Intracoronary Albunex

Its Effects on Left Ventricular Hemodynamics, Function, and Coronary Sinus Flow in Humans

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Background. Albunex is a recently developed ultrasonic contrast agent made from sonicated human serum albumin. The effects on left ventricular hemodynamics, function, and coronary sinus flow of intracoronary Albunex in humans have not been reported.

Methods and Results. Eighteen patients with known or suspected coronary artery disease were examined at the time of coronary arteriography with simultaneous two-dimensional echocardiography and left ventricular catheter-tip manometry. Intracoronary injections of Albunex into the left main coronary artery were performed, as were injections of 5% human serum albumin and iohexol, a widely used angiographic contrast agent. Mean coronary sinus flow was determined before and after injections of iohexol and 2 mL of Albunex. Injection of 1 mL of Albunex induced no changes in any of the measured hemodynamic parameters (heart rate, peak left ventricular [LV] systolic pressure, LV end-diastolic pressure, positive or negative LV dP/dt, or time constant of relaxation) or echocardiographic determinants of LV function (regional wall motion and global ejection fraction). Injection of 2 mL or more of Albunex caused small, transient (less than 30 seconds) changes in measures of isovolumic relaxation (negative LV dP/dt; 95% confidence interval: mean, −2.41 [−4.3, −0.52] and tau_1; confidence interval mean, 3.53; [1.48, 5.58]) but not in functional measures. Intracoronary injection of 5% human serum albumin had no effect. Iohexol induced small but significant changes in both systolic and diastolic parameters, which lasted beyond 30 seconds after injection. Mean coronary sinus blood flow increased.

Conclusions. The effects of Albunex on hemodynamics, left ventricular function, and coronary sinus blood flow compare favorably with iohexol. Albunex can be considered to be an essentially inert contrast agent if used in patients with stable coronary artery disease. (*Circulation*. 1993;88[part 1]:2123-2127.)

KEY WORDS • echocardiography • hemodynamics

Myocardial contrast echocardiography is a relatively new diagnostic tool that uses intravenous or intracoronary injection of solutions containing microspheres of air (microbubbles) in order to enhance myocardial imaging and assess myocardial perfusion.[1] Recently, Albunex (Nycomed, Oslo), a new ultrasonic contrast agent containing human serum albumin and microbubbles of standard sizes and concentration, has been made available for research purposes. Its safety for intravenous injection in humans has been shown,[2] as have its effects in animals after intracoronary injection.[3] The effects of intracoronary injections of Albunex on hemodynamics, left ventricular function, and coronary blood flow in humans are unknown. The aim of the present study is to describe these effects of intracoronary injections of Albunex and to compare them with the effects of a widely used angiographic contrast agent, iohexol, of which the effects on hemodynamics, left ventricular function, and coronary blood flow have been studied before.[4,5] Intracoronary injections of 5% human serum albumin were used as control.

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Methods

Patient Selection

Patients between the ages of 18 and 75 years undergoing cardiac catheterization for suspected coronary artery disease were eligible for the study. Exclusion criteria included clinical evidence of heart failure or unstable angina, recent myocardial infarction (<3 months), left main coronary artery disease, chest pain during cardiac catheterization, hypersensitivity to blood products, neurological disease, and potential for pregnancy. Eighteen patients (15 men and 3 women) fulfilled the inclusion criteria and were chosen for the study. Their mean age was 52.5±9.5 years. Nine of the patients had a myocardial infarction in their medical history, of which seven had a non–Q-wave myocardial infarction. All patients gave written informed consent. The study protocol was approved by the medical ethics committee of the University Hospital Rotterdam, and there were no complications directly related to the research procedure.

Cardiac Catheterization

Cardiac catheterization was performed by the percutaneous approach using both femoral arteries. The ECG from three limb leads was continuously monitored.

Coronary arteriography and left ventriculography were performed before the collection of data, with an interval of at least 15 minutes to allow for recovery from the effects of the angiographic contrast medium. Significant coronary artery disease was defined as the presence of >70% diameter stenosis.

