Effects of Albunex Infusion on Left Ventricular Inflow Velocity in Dogs

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Abstract

This study examined the effects of Albunex® (sonicated 5% human serum albumin) infusion on left ventricular inflow velocity by Doppler echocardiography. Left ventricular pressure and left ventricular inflow velocity were recorded simultaneously under eight different conditions in dogs: 1) baseline 1 (control), 2) Albunex 0.2 ml/kg, 3) baseline 2, 4) Albunex 0.5 ml/kg, infusion of dextran 100 ml, 5) baseline 3, 6) Albunex 0.2 ml/kg, 7) baseline 4, and 8) Albunex 0.5 ml/kg.

In the normal state (no dextran), Albunex (0.2 ml/kg) caused no hemodynamic changes or inflow velocity changes. In contrast, infusion of Albunex (0.5 ml/kg) caused time velocity integrals of early filling to increase from the baseline (5.51 ± 1.13 vs 7.19 ± 1.14 cm, p < 0.05). After dextran infusion (100 ml), Albunex (0.2 ml/kg) caused peak early filling velocity to increase (62.4 ± 6.9 vs 67.3 ± 9.4 cm/sec, p < 0.05), and infusion of Albunex (0.5 ml/kg) also caused peak early filling velocity to increase from baseline (64.6 ± 8.5 vs 73.7 ± 14.5 cm/sec, p < 0.05). Infusion of Albunex (0.5 ml/kg) after dextran infusion caused increases in left ventricular pressure at the mitral valve opening (12.7 ± 3.1 vs 15.2 ± 3.3 mmHg, p < 0.05) and in left atrial driving force (13.5 ± 3.6 vs 16.7 ± 5.9 mmHg, p < 0.05).

Clinicians should be cautious about using Albunex at doses of greater than 0.2 ml/kg when evaluating the pressure gradient of the left ventricle in patients with elevated left ventricular diastolic pressure. In patients with normal hemodynamics, Albunex infusion at doses of less than 0.2 ml/kg apparently did not affect the velocity measurement.

Key Words
Contrast media (Albunex®), Doppler ultrasound, Hemodynamics

INTRODUCTION

Contrast echocardiography was introduced clinically by Gramiak et al., and has been applied to the detection of intracardiac shunt and delineation of the left ventricular cavity. Since then, various echo contrast agents have been tried in vitro. Albunex® (sonicated 5% human serum albumin, Molecular Biosystems, USA) is a Doppler contrast agent for left ventricular flow that can be injected via a peripheral vein. Peripheral injection improves the assessment of right ventricular systolic pressure and the pressure gradient of aortic stenosis.

Peripheral injection of Albunex 0.5 ml/kg causes a
transient increase in left ventricular end-diastolic pressure\textsuperscript{10}. However, there have been no studies of the effects of infused Albunex on left ventricular inflow velocity in normal animals or in those with congestive heart failure. Knowledge of any effects of Albunex on left ventricular inflow velocity is essential if this substance is to be used in the measurement of left ventricular flow clinically.

This study examined the effects of infused Albunex on left ventricular inflow velocity and left ventricular hemodynamics in dogs, in the normal and elevated left ventricular diastolic pressure states induced by the infusion of dextran.

METHODS

In five dogs (5–15 kg of both sexes), general anesthesia was induced by intravenous infusion of fentanyl, midazolam and becnooniumbromide, and maintained throughout the experiment. Respiration was controlled by a ventilator (Model AR 300, Acoma, Tokyo, Japan).

The effects of infused Albunex on left ventricular inflow velocity and hemodynamics were studied by Doppler echocardiography (Aloka SSD660, 2.7 MHz transducer, Tokyo, Japan) and a catheter tip manometer (Model SPR249, Millar Instrument Co., Houston, TX, USA), respectively.

Study protocol

Left ventricular pressure and left ventricular inflow velocity were recorded simultaneously under the following eight conditions:

1) Baseline 1, 2) Albunex 0.2 ml/kg, 3) baseline 2, 4) Albunex 0.5 ml/kg.

