J Cardiol 1997; 29: 283–291

Effects of Albunex Infusion on Left Ventricular Inflow Velocity in Dogs

Masaaki TOMITA, MD*
Hisayasu WADA, MD
Ryuhei TANAKA, MD
Yoko MIWA, MD
Kensaku KAGAWA, MD
Toshiyuki NODA, MD
Kazuhiko NISHIGAKI, MD
Senri HIRAKAWA, MD
Hisayoshi FUJIWARA, MD, FJCC

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 m*l*/kg, 3) baseline 2, 4) Albunex 0.5 m*l*/kg, infusion of dextran 100 m*l*, 5) baseline 3, 6) Albunex 0.2 m*l*/kg, 7) baseline 4, and 8) Albunex 0.5 m*l*/kg.

In the normal state (no dextran), Albunex (0.2 m*l*/kg) caused no hemodynamic changes or inflow velocity changes. In contrast, infusion of Albunex (0.5 m*l*/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 m*l*), Albunex (0.2 m*l*/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 m*l*/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 m*l*/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 m*l*/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 m*l*/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.*[1], and has been applied to the detection of intracardiac shunt[2], and delineation of the left ventricular cavity[3]. Since then, various echo contrast agents have been tried *in vitro*[4]. 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[5–8]. Peripheral injection improves the assessment of right ventricular systolic pressure[9] and the pressure gradient of aortic stenosis[10]. Peripheral injection of Albunex 0.5 m*l*/kg causes a

岐阜大学医学部 第二内科：〒500 岐阜市司町 40; *(現) 平田循環器病院 循環器科：〒511 三重県桑名市中央町 1–32
The Second Department of Internal Medicine, Gifu University School of Medicine, Gifu; *(present) Cardiovascular Division, Hirata Hospital, Mie
Address for reprints : TOMITA M, MD, Cardiovascular Division, Hirata Hospital, Chuo-cho, 1–32, Kuwana, Mie 511
Manuscript received May 27, 1996; revised January 23, 1997; accepted February 19, 1997

Selected abbreviations and acronyms

A=atrial filling velocity
A area=diastolic atrial filling velocity-time integral
A velocity=diastolic maximum atrial filling velocity
E=early filling velocity
E area=diastolic early filling velocity-time integral
E velocity=diastolic maximum early filling velocity
P_{min}=left ventricular diastolic minimum pressure
PMVO=left ventricular pressure at mitral valve opening
PMVO-P_{min}=left atrial driving force
T=time constant

transient increase in left ventricular end-diastolic pressure[11]. 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 becroniumbromide, 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 m*l*/kg, 3) baseline 2, 4) Albunex 0.5 m*l*/kg.

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

Sonicated albumin was prepared according to the manufacturer's instructions. The solution in a 3.5 m*l* 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 m*l*/kg infusion tended to enhance for a longer duration than 0.2 m*l*/kg infusion. Dextran (100 m*l* 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, MP286L) 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

