FEASIBILITY OF MITRAL FLOW ASSESSMENT BY ECHO-CONTRAST ULTRASOUND, PART II: EXPERIMENTAL STUDY ON A MECHANICAL MODEL OF THE LEFT HEART

BRONISLAV HERMAN,* SHMUEL EINAV* and ZVI VERED†

*Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University, Tel-Aviv, Israel; and †Cardiology Institute, Asaf-Harofeh Medical Center, Zrifin, Israel

(Received 6 July 1999; in final form 1 February 2000)

Abstract—The feasibility of assessing mitral flow by means of ultrasonic monitoring of backscattered power from an echo-contrast agent in the left atrium and left ventricle was studied. A mechanical model of the left heart was built in which two thin rubber balloons connected to each other in a feedback loop via two artificial heart valves mimicked the left atrium and left ventricle. The model was driven by compressed air. Its input and output flows were measured as the functions of a pacing rate, driving pressure and artificially introduced mitral regurgitation. These were compared with the corresponding data derived from the ultrasonic measurements that are based on the correlation between echo-contrast agent concentration in the volume of interest and the flow through it. Algorithms for quantitative estimations of forward stroke volume (cardiac output) and mitral regurgitation are given. This study shows, for the first time, both analytically and experimentally, that the pulsating modulation of contrast agent concentration vs. time curves in the ventricle and atrium volumes is closely related to the pulsating nature of the flow in the system. It also shows that the amplitude of the atrium concentration modulation is directly proportional to the maximum value of the incoming (to atrium) flow. © 2000 World Federation for Ultrasound in Medicine & Biology.

Key Words: Ultrasound, Attenuation coefficient, Integrated backscatter, Echo-contrast agent, Mitral flow, Forward stroke volume, Mitral regurgitation.

INTRODUCTION

A reliable noninvasive method of mitral flow assessment would be an extremely valuable tool in the field of cardiac diagnostics. Echo-Doppler velocity-measurement–based methods are currently used for this purpose. However, the Doppler velocity profile of the transmitial flow alone fails to provide a clear-cut assessment of cardiac output, and color Doppler mapping of the mitral retrograde flow provides only qualitative and frequently insufficiently accurate estimation of mitral regurgitation (Garcia et al. 1998; Pu et al. 1996). Recently suggested technique based on 2-D color Doppler mapping of proximal converging flow also suffers from inaccuracy of flow velocity determination, and the alternative 3-D mapping method, although improving the accuracy, is quite elaborate (Anayiotos et al. 1999). Flow measurements based on echo-contrast dilution principles comprise an attractive alternative to echo-Doppler methods because they have the potential of yielding a direct flow estimation in terms of an averaged volume flow over one heart cycle. Such principles were implemented for a qualitative mitral regurgitation estimation in humans (Shuqing et al. 1992a, 1992b) and for a quantitative mitral flow estimation in a canine model (Dent et al. 1992). However, the methods of those investigators (Shuqing et al. 1992a, 1992b; Dent et al. 1992) were based on the use of an intraventricular injection of echo-contrast and subsequent monitoring of its appearance and wash-out rate from the left atrium; thus, making these methods invasive in nature. In the present work, the feasibility of forward and backward mitral flow assessment was studied on a mechanical model of the left heart, where the injection of a contrast agent is made upstream relative to the atrium, thereby mimicking a noninvasive IV injection, because both of the agents we used, Albunex® and Levovist® SHU 508-A, are reported to be capable of crossing the pulmonary vascular bed without loss of their echogenicity (Schlief et al. 1990; Villanueva
et al. 1992; Keller et al. 1989). Similar to other indicator-dilution–based techniques, contrast agent concentration in a certain volume is related to the flow through it. Thus, the question is whether or not simultaneous monitoring of echo-contrast concentrations in the left atrium and left ventricle could provide quantitative data on forward stroke volume (SV) and mitral regurgitation volume (RV). Prerequisite for attempting to answer this question is the ability to determine echo-contrast concentration in the aforementioned volumes. The algorithm of echo-contrast concentration calculation is based on the single-value relationships between integrated backscatter index and attenuation coefficient vs. concentration, which were determined in Part I of this study.

