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Intraoperative contrast transesophageal echocardiography using Albunex

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Abstract: This study was designed to investigate the effect of administration of the contrast material Albunex on intraoperative contrast transesophageal echocardiography for patients with mitral valve disease or coronary artery disease. We studied nine patients scheduled for elective coronary artery bypass grafting (CABG group) and nine patients scheduled for elective mitral valve replacement (MVR group), and used a transesophageal echocardiography probe and an echocardiographic system. During the period of stable hemodynamics before the start of cardiopulmonary bypass, Albunex in doses of 0.1 ml·kg^{-1} was injected at a rate of about 1 ml·s^{-1} from either the peripheral venous line or the distal lumen of the pulmonary arterial catheter, and the effect on contrast was compared. This effect was semiquantitatively assessed by using a grading scale from 0 to 3, with 0 indicating an absence of opacification and 3, full opacification of the cavities examined. In the CABG group, contrast resulting from administration of Albunex from the pulmonary arterial catheter was significantly better than that from the peripheral venous line, whereas in the MVR group, no improvement was found. Furthermore, when it was administered into the pulmonary artery, the effect on contrast for the MVR group was significantly lower than that for the CABG group. The efficacy rate of intraoperative contrast transesophageal echocardiography using Albunex was relatively low, and appeared to be affected by pulmonary circulation or many other factors such as the method of administration, including the route and injection pressure.

Key words: Albunex, Contrast echocardiography, Transesophageal echocardiography, Mitral valve disease

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Introduction

Albunex (Shionogi, Osaka, Japan) is an albumin-capsule agent for contrast echocardiography, containing air-filled microspheres with an average size of 4 μm. In comparison with other contrast agents, Albunex is superior with respect to homogeneity, size, and stability of the air-filled microspheres [1]. Although Albunex enabled us to visualize left cardiac opacification by contrast echocardiography following peripheral venous administration [2], to our knowledge, no such studies have been done regarding intraoperative transesophageal echocardiography (TEE). For this reason, we examined the usefulness of Albunex for intraoperative contrast transesophageal echocardiography in patients scheduled for elective cardiac surgery. The effect of the administration route of Albunex and of mitral valve disease on contrast was also evaluated.

Materials and methods

We studied 18 patients scheduled for elective cardiac surgery (13 men and 5 women with a mean age of 57.0 ± 9.7 years, ranging from 38 to 70 years): 9 patients scheduled for elective coronary artery bypass grafting without mitral valve disease (CABG group) and 9 patients scheduled for elective mitral valve replacement with mitral valve disease (4 patients: mitral valve stenosis; 5 patients: mitral valve regurgitation) (MVR group). Details of this study had been explained to each patient, and informed consent in written form had been obtained from each of them. Anesthesia was induced with intravenous administration of a combination of fentanyl and thiamylal. Muscle relaxation was obtained with intravenous vecuronium. Anesthesia was then maintained with continuous injection of fentanyl and nitrous oxide—oxygen—sevoflurane, or oxygen—sevoflurane.