Infusion of dextran 100 ml, 5) baseline 3, 6) Albunex 0.2 ml/kg, 7) baseline 4, 8) Albunex 0.5 ml/kg.

Sonicated albumin was prepared according to the manufacturer's instructions. The solution in a 3.5 ml vial was blended to a uniform concentration by a gentle, manual rotation of the horizontal vial for a minimum of 3 min. After venting the vial with an 18-gauge needle, the agent was slowly drawn into a syringe through another 18-gauge needle.

A series of two contrast agent injections prepared as described above were administered to each dog through the peripheral veins. Injections were separated by 5-min intervals.

The contrast enhancement of the inflow velocity continued for 30 to 40 beats. Albunex of 0.5 ml/kg infusion tended to enhance for a longer duration than 0.2 ml/kg infusion. Dextran (100 ml bolus) was infused through the peripheral vein, and was repeated until the left ventricular end-diastolic pressure increased by at least 5 mmHg from the baseline.

Data from three consecutive heart beats around the maximum enhancement point were analyzed as follows and averaged.

Data acquisition and analysis

Left ventricular pressure

A catheter tip manometer was introduced through the left carotid artery into the left ventricle. The left ventricular pressure was recorded simultaneously with left ventricular inflow velocity under the eight conditions described in the protocol (paper speed of 100 mm/sec) (Fig. 1). The left ventricular pressure tracings were analyzed using a personal computer (Mitsubishi, MP28SL) and a digitizing tablet (Summa sketch, 5 msec digitizing intervals) as follows:

A) Left ventricular pressure at mitral valve opening (PMVO) (more precisely left ventricular pressure at the beginning of left ventricular inflow was measured)

B) Left ventricular diastolic minimum pressure (P_{min})

C) Left atrial driving force (PMVO-P_{min})

Time constant (T) of left ventricular pressure decay (Weiss), left ventricular peak systolic pressure, left ventricular end-diastolic pressure, and heart rate were also measured.

Left ventricular inflow velocity

Left ventricular inflow velocity was recorded from the apical four-chamber view by pulsed Doppler echocardiography on strip charts (paper speed
of 100 mm/sec). The sampling volume was placed at the mitral annular level (Fig. 1). Once the best Doppler flow gain setting was achieved, the setting was kept the same throughout the series of studies. The obtained left ventricular inflow velocity recordings were analyzed using a personal computer (Mitsubishi, MP286L) and a digitizing tablet (Summa sketch, 5 msec digitizing intervals) as follows:

D) Diastolic maximum early filling velocity (E velocity)
E) Diastolic early filling velocity-time integral (E area)
F) Diastolic maximum atrial filling velocity (A velocity)
G) Diastolic atrial filling velocity-time integral (A area)
H) A velocity/E velocity
I) E area/(E + A) area

In one dog, the data obtained in two series were compared at baseline and after Albunex (0.2 ml/kg) infusion. The average difference of the measurements between the first and the second series of E velocity, A velocity, E area, A area, Psv, PMVO, and Tau was 4.4 ± 1.3%. The reproducibility, therefore, was acceptable. Thus, only the recordings of the first series were used.

**Statistical methods**

Data are expressed as mean ± standard deviation. Comparisons were made using Student's paired t-test. The difference was considered statistically significant when \( p < 0.05 \).

**RESULTS**

**Effects of Albunex on left ventricular pressure and left ventricular inflow velocity**

**Control state**

Infusion of Albunex 0.2 ml/kg: As shown in Table 1, infusion of Albunex (0.2 ml/kg) caused no change in T, PMVO, Psv, and PMVO-Psv.

