are legion. Transpulmonary transmission of echocardiographic contrast from injections in catheters placed in the wedge position are occasionally useful for structure identification in the left heart and left-to-right shunt detection (9-12). Left heart contrast may eventually aid in the diagnosis of aortic abnormalities and proximal arterial diseases.

Until now, the only agents used in our laboratory capable of yielding left heart contrast after peripheral venous injection were ether and hydrogen peroxide (4). However, these would require toxic concentrations for this application in humans. Therefore the success of the saccharide agents reported here in attaining left heart contrast in the majority of experiments is encouraging.

A question raised by these data is why some peripheral injections of Contrast Agent A or B consistently failed to yield left heart echocardiographic contrast. We hypothesize that degradation of the extremely hygroscopic saccharide due to exposure to the atmosphere for brief periods of time during preparation led to degredation and clumping of the smaller particles and eventually to inability to attain transmission. Failure may be related to a storage problem, preparation, or injection technique. Evaluation of Table 1 shows that successful left heart contrast attainment was achieved more frequently with 1 cc or more of contrast agent than with less than 1m cc of contrast agent. This suggests that a critical mass of material is required for consistent left heart contrast effect. Much work remains to enable optimalization of these factors in order to improve the success rate in attaining left heart contrast.

Myocardial perfusion imaging

Myocardial perfusion studies are at present quite cumbersome: in experimental animals radioactive microspheres allow only a limited number of observations to be made using a different isotope for each intervention, and a tedious analysis where data on blood flow are not available until a considerable time has elapsed after the experiment is completed and the animal, of necessity, sacrificed. There are also the ever-increasing problems of radioactive waste disposal afterwards. The technique is not applicable to humans, and only gross estimates of overall and regional flow can be obtained using invasive techniques. With nuclear imaging techniques relative perfusion information with only limited spatial and temporal resolution can be obtained. The ability of minimicrobubble injections during two-dimensional echocardiography to repeatedly yield "real time" information about myocardial perfusion in experimental animals suggests a much more convenient method of studying the effect of interventions on myocardial perfusion.

Potential toxicity

Potential toxicity remains an important unanswered question. However, there are several arguments to suggest that they may be safe enough for human use. First of all, most catheter injections and flushes during routine left heart catheterizations contain microbubbles, which are the cause of ultrasonic contrast. Over 5 years ago, Weyman et al reported on ultrasonic contrast injections into the left main coronary artery in humans, with no adverse reactions (13). Second, the amount of gas necessary to create a strong ultrasonic contrast effect is quite small, and the total gas amount necessary becomes smaller as the average size of the bubbles becomes smaller - contrast intensity is dependent on the scattering cross sectional area rather than the total volume. The total amount ofgas injected during each intra-coronary injection of minimicrobubbles in this experiment was very small - approximately 0.002 cc. The saccharide used in agents A and B is already used for intravenous injection. Extensive toxicity testing remains to be performed in animals, though, before human use can be considered.

Quantitation

Several reports suggest that quantitation of echocardiographic contrast effect may be possible (3,6,14,15). Our experience with quantitative videodensity techniques is that they are currently difficult, quite cumbersome and time-consuming, and of only moderate reproducibility (16). We thus elected to examine efficacy qualitatively in this initial study, especially since the qualitative contrast density seemed to vary on repeat injection. This variation may be due to the fact that we did not use precisely measured doses of precision microbubbles and meticulously standardized injection techniques (dye tubes, repeated flushing to exclude minute amounts of additional air in the injection set-up, etc.). Now that efficacy is shown, the more difficult question of quantitation can logically be examined. However, we feel that even if quantitative methods yield equivocal results, qualitative interpretation is useful: after all, contrast echocardiographic studies are interpreted qualitatively in clinical echocardiographic practice today, and still yield important information.

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13. CONCLUSION

Contrast echocardiography is undergoing a period of rapid development. It will almost certainly assume a more important clinical role in the future: contrast techniques (in addition to new instrumentation and Doppler techniques) are likely to provide the "sonic boom" of the 1980's. How will contrast echocardiography fit into the general picture of echocardiography?