Another very important presumption, which was not verified but merely adopted here is that contrast agent microbubbles move with the same velocity as that of the host liquid. This is supported by the observations of others (Keller et al. 1989; Goldberg et al. 1993; Jayaweera et al. 1994), who stated that echo-contrast microbubbles of the same agents used in this study closely follow the movement of red blood cells.

**MATERIALS AND METHODS**

Figure 1 is a schematic diagram of the mechanical model of the left heart used in the current study. This experimental setup was used for input and output flow measurements, as well as for ultrasonic assessment of the mitral flow in the model. The system is comprised of two thin rubber balloons (Fig. 1, number 2 and 3), mimicking left atrium and ventricle respectively, which were connected to each other in a feedback loop via: “mitral” and “aortic” (Fig. 1, numbers 8 and 10) artificial valves; flexible tubing; open to atmosphere compartment (Fig. 1, number 4), used for volume flow monitoring (see below) and compartment 2, used for injection of fixed doses of contrast agent. The “atrium” 7 and “ventricle” 9 balloons were placed inside two isolated from each other compartments (Fig. 1, number 12 and 13), made of Perspex and filled with water. The balloons, number 7 and 9 were situated one above the other along the axis of the ultrasonic transducer, monitoring backscattered waves from inside “ventricle” and “atrium” volumes simultaneously (Fig. 1, number 11). The system was filled with 1 liter of filtered water for each set of measurements. The ventricle compartment was exposed for 130-ms time periods, with pacing rates of 30.7, 37.6 and 49.6 beats per min to the source of constant compressed air pressure (regulated by the valve 14 in Fig. 1), which made the water circulate through the system. Three pressure settings of that valve 14 in Fig. 1), which made the water circulate through the system. Three pressure settings of that valve (i.e., 0.48, 0.69 and 0.83MPa or 7, 10 and 12 psi). An ultrasonic probe (Fig. 1, number 5) was used to measure the water level in compartment 4 to determine the model’s input and output flows. In other words, the volume output flow was measured when valve 3 was closed to the outside (position a of the valve 3 in Fig. 1), and the volume input flow was measured when valve 3 was opened to the outside (position b of the valve 3 in Fig. 1).

The same pressure and pacing settings were used for ultrasonic mitral flow assessment by means of focusing probe 11 from Harisonic Inc., Stamford, CT focal distance F = 100 mm, nominal frequency f = 7.5 MHz, diameter ø = 11 mm. All the measurements were conducted for two different sets of atrium-ventricle balloons (i.e., setups #1 and #2) and for the two types of contrast agents used for these measurements, Albunex® (Molecular Biosystems Inc., San Diego, CA ) and Levovist® (Schering AG, Berlin, Germany).

Probe 5, the contact probe used for volume flow
measurements, has a nominal frequency of 10 MHz and a diameter of 6 mm. The ultrasonic signal reflected from the water-air interface that was picked up by this probe was sampled at a rate of 32 MHz. The measurements were taken every 20 ms. Stroke volume was determined in two different ways: SV₀ was calculated as maximum-minimum difference of the model output flow volumes (valve 3 in position a) and SVᵢ was calculated as the input flow volume difference for two positions, corresponding to the consequent moments of mitral valve closure (valve 3 in position b).

The ultrasonic monitoring of the signal backscattered from the contrast agent was performed by means of transducer 11. Each monitoring cycle was started shortly before manual injection of a bolus of contrast agent into the V₀ compartment (Fig. 1, number 2) and lasted for 2.5 min. During this time period, records of 4096 bytes each were acquired every 0.125 s with a sampling rate of 32 MHz and stored on the hard disk of the computer. Signal processing was performed off-line by means of the programs written in C-language especially for this purpose.

THEORETICAL BACKGROUND

For the atrium diastolic cycle, the equations governing an echo-contrast agent concentration cₐ in an atrium volume Vₐ are given by:

\[
\begin{align*}
\frac{d(V_c)_a}{dt} &= -\frac{F_{M^+}}{V_a} (V_c)_a + F_{in}c_{in}, \\
\frac{dV_a}{dt} &= -F_{M^+} + F_{in}, \\
\quad c_{in} &= c_0 \exp \left( -\frac{1}{V_0} \int_0^t F_{in}d\tau \right), \quad (1)
\end{align*}
\]

where \( F_{in}, F_{M^+}, \) and \( F_{M^-} \) are incoming atrial and mitral forward and backward volume flows, respectively, and \( V_{in} = V_0 = \text{constant} \) (see Fig. 1). Here, it is assumed that bolus \( Q \) of an indicator was injected upstream relative to the \( V_a \) and its maximum concentration \( c_{in} \) in the volume \( V_{in} \) has been achieved prior to the time point \( t = 0 \), whereas eqn (1) is written for \( t \geq 0 \). It is also assumed that \( F_{in}, F_{M^+}, F_{M^-}, \) and \( V_a \) are a truly periodic function of time with a period \( P \) equal to the average heart cycle.

