Microemboli, developed during haemodialysis, pass the lung barrier and may cause ischaemic lesions in organs such as the brain

Ulf Forsberg¹, Per Jonsson², Christofer Stegmayr² and Bernd Stegmayr²

¹Medicin-Geriatriska Kliniken, Skellefteå lasarett, Lasarettsvägen 29, 931 86 Skellefteå Sweden and ²Department of Internal Medicine, Division of Nephrology, Norrland University Hospital, Umeå Sweden

Correspondence and offprint requests to: Ulf Forsberg; E-mail: ulf.forsberg@gmail.com

Abstract

Background. Chronic haemodialysis (HD) may relieve some medical problems of terminal uraemia, but the life expectancy of patients is still significantly shortened, and there is a greatly increased morbidity. This includes pulmonary morbidity and chronic central nervous system (CNS) abnormalities. Previous studies have shown that a considerable amount of air microbubbles emanate within the blood lines of the dialysis device and pass the air detector without sounding an alarm. The aim of this study was to investigate whether microemboli can pass to the patient and whether they could be detected in the carotid artery.

Methods. A total of 54 patients on chronic HD (16 with central dialysis catheter) were investigated with an ultrasound detector (Hatteland, Røyken, Norway) for the presence of microemboli at the arteriovenous (AV) fistula/graft and at the common carotid artery before and during HD. Measurements were taken for 2 and 5 min, respectively. Non-parametric paired statistics were used (Wilcoxon).

Results. The median number (range) and mean ± SD of microembolic signals detected at the AV access site before commencing dialysis and during HD were 0 (0–3) and 0.2 ± 0.5 versus 4 (0–85) and 13.5 ± 20 (P = 0.000); at the carotid artery, 1 (0–14) and 1.7 ± 2.9 versus 2 (0–36) and 3.5 ± 5.8 (P = 0.008).

Conclusions. The infused and returning fluid from HD devices contains air microbubbles that enter the patient without triggering any alarms. These small emboli pass the lung and may cause ischaemic lesions in organs supported by the arterial circuit, such as the brain.

Keywords: haemodialysis; hazards with haemodialysis; microbubbles; microemboli

Introduction

Venous microair infusion is considered less critical than arterial air infusion since air infused at the venous side ends up in the lungs and is exhaled there [1,2]. If the air is formed as small microbubbles, they are thought to collapse and be absorbed into the blood relatively quickly [3]. The International Electrotechnical Commission (IEC) standards for infusion pumps and dialysis machines thus tolerate some air leakage. Less than 1 mL/15 min, but not including bubbles below the size of 50 μL, is accepted [4]. Less than 0.03 mL/kg body weight and minutes for continuous infusion or 0.1 mL/kg body weight for bolus infusion is tolerated [5].

Spillovers of intravenously infused air to the arterial circulation have been reported but are thought to be the result of either an open foramen ovale or a massive air infusion [1,6].

In a general clinical setting, little attention is paid to smaller amounts of visible air injected by syringe or entering via cannula during infusion since this only usually happens for a brief period. However, frequent injections and infusions are given to patients in intensive care units (ICU) or when on chronic haemodialysis.

During haemodialysis, some of the patient's blood is taken from an access site, usually located in the arm and known as an arteriovenous fistula or graft (AV access). Blood access can also be established by central dialysis catheter (CDC) inserted in or near the right atrium. The blood is then circulated through an extracorporeal tubing system which normally also contains a peristaltic pump, a dialysis filter and, before returning to the venous circulation, a venous chamber to trap any air contamination. When the air is detected, the air trap detector automatically stops the blood pump and thus the blood flow.

The presence of microembolisms in haemodialysis was reported as early as 1975 [7]. In vitro as well as in vivo studies using Doppler ultrasound during haemodialysis sessions have revealed microembolic signals in the veins [8–11]. These microemboli may be composed of fibrinogen, artificial material or air bubbles. In one study, the authors suggested that the composition of the emboli was either synthetic particles or microbubbles due to the intensity of the microembolic signals. They suggested that the roller pump might induce the formation of signals from tube damage or by cavitation [10].

Jonsson et al. [12] found showers of in vitro microbubbles passing the venous chamber without triggering the alarm. These experiments were done without blood

Advance Access publication 19 March 2010

doi: 10.1093/ndt/gfq116


© The Author 2010. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.
For Permissions, please e-mail: journals.permissions@oxfordjournals.org
and therefore ruled out the presence of clots as a reason for embolic signals. Due to the design of the experiment, these signals were unlikely to consist of plastic material derived from the tubing system [12,13]. The presence of air emboli passing the air detector was verified visually. The findings were also verified in vivo during dialysis.