13.1. Clinical applications

The results of a recent study show that contrast echocardiography is never employed in roughly half of all clinical echocardiographic laboratories in the Netherlands (1). The other half employ it occasionally but never frequently. If contrast echocardiography is used, most adult cardiologists do so only to diagnose shunts, particularly atrial septal defects. As can be seen from the foregoing sections, this is only a small field of application. An important reason for the failure to employ contrast more often is that there is such large variability of success in attaining adequate contrast effect with current methodology. One of the most common questions posed by cardiologists in both Europe and America is "why do I sometimes fail to get enough contrast?" I am hopeful that a better understanding of the source of ultrasonic contrast effect (chapter 2) combined with the occasional use of carbon dioxide (chapter 3) will help to solve this problem. If not, the expected marketing of precision microbubbles as an ultrasonic contrast agent may provide another solution. Non-gaseous contrast agents such as aggregated collagen or gelatin spheres may also be developed eventually - these would have the advantage of being able to pass the pulmonary circulation without being removed.

Once echocardiographers get over their reluctance to employ contrast, the list of clinical indications is considerably greater than merely searching for ASD's - as indicated in chapter 6. It is likely that pediatric echocardiographers will take the lead in introducing the regular use of contrast, since they are more frequently faced with the type of flow disturbance where contrast studies are likely to be helpful. This is similar to what is currently occurring with Doppler echocardiography. The similarity is not accidental:

13.2. Contrast echocardiography and Doppler echocardiography

It is not generally realized that in very many aspects M-mode contrast echocardiography and Doppler echocardiography provide quite similar information (Chapter 6, Table I). They both yield the component of blood flow velocity towards or away from the ultrasonic transducer. A multigate Doppler system has been developed by Brandestini at the University of Washington in Seattle capable of color-coding the Doppler signal. This is inserted as a sort of contrast into an M-mode tracing. Thus contrast can give "Doppler information" (velocity) and Doppler can be used to insert

contrast into an echocardiographic tracing! Contrast and Doppler echocardiography are likely to interact in a more direct manner as well: microbubbles are very strong contrast agents, enhancing Doppler signals and possibly improving the signal-to-noise ratio. Contrast studies with microbubbles have just begun in Doppler echocardiography, and they may prove to be an important clinical development, since Doppler is currently one of the most rapidly expanding fields in echocardiography.

13.3. Contrast echocardiography for physiological studies

A unique property of echocardiographic contrast is that the motion of individual contrast particles can be followed and analyzed, as long as they remain in the echo beam. Some authors are now beginning to study flow patterns in the heart, (vortices, turbulence, etc.), or quantifying one vector of the blood velocity by determining slopes of contrast trajectories on M-mode tracings. Though flow velocity has traditionally not been an important parameter to cardiologists, this may only be due to the fact that instrumentation for accurate measurement was not available. Now that 2 different methods for non-invasive measurement of flow velocity are available (Doppler and M-mode contrast trajectory slope), the utility of velocity as a parameter in physiological studies can be re-examined. Currently it is largely unknown whether the time profile of velocity at a specific location in the heart is useful in diagnosing cardiovascular disease, though the qualitative studies using time-interval histogram Doppler echocardiography suggest that indeed this will be the case.

Further, the use of quantitative techniques in contrast echocardiographic analysis from two-dimensional echocardiograms has just begun. In Chapter 11 videodensitometric techniques are being described to obtain indicator-dilution type curves from the appearance and disappearance of contrast. These techniques may eventually be useful in the quantitation of ejection fraction, cardiac output, and intracardiac shunts. Another exciting possibility is that intracardiac pressure measurement may become avialable using resonant frequency analysis of precision microbubbles (2,3).

In Chapter 12 data on organ perfusion with contrast echocardiographic techniques are given. Quantitative techniques such as videodensity analysis applied to this type of data can yield measurements of myocardial perfusion, and preliminary work in this direction in our own laboratory and Dr. Feigenbaum's laboratory in Indianapolis (4) has been encouraging.

13.4. Commercial applications

As with most developments in medical instrumentation today, industry is likely to have an important impact which would be unrealistic as well as ungrateful to ignore. The detailed toxicity testing required before marketing of precision microbubbles as a contrast agent can only be done with the resources of industry. Though the U.S. Food and Drug Administration (FDA) has recently decided that these are a medical "device" rather than a "drug," such testing entails enormous investment.