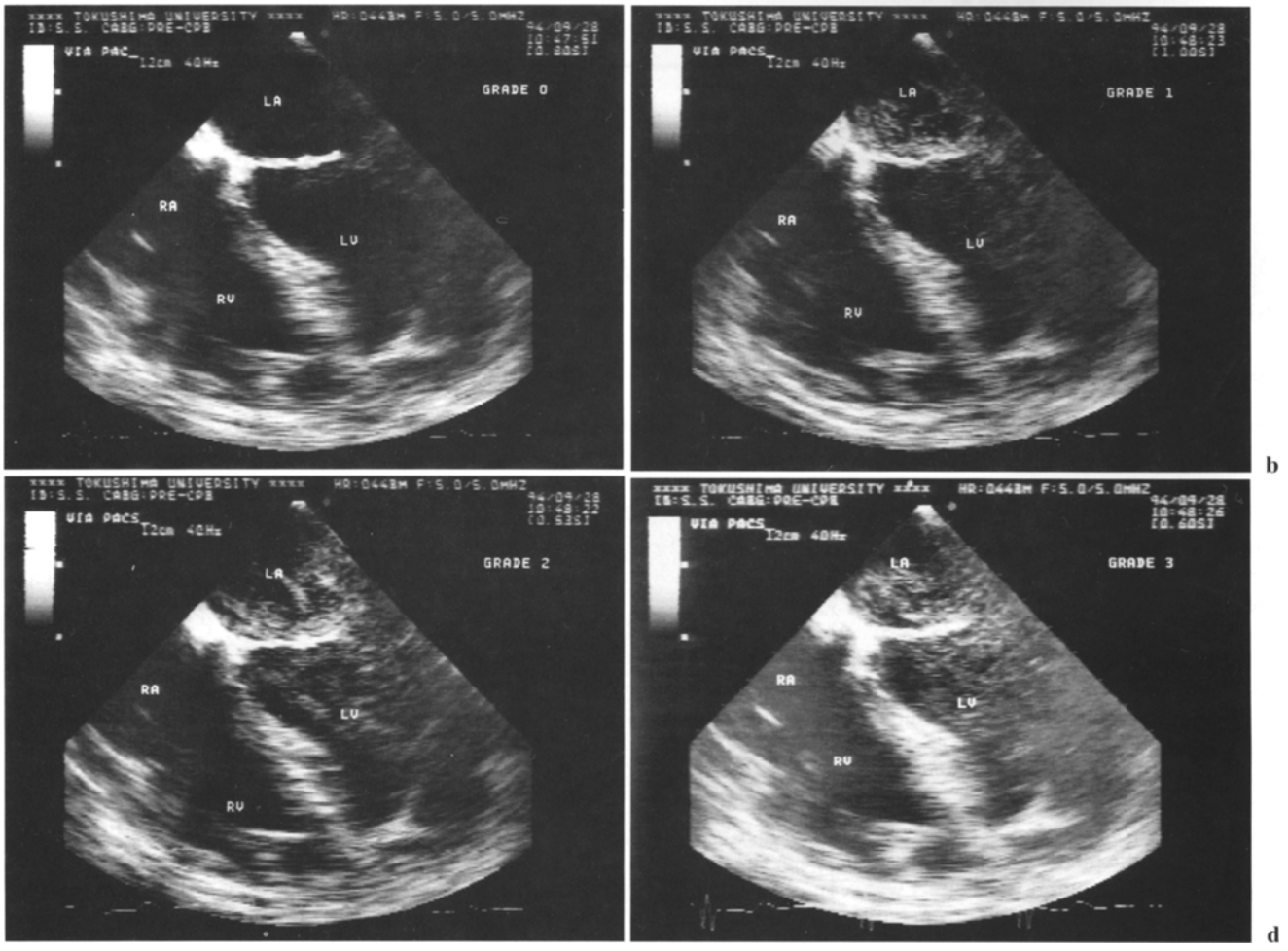

Fig. 1. **a** Grade 0. **b** Grade 1. **c** Grade 2. **d** Grade 3. Visual semiquantitative evaluation of left cardiac opacification. At a long-axis four-chamber view, left ventricular opacification was classified into four grades, ranging from 0 to 3. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle

After induction of anesthesia and tracheal intubation, a TEE probe (5MHZ, UST-5233S-5, Aloka, Tokyo, Japan) was inserted into the esophagus and attached to a color Doppler imaging system (SSD-830, Aloka). Albunex (sonicated 5% human albumin) was used as the medium for contrast echocardiography. Before administration, a vial with Albunex was turned upside down, and the content mixed by gentle spinning between the palms for about 3 min, resulting in a homogeneous milky suspension. To avoid excessive compression or decompression, the vial was pierced with an 18-gauge needle for air flow and the content collected with a syringe with another 18-gauge needle at a rate not exceeding $1\,ml \cdot s^{-1}$. Contrast echocardiography was obtained under hemodynamically stable conditions before cardiopulmonary bypass. Albunex in doses of $0.1\,ml \cdot kg^{-1}$ body weight was injected manually at a rate of $1\,ml \cdot s^{-1}$ through the peripheral venous line larger than 18-gauge or the distal lumen of the 7F pulmonary arterial catheter. As for the injection methods of Albunex, we conformed to the methods of Feinstein et al. [2]. The injection dose and speed used for the present study are considered normal for contrast echocardiography of the left cardiac system. For evaluation of contrast echocardiography, the long-axis four-chamber view was obtained and continuously recorded on an S-VHS video tape. The contrast effect was evaluated postoperatively by means of visually semiquantified grading from 0 to 3: grade 0 = no opacification; grade 1 = faint opacification; grade 2 = intermediate opacification; grade 3 = full chamber opacification (Fig. 1). The contrast effect of Albunex on echocardiography of the right cardiac system was examined by administration from the peripheral venous line, and that of the left cardiac system by administration from the peripheral venous line and the pulmonary arterial catheter. In addition, the contrast effect of Albunex observed in the CABG group was compared with that in the MVR group, as well as the effect of administration routes on contrast enhancement within each group.

