The influence of Albunex on the pulmonary circulation in patients with pulmonary hypertension or left heart failure

R. J. Zotz, S. Genth, V. Mitrovic*, A. Waaler†, R. Erbel and J. Meyer

II. Med Clinic, Johannes Gutenberg University Mainz, *Kerkhoff Clinic, Bad Nauheim, Germany, †Nycomed AS, Oslo, Norway

To determine the safety of the ultrasound contrast agent Albunex, its influence on right and left heart haemodynamics in patients with pulmonary artery hypertension or left heart failure was assessed after intravenous injection. Patients with a left ventricular ejection fraction smaller than 40% or a systolic pulmonary artery pressure greater than 40 mmHg received 0.08 and 0.22 ml kg⁻¹ Albunex and 10 ml albumin in random order during right heart catheterization and transthoracic echocardiography. Right atrial, systolic and diastolic pulmonary artery and capillary wedge pressures were measured at 3 min and 5 min and cardiac output at 5 min after the intravenous injection of Albunex and control. The mean differences of pre- and postinjection values and their confidence intervals were tabulated and significance was anticipated if the confidence interval did not include 0.

Significant changes to pre-injection values could be observed in diastolic pulmonary artery pressure 5 min after the injection of albumin and 0.08 ml kg⁻¹ Albunex, and in right atrial pressure 5 min after the injection of 0.22 ml kg⁻¹ Albunex only. Since intermediate opacification of the left ventricle was seen in only four patients with 0.22 ml kg⁻¹ Albunex, in the patients studied higher doses of Albunex and their safety need to be assessed.

(Eur Heart J 1996; 17: 302-307)

Key Words: Albunex, contrast echocardiography, pulmonary hypertension, heart failure.

Introduction

Myocardial contrast echocardiography is a newly developed method to image cardiac chambers and myocardial perfusion after intravenous injection of air containing microspheres. Albunex (Nycomed, Oslo) is one of the first agents with a defined bubble size and concentration. It should thus be superior to 'home made' solutions and is about to be approved in several European countries.

Release of vasoconstrictors by pulmonary intravascular macrophages underlies the excessive pulmonary hypertension and subsequent death in hoofed animals after the injection of Albunex[11]. Despite many observations in animals and in man that this agent is safe[2-6], it is conceivable that Albunex injection could lead to augmentation of pulmonary artery pressure in man. The aim of this study was thus to assess the influence of an intravenous injection of Albunex on pulmonary artery pressure in patients with pulmonary artery hypertension or left heart failure.


Correspondence: Rainer J. Zotz, MD, Heart Center, Leipzig University, Russenstr. 19, 04289 Leipzig, Germany

Methods

Patients and study protocol

This open-labelled, randomized phase II study which had been reviewed and accepted by the ethics committee of Freiburg, Germany, was based at two centres (Mainz and Bad Nauheim, Germany) and conducted in 18 consecutive patients in whom informed consent had been obtained. Patients had a systolic pulmonary artery pressure greater than 40 mmHg at an ultrasonic screening examination (seven patients, mean age 56 years, 6 males) or were in clinical heart failure with a left ventricular ejection fraction smaller than 40% during the echocardiographic screening examination (11 patients, mean age 55 years, eight males).

Systolic pulmonary artery pressure averaged 50.4 ± 14.3 mmHg in all patients before the study. Main diagnoses were arterial hypertension in seven patients, coronary artery disease in another seven and valvular disease in two patients. Two patients had experienced pulmonary embolism. Exclusion criteria for this study were as follows: age less than 18 and more than 70 years, pregnancy or inadequate contraception, or breast...
feeding women, blood product allergy, protein allergy, HIV- or hepatitis infection, sepsis, adult respiratory distress syndrome, medication with non-steroidal anti-inflammatory drugs, progressive organ dysfunction, mental incompetence, heart transplantation planned or performed, end-stage heart failure, unstable circulatory function, and concomitant investigational drugs within the last 60 days.

In the catheterization laboratory, baseline haemodynamic parameters i.e. pulmonary capillary wedge pressure, systolic and diastolic and mean pulmonary artery pressures as well as right atrial pressures were measured twice and averaged to obtain pre-injection values. During simultaneous transthoracic echocardiographic examination in the catheterization laboratory, patients received in random order 0.08 ml kg⁻¹ and 0.22 ml kg⁻¹ Albunex and 10 ml albumin through the right antecubital vein. During the injection, blood pressure and a six-channel ECG were continuously monitored. At 3 min after injection of every agent pulmonary capillary wedge pressure, systolic, diastolic and mean pulmonary artery and right atrial pressures were recorded and measured. At 5 min after every injection cardiac output, pulmonary capillary wedge pressure, systolic, diastolic and mean pulmonary artery and right atrial pressures were recorded and measured.

