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Venous air embolism, preservation/reperfusion injury, and the presence of intravascular air collections in human donor livers: a retrospective clinical study

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Abstract In human liver transplantation, air embolism is seldom encountered after graft reperfusion. Nevertheless, despite adequate flushing and clamping routines, air emboli have been reported in transesophageal echocardiography (TEE) studies performed during the reperfusion phase. We retrospectively investigated whether air in the donor liver – as observed with pretransplant magnetic resonace imaging (MRI) – resulted in clinical air embolism or contributed to preservation/reperfusion injury. Clinical air embolism was assessed by intraoperative hemodynamics and end-tidal CO_2 monitoring. Preservation/reperfusion injury was assessed in postoperative biochemical measurements. The outcomes were compared between patients receiving livers containing significant intrahepatic air and patients receiving livers without intrahepatic air. Forty-three livers were studied, seven of which had major intrahepatic air and ten of which had no evidence of air collections. Twenty-six livers showed minor amounts of air and were excluded from further study. One patient who received a liver that did not contain intrahepatic air had clinical evidence of air embolism. Clinical air embolism did not appear to be associated with the presence of significant intrahepatic air based upon pretransplant MRI. Intrahepatic air did not seem to affect the amount of preservation/reperfusion injury. Our data indicate that air bubbles in the portal and arterial branches are absorbed during reperfusion and that the majority of intrahepatic air is effectively removed by the specific flushing routines.

Key words Liver preservation, MRI · MRI, liver preservation · Air collection, liver preservation, MRI

Introduction

In human liver transplantation, air embolism is seldom reported after graft reperfusion [4, 5, 9]. Prevention of air embolism is the goal of specific flushing and clamping routines during the implantation phase of a liver transplant. Despite these routines, air embolism has been documented using transesophageal echocardiography (TEE) during graft reperfusion [16]. This indicates that the donor liver itself may have contained air that was released into the recipient circulation during graft reperfusion. Recently, we demonstrated that approximately one-third of donor livers contained intravascular air collections [20]. Apart from potential venous air emboli [7], air bubbles can also cause local complement activation and platelet aggregation, which may lead to thrombosis with subsequent parenchymal damage [2, 8, 17–19].

It is not known whether air released from the donor liver after reperfusion has any hemodynamic effects on the recipient circulation or whether air in the donor liver contributes to preservation/reperfusion injury.

To address these questions, we used magnetic resonance imaging (MRI) to detect intrahepatic air within donor livers prior to implantation. Clinical air embolism was assessed in retrospect from intraoperative hemodynamics and end tidal CO_2 monitoring. Preservation/reperfusion injury was assessed from recipient blood samples. The outcomes were compared between patients receiving livers containing significant intrahepatic air and patients receiving livers without intrahepatic air. In addition, in order to reveal possible causes for intrahepatic air, selected preservation-related events were investigated in relation to the presence of intrahepatic air.

Methods

Donor livers

Forty-three human donor livers were included in the study. Livers were obtained according to a standardized operative procedure [13]. Livers were flushed in situ with 2 l University of Wisconsin (IW) solution (DuPont Critical Care, Waukegan, Ill., USA) via the aorta and portal vein. After explantation, additional UW solution was infused via the hepatic artery and biliary tree until the caval outflow was clear. Livers were then stored, floating in UW solution, in sterile plastic bags on melting ice in styrofoam containers until transplantation. Donor data and data on the organ procurement were obtained from the Eurotransplant Office, Leiden, the Netherlands.

Imaging protocol

All imaging was performed according to a standardized protocol [20]. The plastic bags were never opened, so the livers remained sterile and stored on melting ice all the time. After scoutview imaging, which made it possible to determine the exact position of the liver in its container, the entire liver was imaged in 25–30 intermediately T_1-weighted slices (repetition time ranging from 1000 to 1200 ms, echo time fixed at 20 ms). Depending on the size of the liver, the slice thickness ranged from 2.5 to 3.5 mm. In retrospect, the amount of intrahepatic air was estimated from these images and livers were divided into three groups. Group 1 included livers with no air collections. Group 2 livers had major air collections in the intrahepatic vasculature. Group 3 livers matched neither the characteristics of group 1 nor those of group 2 and was excluded from further statistical analysis. For example, livers containing a few bubbles in the vasculature or major bile ducts were classified in group 3.

