



# “De-airing” in open heart surgery: report from the CVSAP nation-wide survey and literature review

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## Abstract

Since the beginning of cardiac surgery, retained intracardiac air has been an important problem. While transesophageal echocardiography enabled to visualize the air and de-airing procedures have been routinely done, they appear to vary much among institutions not necessarily based on firm scientific evidence. Thus, “de-airing” was chosen as the theme of 2016 CVSAP (cardiovascular surgery and anesthesia and perfusion) symposium and a nation-wide questionnaire survey was carried out prior to it. This paper reports on its results and illustrate “the best of de-airing” based on literature review. The collection rate of the questionnaire survey was 77.9% (278/357) and 83.3% (85/102) from the major institutions of surgeons and anesthesiologists, respectively. More than 90% of both consider de-airing as important, since adverse events of air embolism were actually encountered including critical ones. Most routinely performed de-airing procedures are posture change, lung inflation and aspiration through the vent cannulae. Direct aspiration is performed in one-third of institutions. Carbon dioxide insufflation is performed in 82.5% of institutions (mostly 2–3 L/min). However, not a few surgeons are skeptical for its significance. While many surgeons are grateful for collaboration by anesthesiologists, some expect more information sharing between them. They also expect that clinical engineers understand “de-airing” better and operate the extracorporeal circulation system appropriately to avoid an occurrence of undesirable event. Some surgeons anticipated a convenient device for de-airing. Furthermore, some questions to be solved in the future were raised, including how meticulously the bubbles should be removed or how efficient carbon dioxide insufflation is.

**Keywords** Cardiac surgery · Retained air · Air embolism

## Background

Retention of intracardiac air was thought to be responsible for operative deaths following open heart surgery [1], and a number of de-airing procedures were attempted before the 1970s [2–5]. However, they were blind manipulations because there was no means of visualizing air or assessing the efficacy of its removal. Although two-dimensional (2D) echocardiography was introduced to the operating field in the 1980s [6], assessment with this modality by surgeons was intermittent. M-mode transesophageal

echocardiography (TEE) enabled continuous monitoring of air emboli and assessment of de-airing procedures by anesthesiologists [7–9]. However, it was “bubbles” described as “air emboli” that were visualized and examined, and there was conflict among investigators as to the clinical relevance of detected air [10, 11].

In 1993, a concept of “pooled air” detected by 2D-TEE was reported [12]. It was found to be located mainly in the right upper pulmonary vein (RUPV), left ventricular (LV) apex, and left atrium (LA); it was shown to move along with the blood stream during weaning from cardiopulmonary bypass (CPB) while changing its forms between pooled air and bubbles. The presence of pooled air was significantly associated with the occurrence of cardiac events such as regional wall motion abnormalities, ST elevation, and heart block [13]. As TEE has gained popularity, it has been used for detecting air, guiding de-airing, and assessing the results of de-airing procedures. At the present time, however, the de-airing procedures appear to vary among hospitals and are

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performed based on subjective criteria rather than on scientific evidence. The actual results of de-airing procedures or events related to air embolism have not yet been reported on a national basis.

In 2015, a joint symposium of three societies related to cardiovascular surgery, CVSAP (cardiovascular surgery and anesthesia and perfusion), was started by the Japanese Society of Cardiovascular Anesthesiologists (JSCVA), Japanese Society for Cardiovascular Surgery (JSCVS), and Japanese Society of Extra-Corporeal Technology in Medicine (JaSECT), and “de-airing” was the theme of the second CVSAP symposium at the 21st Annual Meeting of JSCVA in 2016 and the 46th Annual Meeting of JSCVS in 2017. Prior to the symposia, a questionnaire survey was sent to the core members of JSCVA and JSCVS and the topic on de-airing

was discussed by symposiast from the above societies with the report of this survey. The purpose of this paper is to report the current status of de-airing in Japan and unsolved problems based on the results of this survey, and to discuss “optimal de-airing” with some review of the literature.

## Methods

The basic questionnaire was prepared by an author (KO) and was approved by the board of governors of JSCVA and JSCVS after necessary revisions. The questionnaire was sent to anesthesiologists in 102 hospitals qualified by the JSCVA and the surgeons in 357 major training hospitals in the Japanese Board of Cardiovascular Surgery.

The questionnaire included the following items.

### Question 1: Implication of de-airing

How important is de-airing for you? Please choose one of the following grades.

grade 1 (extremely important)

grade 2 (very important)

grade 3 (fairly important)

grade 4 (slightly important)

grade 5 (not important)

### Question 2: Frequency of air-related events

How often do you experience air-related events in your cases? Please choose one of the grades.

grade 1 (frequently)

grade 2 (occasionally)

grade 3 (rarely)

Which organ was involved in them?

cardiac

neurologic

both

others

Please describe some examples of air-related events, especially those that are to be prevented.

