

ORIGINAL ARTICLE

Microemboli induced by air bubbles may be deposited in organs as a consequence of contamination during medical care

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Background. Larger volumes of accidental air infused during medical care may end up as emboli while microbubbles of air are supposed to be absorbed and cause no harm. The aim of this autopsy study was to investigate if microbubbles of air accidentally entering the bloodline may be detected as microemboli (ME) in tissue such as lungs, brain and heart. If so, do differences in prevalence exist between haemodialysis (HD) and amyotrophic lateral sclerosis (ALS) patients.

Methods. Included were data from 44 patients treated by medical healthcare before death. Twenty-five cases had been treated with chronic HD and 19 cases died from ALS. Since air in the bloodline activates coagulation, ME could appear. To discriminate between microbubbles caused by artificial contamination during autopsy versus microbubbles deposited *in vivo*, tissues were stained with a polyclonal fluorescent antibody against fibrinogen, fibrin and fragments E and D. Fluorescence staining was used to visualize ME counted within 25 microscopic fields (600×) of a tissue preparation. One tissue preparation was used if available from the lung, heart and frontal lobe of the brain and in five cases also the cerebellum.

Results. Microbubbles can be verified at autopsy as ME in the lung, heart and brain in tissue from patients exposed to more extensive medical care. There were significantly more ME in the lungs versus the heart or brain. Women had fewer ME than men. The HD group had a higher median of ME per section than the ALS group (lung: 6 versus 3, $P = .007$; heart: 2.5 versus 1, $P = .013$; brain: 7.5 versus 2, $P = .001$) and had more sections with ME findings than the ALS group ($P = .002$). A correlation existed between the time on HD (months) and ME in the lungs.

Conclusions. More ME were present in HD patients compared with those who suffered from ALS. Minimizing air contamination from syringes, infusions and bloodlines will decrease ME and subsequent tissue injury.

LAY SUMMARY

Larger volumes of accidental air infused during medical care may end up as emboli while microbubbles of air are supposed to be absorbed and cause no harm. Microbubbles can be verified at autopsy as microemboli (ME) by air in lung, heart and brain in tissue from patients exposed to dialysis and more cannulation and infusions. Minimizing air exposure from syringes, infusions and bloodlines may decrease the risk of ME by air and subsequent tissue injury.

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Keywords: amyotrophic lateral sclerosis, dialysis, haemodialysis, microbubbles, microemboli

INTRODUCTION

Accidental injection or infusion of larger amounts of air may cause severe pulmonary emboli if entered intravenously or cerebral emboli if entering through the carotid arteries. During a cardiopulmonary bypass, gaseous microemboli (ME) have been recognized with different side effects [1, 2], although air detectors have limited detection capacity [3, 4]. Little is known about smaller volumes of accidental air contamination into the veins during injections and/or infusions of medication or nutrition in patients with severe stages of diseases such as amyotrophic lateral sclerosis (ALS).

Other patients exposed to air contamination by repeated infusions are patients performing chronic haemodialysis (HD) [5–10]. During HD, blood exits the body from a vascular access such as an arteriovenous fistula or central dialysis catheter and enters into a bloodline. The bloodline is for single use and represents the extracorporeal circuit (ECC). The ECC incorporates pump segment connections for anticoagulation and pressure measurements and, after the dialyzer, a venous chamber (air trap) that removes air from the blood and returns it back into the veins of the patient. However, current air traps only partly remove air microbubbles that contaminate the ECC [11]. Residual air microbubbles pass through the venous return line of the access and into the lungs [6, 8]. There are indications by ultrasound that bubbles pass through the lungs and can be detected in the carotid artery [6] and the brain [12]. A shorter dialysis time and lower blood pump speed are variables that lower extracorporeal blood flow during HD [13]. The pump speed is significantly related to air bubble contamination—a faster blood pump speed favours more extensive exposure to microbubbles and subsequent ME [7]. The increased prevalence of pulmonary fibrosis in HD patients has been described [14, 15] and the possibility of a relation with microbubbles has been indicated [15]. In addition, pulmonary arterial hypertension is a frequent finding in HD patients that is not present in peritoneal dialysis (PD) patients [16]. Multiple cerebral emboli have been described in HD patients [17] and an increased prevalence of cerebral stroke is seen in HD versus PD patients [18], as well as increased rates of cognitive impairment [19–22], progression of cerebral atrophy [23], abnormal morphological changes [24] and silent infarction [17], and in elderly HD patients, reduced cerebral perfusion [25]. Two smaller autopsy studies of patients who had been treated by chronic HD before death showed histological findings within tissue sections of microbubbles encapsulated as ME within the vessels of lungs [15], but also in capillaries of the brain and heart of a patient who died during HD [26]. Those data indicate that air entering the veins is not totally resorbed before entering the lungs. A similar concept is also used for contrast medium for ultrasound-guided radiological investigations [27, 28]. A preservation of air microbubbles enables prolonged circulation in the blood since they are embedded, i.e. lipid coating [27, 28].