As shown in Table 2, indexes of early filling velocity (E) and of atrial filling velocity (A) were also not affected. E area and A area did not increase significantly. Pattern of left ventricular inflow A velocity/E velocity, and E area/(E + A) area were also unaffected.
Table 1  Effects of Albunex infusion on hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>PMVO (mmHg)</th>
<th>Pmn (mmHg)</th>
<th>PMVO−Pmn (mmHg)</th>
<th>T (msec)</th>
<th>LVP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.4±3.6</td>
<td>4.3±2.2</td>
<td>9.1±3.4</td>
<td>29.1±4.2</td>
<td>128.4±27.0</td>
<td>13.2±5.4</td>
<td>91±25</td>
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<tr>
<td>SA0.2</td>
<td>13.1±1.8</td>
<td>4.6±1.6</td>
<td>8.5±2.2</td>
<td>30.4±4.5</td>
<td>133.6±21.4</td>
<td>10.4±1.4</td>
<td>90±24</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.7±3.1</td>
<td>4.7±1.6</td>
<td>8.1±2.4</td>
<td>31.9±3.9</td>
<td>131.2±25.6</td>
<td>11.0±0.8</td>
<td>92±24</td>
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<tr>
<td>SA0.5</td>
<td>15.2±3.3*</td>
<td>5.3±1.6</td>
<td>9.8±3.3</td>
<td>33.4±3.5</td>
<td>133.2±24.4</td>
<td>13.6±1.6*</td>
<td>85±23</td>
</tr>
<tr>
<td>Baseline</td>
<td>23.3±3.0</td>
<td>10.5±1.8</td>
<td>12.8±3.7</td>
<td>35.8±4.2</td>
<td>140.4±16.5</td>
<td>21.8±6.7</td>
<td>106±11</td>
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<tr>
<td>SA0.2</td>
<td>24.9±4.5</td>
<td>10.4±1.9</td>
<td>14.5±5.1</td>
<td>37.6±4.8</td>
<td>143.6±15.5</td>
<td>19.2±4.2</td>
<td>106±11</td>
</tr>
<tr>
<td>Baseline</td>
<td>23.8±3.3</td>
<td>10.3±1.8</td>
<td>13.5±3.6</td>
<td>38.7±5.9</td>
<td>140.4±18.8</td>
<td>18.3±2.6</td>
<td>105±17</td>
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<tr>
<td>SA0.5</td>
<td>27.1±6.0*</td>
<td>10.4±2.7</td>
<td>16.7±5.9*</td>
<td>38.8±3.8</td>
<td>141.8±18.1</td>
<td>21.9±4.2*</td>
<td>109±10</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline.
LVP = peak systolic left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; HR = heart rate; SA0.2 = infusion of Albunex 0.2 ml/kg; SA0.5 = infusion of Albunex 0.5 ml/kg.

Table 2  Effects of Albunex infusion on left ventricular inflow velocity

<table>
<thead>
<tr>
<th></th>
<th>A velocity (cm/sec)</th>
<th>E velocity (cm/sec)</th>
<th>A/E</th>
<th>A area (cm)</th>
<th>E area (cm)</th>
<th>E area/(E+A) area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>40.3±14.4</td>
<td>55.4±6.2</td>
<td>0.71±0.21</td>
<td>3.09±1.96</td>
<td>5.66±1.01</td>
<td>6.68±0.13</td>
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<td>SA0.2</td>
<td>41.3±13.9</td>
<td>58.3±3.5</td>
<td>0.70±0.21</td>
<td>3.43±1.75</td>
<td>6.53±0.60</td>
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<td>Baseline</td>
<td>41.9±16.0</td>
<td>56.0±4.7</td>
<td>0.74±0.27</td>
<td>2.92±1.42</td>
<td>5.51±1.13</td>
<td>0.66±0.13</td>
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<td>SA0.5</td>
<td>44.8±13.8</td>
<td>65.9±9.2</td>
<td>0.68±0.20</td>
<td>3.60±1.17*</td>
<td>7.19±1.14*</td>
<td>0.67±0.08</td>
</tr>
<tr>
<td>Baseline</td>
<td>56.5±4.2</td>
<td>62.4±6.9</td>
<td>0.92±0.14</td>
<td>3.84±0.25</td>
<td>5.52±1.54</td>
<td>0.61±0.05</td>
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<td>SA0.2</td>
<td>57.8±2.8</td>
<td>67.3±9.4*</td>
<td>0.87±0.13</td>
<td>4.38±0.73</td>
<td>6.42±1.61</td>
<td>0.59±0.02</td>
</tr>
<tr>
<td>Baseline</td>
<td>55.6±3.3</td>
<td>64.6±8.5</td>
<td>0.87±0.15</td>
<td>4.00±0.66</td>
<td>6.05±1.32</td>
<td>0.60±0.06</td>
</tr>
<tr>
<td>SA0.5</td>
<td>58.7±3.5</td>
<td>73.7±14.5*</td>
<td>0.83±0.17</td>
<td>4.42±0.65</td>
<td>7.11±1.60*</td>
<td>0.62±0.05</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline.
Abbreviations as in Table 1.