Question 3: Routine de-airing procedures

Which of the following de-airing procedures are performed in your institution? Please check all that apply.

postural change

inflation of the lung

air removal via the LV vent

air removal via the root vent

direct aspiration of air from cardiac chamber

Please describe in detail if you have other ingenious attempts or methods of air removal.

Question 4: Carbon dioxide insufflation

Is carbon dioxide insufflation carried out in your institution? Please choose one of the grades.

grade 1 (not performed)

grade 2 (done in selected cases)

grade 3 (routinely done)

If it is done, what is the actual flow rate of insufflation?

Question 5: Significance of carbon dioxide insufflation

How important or reliable is carbon dioxide insufflation for you? Please choose one of the grades.

- grade 1 (essential)
- grade 2 (just to be safe)
- grade 3 (not so reliable)
- grade 4 (insignificant)

Please describe in detail if you have any troubles, concerns, or tips on carbon dioxide insufflation.

Question 6: De-airing in minimally invasive cardiac surgery (MICS)

Do you experience any difficulties or troubles in de-airing in MICS? If yes, what kind of troubles are they in particular? Please describe if you have any tips on de-airing in MICS.

Question 7: De-airing in the right heart

How do you think and deal with air in the right heart? Please choose one of the following answers.

- I do not care about the air in the right heart.
- I care about it but leave it.
- I meticulously remove it.

Please describe if you have experiences of any troubles related to the air in the right heart.

Question 8a (question to surgeons): Request to anesthesiologists and perfusionists

Please describe if you have any particular requests to anesthesiologists or perfusionists regarding de-airing.

Question 8b (question to anesthesiologists): TEE assessment of air retention

When do you check air retention among the following stages? Please check all that apply.

- before aortic declamping
- following aortic declamping
- before weaning from CPB

Do you report the particular sites of air retention to surgeons? Please choose one of the following.

- routinely
- occasionally
- no

Question 9: Future perspective

Please describe if you wish to have any instruments or materials for de-airing. Please describe any questions or concerns or comments regarding de-airing.

After the replies were collected by each society, the answers and comments were summarized and analyzed by KO.