Liver transplantation

All livers were transplanted orthotopically [15] with venovenous bypass used during the anhepatic phase [14]. To avoid the entry of air bubbles and potassium-rich UW solution into the recipient circulation, specific flushing and clamping routines were employed. After completion of the suprahepatic caval anastomosis, the infrahepatic cavae were anastomosed. The anterior row of running sutures of the infrahepatic anastomosis was not tied, allowing the insertion of a cannula into the retrohepatic IVC. After completion of the portal vein anastomosis, the liver was reperfused via the portal vein with the first 500–1000 ml of portal effluent (containg some UW solution) drained via the retrohepatic cava. The cannula was then removed and the infrahepatic anastomosis completed. The suprahepatic clamp was removed, followed by the infrahepatic cava clamp. The time interval between imaging and the start of the implantation procedure ranged from 0.5 to 2 h. The transplanting surgeons were unaware of the MRI findings.

Hemodynamic data

Hemodynamic parameters and end-tidal gas monitoring were recorded using an automated record-keeping system with data recorded every single minute. The unclamping of the suprahepatic inferior caval vein was chosen as the central time point at which hemodynamic changes due to venous air embolism are most likely. The time span around this point (t = 0) was from 10 min before unclamping (t = –10) to 20 min after unclamping (t = 20). The following hemodynamic parameters were recorded: heart rate, systolic blood

pressure, diastolic blood pressure, oxygen saturation, end-expiratory CO_2, systolic pulmonary blood pressure, and diastolic pulmonary blood pressure.

Data analysis

Hemodynamic data of groups 1 and 2 were independently assessed in retrospect for venous air embolism by two anesthesiologists (A. B. and R. V.) who were blinded to the MRI findings. As mentioned, group 3 was excluded from further analysis. Venous air embolism was thought present if diastolic and systolic pulmonary blood pressure suddenly rose with a simultaneous sudden decrease in end expiratory CO_2 and in systemic blood pressure.

To determine whether the occurrence of air was associated with significantly more preservation/reperfusion injury in the immediate postoperative period, groups 1 and 2 were compared with respect to the serum concentrations of alkaline phosphatase (AP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma glutamyl transpeptidase (GGTP), and total bilirubin at days 1,2,3, and 7 after transplantation.

To evaluate whether preservation related events caused air in the liver, groups 1 and 2 were compared with respect to the duration of the cold storage time, whether or not the liver was part of a multiorgan procedure and whether or not the liver had been subjected to repeated alterations of atmospheric pressure during transportation.

For comparison of the two groups of donor livers and their recipients, Wilcoxon's rank sum test was used.

Results

Imaging results

A total of 43 livers were examined with MRI. Of these, ten were categorized in group 1 (no air). Seven livers had major air collections in the vessels and were, therefore, categorized in group 2 (Fig. 1). Air collections were observed in the hepatic veins in all cases in group 2 ($n = 7$), but in some cases, additional air collections were observed in the portal vein branches of the right li-

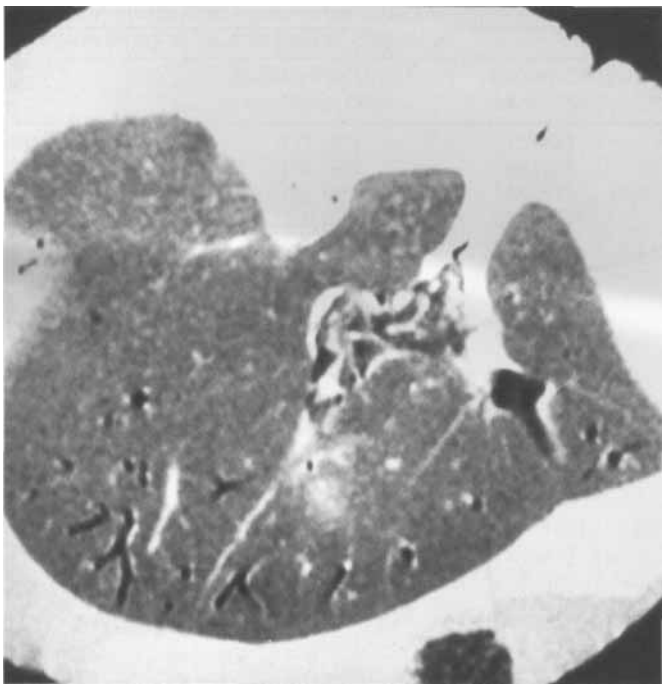

Fig. 1 Magnetic resonance image through a donor liver demonstrating air collections deep into the peripheral hepatic veins

ver lobe ($n = 2$), as well as in hepatic artery branches ($n = 1$). Twenty-six cases were categorized in group 3 and were, therefore, excluded from further statistical analysis.