The solution of the first equation on the interval \( (i-1) \)-th until end of an i-th diastole was given by (Bronson 1973):

\[
V_a(t)c_a(t) = \left[ V_a(ES)c_a(ES_{i-1}) \right]
+ \left[ \int_{ES_{i-1}}^t F_{in} c_{in} \exp \left( \int_{ES_{i-1}}^\tau \frac{F_{M^+}}{V_a} d\tau \right) d\tau \right] \exp \left( -\int_{ES_{i-1}}^t \frac{F_{M^+}}{V_a} d\tau \right) \]
\]

and, after substituting \( c_{in} \) by its average value, one obtains:

\[
V_a(t)c_a(t) = \left[ V_a(ES)c_a(ES_{i-1}) \right]
+ \left( \langle c_{in} \rangle \int_{ES_{i-1}}^t F_{in} \exp \left( \int_{ES_{i-1}}^\tau \frac{F_{M^+}}{V_a} d\tau \right) d\tau \right] \exp \left( -\int_{ES_{i-1}}^t \frac{F_{M^+}}{V_a} d\tau \right). \quad (3)
\]

For short time intervals following the moment of mitral valve opening, it can be assumed that the mitral flow significantly exceeds the input flow:

\[
F_{M^+} \gg F_{in} \Rightarrow F_{M^+} \approx -\frac{d(V_a)}{dt}; \Rightarrow \int_{ES_{i-1}}^t \frac{F_{M^+}}{V_a} d\tau = \int_{ES_{i-1}}^t \frac{d(V_a)}{V_a} = \ln \left( \frac{V(ES_{i-1})}{V_a(t)} \right). \quad (4)
\]

Introducing this into eqn (3) yields:

\[
V_a(t)c_a(t) = \left[ V_a(ES)c_a(ES_{i-1}) + \langle c_{in} \rangle V_a(t) \right]
\times \left( \int_{ES_{i-1}}^t \frac{F_{in}}{V_a} d\tau \right); \quad ES_{i-1} \leq t \leq ES_{i-1} + \delta t \quad (5)
\]
For the relevant time interval, \( F_{in}(t) \) is rapidly increasing and \( V_{a}(t) \) is rapidly decreasing function, so that their ratio is a sharply rising, step-like function. Thus, eqn (5) can be approximated on this time interval by:

\[
c_a(t) = c_a(ES_{i-1}) \frac{V_a(ES)}{V_a(t)} + (c_a(i)) \frac{F_{in}(\tau)}{V_a(\tau)} (t - ES_{i-1}).
\]  
\[
(6)
\]

As the time increases further, \( F_{in} \) decreases toward zero and \( V_a \) starts to rise slowly, so that the integral in the expression, eqn (3) increases at a much slower rate than the rate of decrease of the negative exponent part of the expression. The overall atrium echo-contrast concentration decreases at systolic stage of the heart cycle due to a regurgitant flow of low concentration from the ventricle and continues to do so until the start of the next diastole. It should be noted that, in accordance to this explanation, the presence of elevated mitral regurgitation, which causes atrial over pressure at systole, will impair \( F_{in} \) at early stages of the fast filling and, therefore, will cause a decrease of peak amplitudes of echo-contrast concentration pulses [see eqn (6)]. For this reason, it is suggested to assess mitral regurgitation by the mitral regurgitation index, MRI. It is defined as the value reciprocal to the amplitude of the pulse of mitral echo-contrast concentration, for which the following applies: \( V_a(\tau) = V_a(\text{min}) \), \( F_{in}(\tau) = F_{in}(\text{max}) \) and \( c_a(ES_{i-1}) \approx 0 \)

\[
\text{MRI}(i) = \frac{V_a(\text{min})}{(c_a(i))F_{in}(\text{max})\tau}.
\]
\[
(7)
\]