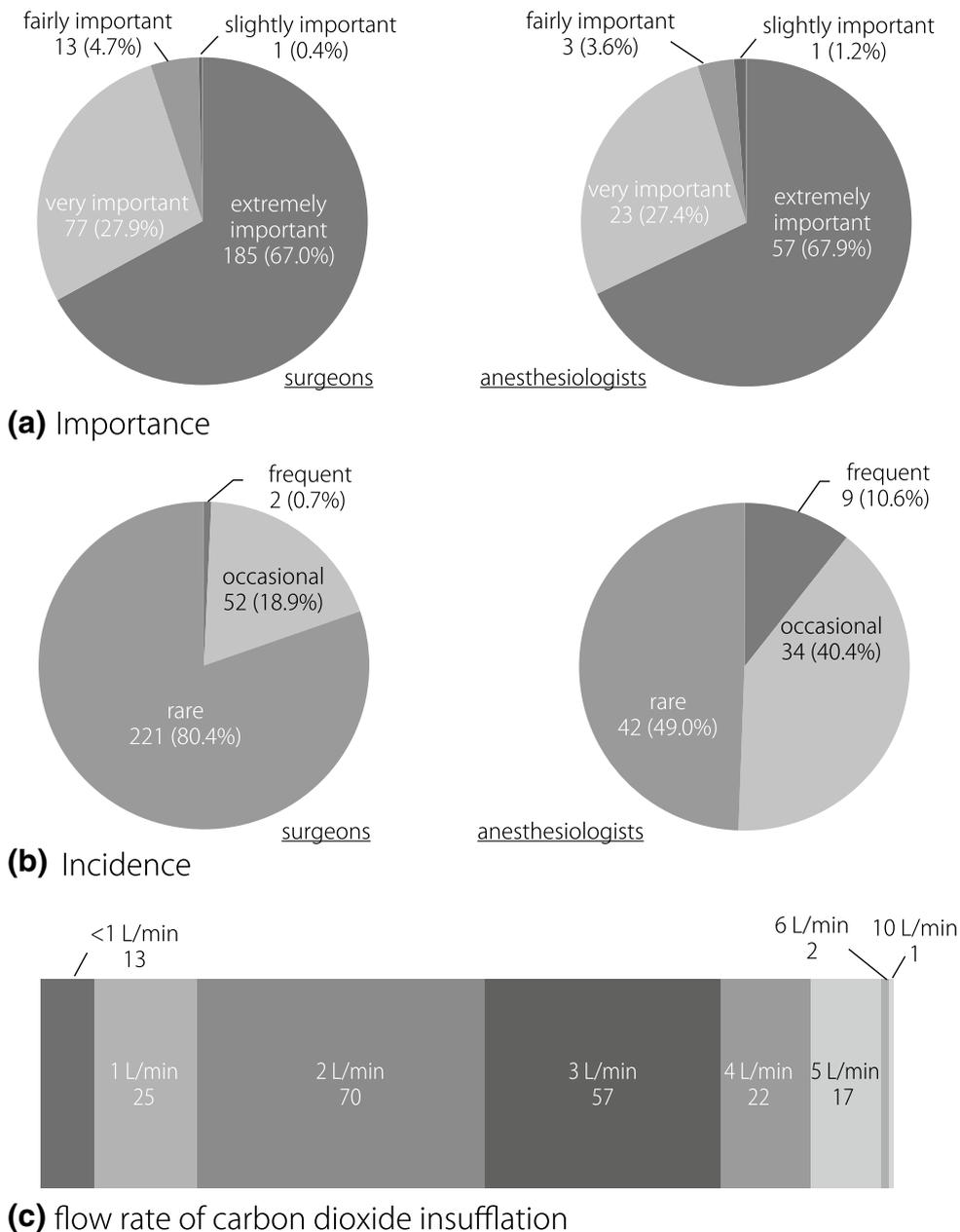
## Results

The replies were collected from 85 of the 102 JSCVA-qualified hospitals (83.3%) and 278 of the 357 core hospitals (77.9%) of the Japanese Board of Cardiovascular Surgery.

## Implications of de-airing and incidence of air-related events

Both surgeons and anesthesiologists consider de-airing as important, with 94.9% (262/276) of surgeons and 95.2% (80/84) of anesthesiologists rating this issue as grade 1 or 2 (Fig. 1). However, the incidence of air-related events recognized as significant was different between them. While only 0.7% and 18.9% of surgeons (2/275, 52/275) chose “frequent” and “occasionally”, respectively, 10.6% and

**Fig. 1** Results of questionnaire survey on de-airing carried out prior to the 2016 CVSAP symposium. **a** Awareness of importance of de-airing. **b** Regarded incidence of air embolism. **c** Flow rate of carbon dioxide insufflation, if performed



40.4% of anesthesiologists (9/85, 34/85) chose “frequent” and “occasionally”, respectively. According to the replies of anesthesiologists, air-related events were mostly cardiac (97.4%, 76/78) and then neurologic (32.1%, 25/78). The specific examples described in the replies are listed in Table 1.

### Routine de-airing procedures

According to the replies of surgeons, four procedures are routinely performed in the majority of institutions: postural change (87.8%, 244/278), inflation of the lung (98.6%, 274/278), air removal via an LV vent (92.4%, 257/278), root vent (99.3%, 276/278), and direct aspiration of air in 33.5% (93/278).

Several methods for de-airing were reported in the replies, such as retrograde terminal cardioplegia, aspiration of the right coronary artery with a 27G needle, and alternative aspiration via the root vent and LV vent; while the cardiac chambers are filled and evacuated repeatedly.

### Carbon dioxide insufflation

According to the replies of surgeons, carbon dioxide insufflation is routinely done in 82.5% of hospitals (227/275) or in selected cases in 4.0% of hospitals (11/275), but is never done in 13.5% of hospitals (37/275). It probably depends on how significant they consider this method. Only 36.7% of surgeons (95/259) think it essential, but as many as 54.4%

**Table 1** Air-related events**1. Cardiac events**

Circulatory collapse when the patient is placed in a sitting position

Transient ST elevation, bradycardia, and right ventricular failure occasionally leading to myocardial infarction, necessitating circulatory support

Air embolism of the right coronary artery following a saline test during mitral valve repair

**2. Neurologic events**

Transient convulsions at awakening but without abnormal computed tomography or magnetic resonance imaging findings or postoperative sequelae

Visual disturbances and hemiplegia

Entry of air into the left heart via a patent foramen ovale during off-pump pulmonary valve replacement

Entry of air into the left heart via the pulmonary circulation during off-pump tricuspid annuloplasty, resulting in delayed awakening and transient neurologic deficit but without postoperative sequelae

**3. Adverse events during CPB**

Aspiration of air into the LV due to excessive negative pressure

Entry of air into the LV due to unexpected reverse rotation of the pump, leading to brain damage (absence of non-return valve and inverted configuration of the circuit was responsible)

Exit of air to the aorta following weaning from CPB with the patient in a head-down position

(141/259) use carbon dioxide insufflation just to be safe. Some surgeons commented that it is done for reducing the time for air removal. Selected cases in which insufflation is performed include mitral valve repair, MICS, and pediatric cases. The flow rate of insufflation varies from 1 to 10 L/min, but most use 2 or 3 L/min. In pediatric cardiac surgery, 0.5–1 L/min is used.