Infusion of Albunex 0.5 ml/kg: T was not changed. PMVO increased significantly (12.7±3.1 vs 15.2±3.3 mmHg, p<0.05), but Pmn and PMVO-Pmn were not increased (Table 1).

E velocity, A velocity and A/E ratio were not changed significantly. However, E area increased from 5.51±1.13 to 7.19±1.14 cm and A area increased from 2.92±1.42 to 3.60±1.17 cm. E area/(E+A) area showed no change (Table 2).

Albunex (0.2 ml/kg) and dextran infusion: As shown in Table 1, T (35.8±4.2 vs 37.6±4.8 msec), PMVO (23.3±3.0 vs 24.9±4.5 mmHg), Pmn (10.5±1.8 vs 10.4±1.9 mmHg), and PMVO-Pmn (12.8±3.7 vs 14.5±5.1 mmHg) tended to increase but the changes were not significant.

E velocity (62.4±6.9 vs 67.3±9.4 cm/sec, p<0.05) increased significantly. A velocity (56.5±4.2 vs 57.8±2.8 cm/sec), E area (5.52±1.54 vs 6.42±1.61 cm), and A area (3.84±0.25 vs 4.38±0.73 cm) tended to increase but the changes were not significant. A/E and E area/(E+A) area were also not changed significantly (Table 2).

Albunex (0.5 ml/kg) and dextran infusion: T was not significantly changed (38.7±5.9 vs 38.8±3.8 msec). PMVO increased significantly (23.8±3.3 vs 27.1±6.0 mmHg, p<0.05). Pmn was not changed. PMVO-Pmn increased significantly (13.5±3.6 vs 16.7±5.9 mmHg, p<0.05; Fig. 2).

E velocity increased significantly (64.6±8.5 vs 73.7±14.5 cm/sec, p<0.05), but A velocity was not changed. A/E was not changed (Fig. 3). E area increased significantly (6.05±1.32 vs 7.11±1.60 cm, p<0.05) and A area (4.00±0.66 vs 4.42±0.65 cm, NS) tended to increase but the changes were not significant. E area/(E+A) area was not changed significantly (Fig. 4).

DISCUSSION

Albunex was developed as a contrast agent with molecules sufficiently small to pass through the pulmonary capillaries. It has been used to improve the delineation of a border, myocardial perfu-

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sion\textsuperscript{14-19}, better estimation of pressure\textsuperscript{9,10}, and blood flowmetry\textsuperscript{20,21} and for evaluation of flow dynamics\textsuperscript{22}. The effects of various contrast agents, including Albunex, on hemodynamics and left ventricular contractility have been reported\textsuperscript{11,23}. In addition to studies of the effects of Albunex injected peripherally, the effects of intracoronary Albunex on left ventricular hemodynamics and function have been studied\textsuperscript{24}. Effects of left ventricular pressure on sonicated albumin microbubbles were also examined\textsuperscript{25}. Pressure assessment non-invasively by Doppler echocardiography is clinically useful and important, and Albunex may affect that assessment. However, the effects of Albunex on flow velocity itself in relation to hemodynamics used have not been studied. Accordingly, we assessed its effects on mitral inflow velocity in dogs in a normal state and in dogs with increased diastolic pressure, as in congestive heart failure.