Patients on haemodialysis have an increased morbidity and mortality compared to the general population [14]. Cardiovascular reasons for morbidity are the most common. Also noteworthy is an increased prevalence of cerebral atrophy and regression of neurocognitive status in long-term haemodialysis (HD) patients [15–17]. Another finding in HD patients is an increased prevalence of pulmonary hypertension [18–21]. It has been suggested that the reason for these findings is partly high pulmonary arterial pressure, elevated due to vasoconstriction and a high cardiac output resulting from fluid overload and AV shunt [22]. Another reason for this risk may be the increased presence of microemboli in HD patients [23].

Aim of this study

The aim of the study was to investigate whether microbubbles passing the air detector during HD were still detectable in the patient's venous system and whether such signals could also be detected on the patient's arterial side—the carotid artery for example.

Materials and methods

The study comprised 54 patients on chronic HD, with a median age of 62 years (range 24–86 years of age). Initially, the number of patients was 55. One was excluded before the measurements were finished since he suffered from muscular fibrillation that did not allow measurements without extensive unintended movements. These movements made the reliable measurements impossible. There were 24 females and 30 males. The primary diagnosis causing end-stage renal function can be seen in Table 1. A standard treatment was carried out, and dialysis conducted using Gambro Lund, Sweden AK 200/200S devices in 27 sessions and Fresenius Bad Homburg, Germany 4008H/S devices in 23 sessions, including online devices in two patients. In one session, a Fresenius 5008 was used. In three cases, the dialysis session protocol did not include the information about what kind of dialysis device was used, although this is routinely requested. The dialysers used were Polyflux 17L, 140H, 170H, 210H, FX80 and F8HPS; all steam sterilized. During the HD sessions, an endovascular microemboli detector was used (EMEX-25, Hatteland Instrumentering, Røyken, Norway), based on the pulsed Doppler principle. A handheld probe was used to investigate the presence of signals at the AV fistula/graft and carotid artery (either at the left or right side of the neck). The corresponding EmmonW software was used and reduced the number of possible false-positive detections caused by unintentional probe movement.

Where a CDC was used for access, the measurement was conducted only at the carotid artery. A recording was taken once before the patient was connected to the HD device and again at least 10 min after the onset of HD. The time the measurement was performed was by random after the first 10 min of HD had passed. This time was not registered since our previous in vivo study showed no difference in the presence of microbubbles after the start compared to before the end of dialysis [24]. Since we expected larger microbubbles to end up in the lungs, the time of measurement was prolonged up to 5 min at the carotid artery versus 2 min at the AV fistula.

The site of measurement on the AV fistula was within 10 cm proximal from the venous needle, at a site where a strong signal could be measured. Another part of the study investigated whether microbubbles were also able to pass an infusion pump. A setup was used comprising an infusion of either 0.9% NaCl Ringer’s with 4% albumin as a replacement fluid (for infusion during, say, aphaeresis) or StructoKabiven Peri-

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy type I and type II</td>
<td>12</td>
</tr>
<tr>
<td>Chronic renal failure; aetiology uncertain</td>
<td>11</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>7</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>4</td>
</tr>
<tr>
<td>Pyleonephritis</td>
<td>3</td>
</tr>
<tr>
<td>Tubular necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>2</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Congenital disease</td>
<td>1</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
<td>1</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
</tr>
</tbody>
</table>

The mean blood flow was 309 ± 52 mL/min at the start and 304 ± 51 mL/min at the end. Blood flow varied between the patients from 200 to 450 mL/min. The men had higher blood flow in the dialysis extracorporeal circulation (P = 0.016). Patients with an AV fistula or graft had a higher blood flow than those with CDC (P = 0.032). There was no difference in the use of either AV access or CDC between the genders. The air detector of the HD device did not give an alarm for any air passage during the dialysis procedures.

There was no significant difference regarding the presence of microemboli during HD between those patients using high- and low-permeability filters, nor was the number of emboli affected by blood flow, age or access type. This applied to both the AV access site and carotid artery.

AV access measurement

The median, range, means and ± SD of embolic signals before the start of dialysis are given in Table 2. There was a significant increase in embolic signals during HD at the AV access (Table 2). The number of microemboli
signals prior to dialysis correlates to the number during treatment at the AV fistula/graft (ρ = 0.41, P = 0.011). Using the HD conditions stated in these patients, there was no difference between males and females in the extent of the microembolic signals. When comparing the devices (Gambro AK 200 and Fresenius 4008), it seemed that those treated using Gambro were exposed to fewer emboli during HD sessions (median 4 versus 16, P = 0.049).