Several pitfalls or concerns were described. Carbon dioxide was failed to be given because of an empty tank or missing connection to the insufflation tube. There were occasions where insufflation was not performed at the second pump-run. There are concerns that carbon dioxide may be aspirated by suction or absorbed into the blood. It is often difficult to fix the insufflation tube, or it accidentally falls out during surgical procedures. For this problem, another surgeon recommended that the tube be placed in the pathway of a thoracic drain in advance.

### De-airing in minimally invasive cardiac surgery (MICS)

The majority of surgeons have no difficulty in de-airing in MICS (90.6%, 106/117). To be more precise, carbon dioxide is insufflated into the thorax during manipulations in the heart, and the flow rate is temporarily increased at suture closure, with the chamber carefully filled with saline. Before the aorta is declamped, the patient is placed in a head-up, left-down position. After air is no longer aspirated from the root vent, the vent cannula is removed. Some surgeons infuse cardioplegic solution during the saline test in mitral valve repair cases, but ST elevation is occasionally encountered. If the root vent is left in for a longer time for meticulous

de-airing, bleeding after decannulation may be a problem for the surgeon.

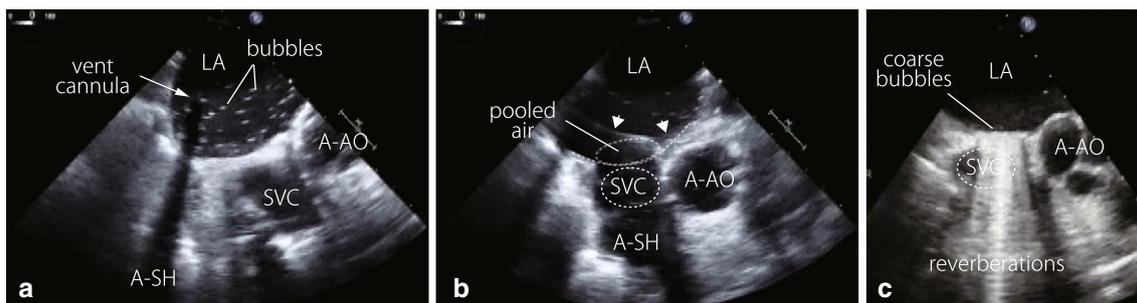
### De-airing in the right heart

Compared with anesthesiologists, more surgeons “do not care” about air in the right heart (6.4%, 5/78 versus 13.3%, 36/271) but rather “meticulously remove air” (35.9%, 28/78 versus 49.4%, 134/271). Some surgeons remove air as this is recommended by anesthesiologists. Air is removed by aspiration or a small incision, but the latter may lead to troublesome bleeding, and this may decrease the motivation for meticulous removal.

### Surgeons and anesthesiologists communication or cooperation

Surgeons are mostly satisfied by the cooperation of anesthesiologists or some even follow their recommendations for de-airing. However, others are not satisfied with the level of collaboration and/or comprehension on de-airing. These surgeons expect the following: (1) timely inflation of lung at inserting or removing a LV vent cannula or suture closure of the heart; (2) more precise information on the site of air retention, hopefully in a repetitive fashion; and (3) better collaboration and communication with perfusionists.

The majority of anesthesiologists (94.1%, 80/85) replied that they routinely share information regarding air retention on the site with surgeons. They check for air following aortic declamping (92.6%, 50/54), but less frequently before weaning from CPB (81.5%, 44/54) and before aortic declamping (35.2%, 19/54).



**Fig. 2** Transesophageal echocardiograms showing three types of intracardiac air. **a** Minute bubbles in the left atrium (LA). Acoustic shadow (A-SH) caused by a vent cannula is seen. **b** Pooled air associated with A-SH which masks superior vena cava (SVC). Strong

echo and side lobes (arrow head) are not apparent. **c** Coarse bubbles depicted as an echogenic line with reverberations which mask the SVC. A-AO ascending aorta

### Request to perfusionists

Many surgeons hope for better collaboration with perfusionists to prevent the following problems with de-airing: (1) reduction of venous drainage at insertion of the LV vent cannula and at de-airing procedures with lung inflation; (2) excessive negative pressure on the vent; and (3) an empty carbon dioxide tank and/or blocked filter. They stressed the importance of education for better comprehension of the surgical procedures, and wanted more communication and information sharing with anesthesiologists and surgeons.

### Future perspectives

Some surgeons wished to have more instruments that facilitate the efficient removal of intracardiac air, while others commented that they are now developing them. There were several questions (shown below) that have not yet been scientifically investigated.