Statistical analysis between groups was performed with the Mann-Whitney test, and analysis within a

Table 1. Patient profiles

	CABG group (n = 9)	MVR group (n = 9)	P value
Age (years)	56.4 ± 10.3	57.6 ± 9.6	NS
Height (cm)	161.4 ± 5.4	162.0 ± 15.1	NS
Weight (kg)	63.4 ± 5.3	58.4 ± 11.0	NS
Male/female	7/2	6/3	NS
sPAP (mmHg)	23.3 ± 3.9	41.7 ± 27.4	P = 0.0153
mPAP (mmHg)	15.3 ± 4.1	26.9 ± 16.3	NS (P = 0.0569)

Values are mean ± standard deviations.
CABG, coronary artery bypass grafting; MVR, mitral valve replacement; sPAP,systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; NS, not significant.

group with the Wilcoxon signed rank test. All values are shown as means with standard deviations, and a probability value of less than 0.05 was considered to be significant.

Results

Patient profiles (Table 1)

No significant differences in age, sex, height, or body weight were observed between the CABG group and the MVR group. However, the preoperative systolic pulmonary arterial pressure for the MVR group was significantly higher than that for the CABG group, while the mean pulmonary arterial pressure tended to be high for the MVR group.

Contrast effect for the right cardiac system

Administration from the peripheral venous line.
The mean contrast-enhancing score for all 18 patients was 1.89 ± 1.02; the score for the CABG group was 2.22 ± 0.83 and for the MVR group 1.56 ± 1.13. No significant difference was observed between these groups.

Contrast effect for the left cardiac system (Fig. 2)

Administration from the peripheral venous line.
The mean contrast-enhancing score for all 18 patients was 0.33 ± 0.59; the score for the CABG group was 0.33 ± 0.50 and for the MVR group 0.33 ± 0.71. No significant difference was observed between these groups.
Administration from the pulmonary arterial catheter.
The mean contrast-enhancing score for all 18 patients was 1.33 ± 1.03; the score for the CABG group was 2.00 ± 0.87 and for the MVR group 0.67 ± 0.71. The contrast effect for the MVR group was thus significantly lower than for the CABG group. When Albunex was administered from the pulmonary arterial catheter, contrast improved significantly for the CABG group, while no improvement was observed for the MVR group.

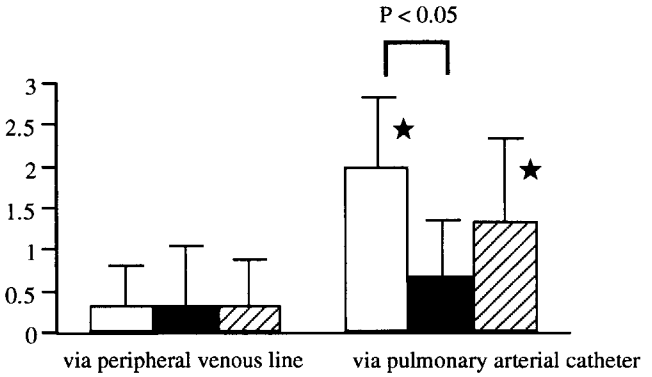

Fig. 2. Contrast effect for the left cardiac system. *Open bars*, coronary artery bypass grafting (CABG) group; *solid bars*, mitral valve replacement (MVR) group; *hatched bars*, total. *Stars*, $P < 0.05$ vs peripheral venous line. Values are shown as means ± SD

Injection pressure

In 5 out of the 18 cases, both the peripheral venous line and the pulmonary arterial catheter were connected to a pressure transducer by means of a three-way stopcock, and the maximum pressure was measured during manual injection of 0.1 ml·kg^{-1} of normal saline at a rate of about 1 ml·s^{-1}. The pressures during administration from both routes were extremely high; that from the peripheral venous line was 330 ± 87 mmHg and from the pulmonary arterial catheter 607 ± 79 mmHg.