A Judkins 7F or 8F coronary catheter (Schneider Inc) was used for the contrast injections necessary for this study. A Cordis (Cordis) 7F catheter-tip manometer then was introduced by the Seldinger technique using the femoral artery approach and advanced under continuous fluoroscopy across the aortic valve into the left ventricular cavity. In 13 of the patients, a 9F Baim catheter also was advanced by the femoral approach into the distal coronary sinus to study changes in coronary sinus flow by the thermodilution method. The position of the distal thermistor was determined by injection of 3 mL of iohexol at the beginning of the study. The main objective of this measurement was to detect changes in global myocardial blood flow due to injections of iohexol and Albunex into the left main coronary artery.

Intracoronary Injections

All intracoronary injections were performed using a Medrad pump injector (Medrad Inc, Pittsburgh, Pa) at a rate of 1 mL/s for a total of 8 mL into the left main coronary artery. A period of 3 minutes between subsequent injections was provided to allow for return to baseline. The following intracoronary injections were performed in order: 2 mL of 5% human serum albumin (HSA) followed immediately by 6 mL isotonic saline; 8 mL of iohexol (Omnipaque, Oslo, Norway); 1 mL of Albunex followed immediately by 7 mL of isotonic saline; and 2 mL of Albunex followed immediately by 6 mL of saline. Higher doses (3 mL and 4 mL) of Albunex were injected in five patients.

The dosages used for this study were based on standard volumes for coronary arteriography using iohexol. The dosages for Albunex in this study were based on our previous experience using sonicated albumin and our animal experience.[6]

Coronary sinus blood flow was determined using the continuous thermodilution method described earlier for our laboratory.[7] Coronary sinus blood flow was measured after the hemodynamic studies had been performed. As mentioned above, at least 3 minutes passed between injections. Coronary sinus blood flow measurements were available in 12 patients after 2 mL Albunex and in 11 patients after iohexol injections. In five patients, we were able to measure coronary sinus blood flow after 5% HSA injections.

Echocardiographic Examination

Simultaneous two-dimensional echocardiography was performed in the apical four-chamber view during intracoronary injections for analysis of wall motion and ejection fraction. A phased-array Hewlett-Packard Sonos 1000 (Hewlett-Packard Inc, Andover, Mass) echocardiographic system with a 3.75-MHz transducer was used. Recordings were begun 30 seconds before and continued for 2 minutes after each injection.

Data Analysis

Coronary arteriograms were analyzed quantitatively using an analysis system described earlier for our laboratory.[8] Ejection fraction was calculated from the volumes measured from the LV cineangiocardiogram in the right anterior oblique position and using Simpson's rule.[7]

The following hemodynamic parameters were calculated on a beat-to-beat basis from the Millar catheter using a computerized method described earlier[7,9]: left ventricular peak systolic and end-diastolic pressure (LVSP and LVEDP, respectively), rate of pressure rise and fall within the left ventricle (positive and negative LV dP/dt), and the time constant of relaxation (tau_1). The mean values of 10 cardiac cycles immediately before injection and of 10 cycles shortly after injection were calculated. The latter cycles were chosen at a point beginning between 20 and 30 beats after the onset of injection, selecting a time free from patient motion artifact, to coincide as closely as possible with the peak effect of the drugs. Finally, 10 cycles occurring approximately 60 seconds after injection were analyzed for late or persistent effects of the drugs.

Echocardiograms were evaluated visually by two independent observers, and regional left ventricular wall motion was graded as normokinetic, hypokinetic, akinetic, or dyskinetic. In addition, a computerized system using Simpson's rule and described in detail elsewhere[10] was used for quantitative analysis of ejection fractions. The cardiac cycles selected for echo analysis were the same as those selected for hemodynamic analysis.

Although after the 2-mL injections of Albunex attenuation of the images occurred for a short period, this period did not last longer than 3 to 4 beats and did not influence the ability to determine the wall motion analysis or the calculation of ejection fraction. This phenomenon of attenuation is caused by the high reflectivity of the echocontrast microspheres so that all ultrasound energy is reflected and no penetration of ultrasound signals is possible. The same order of cardiac cycles used for the hemodynamic parameters were used for the coronary sinus flow measurements.