Clinical examination

Before, immediately after and 24 h after injection, a thorough clinical examination was performed. This included the measurement of systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation and temperature.

Two-dimensional echocardiography

The cross-sectional echocardiographic studies were performed with a Toshiba SSH 160A real-time phased array sector scanner. The radius of the 2.25 MHz transducer was 0.6 cm at the site of skin contact. An 84° sector could be visualized and a depth of 15 cm was selected. Thirty frames s⁻¹ were recorded on a video tape recorder (Panasonic). Real-time and slow motion replays were qualitatively evaluated on a standard television monitor. Echocardiographic images made from an apical transducer position were analysed. From the region of the apex of the heart, they transected the long axis, providing four chamber images of the left ventricle. Satisfactory echocardiograms were obtained in all 18 patients in the supine position. Contrast echocardiograms were semiquantitatively graded in two categories: no or faint opacification of the left ventricle and intermediate or full opacification.

Contrast agent

Albunex injection consists of air-filled microspheres of heat aggregated human albumin suspended in human albumin solution 5% (Pharmacopoeia Europea). The concentration was 200 million air-filled microspheres ml⁻¹ with diameters of 4–10 μm. The product is isotonic and has a pH of 6.7–7.3. The human albumin is prepared from plasma collected from healthy donors, who have been tested and found negative for hepatitis B surface antigen and antibodies to hepatitis C and HIV. In addition, the albumin solution used for production of Albunex injection has undergone virus inactivation by heat treatment at 60°C for 10 h.

Albunex injection is a sterile, pyrogen-free suspension for injection. The product in the non-resuspended form is a clear, light yellow to amber solution with a white layer on top. After resuspension an opaque, white to pale yellow, homogeneous suspension is obtained. Pre-clinical animal safety and toxicity studies had been conducted to predict the potential safety and efficacy of Albunex in man.

Catheterization

The right ventricle was catheterized retrogradely through a percutaneous puncture of the right femoral vein. The patients were fasting and not premedicated. Right heart pressures were recorded through a fluid-filled catheter (Baxter 7F) using a Statham P23 ID transducer, and cardiac output was determined by thermodilution.

Laboratory data

The following were determined before, 10 min and 24 h after the study: haemoglobin, haematocrit, numbers of erythrocytes, leukocytes, neutrophils, bands, segments, basophils, lymphocytes, monocytes, platelets and levels of serum calcium, sodium, potassium, total protein, creatinine, uric acid, urea, total cholesterol, glucose, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase and alkaline phosphatase.

Electrocardiography

Heart rate, P interval, PQ interval, QRS interval and QT interval were measured from the electrocardiograms taken before, 10 min and 24 h after the study.

Statistics

Values before injection of the agents (pre-values) and after injection (post-values) were calculated and tabulated for each variable. This was done for each agent and each variable early and late after injection. The normalized mean difference was calculated for each variable as

\[
\frac{(\text{post-value}) - (\text{pre-value})}{\text{pre-value}} \times 100\%
\]

Eur Heart J, Vol. 17, February 1996
Figure 1  Haemodynamics 3 min after injection (• = albumin 10 ml; ▲ = 0.08 ml Albunex; ▼ = 0.22 ml Albunex). Mean percent differences ± confidence intervals to pre-injection values 3 min after injection. PCW = pulmonary capillary wedge pressure, PAP sys = systolic pulmonary artery pressure, PAP dia = diastolic pulmonary artery pressure, PAP mean = mean pulmonary artery pressure, RA = right atrial pressure, see also table. Confidence intervals not containing zero reflect a statistically significant change. Albunex doses are given per kg body weight.

Figure 2  Haemodynamics 5 min after injection (• = albumin 10 ml; ▲ = 0.08 ml Albunex; ▼ = 0.22 ml Albunex). Mean percent differences ± confidence intervals to pre-injection values 5 min after injection. PCW = pulmonary capillary wedge pressure, PAP sys = systolic pulmonary artery pressure, PAP dia = diastolic pulmonary artery pressure, PAP mean = mean pulmonary artery pressure, RA = right atrial pressure, CO = cardiac output, see also table. Confidence intervals not containing zero reflect a statistically significant change. Albunex doses are given per kg body weight.

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

Clinical examination

The clinical examination revealed no new pathological cardiovascular findings. No changes in respiratory rate, systolic or diastolic blood pressure, heart rate, temperature or oxygen saturation could be observed.