- Should the bubbles depicted by TEE be completely removed?

If it is not essential, the CPB time can be shortened. TEE may visualize bubbles that are not important.

- Do bubbles cause ICU syndrome?

It was not encountered often before when they did not care for de-airing.

- Does the air in the right heart move to the left heart?

They expect scientific verification of intracardiac air and de-airing and hopefully some comprehensive guidelines, recommendations, or instructions, since this would be helpful for education of staff as well as better collaboration with the surgical team.

### Discussion

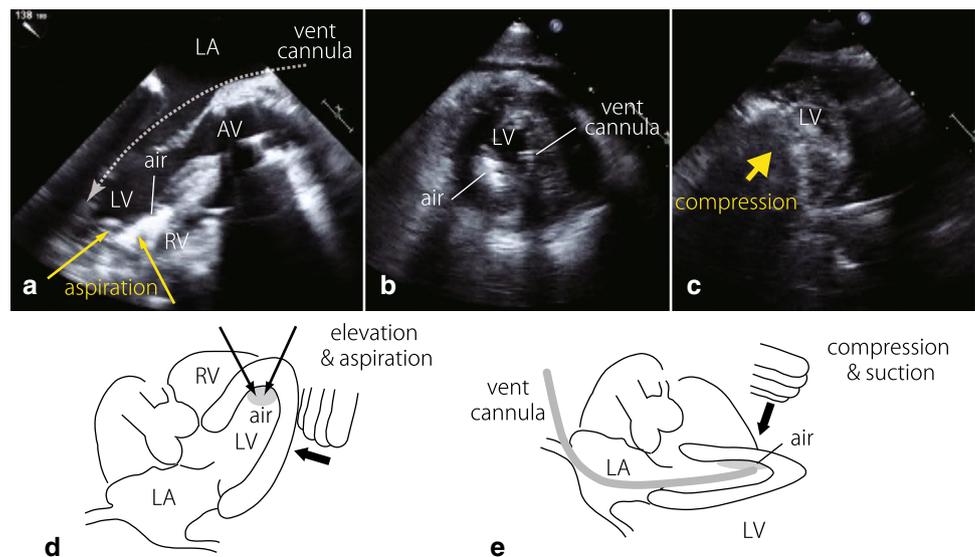
The current survey achieved a high collection rate and has shown several facts. First, both anesthesiologists and surgeons believe that de-airing is important, probably because air-related events are often encountered and can be critical, despite elaborate de-airing procedures. Second, the de-airing procedures are rather similar among institutions but not fully validated scientifically. Third, a problem on safety management has been elucidated. Some problems can be caused by technical errors or ineffective collaboration due to lack of communication or knowledge. Fourth, various recommendations, methods, and ideas have been gleaned from the questionnaires as well as the presentations at the joint symposium. To take full advantage of this information, the “best possible de-airing” as of this moment is described along with some literature review. This should be helpful for sharing common perceptions and knowledge and serve as material for discussion toward further sophistication of de-airing.

### Detection and location of air

The air is visualized by TEE mainly in two forms (Fig. 2). One is “bubbles” depicted as highly echogenic dots that swiftly move along the blood stream (Fig. 2a). They are likely to be “minute bubbles”. “Pooled air” is not so distinct but recognized as an acoustic shadow with a wavering motion that masks the images of structures below such as the RUPV, superior vena cava (SVC) or LV apex [12] (Fig. 2b). A strong echo at its surface with side lobes is another finding, but it is not always present. Besides these two forms, “coarse bubbles” are seen as an echogenic line along the wall of RUPV to LA accompanied by reverberations (Fig. 2c).

When air is detected, surgeons wonder whether it needs to be meticulously removed, since this may prolong the CPB time and cause mechanical stress on the heart due to tapping

**Fig. 3** Removal of air in the left ventricle (LV). **a** Air at the anteroseptal wall near the apex. A vent cannula is located at the posteromedial side and apart from the air. The air can be aspirated from two directions (yellow arrows). **b** Transgastric short-axis view showing the air apart from the vent cannula. **c** Compression of LV approximates the air to the vent cannula. **d, e** Schematic illustration of two de-airing procedures. Air can be aspirated from the LV apex or through the right ventricle (RV) or through the vent cannula with compression of LV. AV aortic valve, LA left ventricle



or agitating. Goldfarb reported that myocardial infarction was caused by 0.1–0.2 mL of air in the canine heart [14], which corresponds to pooled air with an acoustic shadow of 3–4 mm in width according to the approximation formula [15]. However, it is hard to assess the size of bubbles. While echocardiography can visualize bubbles of 5  $\mu\text{m}$  in diameter [16], nearly equal to the size of capillaries, heart block or myocardial ischemia occurs when coarse bubbles are seen. Since larger bubbles should have more buoyancy, coarse bubbles are supposed to be large and need to be removed.

