Clinical Investigation

A New Method for Assessing Right-Sided Heart Pressures Using Encapsulated Microbubbles—A Preliminary Report

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A new noncatheter method for measuring pressures of the right side of the heart uses specially manufactured microbubbles of carbon dioxide injected into the peripheral venous system. Sudden expansion of these bubbles in the cardiac chambers causes bubble oscillations at a frequency that is primarily a function of surrounding pressure. The oscillations are recordable by a microphone on the chest wall. The preliminary experience has been in dogs and further development is needed before we can begin clinical testing of the method. In its current form, the potential for measuring higher systolic pressures seems better than that for lower diastolic pressures.

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Documentation of pulmonary hypertension currently requires catheterization of the right side of the heart. This diagnosis can be suggested by physical examination, chest roentgenography, electrocardiography, Doppler and standard echocardiography, but quantitative confirmation is still most often obtained invasively. The clinical suspicion of pulmonary hypertension (either primary or secondary) arises so commonly that a noninvasive method of quantitating right-sided heart pressures is desirable.

A new, minimally invasive method has been tested previously in vitro[1] and recently tested in vivo in our laboratory. The early results are presented herein. Initial studies in dogs were progressively modified, so data from all available experiments are not directly comparable. But we report this preliminary assessment of a new technology for determining pressures of the right side of the heart mainly to show the principles and methods involved.

Theory

Bubbles behave as simple reflectors and oscillators under certain conditions and theoretically they can be used to measure pressure within the body noninvasively. Because bubbles are resonant scatterers of ultrasound while normal structures within the body, such as erythrocytes and tissue, are not, oscillatory signals from bubbles can be identified. Horton and Wells recognized this and developed an ultrasonic echo-ranging reflection device to detect the existence of microbubbles within the body for management of dysbarism ("the bends").[2] Fairbank and Scully proposed a transmission, absorption method to detect resonating bubbles within the heart that could provide a measure of cardiac pressure.[3] Shortly thereafter, Tickner and Rasor proposed two methods whereby the dynamics of bubbles could be used to measure pressure.[4]

The method used in our studies involved injecting pressurized microbubbles that were spontaneously released within the heart to oscillate by expanding and contracting.[4] This was accomplished by placing the pressurized carbon dioxide microbubble within a fused saccharide particle. These particles begin to dissolve following mixing with blood and, at a critical point, they fracture, releasing the bubble into the circulation. The sudden expansion causes the bubble to oscillate, or "ring," at its natural frequency of compressional oscillation. The oscillation decays in roughly 10 to 12 full cycles. These

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brief oscillation signals can be detected and the frequency data transformed to determine intracardiac pressures (Figure 1).[1]

The ringing frequency of a bubble is given as follows[5-7]:

$$f = 1/\pi d\,(3\gamma p/\rho)^{1/2} \quad (1)$$

where f is the oscillatory frequency of the bubble, d is the diameter of the bubble, p is the absolute pressure of the gas in the bubble, γ is the specific heat ratio of the gas and ρ is the density of the liquid. If the physical properties and bubble diameter are known, then the bubble oscillatory frequency uniquely indicates the surrounding pressure.

Because the diameter of the gas bubble depends on its volume (V) ($d = [6V/\pi]^{1/3}$) and the pressure and volume are related by the compressibility equation (PV^n = constant), equation 1 reduces to

$$P = P_0(f/f_0)^c \quad (2)$$

where the subscript zero refers to the reference condition—that is, atmospheric pressure—and c is a constant depending on the gas. Taking logarithms and differentiating equation 2 yields

$$\Delta P/P_0 = c\Delta f/f_0 \quad (3)$$

Equation 3 indicates that changes in pressure can be directly determined by changes in the resonant frequency of bubbles in the pressure system. *Uniform* microbubbles all "ring" at the same frequency and will show a shift in ringing frequency by a given amount when pressure is changed. In this work the microbubble material was formed at 102 microns diameter and 1 atm pressure.