Statistical Analysis

Values before injection of the agents (prevalues) and after injection (postvalues) were calculated and tabulated for each variable. This was done for each agent and each variable early and late after injection. The normalized difference was calculated for each variable as

$$\left(\frac{\text{postvalue}}{\text{prevalue}}-1\right)\times 100\%$$

The 95% confidence intervals of the mean differences for each of the variables were calculated. If the 95% confidence intervals did not include zero, then the mean change was considered to be statistically significant.

Results

Coronary arteriography revealed significant coronary artery disease in 11 patients. Six of the patients had three-vessel disease and another 5 had one- or two-vessel disease. Seven patients had coronary artery

Mean Percent Differences Between Preinjection and Postinjection for Each Variable After Injection of 5% HSA, Iohexol, and Albunex (2 mL)

	5% HSA		Iohexol		Albunex	
	Mean	**Interval**	**Mean**	**Interval**	**Mean**	**Interval**
Early (within 30 seconds)						
LVEDP	1.60	−0.71, 3.91	6.98*	2.75, 11.21	1.15	−0.66, 2.96
LVSP	−0.21	−1.70, 1.28	−3.62*	−5.72, −1.52	0.98	0.00, 1.91
+LVdP/dt	0.29	−1.38, 1.96	1.84	0.00, 3.67	−0.43	−1.98, 1.12
−LVdP/dt	−1.79	−3.11, 0.47	−9.11*	−3.63, −14.59	−2.41*	−4.3, −0.52
Tau_1	3.20	−0.76, 5.64	10.20*	2.16, 18.24	3.53*	1.48, 5.58
EF	−4.1	−1.1, 9.3	2.5	−11.6, 4.1	0.5	−2.4, 2.6
CSF	8*	1, 12	50*	30, 70	10*	2, 16
Late (beyond 60 seconds)						
LVEDP	1.71	−0.79, 4.21	5.93*	2.33, 9.52	2.58	−0.03, 5.18
LVSP	0.21	−1.70, 2.12	0.14	−0.89, 1.17	0.40	−0.06, 0.74
+LVdP/dt	0.36	−0.38, 1.10	1.42	−0.01, 2.85	0.54	−0.66, 1.74
−LVdP/dt	−1.60	−2.65, 0.55	−3.94	−8.71, 0.83	−1.83	−4.01, −0.35
Tau_1	1.49	−0.61, 3.59	1.73*	0.77, 4.23	1.80	−0.83, 4.43
EF	2.7	−2.6, 8.0	2.6	−2.1, 7.4	3.1	−5.0, 11.1
CSF	4	−2, 8	12.4*	4.7, 17.9	3.8	−2.2, 8.6

The calculated mean differences are tabulated with their 95% confidence intervals. For further explanation see text.

CSF indicates coronary sinus flow; EF, ejection fraction; HSA, human serum albumin; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; +LVdp/dt, first derivative of left ventricular pressure rise; −LVdp/dt, first derivative of left ventricular fall; and Tau_1, time constant of relaxation.

*Confidence intervals not containing zero reflect a statistically significant change.

disease with lesions of less severity. Ejection fraction was less than 50% in 4 patients. Only 3 patients had baseline left ventricular wall motion abnormalities by echocardiography.

Intracoronary injection of Albunex at any of the dosages used caused no complaints or clinically apparent side effects, nor were heart rate or ECG changes observed. Clinical assessment after 24 hours including history, physical examination, routine blood laboratory tests, and 12-lead ECG revealed no abnormalities that could be attributed to the research procedure.

LV Function

No injection of any agent caused any change in ejection fraction or wall motion (see Table).

Hemodynamic Parameters

At a dose of 1 mL, Albunex did not cause any changes in any of the parameters studied. At a dose of 2 mL, Albunex caused a statistically significant decrease in negative LV dP/dt and increase in tau_1, two parameters of isovolumic relaxation (Fig 1). Other hemodynamic parameters did not change, however. Beyond 60 seconds, all observed effects were no longer present (see Table). Intracoronary injection of 3 mL and 4 mL of Albunex, performed in 5 patients, induced similar changes in negative LV dP/dt and tau_1 but did not cause other changes.