Carotid artery measurements
Fewer microembolic signals were measured (P = 0.005) in women compared to men. There was a significant increase in embolic signals during HD at the carotid artery (Table 2). Although measurement was for only 5 min, this study showed an increased number of signals in significantly more patients (38 out of 54) than would be expected if the only explanation for the passage of microemboli was an open foramen ovale (P = 0.000).

Peripheral vein infusion system
No air alarm was triggered during the infusion experiments. An infusion of sodium chloride 1000 ml/h resulted in one count during a 55-min measurement. The median amount of microbubbles during 11 runs was 206 counts per minute (range 34–443) when the infusion was conducted with a Ringer’s–albumin solution. During the infusion of StructoKabiven Perifer (speed 200 mL/h), a median was measured of 0 counts per 5 min (n = 17 runs, 13 runs with 0 and 4 runs with one count per 5 min).

Discussion
The extended study confirmed our previous preliminary report [25] that, once HD has started, there is a significant increase in embolic signals in both the AV fistula and carotid artery of the patients. Such microemboli are also infused to a greater or lesser extent by a regular infusion pump.

The data indicate that intravenous infusion of microbubbles also leads to microembolic signals in the arterial circulation.

This finding is important for infusion and venous extracorporeal circulation procedures, especially in frequently exposed patients, such as those in ICU or on chronic HD. Dialysis patients are often suffering from atherosclerosis and vascular lesions. Even if the endovascular microemboli detector, EMEX-25, has a corresponding software with an artefact removal algorithm, it can give false-positive detection signals induced by blood aggregates, caused by coagulation. Another source of possibly false detections is unintended movements of the probe or patients, which may happen both before and during HD measurements. That may well explain why signals were detected before commencing dialysis.

Previous in vitro data, conducted with a dextran–albumin solution that mimics the viscosity of blood, showed that air microbubbles passed the air trap without triggering an alarm during the dialysis procedure [12]. In vivo investigation of the presence of microembolic signals after the air trap detector revealed up to 900 signals per minute. This was similar to the in vitro findings and confirmed such passage within the venous blood part of the tubing system [26]. This strongly indicated that microembolic signals were caused by air microemboli.

There is a greater variability in the number of microbubbles at the AV access compared to at the carotid artery (0–85 versus 0–14, Table 2). Vascular access with a high recirculation would have greater proportion of blood from extracorporeal system, which can influence the total number of microemboli measured. We have not measured the recirculation of AV fistula during the study. However, the recirculation is measured regularly in our dialysis unit. The high recirculation is corrected routinely by reconstructive intervention of stenosis. Another factor inducing the variability in results is that microbubbles with larger diameters will be retained in the capillaries of the lung. Results from canine experiments showed the lungs to be superb bubble filters if the diameter is >22 μm [27]. The clinical consequences of such microbubbles might involve some of them being trapped in the lungs where they could cause circulatory obstruction and subsequent ischaemia. Air bubbles by themselves cause tissue damage in a number of other ways, further aggravating their adverse effect and possibly resulting in clinical relevant ischaemic injuries [23]. Such injuries, even in a minor range, can result in fibrotic scarring in afflicted areas and progressive pulmonary dysfunction. This may be strengthened by the findings of greater than expected fibroid pulmonary scarring in HD patients than in the general population [19,20]. Such scarring could result in pulmonary hypertension, a complication present in HD patients. The incidence of pulmonary hypertension is higher in patients treated with HD compared to those receiving peritoneal dialysis (PD) and pre-dialysis patients [21].

In addition to air microemboli, the increased extent of embolic signals in the carotid artery found in this study may be due to an increase in microemboli deriving from blood membrane interaction in the dialysis circuit and by activation of the coagulation system through the dialysis process itself [28–31]. Even if a generalized activation of the complement and coagulation system appears through exposure to air [23,32,33], there is no evidence that the exposure to air in the veins would induce coagulation pro-

### Table 2. Microembolic signals prior to haemodialysis (no-HD) and during HD (d-HD) at AV fistula/graft and carotid artery

<table>
<thead>
<tr>
<th></th>
<th>AV access no-HD (n = 38)</th>
<th>AV access d-HD</th>
<th>P</th>
<th>Carotid artery no-HD (n = 54)</th>
<th>Carotid artery d-HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0–3)</td>
<td>4 (0–85)</td>
<td>0.000</td>
<td>1 (0–14)</td>
<td>2 (0–36)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>0.2 ± 0.5</td>
<td>13.5 ± 20</td>
<td></td>
<td>1.7 ± 2.9</td>
<td>3.5 ± 5.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range) (first row) and means ± SD (second row).
cesses and produce microemboli on the arterial side. If so, this would be disadvantageous to the patient.