The aim of this autopsy study was to investigate if microbubbles of air accidentally entering the bloodline may be detected as ME in tissue such as lungs, brain and heart. If so, do differences in prevalence and distribution exist between HD and ALS patients?

MATERIALS AND METHODS

The study included samples or tissue from patients who died in the course of medical healthcare that included exposure to interventions such as infusions, injections, surgery and chronic HD. Tissue sections from 44 autopsied patients were investigated for the presence of ME including air. Patients investigated were those who died while on chronic intermittent HD (HD group, 25 patients: 17 men and 8 women), patients who died in the course of treatment for ALS (ALS group, 19 patients: 10 men, 8 women and 1 patient who was undefined by gender and age due to missing data).

The study was performed at the University of Umeå and approved by the Ethical Committee of Umeå University (Dnr 2009-0096M) and adhered to the tenets of the Declaration of Helsinki.

A total of 109 tissue sections were available (Table 1). They included 54 from patients who were treated with chronic intermittent HD and 55 from ALS patients. The sections were taken from the lung, heart and brain (frontal lobe, and in five instances also cerebellum) from the same HD patients ($n = 20, 20$ and 8 , respectively) and ALS patients ($n = 17, 19$ and 19 , respectively). Tissue sections were not always available from all three organs, because in some the autopsy was focused only on clarifying the reason of death.

The collected tissue sections were immersion fixed in 4% paraformaldehyde in 0.1 M sodium phosphate, pH 7.4, and paraffin embedded. Tissue sections were stained with haematoxylin and eosin.

The autopsy procedure per se may induce air bubble contamination into the tissues. To visualize such air contamination post-mortem from air bubbles deposited before death, a specific analysis was necessary. Therefore, all tissue sections were stained using a polyclonal fluorescent antibody against fibrinogen for immunohistochemistry. This method was used to calculate microbubbles (open spaces) present in ME. The polyclonal antibody reacts against fibrinogen, fibrin and fibrinogen fragments D and E (fluorescein isothiocyanate-conjugated rabbit fibrinogen anti-human antibody; F0111; Dako, Stockholm, Sweden). Fragments D and E constitute the D-dimer [29].

Table 1: Number of tissue sections with and without ME findings in HD and ALS patients.

Tissue	HD		ALS	
	No ME	ME	No ME	ME
Lung	0	20	4	13
Heart	3	17	8	11
Brain				
Frontal lobe	0	9	4	15
Cerebellum	0	5	No sample	No sample
Total	3	51	16	39

HD patients had more tissue sections with ME findings compared with ALS patients [Fisher's test, $P = .002$, risk ratio 3.6 (confidence interval 1.25–10.3)]. Tissue sections from cerebellum were collected in parallel with tissue from the frontal lobe in five patients. In one patient, two samples from the frontal lobe were collected and analysed.