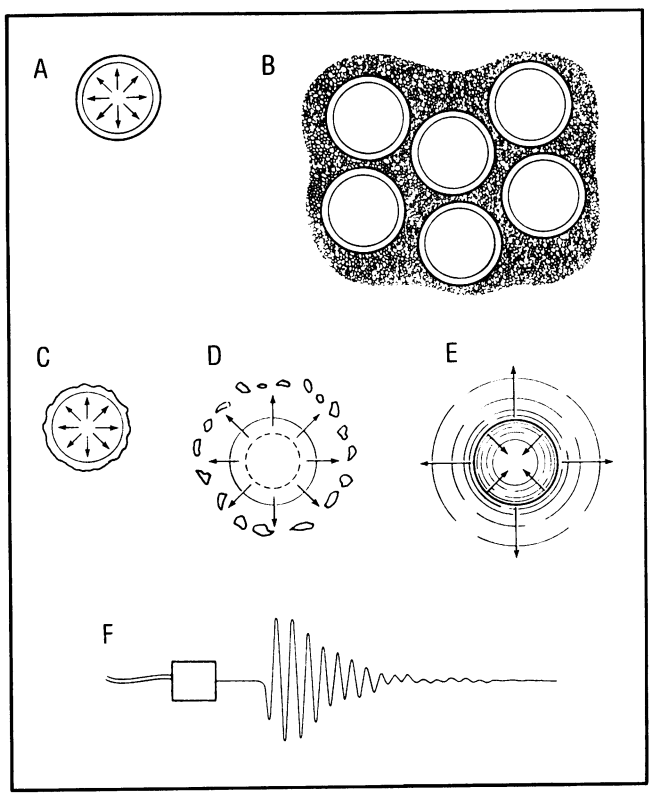

Figure 1.—Schematic representation of the origin of the signals recorded for conversion to pressure measurement. **A,** Carbon dioxide is used to form a bubble, which is incorporated into a fused saccharide particle at greater than atmospheric pressure. The particles and bubbles are uniform in size. **B,** Several thousand particles are suspended in a nonaqueous vehicle for intravenous injection. **C,** The saccharide shell begins dissolving in serum as the particles disperse in the cardiac chambers. **D,** The thinning saccharide shell fractures, releasing the pressurized gas. **E,** The gas bubble expands to a size related to the surrounding intracardiac pressure and briefly oscillates. **F,** The oscillatory signals are of ultrasonic frequency but can be recorded by an appropriate microphone.

Release of these uniform bubbles from their saccharide coat depends both on their separation from the carrying vehicle and the time necessary to fracture their capsules. Because the release of all bubbles is not simultaneous, signals occur continuously throughout the cardiac cycle and a precise signal-time record can be obtained. These data can be transformed to a pressure-time plot spanning the cardiac cycle. Electrocardiographic (ECG) gating allows signals from various periods in the cardiac cycle to be analyzed; hence, diastolic and systolic pressures can be determined.

The accuracy of this method of detecting free-ringing signals and converting them into pressure depends on uniformity of the bubble size, as mentioned. Aside from nonuniformity of bubbles, signal error can occur when bubbles are not released as perfect spheres. These deformational oscillations create frequency characteristics quite different from the uniform frequency emitted through compressional oscillation of spherical bubbles. Reflections and transducer artifacts are additional sources of error. Artifactual signals, deformational oscillation and coincident signals may be identified by their form and electronically eliminated.

Figure 2 presents a schematic of the electronic package required to transform the free-ringing oscillatory signals into pressure data. The individual components of this package and their functions are as follows:

Ultrasonic Detector (Microphone Transducer)

Signals from the oscillating bubbles are compression waves with ultrasonic frequencies of about 40 kHz. Sound signals in this range are transmitted through body tissues with little attenuation.[8] An ultrasonic microphone properly positioned on the chest wall can detect the signals coming from within the heart.

ECG Electrodes

An electrocardiographic recording is necessary to "gate" data acquisition during various intervals in the cardiac cycle. This gating technique organizes the data so signals during a given interval of time, such as systole, can be separated from other periods of the cardiac cycle. This results in grouping the pressure data into bins or ranges related to time intervals during the cardiac cycle.

Signal Conditioners

Signal conditioners serve to amplify both the oscillation and ECG signals while filtering extraneous high- and low-frequency noise. Some extraneous signals are excluded by this stage, such as deformational oscillation of nonspherical bubbles.