Correlation of air with the hemodynamic recordings during the implantation phase

The evaluating anesthesiologists identified one case of possible pulmonary air embolism in which hemodynamic data were characterized by a massive increase in the pulmonary blood pressure with a simultaneous decrease in end-expiratory CO_2 and systemic blood pressure (Fig. 2). That case had been categorized in group 1 (no air in the liver) according to the imaging criteria.

Correlation of air with parameters for preservation/reperfusion damage (Table 1)

Statistical analysis demonstrated a significant difference between the two groups for AP on day 7 (group 1: 230 ± 99 U/l, group 2: 133 ± 44 U/l). No other parameters for preservation/reperfusion injury were significantly different.

Correlation of air with preservation related events

Mean duration of cold ischemia was 5.5 ± 1.7 h for group 1 livers and 6.5 ± 1.8 h for those in group 2 (P = NS). The mode of transportation was not different between the two groups. Specifically, there was no difference between livers obtained from donors in our own hospital and livers transported by aircraft without pressure cabins. No differences were observed when only the liver was used for donation versus when it was obtained in a multiorgan procedure.

Other findings

In the two cases of proven portal venous air, a transient, bluish, spotty discoloration during portal reperfusion was observed that may have been caused by a temporary obstruction of blood flow due to air embolism (R.F.E. Wolf, personal observation). With respect to the indicators for preservation/reperfusion injury, no significant differences were observed in these two livers compared to the rest of the air-containing group. Also, the one liver with intra-arterial air collections was not significantly different from the rest of the livers in group 2.

Discussion

Air embolism has seldom been reported after graft reperfusion during human liver transplantation [4, 5, 9]. However, in cases where it has been documented, the air embolism caused massive hemodynamic disturbances and was, therefore, readily recognized by the attending anesthesiologists. Evidence for air embolism on a more modest scale was observed in TEE studies [16, T.H.N. Groenland, unpublished data]. In these studies, highly echogenic material suggestive of air bubbles was observed passing from the IVC into the right atrium during graft reperfusion. Since, in the abovementioned studies, all necessary flushing and clamping routines during the implantation phase were properly employed, the entrance of air into the venous circulation due to leaking vascular anastomoses was practically excluded. This suggests that there was another source for the observed air emboli. Perhaps the air emboli in the recipient circulation were released from the donor liver itself, indicating that the donor liver must have contained air before the start of the implantation. Evidence that supports this hypothesis was found in the observation of an abundant presence of air in isolated donor livers before transplantation [20]. The observed air collections were found – widespread in some cases – in the vessels of the donor livers. This location raised additional concern since intravascular air bubbles have the