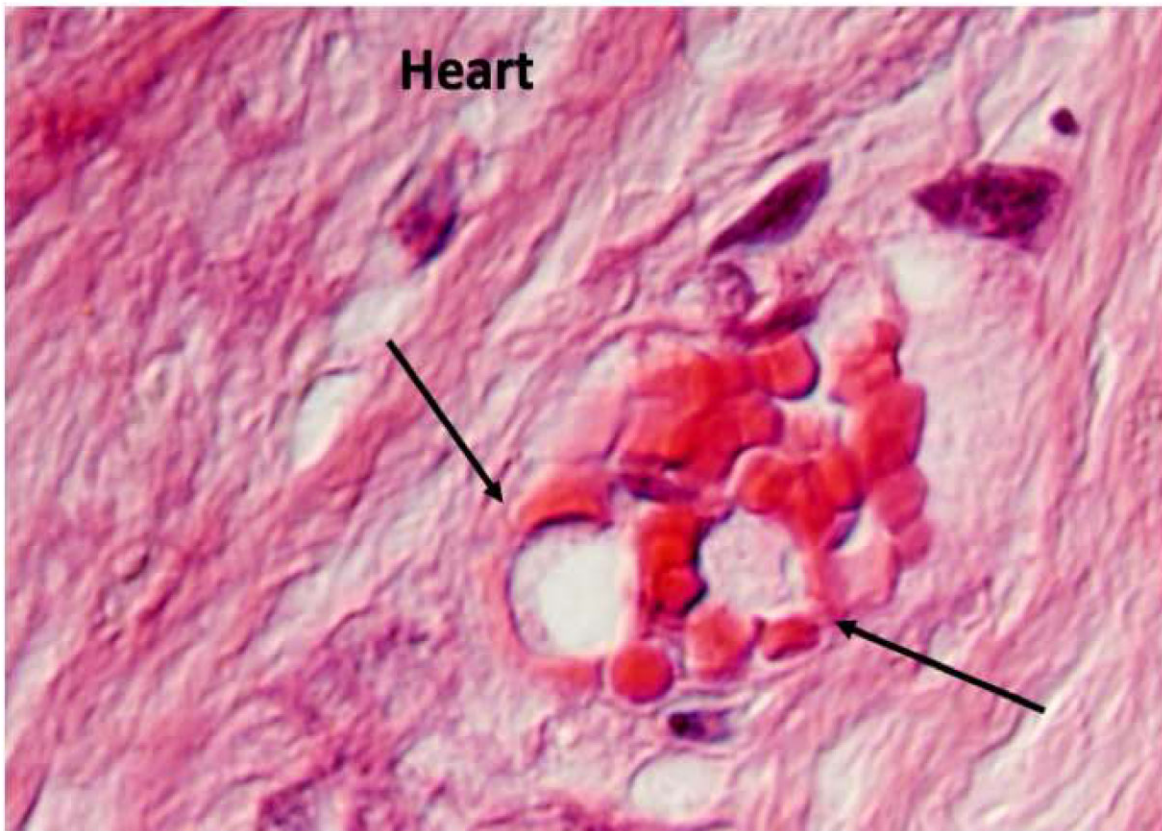


Figure 1: Tissue section of the myocardium stained with haematoxylin and eosin. Within the vessel, an air emboli is visible.

Positive staining was interpreted as a pre-mortem exposure to microbubbles and subsequent development of surrounding clots.

Each microbubble of gas that was visible by an illuminated surrounded sheath was counted as an ME. Each tissue preparation was investigated for ME per 25 microscopic fields (600 \times). We intended to collect a single tissue preparation for analysis of ME from available tissue sections from the lung (peripheral tissue), heart and brain (from frontal lobe). To investigate if exposure varies within, for example, the brain in a patient, separate paired comparisons of brain tissue data from five patients were analysed both from the frontal lobe and the cerebellum. In one HD case, two tissue sections from the frontal lobe were analysed.

Statistical analysis

The Fisher's test was used for comparison of ratios of ME findings in tissue sections between the HD and ALS group. Analysis of variance (ANOVA) and the Mann-Whitney U test were used for comparisons of the number of ME/tissue sections between groups and Wilcoxon analysis used for paired comparisons of the total number of ME per 25 fields in different brain tissue sections of five cases. Correlation analyses (r) were performed with the Pearson method (see Figs. 3–5) and Spearman values (ρ) were used to adjust for outlier effects. Two-sided P -values $< .05$ were considered significant. SPSS version 25 (IBM, Armonk, NY, USA) was used for the analyses.