However, the data does not rule out the fact that air microemboli also may enter into the carotid arteries and arterial blood stream. This might happen by passage through an open foramen ovale present in up to 30% of the patients [1]. In those patients, even larger volumes of air and microemboli may pass into the arterial circuit. However, our data strengthen the hypothesis that air microbubbles or clots also pass to the arterial side in patients with no open foramen ovale. This is because a significantly higher number of patients had elevated embolic counts on the arterial side than would be expected if an open foramen ovale was the only option. Therefore, a considerable number of microemboli seem to pass the lung. One factor that would enable the microbubbles by air to pass through the lungs would be if they were smaller in size and not rapidly resorbed. We consider this to be possible since previous reports explain the dynamics of bubbles in a streaming fluid [23,24]. Thus, smaller bubbles more easily pass the air trap because their lift force is weaker than the driving force of the fluid flow. It is worth noting that our previous data showed the greatest number of microbubbles to have a diameter of 10 μm or less [12,13,24,26]. Such small bubbles may pass vessels and block even smaller capillaries [1] since they are of the magnitude of erythrocytes or less.

Additionally, the lifespan of gas bubbles could be considerably higher in human circulation than earlier stated [23]. In vessels, the microbubbles remodel into cylinders which extends their dissolution time by at least 50% [34]. Also, a layer of denatured proteins has been seen at the bubbles’ surface protecting them from dissolution [35,36]. Thus, smaller microbubbles might be able to pass through the pulmonary capillaries and enter the bloodstream to the left side of the heart. There they are ejected into the arteries, including the cardiac vessels, brain and other organs. This can result in microemboli and subsequent ischemic injuries in those organs.

Chronic renal failure maintained by HD increases the prevalence of silent cerebral infarction [37]. A consequence of such brain damage would increase the risk of premature cerebral dysfunction including dementia [15,17,38–43]. Previous studies suggest that the prevalence of cognitive impairment is worse in HD versus continuous ambulatory peritoneal dialysis (CAPD) patients [44–46]. These results may reflect the procedure itself.

Through small movements on the part of the patient or the investigator, the handheld probe can cause extra signals. A similar error appears before and during dialysis, but there is still a risk of evaluation bias due to lack of blinding. Further experiments had to be done to confirm this data.

In conclusion, this data shows that the infusing and returning of fluid from HD devices to the patient contains air microbubbles that enter the patient without triggering an alarm. The small emboli pass the lung and may cause ischemic lesions in organs supported by the arterial circuit, such as the brain. In addition to patients with HD, the problem should also be considered in patients who receive frequent infusions, especially if the infusion speed and viscosity are higher, as is the case with albumin and dextan infusions, and blood transfusions.

Acknowledgements. We thank all the personnel at the dialysis units in Skellefteå County Hospital and Norrland University Hospital, Umeå. We also thank the Department of Medicine, Norrland University Hospital, Umeå, Sweden and Njuruföreningen Norrland for their financial support. We thank Robert Tavoniku, Biomedical Engineering, Norrland University Hospital for advice about infusion pumps.

Conflict of interest statement. None declared.

References

Intradialytic exercise training reduces oxidative stress and epicardial fat: a pilot study

Kenneth R. Wilund1,2, Emily J. Tomayko2, Pei-Tzu Wu1, Hae Ryong Chung1, Srikanth Vallurupalli4, Batlagundu Lakshminarayanan3 and Bo Fernhall1

1Department of Kinesiology and Community Health, 2Division of Nutritional Sciences, 3Department of Internal Medicine, University of Illinois, Urbana–Champaign, USA and 4Department of Medicine, Southern Illinois University School of Medicine, Springfield, USA

Correspondence and offprint requests to: Kenneth R. Wilund; E-mail: kwilund@illinois.edu

Abstract

Background. Cardiovascular disease (CVD) mortality rates are greatly elevated in chronic kidney disease patients receiving maintenance haemodialysis therapy. The purpose of this study was to evaluate the efficacy of intradialytic endurance exercise training on novel risk factors that may contribute to this excessive CVD risk.

Methods. Seventeen haemodialysis patients were randomized to either an intradialytic exercise training (cycling) group (EX; n = 8) or a non-exercising control group.