Some of the foregoing possibilities (pressure measurement and cardiac output measurement) allow one to envisage a future "ultrasonic Swan-Ganz

catheter" which would consist of a small piece of electronic equipment held over the precordium that would sense intracardiac signals from peripherally injected precision microbubbles. Development of such an instrument, with its obvious salutory affect on patient care, is quite properly a field for cooperation between industry and the university.

13.5. Other applications

Transmission of echocardiographic contrast through the lungs after peripheral venous injection has been achieved in experimental animals (chapters 5 and 12). If safely achieved in humans, this would enhance our ability to image left heart structures, and might particularly aid proximal coronary artery visualization.

Better understanding of the phenomenon of "spontaneous contrast" on both the left and right side of the heart is needed: this might shed light on whether spontaneous cavitation can be present in the human circulation in the absence of decompression. Decompression disease is another area where experimental studies of microbubble dynamics have much to offer, and the knowledge of microbubble behavior thus obtained may help in the development of improved contrast agents.

13.6. Toxicity

Perhaps the main impetus for the rapid growth of echocardiography has been that it is entirely safe. Also, over the past dozen years since the contrast effect was described, there has been no published report of its clinical toxicity. This is not at all surprising, since we know that microbubbles are present in all left heart injections performed in the catheterization laboratory, and if gross air bubbles are excluded the toxicity of left heart injections seems to be acceptable (that is, there are no reports of toxicity that are likely due to their microbubble content). I have never seen a major or permanent adverse effect due to contrast echocardiography, with a personal clinical experience of about a thousand patients. Further, Reale and coworkers in Rome have used 0.5 cc carbon dioxide for injections in the pulmonary wedge position to cause contrast in the left heart, and have reported no toxicity in a small initial series (5).

Nevertheless, the possibility of toxicity due to air embolism or some other effect should always be borne in mind. For example, it is known that proteins are altered at the plasma-air interface (6,7) and this might theoretically affect important homeostatic mechanisms in the blood. There are several unpublished cases of transient neurologic defecits after contrast echocardiography of which the author is aware. All were in patients with known large right-to-left shunts. The American Society of Echocardiography has a Committee on Contrast Echocardiography of which I am a member, and reports of adverse effects of contrast echocardiography are being collected for eventual publication. It should be stressed that an awareness of potential toxicity is important in both clinical and research work. Since some toxicity will surely be reported eventually, it will be important to weigh it in an objective manner, so that what might be only a careless action on the part of some individual will not unnecessarily impede further work.

13.7. The place of contrast echocardiography in the integrated ultrasonic diagnosis of the future

The past development of echocardiography has concentrated first of all on the delineation of anatomy. The emphasis has been shifting towards physiology as deduced from motion of the anatomic structures. Nevertheless, ultrasonic cardiac diagnosis remains limited to cardiac imaging. This is unfortunate, since a cardiologist would like to have several levels of information potentially available when investigating the cardiovascular system. Flows and pressures are the traditional variables considered, since they have been available for measurement over the past decades. In the future ultrasonic diagnosis will be increasingly able to address other levels of information. In addition to anatomic information, physiologic information on flows, velocities, and even pressures may be available. Perhaps some of this physiologic information will be somewhat difficult to relate directly to former modes of thinking for a cardiologist, since a parameter such as flow velocity has thus far not been intensively investigated. It is currently too early to know whether this parameter will be very helpful clinically. Other ways of looking at tissue perfusion and even tissue characterization are on the horizon. We can envisage a multi-purpose instrument that will not only image cardiac anatomy with very good time resolution for cardiac motion, but that also will be used to interrogate specific parts of the heart with respect to flow, pressure, tissue characteristics (?ischemia, scar) etc. It is my belief that contrast studies will have an increasingly important part in the more physiologically oriented aspects of echocardiography in the 1980's and 1990's.

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CURRICULUM VITAE

The author was born in New York City in 1948 and raised in the New York suburbs. He graduated first in his class from Valhalla High School and entered Harvard College, Cambridge, Massachusetts, in 1966. The Bachelor of Arts (B.A.) degree was awarded magna cum laude in 1970, with a major in chemistry and physics. Harvard Medical School, Boston, Massachusetts, was attended from 1970 through 1974, and the M.D. degree was received in 1974.