RESULTS

For the HD and ALS groups, the median ages were 66 years (range 29–81) and 66 years (16–79), respectively, and the gender distribution in the groups was similar.

The indications for dialysis in the HD group were diabetic nephropathy [$n = 7$ (28%)], glomerulonephritis [$n = 6$ (24%)], nephrosclerosis [$n = 3$ (12%)], polycystic kidney diseases [$n = 1$ (4%)] and other reasons [$n = 8$ (32%)].

Any presence of ME

As an indication that infused air was not fully absorbed when entering the blood, 90 of 109 tissue sections showed the presence of ME (Table 1). Fig. 1 shows ME in the heart of an HD patient and Fig. 2 shows ME in the brain tissue of an HD patient (visualized by delimited fluorescent material).

Both groups of chronic exposure had findings of microbubbles that were delimited by fluorescent material. Overall, women had fewer ME than men in the brain and heart tissue ($P = .013$ and $P = .007$, respectively).

Taking all data together, more ME were present in the lung tissue versus the heart ($P < .001$). No significant differences were found between the brain and heart or lung and brain.

Paired analyses of the number of ME in the cerebellum versus the frontal brain lobe were not significantly different (5 pairs, median 4 versus 7, respectively; $P = .088$) while a paired sample correlation existed ($P = .047$). Analysing all