A pitfall related to pooled air should be kept in mind. Side lobes generated by pooled air in the LA extend in various directions and may appear as a mass-like image in the LA in a different scanning plane [17]. Knowledge of this artifact is helpful for avoiding an unnecessary second pump-run due to misinterpretation.

### Carbon dioxide flooding

While carbon dioxide flooding of the operative field was shown to reduce the risk of arterial embolism [18, 19], Giordano et al. reported that there was no evidence of reduced postoperative cerebrovascular events, despite the intraoperative benefit of reducing air bubbles [20]. Despite elaborate preparation of insufflation, carbon dioxide can be absorbed in blood or water or aspirated by suction in the operative field, but there is no way to know whether any carbon dioxide remains. Such uncertainty might have led to the varying opinions among surgeons in the current survey. The best strategy may be to consider the worst-case scenario that the retained gas detected in the heart during weaning from CPB is just “air” after all carbon dioxide is absorbed.

### Air removal at each retention site

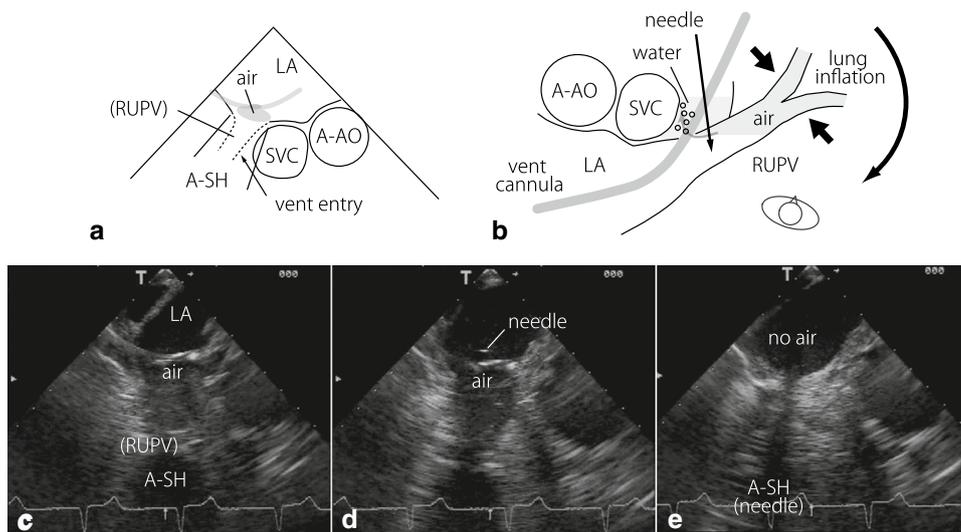
Before aortic declamping, pooled air is found mainly in the RUPV, LA, and LV apex and moves from moment to moment while transforming to bubbles or re-collecting as the pooled form or coarse bubbles during weaning from CPB. To minimize the total amount of air that enters the systemic circulation, efficient and timely collaboration among surgeons, anesthesiologists, and perfusionists is essential. It is necessary to visualize the air at each stage of weaning, retention site, and forms of air based on the knowledge of the behavior of air and TEE images. The best possible method for de-airing at each retention site is described below, and this was created with information collected from the survey and will require further refinement in the future.

#### Air in the LV apex

Most often seen is minute bubbles flowing off along the blood stream toward the aorta during weaning from CPB. They are probably too small to cause embolic events and actually no bubbles are visible in the vent circuit in this situation. However, the LV apex needs to be checked for pooled air or coarse bubbles before aortic declamping. It can stay there even after LV contraction recovers because of buoyancy. Unless properly removed, it may move to the aorta in a bolus at the time of a posture change and cause sudden circulatory collapse, as reported in the questionnaire (Table 1).

Although the pooled air is commonly crushed into coarse bubbles with vigorous agitation that can be aspirated from the root cannula, the efficacy of removal is questionable. It should be aspirated from the LV through a vent cannula or a needle. Despite expectations, however, the vent cannula is

**Fig. 4** Removal of air in the right upper pulmonary vein (RUPV). **a, b** Schematic illustration of visualization and removal procedures of air in the RUPV. Acoustic shadow (A-SH) caused by air masks the RUPV. Lung inflation at the right lower position with pulmonary venous return squeezes the air toward the left atrium (LA) and can be removed through the vent entry or aspirated through a needle. **c–e** Transesophageal echocardiograms of de-airing by a needle. The image of air and A-SH instantaneously disappears. A-AO ascending aorta, SVC superior vena cava



often located at the inferior side in the LV away from the air due to the stiffness of the cannula [21] (Fig. 3a). By compressing the LV apex dorsally, the air reaches the cannula and is aspirated with complete removal of air from the LV (Fig. 3b, c, e). The air may also be aspirated with a needle through the LV apex or via the right ventricle and interventricular septum (Fig. 3a, d). It is recommended that these procedures be done before full restoration of LV contraction to avoid an unnecessary injury of the heart. Occasionally, coarse air is seen but is not displaced despite tapping or agitation. Such air is probably minute bubbles trapped in the trabeculae or embolized in the myocardium and does not require removal.