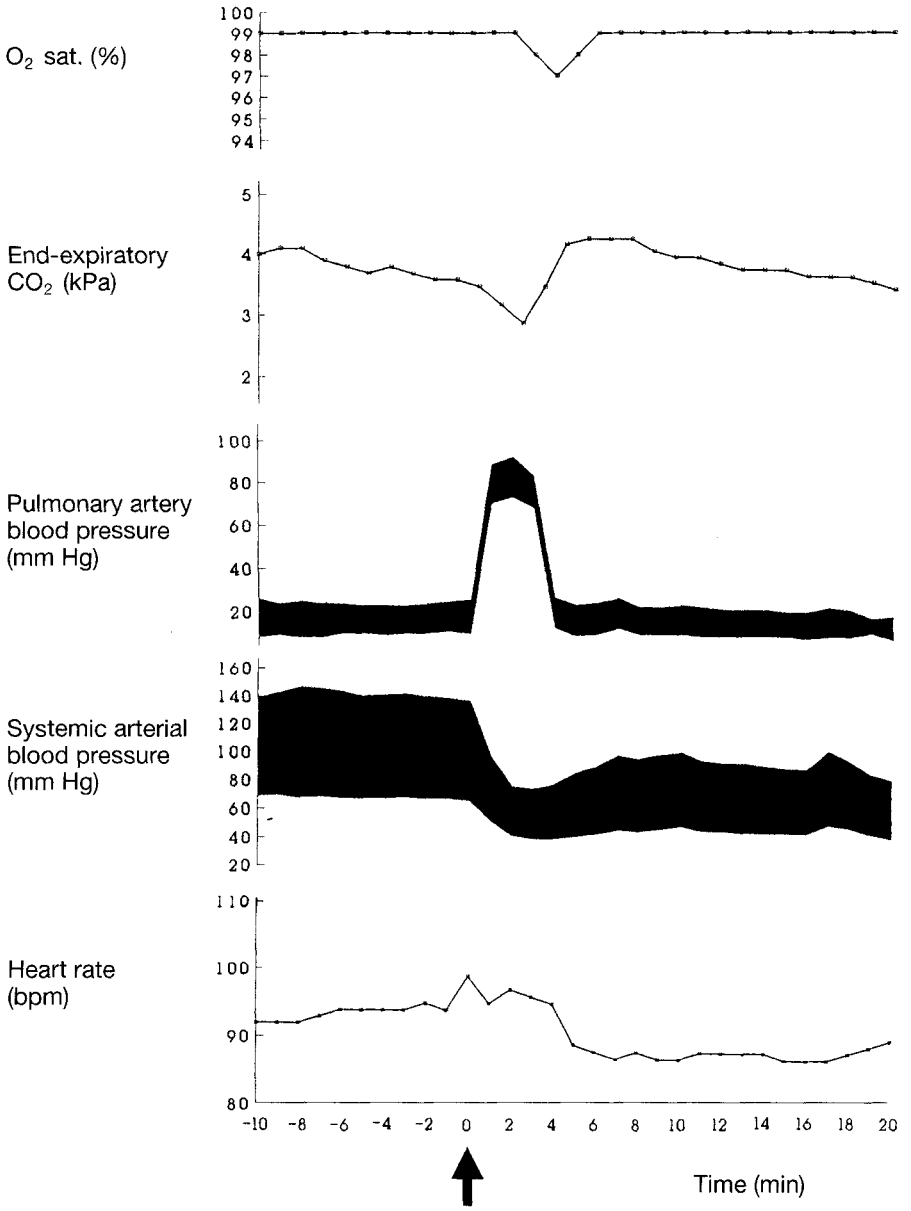

Fig. 2 Anesthesiological recordings suggesting the occurrence of air embolism in the pulmonary circulation. *Arrow* indicates the moment of unclamping of the suprahepatic IVC

ability to act as foreign bodies, possibly causing local damage to the vascular endothelium [2, 8, 17–19].

The present study demonstrates that the presence of air in donor livers does not have clinically important hemodynamic consequences during reperfusion. Additionally, recipient biochemical parameters show that intrahepatic air does not cause additional preservation/reperfusion injury to the graft.

One of the main findings of this study was that intrahepatic air is not a cause of major venous air embolism in the recipient during or after graft reperfusion. Two theoretical explanations are possible. The first is that the air remains in the vessels and is not released into the circulation during reperfusion. However, this would have been noticed on post-transplant liver ultrasound, which was routinely performed in all recipients. The second explanation, which appears more likely, is that the prereperfusion flush removes the preservation solution together with the major portion of air from the hepatic veins. A small amount of air may remain in the liver and be released into the recipient circulation upon portal reperfusion. This may be the explanation for limited air embolism, detectable with TEE, but not causing major circulatory disturbances and, as such, not manifest in the hemodynamic recordings. It proves that the prereperfusion flush procedure is, indeed, effective in the way that it was intended to be, namely, in removing the preservation solution and air bubbles before complete

Table 1 Postoperative biochemical indicators for preservation/reperfusion injury in the two patient groups

	Group 1[a] ($n = 10$) Mean (SD)	Group 2[b] ($n = 7$) Mean (SD)
AP day 1	117 (87)	72 (62)
2	141 (92)	89 (60)
3	161 (89)	108 (57)
7	230 (99)*	133 (44)*
ASAT day 1	900 (1074)	543 (406)
2	756 (973)	433 (305)
3	312 (240)	257 (192)
7	127 (168)	286 (567)
ALAT day 1	765 (877)	513 (366)
2	934 (1060)	774 (632)
3	682 (665)	795 (745)
7	282 (184)	215 (148)
GGTP day 1	73 (36)	45 (24)
2	94 (71)	34 (11)
3	191 (141)	137 (131)
7	301 (163)	198 (55)
Total bilirubin day 1	129 (83)	139 (79)
2	101 (72)	101 (63)
3	95 (64)	104 (84)
7	132 (100)	134 (135)

* $P < 0.05$

[a] Livers with no air

[b] Livers containing large amounts of air

reperfusion. The signs of air embolism that we found in retrospect in the case in the group containing no air may have been caused by remaining air in the inferior caval vein or air that entered during the removal of the cannula in the infrahepatic anastomosis; however, proof is lacking. In the case of venous air embolism in a recipient with a patent foramen ovale, the elevated right atrium pressure can possibly force air bubbles into the systemic circulation with all of the associated consequences. This is not completely hypothetical since it has been reported that shortly after graft reperfusion a right-left shunt can develop [12].