Microprocessor

The microprocessor decodes oscillation signals and time relative to the electrocardiographic QRS signal and subsequently converts these data into pressure-time pairs. The microprocessor also handles the statistics for the large number of sampled data.

Graphics Terminal

The graphics terminal displays oscillation frequency-time and pressure-time plots. Figure 3 shows a hypothetical idealized plot of frequency of oscillation versus time and a hypothetical plot of derived pressures versus time for the right side of the heart. This figure is included only to show the conceptual possibilities of the apparatus in the future.

Methods

Several protocols were used in ten animals while developing a useful model for evaluating the optimal microbubble expansion technique material and a suitable vehicle. The following is a description of our final working model.

Healthy 25-kg (55-lb) mongrel dogs were premedicated with morphine sulfate (2 mg per kg of body weight) intramuscularly, then anesthetized with chloralose (85 mg per kg) and urethane (625 mg per kg) given intravenously. A cuffed endotracheal tube was inserted and the animals were ventilated with room air using a Harvard respirator. Arterial blood specimens were analyzed frequently using a Corning blood gas analyzer (Model 165), and tidal volume and respiratory rate were adjusted to maintain the level of arterial oxygen pressure above 80 mm of mercury and the pH between 7.35 and 7.45. The dogs were placed on a heating pad in the supine position and four limb leads were attached for ECG monitoring. A fluid-filled catheter was placed in the descending aorta by way of the left femoral artery. A second fluid-filled catheter was placed in the superior vena cava by way of the right internal jugular vein, and a small catheter was inserted percutaneously into the left cephalic vein to be used as a conduit for infusing fluids and drugs. The chest was opened using a midline sternotomy and the heart was exposed in a pericardial cradle. A solid-state pressure transducer (Biotec, BT-250) was placed through a stab wound into the right ventricular outflow tract. A thermocouple was placed in the left ventricular apex through a stab wound to monitor blood temperature using a YSI-telethermometer.

Hemodynamic recordings were made using a multichannel electrostatic recorder (Gould ES 1000). Aortic pressures were recorded using a Statham P23Db transducer. The zero level for all pressure measurements was estimated at the mid-chest.

Compressional oscillation signals were detected over the right ventricle using an ultrasonic microphone (Bruel and Kjaer hydrophone Model #8103) and recorded on a Tektronix (Model #7603) oscilloscope. Simultaneous pressure, ECG and oscillation frequency data were recorded on high-fidelity frequency-modulation magnetic tape. Paired hemodynamic and gated frequency data were subsequently analyzed using a microprocessor (Hewlett-Packard 9826 desk-top calculator). Plots were made of the measured right ventricular pressure (solid-state transducer) versus signal frequency or signal-derived pressure (or both). Signal frequency points on these plots represent the average from more than 100 bubbles sampled.

Precision microbubble material* consisted of pressurized (1 atm) carbon dioxide bubbles (102 microns) in a fused saccharide capsule (external diameter = 144 microns) (Figure 4). The carrying vehicle was a polyalcohol.

Following instrumentation of the dog, multiple short injections of the microbubble material were delivered while varying the right ventricular pressure. Increases in right ventricular pressure were initially achieved pharmacologically by peripheral infusions of prostaglandin $F_{2\alpha}$ (Upjohn Company, Kalamazoo, Michigan), which produces pulmonary hypertension.[9,10] Right ventricular pressures were also raised abruptly by partial mechanical obstruction of the pulmonary artery with finger pressure. The microbubble material was

*Supplied by Rasor Associates, Sunnyvale, California.