The equation governing ventricle echo-contrast concentration \( c_v \) in the volume \( V_v \) on a diastolic cycle is:

\[
\frac{d(V_v c_v)}{dt} = F_{M,v} c_a + F_{in} c_m - \frac{d(V_v c_v)}{dt}.
\]
\[
(8)
\]

Assuming that \( c_v \) does not change on systole, it can be shown that the drops of the value \((c_v V_v)\) on diastole and on full heart cycle are:

\[
\Delta(V_v c_v) = \Delta_{i-1}(V_v c_v) \exp\left(-\frac{SV}{V_{in}}\right); \quad \Delta_f(V_v c_v) = \Delta(V_v c_v)
\]

\[
- (SV + RV)c_v(ED_i).
\]
\[
(9)
\]

By now taking the ratio of two consequent values of \( \Delta_f(V_v c_v) \), one obtains:

\[
\frac{\Delta_f(V_v c_v)}{\Delta_{i+1}(V_v c_v)} = \frac{\Delta_{i}c_v}{\Delta_{i+1}c_v} = \frac{\Delta_i(V_v c_v) + (SV + RV)c_v(ED_{i+1})}{\Delta_i(V_v c_v)\exp\left(-\frac{SV}{V_{in}}\right) + (SV + RV)c_v(ED_{i+1})},
\]
\[
(10)
\]

from which, it follows that, if the assumption is made that the descending portion of the \( c_v(t) \) curve can be approximated by an exponential function \( A \exp(-\alpha t) \), then \( \alpha \) will be equal to:

\[
\alpha = \frac{SV}{V_{in}P}; \quad SV = \alpha V_mP
\]
\[
P = \text{heart cycle period.}
\]

RESULTS

Figure 2 depicts typical records of input and output flow volumes and their corresponding 7th order polynomial fits for balloon setup #1 (pressure 0.69 Mpa, pacing rate 30.7 bpm of the model with artificial regurgitation). The results of calculated stroke volumes are summarized in Table 1.

Data acquired by the transducer (Fig. 1, number 11) were used for calculating echo-contrast concentration values in the corresponding volumes based upon the relationships determined in Part I of this study, and accounting for the time-dependent attenuation. Figures 3 and 4 provide examples of “ventricular” and “atrial” contrast concentration vs. time-dependencies for the cases corresponding to the balloon setup #1 obtained with the Albunex® contrast agent, and Figs. 5 and 6 show these results using the balloon setup #2 and the Levovist® contrast agent. Two features should be noted here: the first is the fact that, for Albunex®, the “atrium” is overshadowed by the “ventricle” so that its concentration data cannot be resolved from the background noise; the second is that, when they are available, there is a well-defined cyclic modulation of the concentration patterns of the “ventricle” and “atrium.” This cyclic modulation is among the common findings of all the research studies dealing with echo-contrast echocardiography (Wilson et al. 1993; De Pieri et al. 1988; Rovai et al. 1987) and, as was shown above, is related to the pulsating nature of the flow in the system.

Several parameters were calculated from the “atrial” and “ventricular” contrast agent concentration data to characterize forward stroke volume and mitral regurgitation volume:

1. \( SV_1 \) = forward stroke volume parameter calculated in accordance with the indicator dilution principle, which states that the amount of the washed-out indicator should be equal to the bolus (Zierler 1962):
where

\[ Q = \text{bolus}; \quad P = \text{heart cycle period.} \]

2. \( SV_2 \) = forward stroke volume parameter calculated in accordance with the \( SV_2 = V_i aP \), where \( \alpha \) was attenuation coefficient of the LMS-fitted function \( y = A \exp(-\alpha t) \) to the descending part of each ventricle concentration curve;

3. The mitral regurgitation index (MRI) was calculated as a reciprocal of the first discernible impulse of the \( c_i(t) \) pattern.

4. The area under the \( c_i(t) \) curve, \( Avc = \sum c_i \Delta t \), was calculated to check how it is related to artificial mitral regurgitation and to provide evidence of fluctuation of contrast agent backscatter activity, which is prone to change from test to test.