Another important finding was that intrahepatic air does not cause significant additional preservation/reperfusion injury to the graft. In theory, air in (afferent) hepatic artery branches or portal venous branches could have consequences for post-transplant organ function. During reperfusion, the organ is regaining its original body temperature. Since the passage of bubbles through the capillary network is highly unlikely [10], obstruction of blood flow by air bubbles could cause warm ischemic damage downstream. Reperfusion of these ischemic areas will increase the amount of parenchymal damage [11]. This, in turn, will cause liver viability to deteriorate by impairing the adenosine triphosphate (ATP)-regenerating capacity of the hepatocytes [6]. Inevitably, this would result in more preservation/reperfusion injury with an elevation of serum liver enzymes. Our findings indicate that clinically important additional parenchymal damage due to obstruction of afferent liver vessels by air bubbles does not occur. The bubbles that were clearly demonstrated in hepatic artery and portal vein branches were probably rapidly absorbed by the blood after reperfusion. The other potential danger of intravascular air bubbles is their ability to act as foreign bodies. Extensive research on the pathophysiology of air embolism has shown that the blood-air interface itself can cause complement activation and that it can induce platelet aggregation with thrombus formation [2, 8, 17–19]. In our study we found a significantly lower AP only on day 7 in the group containing air. In view of the absence of any other significant relationships between the amount of preservation/reperfusion injury and the presence of air, we consider this correlation to be of no clinical importance. Therefore, we have to assume that if platelet activation by the air bubbles occurs, it is probably induced at a very limited scale and goes unrecognized in the massive Derangement of the clotting system that always occurs during liver transplantation.

The origin and composition of the air bubbles are still unclear. In an earlier study, we postulated that air in the portal vein or in the hepatic artery branches may have been caused by leaking perfusion catheters during in situ hypothermic perfusion or during subsequent workbench procedures [20]. Support for this hypothesis was found in the observation that when portal venous air was present, it was predominantly found in the right liver lobe. This location can only be explained by the preference for air bubbles to enter the right portal vein during workbench perfusion since, during this procedure, its direction is slightly upwards as compared to the left portal vein. Air entrapment in the hepatic veins is most likely caused by regurgitation of air after transection of the suprahepatic and infrahepatic caval veins during donor hepatectomy after in situ perfusion. Repeated alterations in atmospheric pressure, for example, as they occur during air transportation, could possibly force bubbles deeper into the liver vasculature, but we have no proof of this. Also, uptake of preservation solution from the vascular bed could suck regurgitated air deep into the terminal hepatic vein branches (Fig. 1). The suggestion that the air bubbles might consist of CO_2 as a sign of continuing metabolic activity of the hepatocytes is highly unlikely since, during cold storage, the remaining low metabolic activity consists of (anaerobic) glycolysis, which does not generate CO_2. Gaseous anesthetics are unlikely to be a source of bubbles since all of our liver donors were ventilated with air/oxygen mixtures during donor hepatectomy. Interference of the ice-cold organ preservative with blood with a possible intrahepatic release of dissolved or bound gases, either from blood or from the preservation solution, could be possible, but if that were the

case, we would have observed air bubbles in equal amounts in all donor livers. A sample of air bubbles might reveal the origin of air bubbles in cold-stored livers. Up to now, due to logistic limitations, we have not been able to obtain a sample of the air bubbles.

It should also be noted that during the time interval between imaging and actual implantation, the liver is manipulated. There may be passive drainage of fluid (and possibly air) when the liver is picked up out of the solution and when the vascular anastomoses are created. This may also be one of the reasons for the absence of clinical air embolism in the livers containing air.

Our data do not indicate that air in the graft after transplantation – an alarming sign that is associated with graft dysfunction [1, 3, 10] – is related to air bubbles in the donor organ before transplantation.

In summary, it was demonstrated that air bubbles in the vasculature of the explanted donor liver, are not associated with the incidence of clinically significant air embolism during reperfusion, nor do they have clinically significant consequences for early graft function. Our data indicate that air bubbles in the portal and arterial branches are most likely absorbed during reperfusion and that air bubbles in the hepatic veins are effectively flushed out by the specific flushing routines.

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