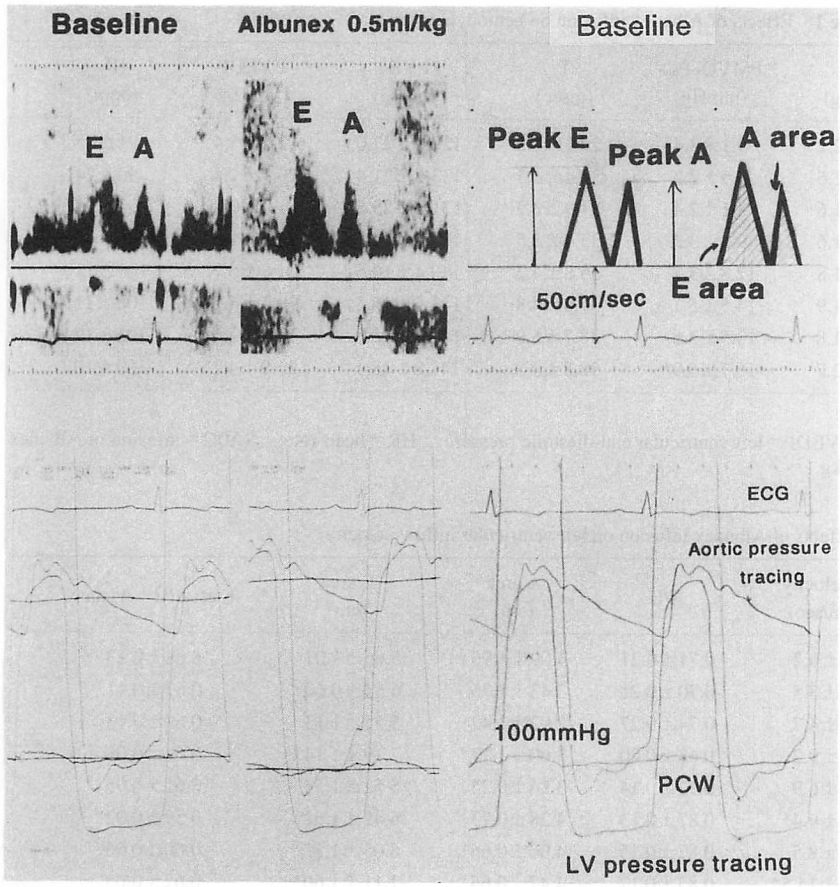

Fig. 1 Left ventricular inflow and left ventricular pressure

Left: Records in a representative case (baseline and after infusion of Albunex 0.5 ml/kg).
Right: Schema of left ventricular inflow (*upper*) and schema of left ventricular pressure (*lower*).
ECG = electrocardiogram; LV = left ventricular; PCW = pulmonary capillary wedge pressure.

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, P_{min}, 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, P_{min}, and PMVO-P_{min}.

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

	PMVO (mmHg)	P_{min} (mmHg)	PMVO–P_{min} (mmHg)	T (msec)	LVP (mmHg)	LVEDP (mmHg)	HR (bpm)
Baseline 1	13.4±3.6	4.3±2.2	9.1±3.4	29.1±4.2	128.4±27.0	13.2±5.4	91±25
SA0.2	13.1±1.8	4.6±1.6	8.5±2.2	30.4±4.5	133.6±21.4	10.4±1.4	90±24
Baseline 2	12.7±3.1	4.7±1.6	8.1±2.4	31.9±3.9	131.2±25.6	11.0±0.8	92±24
SA0.5	15.2±3.3*	5.3±1.6	9.8±3.3	33.4±3.5	133.2±24.4	13.6±1.6*	85±23
Baseline 3	23.3±3.0	10.5±1.8	12.8±3.7	35.8±4.2	140.4±16.5	21.8±6.7	106±11
SA0.2	24.9±4.5	10.4±1.9	14.5±5.1	37.6±4.8	143.6±15.5	19.2±4.2	106±11
Baseline 4	23.8±3.3	10.3±1.8	13.5±3.6	38.7±5.9	140.4±18.8	18.3±2.6	105±17
SA0.5	27.1±6.0*	10.4±2.7	16.7±5.9*	38.8±3.8	141.8±18.1	21.9±4.2*	109±10

*$p<0.05$ 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

	A velocity (cm/sec)	E velocity (cm/sec)	A/E	A area (cm)	E area (cm)	E area/(E+A) area
Baseline 1	40.3±14.4	55.4±6.2	0.71±0.21	3.09±1.96	5.66±1.01	6.68±0.13
SA0.2	41.3±13.9	58.3±3.5	0.70±0.21	3.43±1.75	6.53±0.60	0.67±0.11
Baseline 2	41.9±16.0	56.0±4.7	0.74±0.27	2.92±1.42	5.51±1.13	0.66±0.13
SA0.5	44.8±13.8	65.9±9.2	0.68±0.20	3.60±1.17*	7.19±1.14*	0.67±0.08
Baseline 3	56.5±4.2	62.4±6.9	0.92±0.14	3.84±0.25	5.52±1.54	0.61±0.05
SA0.2	57.8±2.8	67.3±9.4*	0.87±0.13	4.38±0.73	6.42±1.61	0.59±0.02
Baseline 4	55.6±3.3	64.6±8.5	0.87±0.15	4.00±0.66	6.05±1.32	0.60±0.06
SA0.5	58.7±3.5	73.7±14.5*	0.83±0.17	4.42±0.65	7.11±1.60*	0.62±0.05

*$p<0.05$ 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 P_{min} and PMVO-P_{min} 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), P_{min} (10.5±1.8 vs 10.4±1.9 mmHg), and PMVO-P_{min} (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, $p<0.05$). P_{min} was not changed. PMVO-P_{min} 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[5–8]. It has been used to improve the delineation of a border[12,13], myocardial perfu-