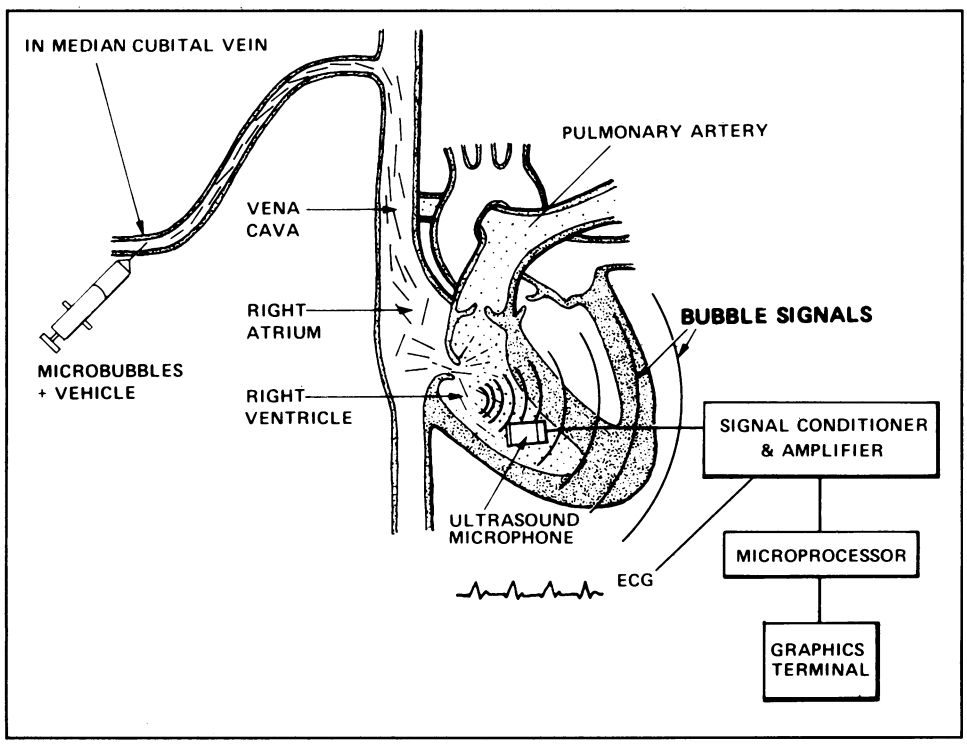

Figure 2.—Schematic representation of the electronic package required to transform the free-ringing oscillatory signals into pressure data. See text for full explanation. ECG = electrocardiogram

TABLE 1.—*Raw Data Relating Catheter-Measured Pressure to Pressure Calculated From Microbubble Frequency Data*

Pressure Range	Average Bubble Oscillation Frequency kHz	Number of Data Points*	Average Calculated Pressure mmHg	Average Catheter Pressure mmHg
−3 to −0.1	34.54	5,180	− 1	− 2.5
0.0 to 9.9	34.01	1,730	−11	2.0
10.19 to 10.9	35.94	761	27	17.0
20 to 24.9	36.15	1,660	31	22.2
25 to 30.9	36.19	1,778	32	27.0
31 to 39.9	36.04	1,852	29	35.3
40 to 51.9	36.66	931	41	45.5

*Each point represents the average of more than 100 discrete bubble oscillations.