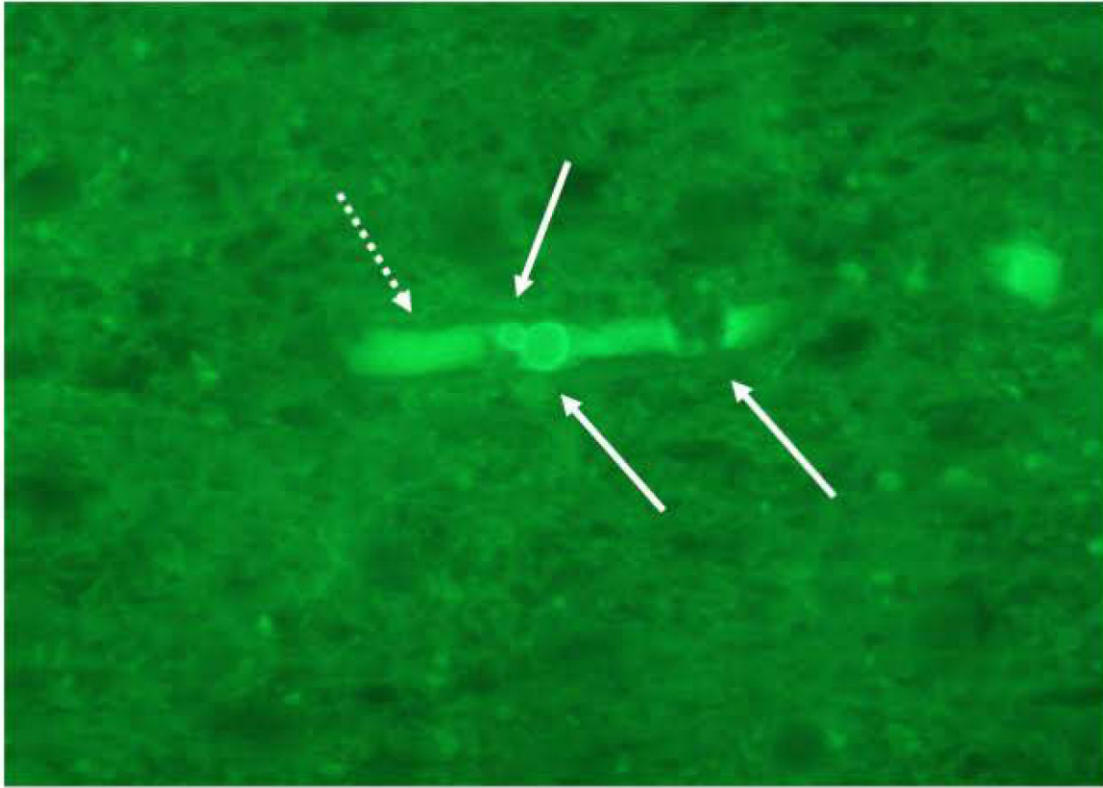


Figure 2: ME with microbubbles of air (open space) in a vessel of brain tissue from one HD patient (visualized by polyclonal fluorescent antibody against fibrinogen and fibrin). The shape of the emboli shows a tail (marking a thrombus area) that indicates the direction of the prior blood flow in the vessel.

cases revealed a correlation between the extent of ME in the lung versus the heart (Fig. 3; Spearman's $\rho = 0.621$, $P < .001$) and the heart versus the brain (Fig. 4; Spearman's $\rho = 0.506$, $P = .004$).

HD versus ALS

Tables 1 and 2 show the tissue distribution of ME between the two groups of patients with chronic exposure. The number and prevalence of ME were more pronounced for HD patients than for ALS patients.

ANOVA comparing HD versus ALS revealed similar numbers of ME/section in the lung [mean \pm standard deviation (SD) 6.65 ± 4.1 versus 4.41 ± 7.0] and more extensive in the heart (3.30 ± 2.8 versus 1.26 ± 1.6 ; $P = .009$) and brain (7.38 ± 3.9 versus 2.42 ± 4.4 ; $P = .011$). Non-parametric analysis (Mann-Whitney U test; Table 2) revealed significantly more findings in the HD patients in tissue from the lung ($P = .007$), heart ($P = .013$) and brain ($P = .001$).

Subgroup analysis revealed that HD patients versus those with ALS had a higher number of ME/section in the lung versus the heart ($P = .004$) and in brain tissue versus the heart ($P = .012$). The ALS patients had a higher number of ME/section in lung tissue versus heart tissue ($P = .025$).

Table 1 shows that more tissue sections included ME if the patients had been on HD versus those who suffered from ALS. For HD patients there was a significant correlation between the extent of ME in lung tissue and the number of years on dialysis (Fig. 5; Spearman's $\rho = 0.619$, $P = .006$).

Gender analysis of the HD group revealed that women had fewer ME than men in the brain ($P = .036$), while women in the ALS group had fewer ME than men in heart tissue ($P = .016$).

DISCUSSION

The present study verified ME with incorporated air bubbles. The air bubbles verified were all covered by a fibrin sheath and were seen as clots. The majority of ME were in lung tissue, followed by brain and heart tissue. As most ME were found in lung tissue, this indicates that the main entry for air in these patients was through the venous route. Women were less exposed than men.

HD patients had more extensive and more frequent findings of ME than ALS patients. A longer duration of dialysis showed an accumulation of emboli over the time of exposure. This relation also indicates that absorption of microbubbles is slow, probably due to the fibrin that covers the air bubbles.

The method of using fluorescent polyclonal antibodies to fibrinogen and fibrin to detect ME developed before death was based on the knowledge that an air bubble surface contains hydrophobic properties [30]. This hydrophobic action induces the activation of platelets and coagulation in the area closest to the bubble [31–34] and may also activate the binding of platelets [33, 35, 36]. Evidence of subsequent tissue damage by prolonged exposure to ME was also noted in a previous study where HD cases had signs of chronic pulmonary changes that were not noted in the ALS patients [15].