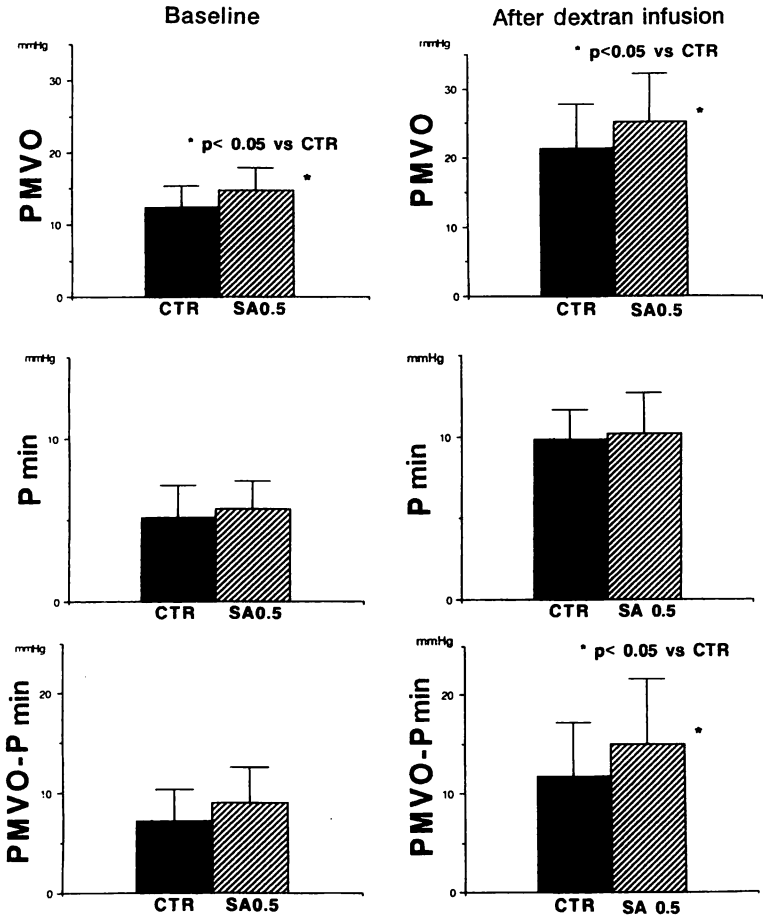

Fig. 2 Hemodynamic changes after infusion of Albunex (0.5 m*l*/kg) at baseline (*left*) and after infusion of dextran (100 m*l*) (*right*)

Black bar (CTR=control) shows the baseline and shaded bar after dextran infusion. PMVO increased significantly after infusion of Albunex (0.5 m*l*/kg) both at baseline and after dextran infusion. PMVO-P_{min} increased significantly only after dextran infusion.
Abbreviation as in Table 1.

sion[14–19], better estimation of pressure[9,10], and blood flowmetry[20,21] and for evaluation of flow dynamics[22]. The effects of various contrast agents, including Albunex, on hemodynamics and left ventricular contractility have been reported[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[24]. Effects of left ventricular pressure on sonicated albumin microbubbles were also examined[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.

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

Normal state

Infusion of Albunex (0.2 m*l*/kg) did not alter any hemodynamic parameters, but 0.5 m*l*/kg caused a significant increase in PMVO. Albunex (0.5 m*l*/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 m*l*/kg) would affect pressure evaluation by Doppler echocardiography and that infusion of Albunex (<0.2 m*l*/kg) appeared not to affect pressure measurement in the normal state.

Elevated left ventricular diastolic pressure state

Hemodynamically, both PMVO and PMVO-P_{min} were elevated by an infusion of Albunex 0.5 m*l*/kg, but not 0.2 m*l*/kg. As a result, E velocity, E area, and A area were also increased significantly by an infusion of Albunex (0.5 m*l*/kg). Again these data