Discussion

Contrast echocardiography was developed to obtain clearer images and more useful information. This method is based on the formation of an interface between the air and blood or organs by administration of air, the acoustic impedance of which is greatly different from that of blood and organs. Since its first clinical application by Gramiak and Shah [3] in 1968, contrast echocardiography has been used for the identification of abnormal cardiac anatomy [4], demonstration

of intracardiac shunts [5,6] assessment of valvular regurgitation [6], clear visualization of the surface of the endocardium [7], evaluation of myocardial perfusion by intracoronary injections of contrast agents [8,9], and enhancement of transvalvular Doppler signals [10]. Although this contrast echocardiography seems to be particularly useful for intraoperative transesophageal echocardiography that has restrictions including the angle of the probe, no detailed examination of intraoperative contrast echocardiography has been performed.

In previous studies, several echocardiographic contrast agents containing air-filled microspheres have been prepared by hand agitation or ultrasonication; these agents used iodine-containing contrast media, normal saline, albumin solution, and glucose solution as their basal medium. However, air bubbles in the contrast media prepared by such methods are difficult to pass through the pulmonary capillary circulation after intravenous administration, so that good contrast enhancement in the left heart could not be achieved. Reproducibility of these media was also a problem, because the size and concentration of air bubbles varied. Albunex (sonicated 5% human albumin) is a new agent for use in contrast echocardiography and its active components are air bubbles of 4 μm in mean diameter. It was developed by Feinstein et al. [2] in 1990. One ml of Albunex contains 4×10^8 air-filled microspheres, so that a 5-ml vial contains 2×10^9 microspheres. Since the diameter of the air-filled microspheres is smaller than that of erythrocytes (about 8μm on average), the microspheres can pass through the pulmonary capillary bed, and contrast echocardiograms of the left heart can be obtained by intravenous injection of this agent [1,2,11]. One ml of Albunex contains about 0.02ml of air, but intravascular injection of this amount of air is considered safe. Although no difference in the contrast-enhancing effect was found between Albunex and the conventional albumin medium prepared by ultrasonication, the former is superior with respect to homogeneity, reproducibility, and stability of the air bubbles [1]. Moreover, the stability of the air bubbles of Albunex is guaranteed for about 10 months.

In the present study, Albunex was injected from the peripheral venous line to examine its efficacy for contrast echocardiography during cardiac surgery; however, its contrast-enhancing effect in the left heart was not satisfactory. Hence, Albunex was administered from the distal lumen of the pulmonary arterial catheter so as to decrease its dilution with blood and to introduce it at a high concentration into the left cardiac system. As the result, an improvement in contrast was observed. Evaluation of the influence of mitral valve disease on contrast-enhancing effect showed that in the MVR group, administration from the pulmonary arterial catheter did not result in significant improvement in contrast. Thus, the contrast enhancement for the MVR group was significantly lower than that for the CABG group. It has been reported that the effect of Albunex on contrast enhancement in the left cardiac system is not significant for patients with dysfunction of the pulmonary circulation such as pulmonary embolism, pulmonary hypertension, and mitral valve disease. According to Machii et al. [12], the efficacy rate of contrast produced with Albunex was 96.3% for patients with angina pectoris, while that for patients with mitral valve disease was 41.5% when grade 2 contrast enhancement or higher was considered effective. It was speculated that a high pulmonary arterial pressure might have caused some changes in the pulmonary capillary beds which affected the pulmonary passage of Albunex, thus leading to a poor contrast effect in the left ventricle of patients with mitral valve disease. In the present study, preoperative systolic pulmonary arterial pressure for the MVR group was significantly higher than for the CABG group, indicating an increase in pulmonary vascular resistance in the former group. It has also been reported that the contrast-enhancing effect of Albunex is affected by not only pulmonary circulation but also systemic hemodynamics including cardiac output [13]. Since the present study was performed during cardiac surgery under general anesthesia, the intraoperative changes in hemodynamics could affect the contrast enhancement obtained with Albunex.