Laboratory data

There were no significant changes in any of the laboratory parameters tested which could be attributed to any of the injections.

Haemodynamic results

At 3 min after injection (Table 1 and Fig. 1) no significant changes to pre-injection values could be observed, as regards all parameters measured at this time point i.e. pulmonary capillary wedge pressure, systolic and diastolic pulmonary artery pressure and right atrial pressure.

At 5 min after injection (Table 1 and Fig. 2): diastolic pulmonary artery pressure increased significantly following the injection of control and 0.08 ml·kg⁻¹ Albunex, while with the higher dose of Albunex (0.22 ml·kg⁻¹) no significant change was observed; right atrial pressure rose significantly after the injection of 0.22 ml·kg⁻¹ Albunex, while with control and 0.08 ml·kg⁻¹ Albunex right atrial pressure remained unchanged. No significant changes could be observed for pulmonary capillary wedge pressure measurements, systolic pulmonary artery pressure and cardiac output. The calculated pulmonary artery resistance showed no changes when post-injection values were compared to pre-injection values.

Electrocardiographic results

No significant changes were observed after any of the injections in any of the electrocardiograms compared to pre-injection electrocardiograms.

Echocardiographic efficacy

The higher dose of Albunex 0.22 ml·kg⁻¹, led to intermediate or full opacification of the left ventricle in four patients, while the lower dose of 0.08 ml·kg⁻¹ was able to opacify the left ventricle in one patient. The control injection of albumin did not cause any echo contrast in any heart chamber in any patient.

Discussion

Since the original observation of Gramiak and Shah(7) that the injection of indocyanine green causes opacification of blood flow, the need and possibility of...
visualizing intracavitary and parenchymal blood flow has been recognized and stimulated worldwide research to develop biocompatible and efficacious contrast agents. Albunex is one of the first agents which is expected to be approved in the near future. Its efficacy has been proven in numerous studies, however, with a variety of results and a high inter-observer variability. This variability could perhaps be attributed to different haemodynamic conditions in different patient groups. With another agent, SHU508A, good correlation could be demonstrated between pulmonary artery pressure and left heart opacification in patients with normal as well as with a wide range of abnormal pressures. Our study was designed to look at the safety of Albunex in patients with severely elevated pulmonary artery pressure and in patients with left heart failure. While in other studies up to one third of patients complained of changes in the senses of taste and touch, we did not observe this in our patients. No significant change in the haemodynamic parameters tested could be found 3 min after injection of control, and the lower and higher dose of Albunex. Five minutes after injection, diastolic

Table 1  Haemodynamic measurements

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Albumin 0.22 ml</th>
<th>0.08 ml</th>
<th>PAP sys (mmHg)</th>
<th>PAP dia (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre 3 min 5 min</td>
<td>pre 3 min 5 min</td>
<td>pre 3 min 5 min</td>
<td>pre 3 min 5 min</td>
</tr>
<tr>
<td>1</td>
<td>43 40 39 43 41 40 43 42 41 15 14 16 15 14 17 15 16 19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>47 54 55 47 57 58 47 56 54 22 24 24 22 28 27 22 25 27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45.5 40 43 45.5 35 42 45.5 41 40 19.5 21 25 19.5 20 22 19.5 25 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>45 46 48 45 46 47 45 48 44 21.5 24 25 21.5 25 24 21.5 23 21 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>53.5 57 57 53.5 54 55 53.5 50 54 27 28 33 27 30 26 27 23 29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>42 33 33 42 40 42 42 40 35 20 18 16 20 25 24 20 14 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50.5 46 49 50.5 49 46 50.5 48 49 12.5 17 17 12.5 11 17 12.5 13 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>19.5 20 17 19.5 25 24 19.5 19 19.5 9.5 10 9.5 11 10 9.5 11 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60 61 54 60 61 54 60 62 61 32 28 24 32 28 24 32 26 26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>63 63 64 63 65 62 63 67 66 48 56 55 48 52 51 48 56 54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>32 36 33 32 38 37 32 37 35 19 22 19 19 22 23 19 22 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>83 90 96 83 88 82 83 84 90 38 40 40 38 36 38 38 38 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>74 80 80 74 88 90 74 86 76 37 38 40 37 40 42 37 38 30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>38 46 44 38 41 42 38 40 44 15 20 20 15 18 18 15 19 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>55 56 56 55 54 54 55 54 54 35 34 35 34 35 34 35 36 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>56 60 56 56 60 60 56 60 64 34 34 36 34 36 34 34 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>41 41 41 41 42 41 41 42 41 24 24 24 24 24 22 24 23 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>56 43 39 56 44 35 56 39 48 29 17 27 29 25 11 29 27 26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>50.2 50.7 50.2 50.2 51.6 50.6 50.2 50.8 51.5 25.4 26.0 26.9 25.4 26.4 26.1 25.4 26.0 26.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>14.7 16.7 17.9 14.7 16.7 16.2 14.7 16.6 15.4 10.3 11.2 11.0 10.3 10.4 10.9 10.3 11.1 10.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eur Heart J, Vol. 17, February 1996
efficient in patients with elevated pulmonary artery pressure. This can be explained by the addition of volume and its osmotic effects, especially in patients with left heart failure which leads to increased right atrial and diastolic pulmonary artery pressures.