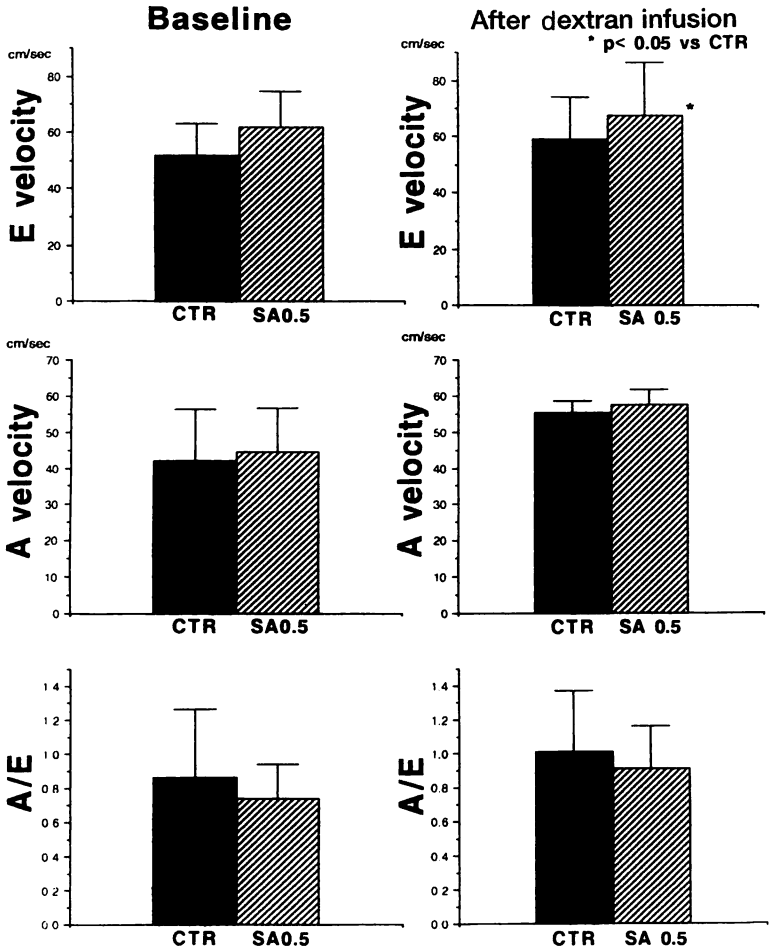

Fig. 3 Changes in E velocity, A velocity, and A/E
Infusion of Albunex (0.5 m*l*/kg) caused E velocity to increase significantly after dextran infusion.
Abbreviation as in Table 1.

suggest that infusion of Albunex (0.5 m*l*/kg) would affect the evaluation of pressure by Doppler echocardiography. Infusion of Albunex (0.2 m*l*/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.*[11] 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[11,24]. Matsuda *et al.*[11] reported that Albunex (0.5 m*l*/kg) caused elevation of left ventricular peak systolic pressure and end-diastolic pressure. When given by intracoronary injection, however, Albunex (1 m*l*/kg) did not affect any pressure[24]. In the present study, left ventricular peak systolic pressure tended to increase. Left ventricular end-diastolic pressure