Injection of 5% HSA exerted no measurable change in left ventricular hemodynamics. Iohexol caused an increase in left ventricular end diastolic pressure that persisted beyond 30 seconds as well as a transient decrease in left ventricular systolic pressure. It had a small negative effect on isovolumic relaxation parameters (negative LV dP/dt and tau_1) (see Fig 1 and Table). As can be seen from Fig 1, the effects of iohexol on isovolumic relaxation parameters were more extensive than for Albunex (2 mL).

Coronary Sinus Flow

Fig 2 shows the mean percent differences between prevalues and postvalues for mean coronary sinus blood

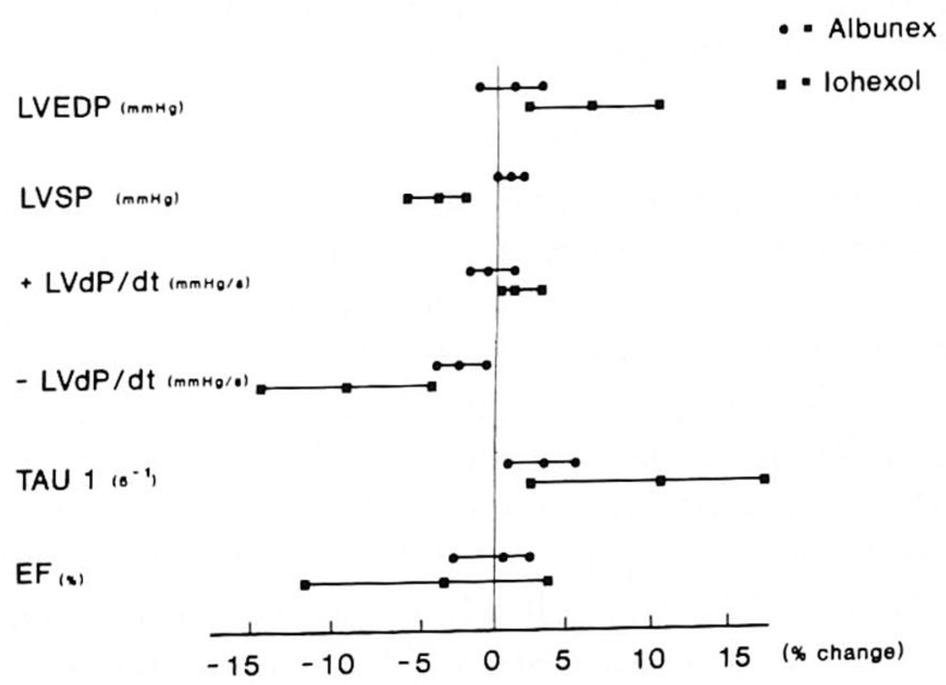

FIG 1. Percent differences between preinjection and postinjection values for iohexol and Albunex (2 mL). EF indicates ejection fraction; +LVdP/dt, first derivative of LVP rise; −LVdP/dt, first derivative of LVP fall; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; and tau_1, time constant of relaxation (also see Table).