Fig. 2 Hemodynamic changes after infusion of Albunex (0.5 ml/kg) at baseline (left) and after infusion of dextran (100 ml) (right)
Black bar (CTR = control) shows the baseline and shaded bar after dextran infusion. PMVO increased significantly after infusion of Albunex (0.5 ml/kg) both at baseline and after dextran infusion. PMVO-P\textsubscript{min} increased significantly only after dextran infusion. Abbreviation as in Table 1.

Effects of Albunex infusion on left ventricular inflow velocity in relation to hemodynamic changes

Normal state
Infusion of Albunex (0.2 ml/kg) did not alter any hemodynamic parameters, but 0.5 ml/kg caused a significant increase in PMVO. Albunex (0.5 ml/kg) caused E velocity to increase significantly. Infusion of Albunex tended to increase A velocity, but not to a statistically significant extent. These data suggest that the infusion of Albunex (0.5 ml/kg) would affect pressure evaluation by Doppler echocardiography and that infusion of Albunex (<0.2 ml/kg) appeared not to affect pressure measurement in the normal state.

Elevated left ventricular diastolic pressure state
Hemodynamically, both PMVO and PMVO-P\textsubscript{min} were elevated by an infusion of Albunex 0.5 ml/kg, but not 0.2 ml/kg. As a result, E velocity, E area, and A area were also increased significantly by an infusion of Albunex (0.5 ml/kg). Again these data
suggest that infusion of Albunex (0.5 ml/kg) would affect the evaluation of pressure by Doppler echocardiography. Infusion of Albunex (0.2 ml/kg) caused an increase in E velocity, although this dose did not affect the left ventricular pressure significantly. The reason may be that the left ventricular inflow velocity is more sensitive to left ventricular volume changes than the left ventricular pressure.

The effects of Albunex on pressure have been ascribed to the volume effects of albumin. Matsuda et al. observed that infusion of Albunex via a pulmonary vein did not raise the peak left ventricular pressure more than did normal albumin, but an identical infusion via a pulmonary artery did. Those authors suggested that some other mechanism, such as release of a vasoconstrictor mediator, may be induced by the passage of Albunex through the pulmonary capillary beds.

In the normal state, the effect of Albunex on left ventricular inflow was first evident in the time velocity integrals (E area), however in the elevated left ventricular diastolic pressure state, that effect was first evident in the peak filling velocity (E). This difference may be due to left ventricular diastolic stiffness. In the normal state, with the left ventricle more compliant, the volume effects of Albunex appeared in time-velocity changes. However, in the elevated left ventricular diastolic pressure state, with the left ventricle stiffer, the volume effects of Albunex may be evident in peak flow velocity changes.

**Comparison of Albunex effects on hemodynamics with other studies**

Albunex has been shown to be essentially safe for use in studies of left ventricular function. Matsuda et al. reported that Albunex (0.5 ml/kg) caused elevation of left ventricular peak systolic pressure and end-diastolic pressure. When given by intracoronary injection, however, Albunex (1 ml/kg) did not affect any pressure. In the present study, left ventricular peak systolic pressure tended to increase. Left ventricular end-diastolic pressure.
increased significantly [Albunex (0.5 ml/kg) in both the normal state and after dextran infusion]. Our results almost conformed to those of Matsuda et al.