Next came 3 years of training in Internal Medicine at New York Hospital - Cornell Medical Center in New York City, and certification in Internal Medicine in 1977. Cardiology subspeciality training was done from 1977 through 1979 at Stanford Medical Center in Stanford, California, where the author went to learn echocardiography under Dr. Richard Popp. Certification in Cardiology was obtained in 1979.

From September, 1979 to the present the author has been a cardiologist on the staff of the Thoraxcenter, Academisch Ziekenhuis Dijkzigt, in Rotterdam, and a "wetenschappelijk medewerker" of Erasmus University. He has received a Clinician-Scientist Award from the American Heart Association which was activated in 1980 and has allowed him to stay a third year in Rotterdam. The topic of this Award is "Contrast Echocardiography." During his stay in Rotterdam he has concentrated on research in this field. He was registered as a cardiologist in the Netherlands in 1981.

After 6 months further research in contrast echocardiography at Tel Hashomer Hospital in Israel the author will return to the U.S. to join the Cardiology faculty at Mt. Sinai Medical School in New York City.

He is a Fellow of the American College of Physicians and American College of Cardiology, and a member of the American Federation for Clinical Research, the American Society of Echocardiography, the Laennec Society, the American Heart Association, and its Council on Clinical Cardiology.

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63. Meltzer RS, Roelandt J: The dangers of quantification in echocardiography (MS 81-17)
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65. Pierard LA, Meltzer RS,Simoons ML,Roelandt J: Detection et localization par echocardiographie bi-dimensionelle des troublesde contractile regionale secondaire à un infarctus myocardique aigue. (MS 81-21)
66. Santoso T, Meltzer RS, Castellanos S, Roelandt J: Small shunts may persist after atrial septal defect repair. (MS 80-16)
67. Bastiaans OL, Honkoop J, Vogel JA, Meltzer RS, Verheel PW: Hardware and software configuration of an interactive device for medical image processing. (MS 80-22)
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77. Meltzer RS, Roelandt J (ed): Contrast echocardiography (multi-authored text) The Hague: Martinus Nijhoff to appear in 1982

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78. Meltzer RS: Uncle Sam pushes cigarettes. The Phoenix 3: 25, 1971(Boston)
79. Meltzer RS: Mad. Ave & Tobacco Road. The Real Paper 1: 19, 1972 (Boston)

Contrast echocardiografie is onderzoek waarbij gebruik gemaakt wordt van een ingespoten stof die andere akoestische eigenschappen heeft dan bloed om de bloedstroom op het beeldscherm zichtbaar te maken. Bijna alle intraveneuze inspuitingen bevatten zeer kleine hoeveelheden lucht en kunnen dus als echo contrast middel gebruikt worden. Kleine hoeveelheden steriel koolzuur kunnen aan de oplossing worden toegevoegd en verhogen het echo contrast effect. Zeer kleine gasbellen passeren gewoonlijk niet door capillairen. Dit gebeurt wel wanneer men in de pulmonale "wedge" positie inspuit zodat zij in de linker kant van het hart aankomen. Het mechanisme van deze transmissie van gasbellen werd onderzocht in dierexperimenteel onderzoek met behulp van verschillende agentia.

Er zijn veel belangrijke klinische vraagstellingen waarbij contrast echocardiografie nuttige informatie kan geven: structuur identificatie, het aantonen of uitsluiten van intracardiale of intrapulmonale rechts-links shunts, de diagnose van congenitale hartziekten, en de diagnose van tricuspidalis insufficientie. Wij hebben aangetoond dat postoperatieve shunts nog aanwezig kunnen zijn lang na succesvolle sluiting van interatriale communicaties.

De toekomstmogelijkheden voor contrast echocardiografie zijn indrukwekkend. Theoretisch is het mogelijk dat de graad van doorstroming van het myocard, het hartminuutvolume, de grootte van een shunt, en zelfs de intracardiale druk gemeten kunnen worden met behulp van speciaal ontworpen microbellen.