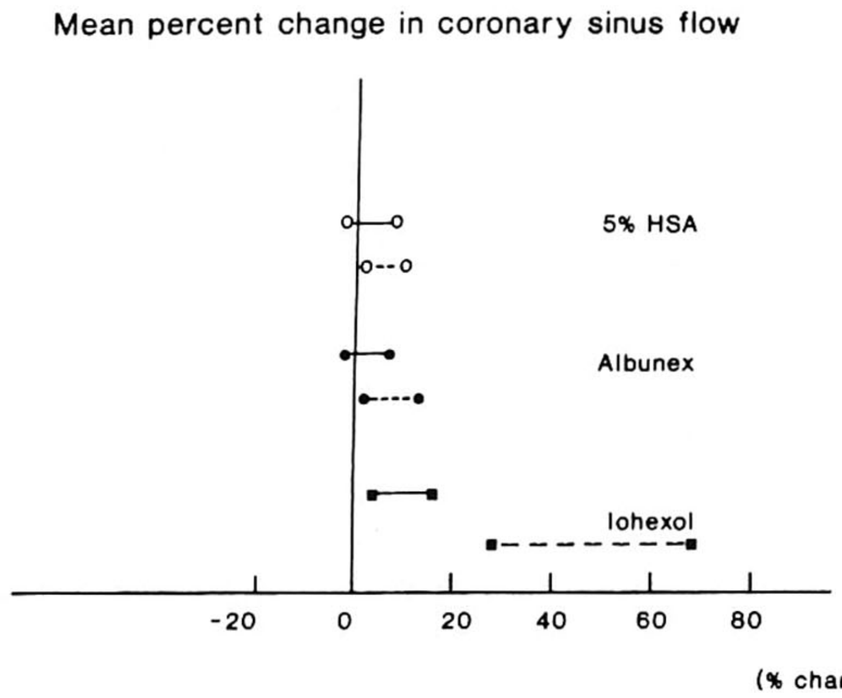

FIG 2. Mean percent change in coronary sinus flow after 5% HSA, iohexol, and Albunex. It can be seen that both 5% HSA and Albunex showed similar changes in coronary sinus flow (CSF). Iohexol showed more extensive increase in CSF, which lasted longer. Dotted lines represent the early values, whereas the uninterrupted lines represent the later values for each agent.

flow after injection of 2 mL of Albunex and iohexol, respectively. The changes in coronary sinus blood flow are significantly higher for iohexol than for Albunex. In addition, the hyperemic effects of iohexol persisted beyond 60 seconds, whereas the changes caused by Albunex had already returned to baseline values (see Table). It is also apparent that the changes in coronary sinus flow caused by Albunex and 5% HSA were similar (see Fig 2).

Patients With Severe Heart Disease

To examine the possibility that intracoronary Albunex has a greater effect in the presence of more severe disease,[11] a subgroup of patients with more extensive heart disease who had either an ejection fraction <50%, significant three-vessel disease, or severe left anterior descending artery stenosis >90%, were separately analyzed. In the 6 patients who met these criteria, Albunex showed no hemodynamic or functional effects, whereas iohexol caused a rise in left ventricular end diastolic pressure and isovolumic relaxation.

Discussion

The present first human study of intracoronary injections of Albunex shows that Albunex is safe and well tolerated if used in patients with stable coronary artery disease. A dose of 1 mL exerts no significant effects on left ventricular function, hemodynamics, or wall motion. At higher doses, small transient effects on isovolumic relaxation are found, namely, a decrease in the rate of pressure decay (negative LV dP/dt) and an increase in the time constant of relaxation (tau_1). In this respect, the effects of intracoronary Albunex in humans are similar to those found in animals, as reported by Keller et al.[3] This was also true for doses up to 4 mL.

Keller[3] found no effect of Albunex on epicardial coronary blood flow in animals and showed[12] that no changes in epicardial coronary blood flow were seen using different sizes of sonicated albumin microspheres produced in their own laboratory.

Contrary to the findings in animals, the present human study showed a small transient increase of mean coronary sinus blood flow by Albunex. The changes in coronary sinus flow caused by 5% HSA are in agreement with a previous study that has described the factors that modify the flow response to intracoronary injections.[13] Since the changes in coronary sinus flow by Albunex and 5% HSA are similar, it can be concluded that Albunex exerts no hyperemic effect.

The differences between the present study and the studies of Keller[3,12] can be explained by the fact that the last author defined the change in coronary blood flow after sonicated albumin as a percentage of the maximal hyperemic response after a short occlusion of the epicardial coronary artery. It is evident that we were not able to repeat this procedure in humans.

Earlier studies using angiographic contrast agents showed potential deleterious effects on patients with severe heart disease.[4,5] We performed a subgroup analysis on patients with depressed ejection fraction, critical left anterior coronary artery stenosis, and/or diffuse three-vessel disease to determine whether these effects were also present after Albunex injections. While only 6 patients in our study met these criteria, the effects of Albunex were similar for these patients and the other patients who did not meet these criteria. Since patients with severe heart disease are precisely the patients likely to benefit most from an investigation using myocardial contrast echo, this finding is encouraging. However, more studies are needed in patients with unstable hemodynamic status before definite conclusions can be drawn about the safety of intracoronary Albunex injections.