**DISCUSSION AND CONCLUSIONS**

The results of the input/output flow measurements that were derived from our model can be summarized as follows:

1. The dependence on driving pressure (this is obvious and needs no further comments: it serves more for checking the validation of the measurement procedures);

2. The dependence on pacing rates. This feature is worthy of closer attention. Apparently, the lower the pacing rate, the higher the output stroke volume (both \( SV_o \) and \( SV_i \)). (i.e., the longer the time allowed for the “ventricle” to accomplish its filling-up cycle, the higher the output stroke volume). This is similar to the Franklin–Starling law. This effect apparently has to be ascribed to the properties of the aortic valve. The underlying explanation is that a greater ventricle end-diastolic volume means a smaller negative pressure drop on the aortic valve, so that the ensuing pulse of the same driving pressure will open the valve wider to provide greater forward stroke volume.

3. Unlike what occurs in real hearts, the model does not have a suction phase (the phase in which ventricular pressure decreases despite increasing volume) of the rapid filling cycle. That is why the diastolic cycle was made relatively long to allow the “ventricle” enough time for the filling process. The model fails to produce an adequate output, however, at pacing rates higher than 50 bpm.

4. The model output flow pattern (see Fig. 2) is very much like real heart aortic flow. The input flow pattern, however, differs considerably because there is
no atrial systole in the model, and the “mitral annulus” does not descend during systole. The corresponding phases of the incoming flow are, therefore, absent.

5. The balloon setup #1 reacts to the introduction of the artificial regurgitation in an expected manner; namely, the output stroke volume $SV_o$ decreases. The fact that $SV_i > SV_o$ suggests that mitral valve opening occurs while compliance compartment filling is still in progress. The introduction of regurgitation causes overinflation of the “atrium,” which retards the input flow. On the other hand, the behavior observed with balloon setup #2 was quite different: the measured stroke volumes were $SV_i \approx SV_o$ and the introduction of artificial regurgitation caused an increase of the output stroke volume in all the cases, except when the driving pressure was 0.83 MPa. The ventricle balloon of this setup was twice as thick as its counterpart in setup #1 and, therefore, it was stiffer, which explains the lower values of the observed stroke volume. Because of these small values of forward stroke volume, the filling of the compliance compartment ceases before the moment of mitral valve opening and, therefore, $SV_i \approx SV_o$. The introduction of artificial mitral regurgitation causes a more positive pressure drop on the mitral valve during diastole and, therefore, greater ventricle end diastolic volume which, in turn, causes the aforementioned greater forward stroke volume, apparently prevailing over the mitral regurgitation loss. For the high driving pressure of 0.83 MPa, the aortic valve exhausts its

<table>
<thead>
<tr>
<th>Bpm (min⁻¹)</th>
<th>30.7</th>
<th>37.6</th>
<th>49.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pres. (psi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$SV_o$ (mL)</td>
<td>53.3</td>
<td>47.7</td>
<td>45.5</td>
</tr>
<tr>
<td>$SV_i$ (mL)</td>
<td>62.8</td>
<td>55.1</td>
<td>47.4</td>
</tr>
<tr>
<td>$SV_o$ (mL)</td>
<td>–</td>
<td>47.4</td>
<td>65.3</td>
</tr>
<tr>
<td>$SV_i$ (mL)</td>
<td>–</td>
<td>65.3</td>
<td>45.5</td>
</tr>
<tr>
<td>$SV_o$ (mL)</td>
<td>44.7</td>
<td>49.4</td>
<td>45.9</td>
</tr>
<tr>
<td>$SV_i$ (mL)</td>
<td>65.9</td>
<td>70.8</td>
<td>50.8</td>
</tr>
<tr>
<td>$SV_o$ (mL)</td>
<td>–</td>
<td>41.4</td>
<td>39.0</td>
</tr>
<tr>
<td>$SV_i$ (mL)</td>
<td>–</td>
<td>65.4</td>
<td>48.7</td>
</tr>
<tr>
<td>$SV_o$ (mL)</td>
<td>55.8</td>
<td>–</td>
<td>39.3</td>
</tr>
<tr>
<td>$SV_i$ (mL)</td>
<td>57.9</td>
<td>–</td>
<td>47.5</td>
</tr>
<tr>
<td>Mean</td>
<td>51.3</td>
<td>48.6</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>56.3</td>
<td>56.0</td>
<td>48.4</td>
</tr>
<tr>
<td></td>
<td>56.9</td>
<td>55.6</td>
<td>51.4</td>
</tr>
<tr>
<td>Mean</td>
<td>56.6</td>
<td>55.8</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>58.5</td>
<td>55.8</td>
<td>46.2</td>
</tr>
<tr>
<td></td>
<td>59.7</td>
<td>59.4</td>
<td>46.8</td>
</tr>
<tr>
<td>Mean</td>
<td>59.1</td>
<td>59.1</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Fig. 3. Albunex® concentration vs. time relationship obtained for balloon setup #1 (pres. -0.69 MPa; bpm 30.7 min⁻¹; without regurgitation). Panel a represents the “ventricle” and panel b represents the “atrium.”
capability to open up considerably wider and the increase in the forward stroke volume can no longer compensate for the losses due to mitral regurgitation, and the model returns to the “normal” relationships \( SV_i > SV_o; SV_i(\text{reg}^-) > SV_o(\text{reg}^+) \).