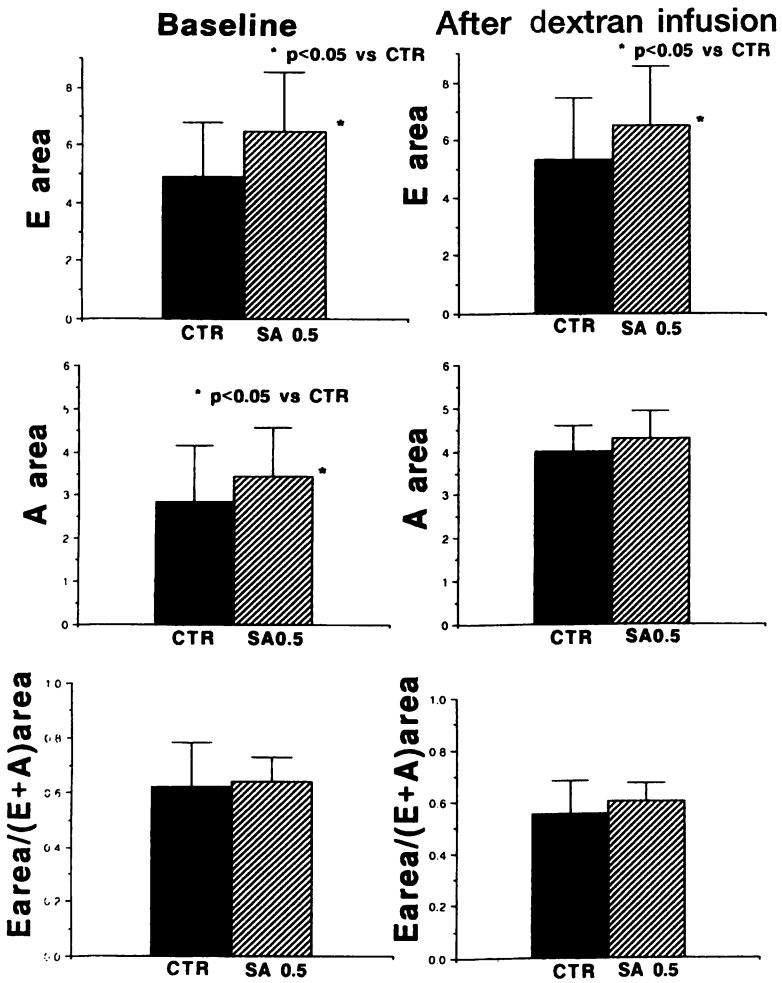

Fig. 4 Changes in time-velocity integrals of left ventricular inflow

Infusion of Albunex (0.5 m*l*/kg) caused E area to increase both at baseline and after dextran infusion; A area increased only at baseline. Abbreviation as in Table 1.

increased significantly [Albunex (0.5 m*l*/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 m*l*/kg) is often necessary for contrast enhancement of the left ventricle. An Albunex dosage of more than 0.2 m*l*/kg is not preferable clinically according to the manufacturer's recommendation. As shown in this study, the dosage of Albunex (0.2 m*l*/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 m*l*/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)[26], 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.*[11] 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 m*l*/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 m*l*/kg appeared not to affect the velocity measurement.

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　憲作　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を用いて検討した．イヌを使って以下の8条件下で左室圧と左室流入血流を同時記録した．

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

正常心においては，アルブネックス 0.2 m*l*/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 m*l*/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, $p<0.05$)．Dextran 100 m*l* 静注後では，アルブネックス 0.2 m*l*/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 m*l* 静注後は，アルブネックス 0.5 m*l*/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, $p<0.05$)，僧帽弁開放時左室圧 (12.7±3.1 vs 15.2±3.3 mmHg, $p<0.05$) と左房左室圧較差 (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 m*l*/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 m*l*/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．

J Cardiol 1997; 29: 283–291

References

1) Gramiak R, Shah PM, Kramer DH : Ultrasound cardiography : Contrast studies in anatomy and function. Radiology 1969; **92** : 939–948
2) Valdes-Cruz LM, Sahn JD : Ultrasonic contrast studies for the detection of cardiac shunts. J Am Coll Cardiol 1984; **3** : 978–985
3) Feigenbaum H, Stone JM, Lee DA, Nasser WK, Chang S : Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green. Circulation 1970; **41** : 615–621
4) Feinstein SB, Ten Cate FJ, Zwehl W, Ong K, Maurer G, Tei C, Shah PM, Meerbaum S, Corday E : Two-dimensional contrast echocardiography : 1. In vitro development and quantitative analysis of echo contrast agents. J Am Coll Cardiol 1984; **3** : 14–20
5) Keller MW, Feinstein SB, Watson DD : Successful left ventricular opacification following peripheral venous injection of sonicated contrast agent : An experimental evaluation. Am Heart J 1987; **114** : 570–575
6) Feinstein SB, Cheirif J, Ten Cate FJ, Silverman PR, Heidenreich PA, Dick C, Desir RM, Armstrong WF, Quinones MA, Shah

PM : Safety and efficacy of a new transpulmonary ultrasound contrast agent : Initial multicenter clinical results. J Am Coll Cardiol 1990; **16** : 316–324