In comparison to Albunex, intracoronary injection of iohexol had greater hemodynamic effects, including an increase in left ventricular end diastolic pressure and a decrease in left ventricular systolic pressure, as well an even greater negative effect on isovolumic relaxation. The effects we observed parallel those reported elsewhere.[5,11,13] While most were small and transient, the effect on left ventricular end diastolic pressure and tau persisted beyond 60 seconds, indicating that in our group of patients, diastolic function was definitely influenced by this radiographic contrast agent.

Albunex for myocardial contrast echocardiography offers a significant advantage over echo contrast agents that are produced at the bedside because it contains microbubbles of a consistent size and concentration. Furthermore, Albunex can be be stored without deterioration for several months.[2] The agents that we have used in the past by sonication of radiographic contrast media have been shown to be safe and effective, but they suffer from instability and had a relatively wide variation in size and concentration.[6,15] For research in the field of contrast echocardiography and perfusion to progress, investigators will need to work with standardized agents under reproducible conditions. We therefore chose to compare Albunex, currently the only manufactured echocardiographic contrast agent available for intracoronary injections in humans, with iohexol, a commonly used radiographic contrast agent, and not to our "homemade" contrast agents, such as sonicated iopamidol.

Our experience with intravenous injection of Albunex[2] suggests that the doses used in the present intracoronary study (up to 4 mL) are extremely high.

Figuring output to the coronary arteries to be 5% to 10% of total cardiac output, direct intracoronary injection of 2 mL of Albunex delivers about 5 to 10 times what is normally achieved by way of an intravenous injection.[2] Such high doses of Albunex usually cause attenuation of the ultrasound signal, which limits one's ability to visualize the myocardium continuously. In this study, we chose to image during the 2-mL injection because this is the optimal dose with which to assess both its hemodynamic and functional effect. In future studies, however, smaller doses of Albunex, perhaps even less than 1 mL, should be used to obtain the maximum image quality.

Advantage of Myocardial Contrast Echocardiography

Recent studies[16,17] have shown that myocardial contrast echocardiography can provide prognostic information after acute myocardial infarction and thrombolysis. It also offers the possibility of studying viable myocardium perfused by collaterals at the time of cardiac catheterization.[17] In both of these studies, the sonicated radiographic agents that were used were produced by the authors themselves. Thus, the availability of a standardized, safe ultrasound contrast agent that has no hemodynamic effects and does not influence wall motion or ejection fraction is a significant advantage for use during cardiac catheterization.

We have shown for the first time that this standardized agent can be used in patients with extensive coronary artery disease, a specific population of interest to clinicians who might wish to determine the presence of viable muscle and collaterals.[17] The study of coronary flow reserve has recently been validated in human heart transplant patients using sonicated human serum albumin.[18]

The properties of Albunex, without hemodynamic effects or reactive hyperemia, make it an extremely valuable agent for coronary physiological studies[18] because quantitation of myocardial perfusion is now possible, contrary to earlier experience.[6]

Limitations of the Study

There were several limitations to this study. Because this was the first safety study of Albunex in humans, we selected patients with stable disease. Second, we allowed substantial time between the individual injections, which prolonged the catheterization considerably. Third, since two-dimensional echocardiography is a tomographic imaging technique, we were only able to perform one cross section at a time, and this may have influenced the assessment of wall motion abnormalities.

Conclusions

This study shows that Albunex, a new ultrasound contrast agent, is safe and well tolerated for intracoronary injections in humans with stable coronary artery disease. Because the size and concentration of microbubbles in Albunex are standardized, studies of myocardial perfusion using Albunex are reproducible. More importantly, this study demonstrates that intracoronary injection of Albunex exerts no important effects on left ventricular function, hemodynamics, or coronary blood flow. This makes it a superior agent to currently used agents such as "homemade" sonicated iohexol or albumin for studying coronary physiology. Albunex compares favorably with a widely used angiographic contrast agent in all aspects studied.

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