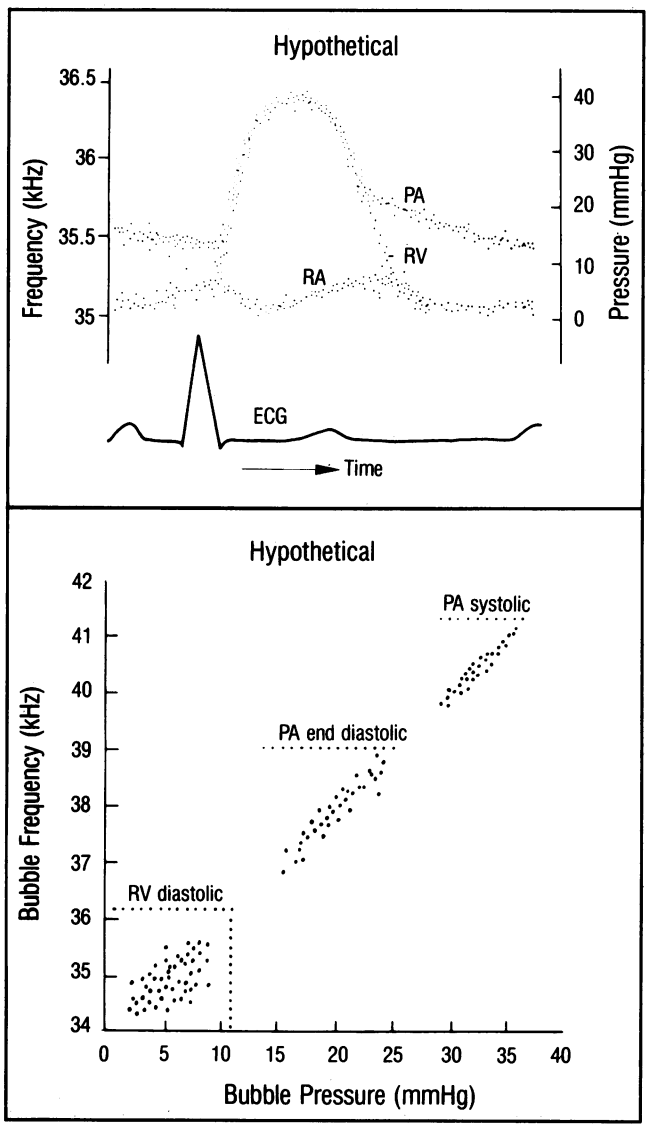

Figure 3.—Illustration of hypothetical data showing idealized frequency of bubble oscillation (corresponding to pressure) versus time relative to the electrocardiogram (ECG), with microbubble oscillations recorded from all right-sided heart chambers (upper panel). The lower panel displays grouped data derived from bubble ultrasonic ringing frequency for converting pressure with labels on areas assumed to represent right ventricular (RV) and pulmonary artery (PA) pressure levels.

infused through the catheter in the superior vena cava and the ultrasonic microphone was handheld over the anterior wall of the right ventricle. Following conclusion of the multiple infusions, the dogs were killed by barbiturate overdose.

Results

Data for one animal only will be presented for illustration of the technique. A total of 20 microbubble injections were carried out with right ventricular systolic and diastolic pressures varying from 16/−3 to 51/0 mm of mercury. Right ventricular pressures were first elevated by peripheral infusions of prostaglandin $F_{2\alpha}$. Right ventricular pressures rose from a baseline of 22/−3 mm of mercury to a peak of 30/−2 mm of mercury with a maximum prostaglandin infusion rate of 5 mg per minute. Heart rates were persistently in the 150 to 160 beats-per-minute range during the prostaglandin infusion. Subsequent elevations of the right ventricular pressure were reliably obtained by partial obstruction of the proximal pulmonary artery with finger pressure. The aortic pressure did not change significantly with either intervention.

A summary of the average catheter pressures, corresponding microbubble oscillation frequencies and derived pressures is presented in Table 1. From 100 to 1,000 discrete signal measurements were averaged to give an "individual" frequency for comparison with the pressure recorded simultaneously. The catheter pressure-bubble frequency and catheter pressure-bubble estimated pressure data using "individual" data points are plotted (Figures 5 and 6). Linear-regression analysis of the right ventricular transducer pressure versus this microbubble oscillation frequency result yields a correlation coefficient of .77 and the standard error in derived pressure was ± 14 mm of mercury using individual data.

Discussion

We first reported the use of pressurized microbubbles to determine cardiac pressures in an in vivo model in 1981.[10] The present data only show the principle and feasibility of using microbubble oscillation signals for determining right-

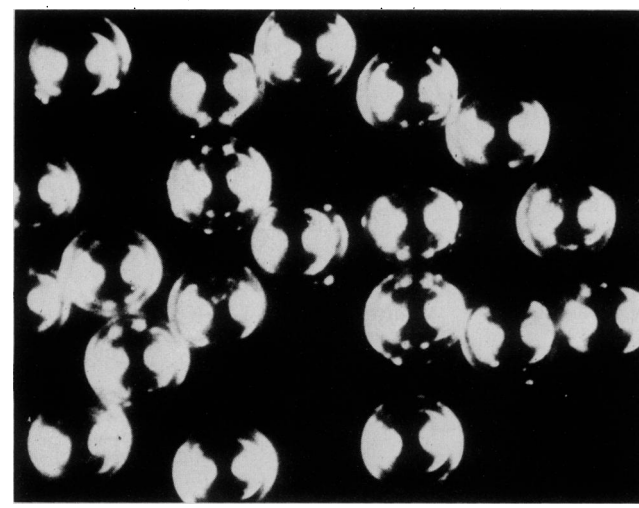

Figure 4.—Photomicrograph of the encapsulated microbubbles. Note their size uniformity. The bubbles are consistently contained in the center of the saccharide shell. The individual spheres used in this work had a mean diameter of 144 microns and the bubbles have a mean diameter of 102 microns. (The photography results in a bright pair of reflections in each sphere.)