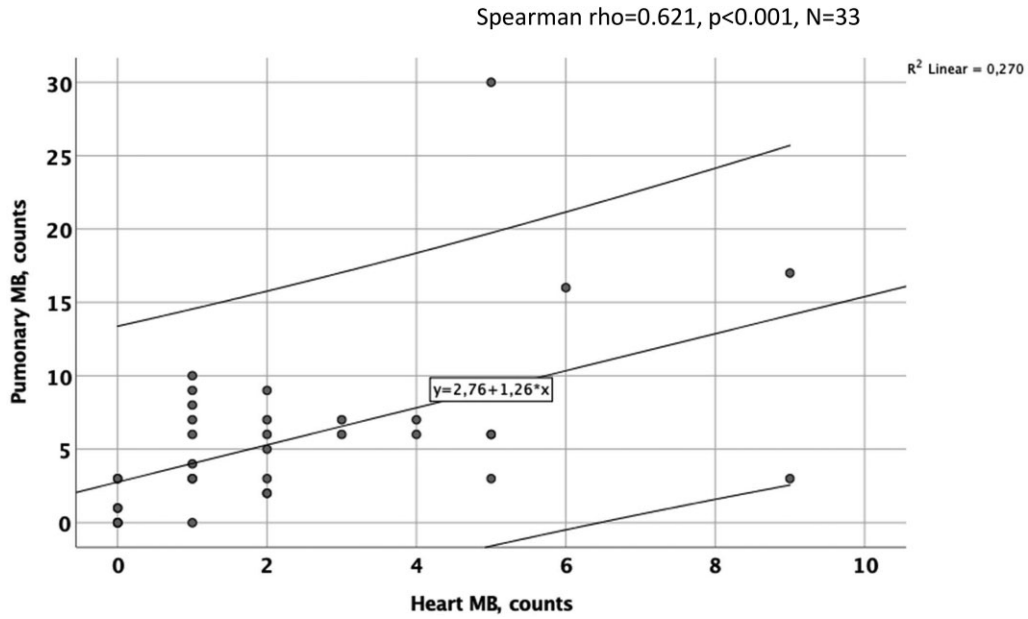


Figure 3: Correlation comparison of all patients between the extent of ME findings in the lung versus the heart.

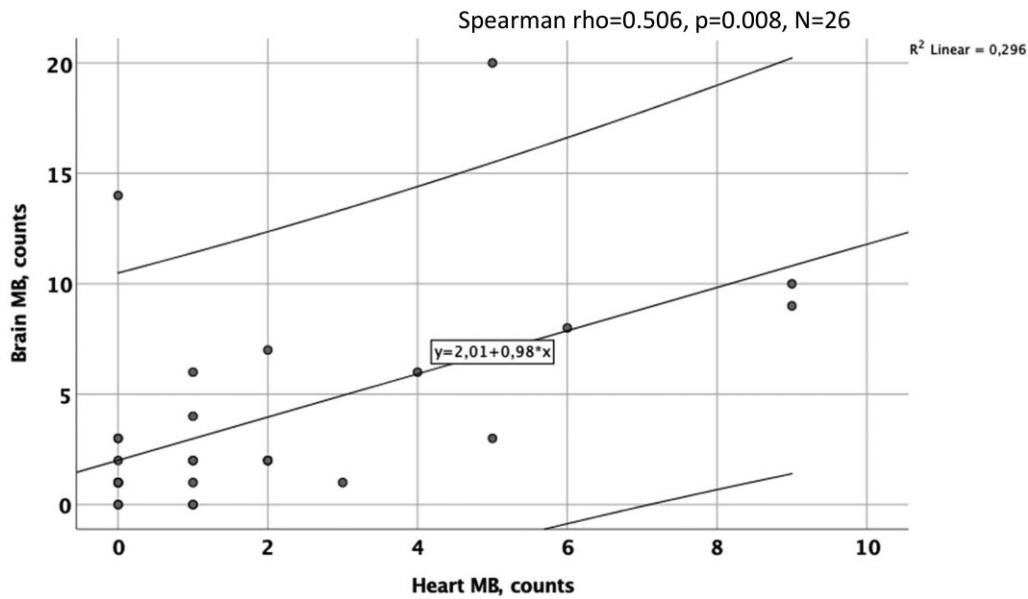


Figure 4: Correlation comparison of all patients between the extent of ME findings in the heart versus the brain.

Table 2: Median and range (minimum–maximum) of ME/tissue section.