In MICS, air is unlikely to remain in the LV because of the head-up, left-down position of the patient and compression of right lung. However, the above procedures are difficult when air is retained in the LV. To address this problem, Gundry et al. recommend flooding the LV with blood to scatter the air and then aspiration of the air via the vent cannula [22].

### Air in the RUPV

Among the four pulmonary veins, the RUPV is the most common site of air retention because it is easily emptied during atriotomy. It has been described as an inverted tube model [23] and potentially contains several mL of air that could cause circulatory collapse postoperatively. Lung inflation with the patient in a right-down/head-down posture is helpful for squeezing air toward the LA while accelerating blood flow velocity in the RUPV, which is further augmented by adequate pulmonary venous return [24].

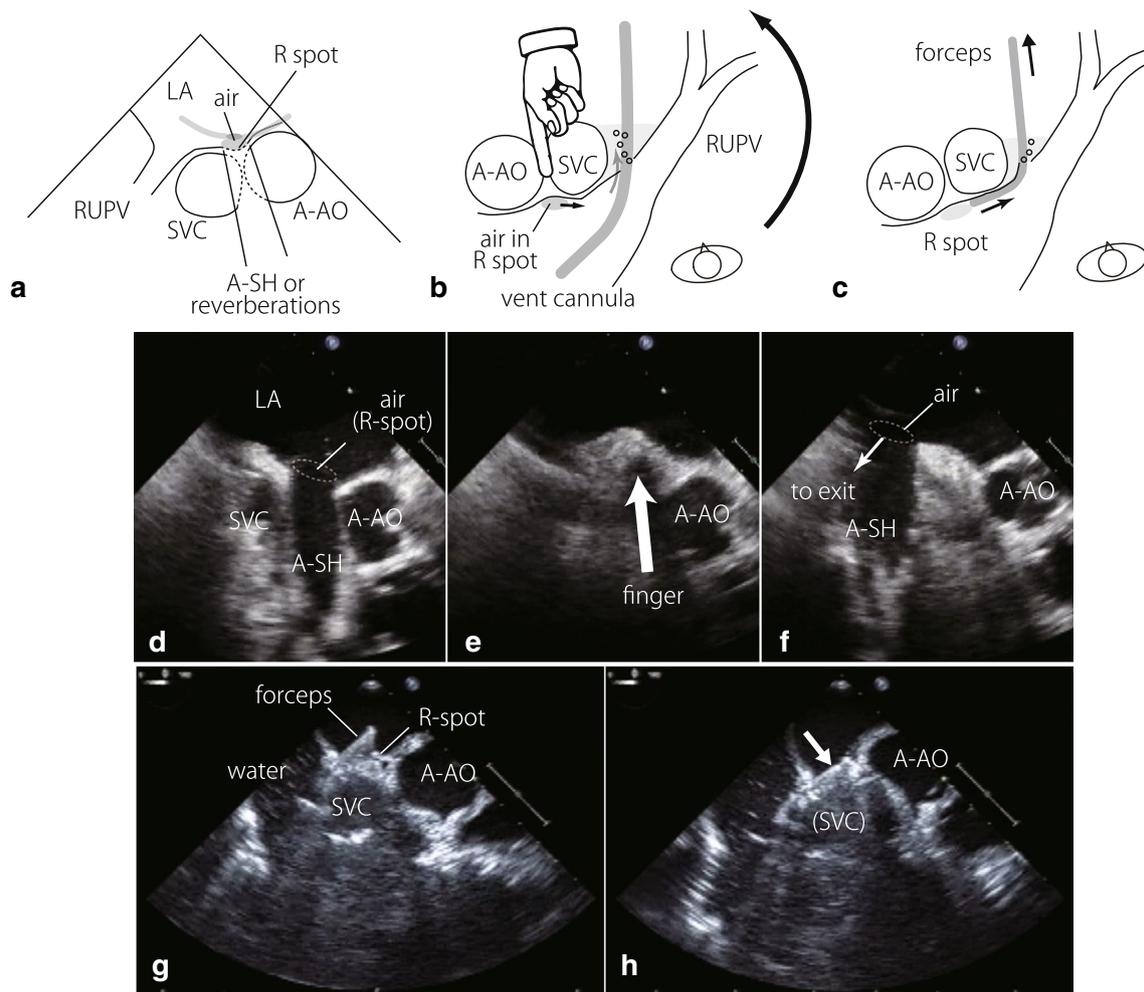
The RUPV should be checked for pooled air before aortic declamping because it can fill the RUPV up to the atrial orifice, which appears as a wide acoustic shadow on TEE that masks the RUPV and SVC (Fig. 4a, d). There are three ways to remove it. First, it is aspirated by a needle. As 1 mL or more of air is