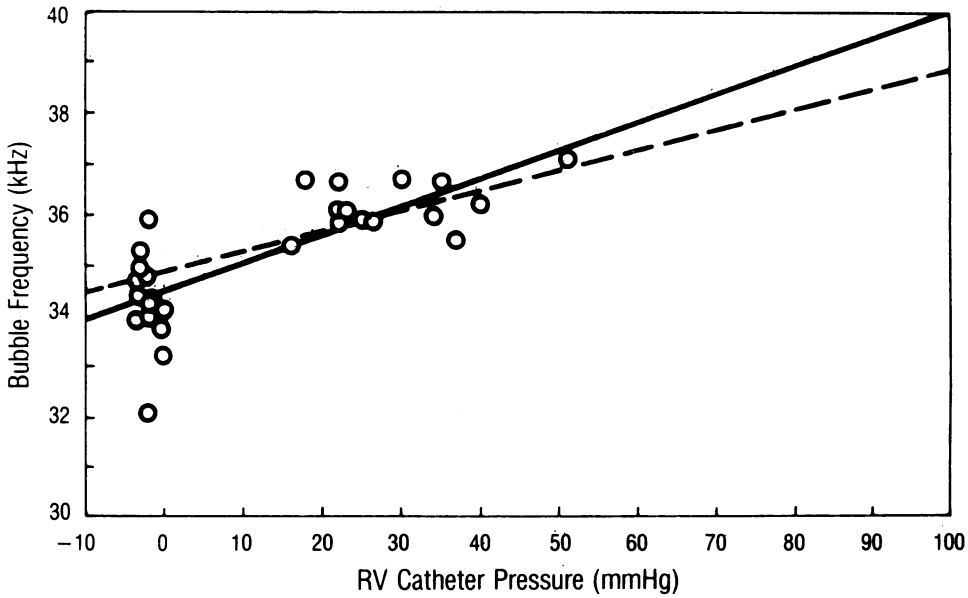

Figure 5.—Recorded bubble oscillation frequencies and corresponding right ventricular (RV) pressures as measured by solid-state manometer. These "individual" data points (see text) are expressed with the solid regression line and the dashed line expected from equation 3. Least-squares analysis: $Y = .055 \times X + 34.508$, $r = .7662$, c (constant) = 1.2.

sided heart pressures that may be developed for clinical use in the future. Significant research and development have been carried out using in vitro models, including a heart-lung model with pulsatile flow.[1] The standard error in derived pressures in the present work in dogs was greater than 10 mm of mercury, which is not sufficiently accurate for clinical use at this time. However, the results of this initial effort provide for optimism concerning the possible use of such material in an improved form.

Further refinements in the microbubble oscillation technique are needed. The current ultrasonic microphones were not built for our purpose, lack directionality and can be used only in open-chest procedures where the transducer can be positioned over the cardiac chamber or vessel of interest. Producing precision microbubbles is a major challenge for this technique and further developments in the mass production of these bubbles, as well as defining an optimal vehicle,