Since the two patients with a recent history of thromboembolism still showed left heart contrast as opposed to two patients of a different study with chronic thromboembolism, the interaction of the pulmonary endothelium with the air microspheres might need further investigation. In this study, no significant left heart opacification could be observed in the majority of patients using Albunex. This might have been caused by the high intravascular pressure in the pulmonary bed, but more probably reflects the longer passage of contrast particles through the pulmonary circulation arising from decreased cardiac output. This could also give rise to gas diffusion out of the microbubbles into the blood and thus explain lack of suitable surfaces for ultrasound scattering. This study suggests that Albunex does not augment pulmonary artery pressure, but is also not efficient in patients with elevated pulmonary artery pressures.

Albunex has been shown to be affected by aspiration through small needles resulting in microparticle disruption. A similar phenomenon may arise from passage of microparticles through a high pressure pulmonary system and account for the poorer efficacy in left ventricular opacification in this study.

The data from this study do not concur with the results of a study testing the efficacy of Albunex in 50 patients with normal pulmonary artery pressures, where good echo contrast in the left ventricle could be observed in two-thirds of patients. In this study, the authors could not find a direct correlation between the degree of pulmonary hypertension and left ventricular opacification, possibly a middle range of pulmonary artery pressures was excluded. It is conceivable that such a relationship could have been established if the entry criterion had permitted patients with normal, moderately elevated and severely elevated pulmonary artery pressures. In this study, the authors could significantly improve the performance of Albunex by use of mini valve spikes for aspiration and by elevation of the injection arm facilitating flow through the injection arm. It is possible that large amounts of microparticles could cause pulmonary vasoconstriction more rapidly than smaller amounts and our data concerning the safety of Albunex in man with pulmonary hypertension is valid only with respect to the dosage used.

The local concentration of air bubbles with the capillaries could cause coronary plugging or under-oxygenation, leading to serious haemodynamic consequences. A study looking at left ventricular myocardial contractility, haemodynamics and coronary sinus flow did not show any side effects. Since no significant clinical, electrocardiographic or laboratory data changes were observed during this study, Albunex can be regarded as a safe ultrasonic contrast agent. Further studies using intracoronary injections of Albunex with
respect to coronary perfusion and oxygenation are warranted.

Pulmonary intravascular macrophages are responsible for a dramatic increase in pulmonary artery pressure in hoofed animals[1]. This could at least in part be the case in man as well. However, our data do not confirm a consistent pulmonary artery pressure increase in our patients. In healthy man, intravascular pulmonary macrophages are not found but were found in lung specimens of patients with infectious disease[14]. In patients with adult respiratory distress syndrome[14,15] and in patients with various liver diseases[16]. Pulmonary hypertension has been observed in these patients after lipid containing infusions[16].

At the beginning of our study, 673 subjects (592 patients and 81 volunteers) had been tested in 17 studies. In healthy volunteers Albunex usually produced good left heart opacification while in patients results varied with the severity of the underlying heart disease. In a study in 50 patients looking at improved left ventricular endocardial border delineation[15], left heart opacification was obtained in 59% of all patients. The authors could not find any correlation between haemodynamic parameters and the degree of opacification. However, during systole, opacification was significantly less than during diastole.

It is conceivable that very high doses of Albunex are able to demonstrate myocardial perfusion after intravenous injection. However, this procedure does not seem to be efficacious, since most of the contrast particles are lost during transpulmonary passage and their remnants have to be removed by phagocytosis. It should thus be worthwhile to look at white blood cell fractions produced by a completely different procedure, i.e. rotational atherectomy[17].

**Conclusion**

This safety study did not show a significant alteration in right and left heart haemodynamics in the doses tested after intravenous injection of Albunex. However, in the patients in whom this agent was tested, i.e. in patients with pulmonary artery hypertension and left heart failure, in only a minority was intermediate opacification of the left ventricle observed. Since an increase of dosage might appear useful in these patients, safety data for higher doses are needed.

**References**