Machii et al. [12] reported that a high efficacy rate was observed in contrast enhancement of the left cardiac system with intravenous administration of Albunex at a dose of 0.08–0.22 $ml \cdot kg^{-1}$ when grade 2 contrast enhancement or higher was considered effective (0.08 $ml \cdot kg^{-1}$: 47.4%; 0.15 $ml \cdot kg^{-1}$: 62.6%; 0.22 $ml \cdot kg^{-1}$: 71.6%). In the present study, the observed contrast-enhancing effect was less than expected for the right as well as the left cardiac system. As for the injection dose, 0.01–0.04 $ml \cdot kg^{-1}$ for contrast echocardiography of the right heart and 0.08–0.51 $ml \cdot kg^{-1}$ for the left heart are considered reasonable, as are the maximum single dose of Albunex of 0.22 $ml \cdot kg^{-1}$ and the maximum cumulative dose of 0.45 $ml \cdot kg^{-1}$ [12]. Although repeated administration of 0.2 $ml \cdot kg^{-1}$ was used in several cases, little improvement in contrast was obtained. Therefore, it seemed that no improvement in contrast enhancement could be expected from increasing the dose. Air-filled microspheres, the effective component of Albunex, consist of a membrane portion (human serum albumin) and air. The membrane is very thin and appears to be susceptible to stresses, such as rapid changes in pressure and excessive mechanical shock and vibration. Since a high pressure was recorded during injection from the peripheral venous line and the pulmonary arterial cath-

eter in the present study, collapse of the air bubbles by this high pressure at injection may have caused the low efficacy of the contrast effect.

In most previous studies, contrast echocardiography was performed in awake patients under spontaneous respiration. In the present study, on the other hand, it was performed with the patients under general anesthesia and artificial respiration. Collapse or trapping of air bubbles may have been caused by a pressure rise in the thoracic cavity or an increase in pulmonary vascular resistance due to compression of pulmonary capillaries attributable to positive pressure breathing. Moreover, the effect of oxygen administration on contrast enhancement has been reported on recently [14]. Briefly, this effect functions as follows: oxygenation raises the partial pressure of oxygen and lowers the partial pressure of nitrogen in the arterial blood. Since oxygen in the blood is consumed in the periphery, gas pressure in the venous blood decreases; as a result, the total blood gas pressure becomes extremely low compared with that during air respiration. This decrease in the total blood gas pressure causes the air in Albunex to diffuse into the blood and the bubbles to shrink. Since a high concentration of oxygen was administered under general anesthesia and artificial respiration in our study, this effect cannot be ruled out. In addition, nitrous oxide may also affect the size of air bubbles, but the influence of this gas has not been studied yet.

One limitation of the present study is that it does not contain an analysis of the elapsed time until contrast can first be noted or the length of time that contrast continues to be visible. When contrast agent is infused into blood vessels for subsequent investigation of its transfer and fate, analysis over time is indispensable. The present study was undertaken to study the contrast level on the left side of the heart system especially in relation to passage of the contrast agent through the pulmonary circulation. In this study, the contrast agent was used as a deposit tracer rather than as a free-passing tracer. This is why only the contrast level was analyzed in this study. Another limitation of this study is that cases of mitral valve stenosis and mitral valve regurgitation were both assigned to the MVR group, on the grounds that the same surgical procedure was used on all these cases. It is possible that the contrast effect and the time it takes for such an effect to appear may differ slightly between cases of mitral valve stenosis and mitral valve regurgitation. However, we assigned these cases to the same group, as did Machii et al. [12], taking note of the fact that both conditions involve disturbed passage of Albunex, due to increased pulmonary vascular resistance and pulmonary arterial pressure caused by organic changes of the pulmonary capillaries. We cannot rule out that this grouping may involve some problems.

In conclusion, the efficacy rate of Albunex for intraoperative contrast transesophageal echocardiography was relatively low, but the contrast effect was improved significantly when Albunex was administered from the pulmonary arterial catheter rather than from the peripheral venous line. The contrast effect thus appeared to be affected by pulmonary circulation. Further examination of intraoperative contrast transesophageal echocardiography is necessary to determine the effect of factors such as the method of administration, including the route and injection pressure, the effects of systemic homodynamics, positive pressure breathing, and inspired oxygen concentration.

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