aspirated, the acoustic shadow on TEE disappears (Fig. 4b–f). Second, the tourniquet around the LV vent cannula is loosened; while it is covered with some saline to avoid air entry (Fig. 4b). Air comes out through the gap around the cannula. Another way is to aspirate the air via the vent cannula after it is moved into the LV, but this is not optimal because it is difficult to remove the re-collected air in the LV at this stage.

During weaning from CPB, numerous bubbles come out of the RUPV as pulmonary venous return recovers, indicating that air still remains in the distal portion of RUPV. When bubbles are dense, aspiration through the vent cannula is temporarily augmented. If dense bubbles continuously come out even after weaning from CPB, an alveolar–venous fistula should be considered [25].

### Air in the LA

Besides minute bubbles passing in the LA, coarse bubbles and pooled air are often found. The latter is located at the small recess between the SVC and ascending aorta, and it is called the “R spot” [21] (Fig. 5a). It persists despite changes in posture or tapping of the heart but can be moved into the LV by vigorous agitation, which is commonly done. At this stage, however, the air that re-collects in the LV is difficult to remove, or it may cause heart block associated with echogenic dots in the interventricular septum. Thus, it is better to remove this air, while it is in the LA. The air can be moved toward the RUPV with the patient in a left-down position and removed through the site of vent entry. Bubbles are often seen to come out. If they cannot cross over the ridge of the SVC, digital compression of the R spot may be effective, which is visualized by TEE as an inversion of the R spot into the LA (Fig. 5b, d–f). Or the ridge of SVC may be lifted with forceps or other instruments (Fig. 5c, g, h). Prior to these procedures, however, an exit needs to be ready to avoid the return of air into the RUPV.



**Fig. 5** Removal of air in the left atrium (LA). **a–c** Schematic illustration of visualization and de-airing. The air stays at the R spot associated with acoustic shadow (A-SH). Digital compression of R spot or elevation of superior vena cava (SVC) moves the air toward the vent

entry. **d–h** Transesophageal echocardiograms showing removal of air by digital compression and SVC elevation by a forceps. A-AO ascending aorta

**Other devices for de-airing in the literature**

Zhong et al. reported a device for removing air from the LV, which was composed of a transparent bulb and a needle [26]. The LV apex was elevated and punctured, and the air was replaced with blood by compressing and releasing the bulb, although this method was not feasible in MICS. Kuralay et al. reported de-airing of the LV through a 16G catheter, which was inserted through the prosthetic valve in cases that had aortic valve replacement [27]. However, this method has limitations. It is not applicable in cases with mechanical valve implantation, and damage of the bioprosthesis is a concern. When air appears again after the catheter is withdrawn, re-insertion of the catheter may be difficult. Koul et al. collapsed the lungs bilaterally to remove air from the pulmonary vein [28], and the efficacy of this maneuver was verified [29]. However, it necessitates bilateral pleurotomy and is not suitable in MICS cases or patients

with a history of lung surgery. Viewed from the opposite side, intentional pleurotomy causes pleural adhesion and limits the option of thoracoscopic surgery in case this patient develops lung cancer in the future, and necessitates thoracotomy. Since many patients with atherosclerotic diseases are smokers and potentially develop lung cancer, potential restriction of treatment option in other field should be taken into consideration [30].

The report and discussion in this paper are under restricted circumstances. In the current survey, the interviewed hospitals were not identical between surgery and anesthesiology, because the number of JSCVA-qualified hospitals is still small, which might have been responsible for the inconsistent responses between surgeons and anesthesiologists. As the number of qualified anesthesiologists increases, this discrepancy may be reduced as well as the requests by surgeons to anesthesiologists may decrease. Because the survey was aimed just to clarify the

current status, no statistical analysis was done. Despite such limitations, this report probably serves as a material for further discussion.

## Conclusions

De-airing is a long-standing but still pending issue in cardiac surgery. The survey elucidated the current situation in Japan as well as problems to be studied in a scientific basis. Furthermore, it is anticipated that surgeons, anesthesiologists and clinical engineers collaborate timely and efficiently to avoid the preventable troubles. The authors hope that this report will contribute to this purpose in the future.

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## Compliance with ethical standard

**Conflict of interest** The authors have no conflict of interest.

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