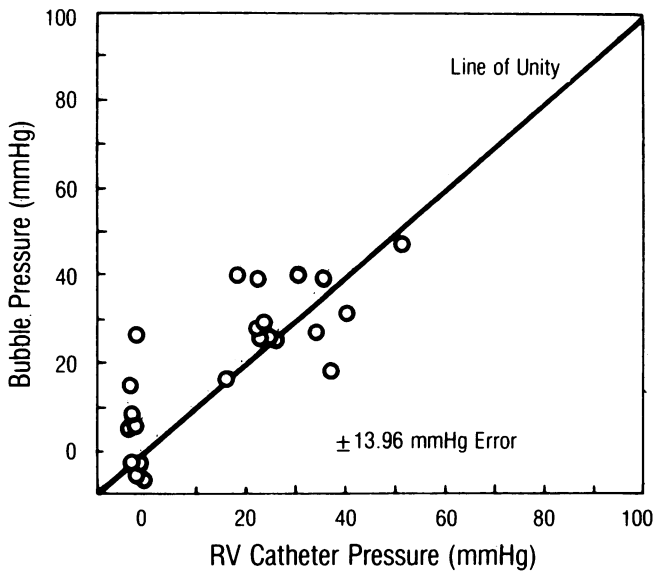

Figure 6.—Pressures derived from bubble oscillation and corresponding measured right ventricular (RV) pressures for "individual" data (see text).

are necessary. The vehicle must be designed to carry the microbubble material and protect it from dissolving until the material reaches the heart. Turbulence in the right side of the heart shears the vehicle away from the encapsulated microbubble and allows capsule dissolution and gas release. Delayed release will carry the bubble through the heart and into the pulmonary capillary bed without release from its capsule.

Modifications of both the microbubble material and the delivery by its vehicle are necessary so a maximum number of signals can be detected over several cardiac cycles. Toxicity studies are currently under way to analyze possible damage from either the microbubble material or the vehicle. Carbon dioxide has been chosen as the optimal gas for the pressurized microbubbles because of its short life in the circulation and its biologic compatibility.[11] Carbon dioxide bubbles that do not dissolve in the lungs will be filtered by the pulmonary capillary circulation.[12] Likewise, the lungs should serve as filters for the saccharide capsules in the unlikely event that they do not dissolve. Preliminary results indicate that no microscopic damage to the pulmonary capillaries or parenchyma occurs following multiple injections of the microbubble material.[1] There may be concern over the potential for injecting significant amounts of gas into the circulation; the volume of carbon dioxide, however, in each injection of 30,000 microbubble particles is about 0.07 ml of gas at 1 atm pressure.

There is a theoretic possibility that hemolysis could occur due to vibratory damage from the oscillating bubbles. Initial experience indicates that significant hemolysis does not occur when the microbubble material is fully diluted in the circulation at the time of bubble release in the right side of the heart.[1] Microscopic examination of the right ventricles of dogs receiving 10 to 100 times the standard amount of microbubble material has failed to show damage to the myocardium when studied one to three hours after infusions.[1]

The microbubble expansion technique provides an interesting approach to measuring intracardiac pressures. Much further work needs to be done before this could become a clinically testable technique. At present the potential for measuring higher—systolic—pressures seems more likely than for lower—diastolic—pressures. Even if acceptable accuracy

for lower pressures is not achieved, we can envision the possible use of the method as a screening tool for pulmonary hypertension.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Transmission of Disease Via Mouth-to-Mouth Resuscitation

QUESTION:

Is there a proved relationship between the use of mouth-to-mouth resuscitation and the transmission of communicable and infectious diseases?

OPINION:

In the opinion of the Scientific Advisory Panels on Emergency Medicine, Internal Medicine and Preventive Medicine and Public Health, there is no proved relationship between the use of cardiopulmonary resuscitation (CPR) training mannequins and the transmission of communicable and infectious diseases. The American Heart Association, American Red Cross and the Centers for Disease Control concur that, if recommended mannequin decontamination procedures are followed and precautions are taken to prevent CPR students with known infectious oral, facial cutaneous of respiratory disease from participating in mouth-to-mannequin practice, the risk of the spread of communicable disease is extremely small.

The larger question whether actual mouth-to-mouth resuscitation is likely to transmit a communicable disease is difficult to answer. Since diseases such as the acquired immunodeficiency syndrome (AIDS), mononucleosis, herpes simplex and hepatitis B are known to be or have the potential to be transferred by saliva, it is theoretically possible that mouth-to-mouth resuscitation can transmit communicable disease.

In spite of the widespread use of CPR training mannequins and actual mouth-to-mouth cardiopulmonary resuscitation in recent years, the risk of disease transmission appears to be minimal. Since most resuscitative efforts take place in health care institutions, however, it is prudent to have other means of resuscitation available.