**Clinical implications**

A dosage of Albunex (0.2 ml/kg) is often necessary for contrast enhancement of the left ventricle. An Albunex dosage of more than 0.2 ml/kg is not preferable clinically according to the manufacturer’s recommendation. As shown in this study, the dosage of Albunex (0.2 ml/kg) generally does not affect velocity measurement in patients with normal hemodynamics. However, clinicians should be cautious when using Doppler echocardiography to evaluate the pressure gradient in patients with aortic stenosis, specifically patients with elevated left ventricular diastolic pressure using Albunex infusion (0.2 ml/kg). Infusion of Albunex affects left ventricular diastolic pressure to some degree, and through the Frank-Sterling mechanism the left ventricular systolic pressure may be elevated to some extent. This effect may cause the pressure gradient between the aortic pressure and left ventricular pressure to increase at systole.

In evaluating the right ventricular pressure by Doppler echocardiography, a low dose of Albunex is usually used, so Albunex may not affect the flow velocity and right ventricular pressure measurement.

**Limitations**

Although the gain setting may affect the measurement of velocity, we measured the modal velocity (darkest line method)\(^{20}\), not the leading edge, so we believe the effects of gain setting, if any, were minimal. We also tried to keep the gain setting constantly at the same level.

Our elevated left ventricular diastolic pressure state does not duplicate real heart failure, so a true heart failure model experiment would be preferable.
We did not compare the effects of Albunex on the hemodynamics to those of albumin solution. Thus these results may not be a unique reaction of Albunex on the hemodynamics. Matsuda et al.\(^1\) compared the effects of Albunex and non-sonicated albumin on hemodynamics, and found the effects of Albunex on left ventricular peak pressure were more evident than those of non-sonicated albumin. To find the sole feature of the effects of Albunex on hemodynamics and inflow velocity, further studies might be necessary.

**CONCLUSION**

Clinicians should be cautious about using Albunex at a dose greater than 0.2 ml/kg when evaluating the pressure gradient of the left ventricle in patients with elevated left ventricular diastolic pressure. In patients with normal hemodynamics, Albunex infusion at a dose less than 0.2 ml/kg appeared not to affect the velocity measurement.

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**要約**

アルブネックス静注の左室流入血流速計測に及ぼす効果：

イヌでの実験的検討

富田 政明 和田 久泰 田中 隆平
三輪 陽子 加川 惠作 野田 俊之
西垣 和彦 平川 千里 藤原 久義

左室流入血流速計測に対するアルブネックス静注の効果をドップラー心エコー図法の用いて検討した。イヌを使って以下の8条件下で左室圧と左室流入流速を同時記録した。

1) ベースライン (対照), 2) アルブネックス 0.2 ml/kg, 3) ベースライン, 4) アルブネックス 0.5 ml/kg, dextran 100 ml 静注後, 5) ベースライン, 6) アルブネックス 0.2 ml/kg, 7) ベースライン, 8) アルブネックス 0.5 ml/kg。

正常心においては、アルブネックス 0.2 ml/kg 静注では血行動態や流入血流速には変化を与えなかった。アルブネックス 0.5 ml/kg の静注では、左室急速流入血流面積を増加させた (5.51±1.13 vs 7.19±1.14 cm\(^2\), p<0.05)。Dextran 100 ml 静注後では、アルブネックス 0.2 ml/kg の用量で最大左室急速流入血流速度が増大した (62.4±6.9 vs 67.3±9.4 cm/sec, p<0.05)。Dextran 100 ml 静注後は、アルブネックス 0.5 ml/kg の用量では最大左室急速流入血流速度が増大し (64.6±8.5 vs 73.7±14.5 cm/sec, p<0.05)、僧帽弁開閉時左室圧 (12.7±3.1 vs 15.2±3.3 mmHg, p<0.05) と左房左室圧差 (13.5±3.6 vs 16.7±5.9 mmHg, p<0.05) も増大した。

拡張期左室圧が上昇している状況下では、アルブネックス 0.2 ml/kg 以上の静注では左室流入血流速計測に影響を与えることが推測された。正常心においては、アルブネックス 0.2 ml/kg 未満の用量では左室流入血流速計測に影響がないことが示唆された。

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**References**


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