7) Bleeker HJ, Shung KK, Barnhart JL : Ultrasonic characterization of Albunex, a new contrast agent. J Acoust Soc Am 1990; **87** : 1792–1797
8) Barnhart J, Levene H, Villapando E, Maniquis J, Fernandez J, Rice S, Jablonski E, Gjoen T, Tollleshaug H : Characteristics of Albunex : Air-filled albumin microspheres for echocardiography contrast enhancement. Invest Radiol 1990; **25** : S162–S164
9) Beppu S, Tanabe K, Shimizu T, Ishikura F, Nakatani S, Terasawa A, Matsuda H, Miyatake K : Contrast enhancement of Doppler signals by sonicated albumin for estimating right ventricular systolic pressure. Am J Cardiol 1991; **67** : 1148–1150
10) Nakatani S, Imanishi T, Terasawa A, Beppu S, Nagata S, Miyatake K : Clinical application of transpulmonary contrast-enhanced Doppler technique in the assessment of severity of aortic stenosis. J Am Coll Cardiol 1992; **20** : 973–978
11) Matsuda H, Beppu S, Nakatani S, Ohta T, Miyatake K : Transpulmonary contrast echocardiographic opacification of left ventricle and its hemodynamic action : A comparative experimental study between Albunex and sonicated human albumin. Jpn J Med Ultrasonics 1992; **19** : 9–16
12) Crouse LJ, Kramer PH : Opacification and border delineation improvement in patients with suboptimal endocardial border definition on routine echocardiography : Results of a phase 3 trial of sonicated albumin microspheres. Clin Cardiol 1991; **14** (Suppl 5) : 19–22
13) Crouse LJ, Cheirif J, Hanly DE, Kisslo JA, Labovitz AJ, Raichlen JS, Schutz RW, Shah PM, Smith MD : Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography : Results of the phase III Albunex multicenter trial. J Am Coll Cardiol 1993; **22** : 1494–1500
14) Keller MW, Segal SS, Kaul S, Duling BR : The behavior of sonicated albumin microbubbles in the microcirculation : A basis for their use during myocardial contrast echocardiography. Circ Res 1989; **65** : 458–467
15) Kaul S : Quantification of myocardial perfusion with contrast echocardiography. Am J Cardiac Imag 1991; **5** : 200–216
16) Porter TR, D'Sa A, Turner C, Jones LA, Minisi AJ, Mohanty PK, Vetrovec GW, Nixon JV : Myocardial contrast echocardiography for the assessment of coronary blood flow reserve : Validation in humans. J Am Coll Cardiol 1993; **21** : 349–355
17) Reisner SA, Ong LS, Lichtenberg GS, Amico AF, Shapiro JR, Allen MN, Meltzer RS : Myocardial perfusion imaging by contrast echocardiography with use of intracoronary sonicated albumin in humans. J Am Coll Cardiol 1989; **14** : 660–665
18) Keller MW, Glasheen W, Kaul S : Albunex : A safe and effective commercially produced agent for myocardial contrast echocardiography. J Am Soc Echo 1989; **2** : 48–52
19) Klein AL, Bailey AS, Moura A, Murray RD, Morehead AJ, Brum J, Pearce G, Stewart WJ, Thomas JD : Reliability of echocardiographic measurements of myocardial perfusion using commercially produced sonicated serum albumin (Albunex). J Am Coll Cardiol 1993; **22** : 1983–1993
20) Bleeker H, Shung K, Barnhart J : On the application of ultrasonic contrast agents for blood flowmetry and assessment of cardiac perfusion. J Ultrasound Med 1990; **9** : 461–471
21) Rovai D, Nissen SE, Elion J, Smith M, L'Abbate A, Kwan OL, DeMaria AN : Contrast echo washout curves from the left ventricle : Application of basic principles of indicator-dilution theory and calculation of ejection fraction. J Am Coll Cardiol 1987; **10** : 125–134
22) Mizushige K, DeMaria AN, Toyama Y, Morita H, Senda S, Matsuo H : Contrast echocardiography for evaluation of left ventricular flow dynamics using densitometric analysis. Circulation 1993; **88** : 588–595
23) Lang RM, Borow KM, Neumann A, Feinstein SB : Echocardiographic contrast agents : Effect of microbubbles and carrier solutions on left ventricular contractility. J Am Coll Cardiol 1987; **9** : 910–919
24) Ten Cate FJ, Widimsky P, Cornel JH, Waldstein DJ, Serruys PW, Waaler A : Intracoronary Albunex : Its effects on left ventricular hemodynamics, function, and coronary sinus flow in humans. Circulation 1993; **88** : 2123–2127
25) Mor-Avi V, Shroff SG, Robinson KA, Ng AF, Cholley BP, Marcus RH, Lang RM : Effects of left ventricular pressure on sonicated albumin microbubbles : Evaluation using an isolated rabbit heart model. J Am Coll Cardiol 1994; **24** : 1779–1785
26) Dubin J, Wallerson DC, Cody RJ, Devereux RB : Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determination. Am Heart J 1990; **120** : 116–123