Ultrasonic monitoring of echo-contrast backscatter activity in the “atrial” and “ventricular” volumes

Two parameters were derived from echo-contrast concentration vs. time relationships in an attempt to find their correlation to the previously measured stroke volume \( SV_i \), and one further parameter to characterize mitral regurgitation volume.

The \( SV_2 \) parameter. This was determined in accordance with eqn (9) and exhibited reasonably good correlation with the \( SV_i \) values measured independently (see Fig. 7).

\( SV_1 \) parameter. This did not exhibit any correlation with the model’s forward stroke volume, but was dispersed over a very wide range of values, even for the same pulse rate and driving pressure because of the fluctuation of the contrast agent’s backscatter activity as had been evidenced by the dispersion of the \( Avc \) parameter. The reasons for this with regard to Albunex® are not clear: they cannot be explained by relatively small deviations in the amounts of injected bolus, nor by any other reason related to how the measurements were carried out. The situation is clearer for Levovist®: for which initial contrast concentrations depend on the time expired since the moment of its preparation: they drop significantly.

Fig. 4. Albunex® concentration vs. time relationship obtained for balloon setup #1 (pres. \(-0.69\) MPa; bpm \(30.7\) min\(^{-1}\); with regurgitation). Panel a represents the “ventricle” and panel b represents the “atrium.”

Fig. 5. Levovist® concentration vs. time relationship obtained for balloon setup #2 (pres. \(-0.69\) MPa; bpm \(30.7\) min\(^{-1}\); without regurgitation). Panel a represents the “ventricle” and panel b represents the “atrium.”
after 10 min, and 10 min was approximately the time span between two consecutive sets of measurements carried out with the same echo-contrast preparation. In any event, the method of stroke volume assessment by the formula $SV = \frac{QP}{Avc}$ is not altogether suitable for echo-contrast cardiography because some loss of the agent on its passage through a pulmonary vascular bed following an IV injection is highly possible.

The MRI parameter. This was not suitable for Albunex® because of the very high attenuation coefficient of the agent and low “atrial” signal-to–noise ratio. Reliable measurements of “atrial” concentrations of Albunex®, overshadowed by the “ventricular” ones are, therefore, impossible. For Levovist®, the MRI parameter correctly characterizes the regurgitant mitral flow (it is higher whenever artificial regurgitation is introduced) for those cases where the $Avc$ parameter was high enough ($Avc > 1.0\% \times s$). Note how the introduction of artificial regurgitation impairs the normal behavior of the “atrial” concentration curve, which is in good agreement with the relationships in eqn (3) and (5) (see Figs. 5 and 6). The measured MRI, however, exhibited a very wide range of variation, so that the presence of mitral regurgitation could be identified only by comparison of the value of the index with that obtained in the test performed without artificial regurgitation. The possible reasons for this are: 1. the degree of artificial regurgitation used in this study was uncontrolled so that repeatability of MRI values could not be expected; 2. MRI strongly depends on initial contrast concentration of the agent; 3. “atrial” echo-contrast concentration

---

Fig. 6. Levovist® concentration vs. time relationship obtained for balloon setup #2 (pres. –0.69 MPa; bpm 30.7 min⁻¹; with artificial regurgitation). Panel a represents the “ventricle” and panel b represents the “atrium.”

Fig. 7. Average stroke volume $SV_2$ determined by echo-contrast US measurements vs. average stroke volume $SV_1$, measured independently. Panel a represents the balloon setup #1 using the contrast agent Albunex® and panel b represents the contrast agent Levovist® in a combination of the data from balloon setups #1 and #2.
data were acquired with a low signal-to-noise ratio, which strongly depends on the proper angle adjustment of the ultrasonic probe.

The \textit{Avc parameter}. This was measured to provide $SV_i$ values and to indicate variance of the initial concentration of the contrast agent’s microbubbles. It is interesting to note that this parameter was found to be correlated to the introduction of mitral regurgitation (\textit{i.e.}, it was lower than its counterpart whenever artificial regurgitation was introduced compared to when there was no mitral regurgitation).

**SUMMARY**

A mechanical model of the human left heart especially designed for this study was capable of producing adequate “cardiac” output for low pacing rates (bpm $\leq$ 50 min$^{-1}$). Its input/output flow was regulated in three different ways: 1. by changing driving pressure; 2. by changing pulse repetition rate; and 3. by introducing artificial mitral regurgitation. Forward stroke volume was measured by ultrasonically monitoring the volume of the incoming fluid over a given period (heart cycle). This method, although possessing very good time and amplitude resolutions, provided apparently poor accuracy due to the concomitant wavy motion on the surface of the water column, the height of which was the indicator of the “consumed” (incoming) volume. However, because the primary concern of this study was not the accuracy, but the feasibility, of mitral flow assessment by echo-contrast US, this method was judged as being altogether satisfactory. Indeed, on the average, the measured forward stroke volume, $SV_i$, provided reasonable results both for changing driving pressure and changing pulse-repetition rates. The results for artificial mitral regurgitation were ambiguous: for the set of thin compartments, the introduction of artificial mitral regurgitation caused a decrease of the forward stroke volume, but resulted in an increase in the other set of thicker (more rigid) balloons.

The model mitral flow assessment by echo-contrast US was performed in a configuration mimicking an echocardiographic 4-chamber long axis view (\textit{i.e.}, the interrogating transducer “saw” the “atrial” compartment overshadowed by the “ventricular” one). This imposed formidable difficulties on reliable data acquisition on the “atrium,” and these could not be overcome when applying Albunex®. For this contrast agent, only the forward stroke volume characteristic of the flow could be obtained, based on the data derived from the “ventricular” contrast concentration vs. time dependency. This parameter correlates reasonably well with the forward stroke volume measured as described in the section above. Good correlations between the same parameters were also obtained for Levovist®, the second contrast agent used in this study. The conclusion that “ventricular” contrast concentration vs. time dependency can be used for estimating forward stroke volume (cardiac output) is identical to what had been reported by Wilson et al. (1993); De Pieri et al. (1988) and Rovai et al. (1987). The innovative feature of the current study is the fact that the commonly observed cyclic modulation of the ventricle echo-contrast concentration curve was found (both theoretically and in actual measurements) to be related to the amplitude and timing of the incoming flow on its early stage of diastolic fast filling. This cyclic modulation is most pronounced in the “atrial” echo-contrast concentration vs. time-dependency curve and can be used for mitral regurgitation assessment because the latter strongly affects the amplitude of the incoming flow during the early stages of fast filling. Full range “atrial” concentration curves could be obtained only for those tests carried out with Levovist® for which the initial concentration of the agent was sufficiently high. Here, the presence of elevated regurgitation could be determined qualitatively by observation of the differences in the “atrial” echo-contrast concentration pattern, which was supported by quantitative estimation of mitral backward flow (\textit{i.e.}, by calculation of the MRI).

Finally, in spite of the fact that the results of the present study need further confirmation by means of more precise measurements, we believe that we can confidently conclude that echo-contrast US has the potential to serve as the basis for a noninvasive method for mitral flow assessment.

**Acknowledgements**—The authors thank S. Akselrod from the Tel-Aviv University for her kind assistance, which made this study possible. We are also very much obliged to Mrs. E. Eshkol from the Tel-Aviv Ichilov Hospital, whose advice was so useful in editing part of this work. The support of the Drown Foundation is greatly appreciated.

**REFERENCES**