Tissue	HD	ALS	P-value
Lung ME	6 (0–17)	3 (0–30)	.007
Heart ME	2.5 (0–9)	1 (0–5)	.013
Brain ME	7.5 (1–14)	2 (0–20)	.001

Non-parametric comparisons of the number of visible ME in tissues of the lung, heart and brain.

The relation of ME found in lung tissue versus the heart and brain strengthens the assumption raised in a previous study that

microbubbles of air pass through the lungs into the arterial circuit through anastomoses [6]. Such anastomoses [37] would enable cross-transport of microbubbles into the left heart and subsequently into the arterial circuit.

A reason that women had fewer findings of ME may fit well with the fact that they usually have a shorter dialysis time and lower extracorporeal blood flow during HD [13]. In addition, they often have a lower pump speed, a factor that is significantly related to less air bubble contamination [7].

We believe it is plausible that ME exposure may well contribute to the increased prevalence of pulmonary fibrosis in HD patients that has been described by others [14, 15]. In

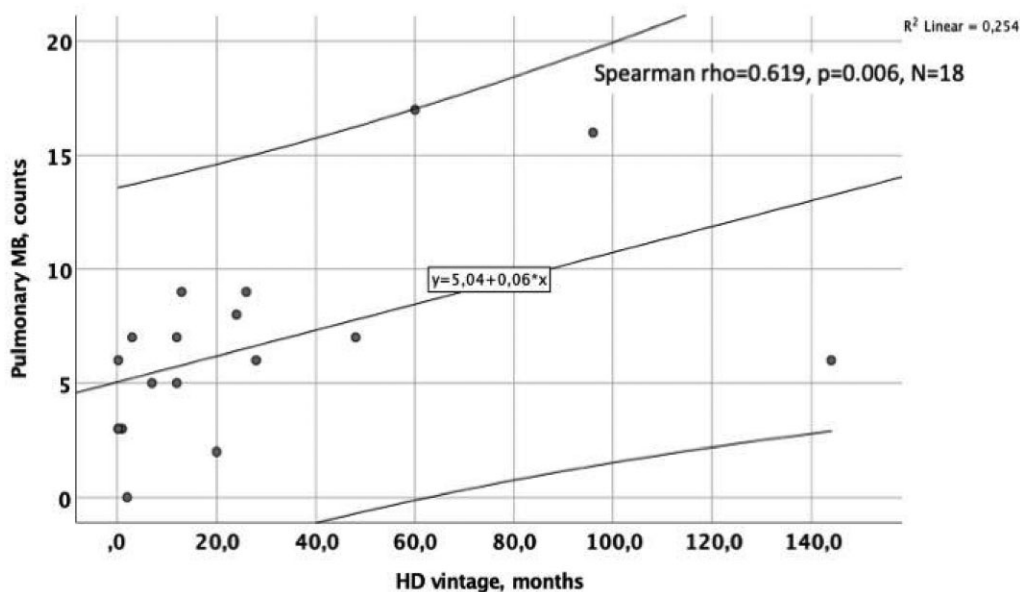


Figure 5: Correlation comparison in HD patients only between the extent of ME findings in lung tissue and the time on HD (months).

addition, pulmonary arterial hypertension is a frequent finding in HD patients that is not present in PD patients [16]. In addition, the present study also verified multiple cerebral ME, especially in HD patients. This would corroborate findings by others of an increased prevalence of cerebral stroke in HD patients versus PD patients [18], as well as increased rates of cognitive impairment [19–22], progression of cerebral atrophy [23], abnormal morphological changes [24] and silent infarction [17].

Myocardial stunning, a state that is assumed to be due to rapid fluid removal during HD in patients with volume overload [39–42], may be worsened by ME in the heart that develops during HD, as verified in the present study. This may also be supported by cardiac tissue strain and damage detected by elevated pro-brain natriuretic peptide [43, 44] and troponin T levels during HD [44, 45].

Exposure of patients to microbubbles during medical care has been previously demonstrated by others who detected microbubbles by ultrasound in patients in intensive care, especially during HD [12].

A limitation of the study is that we were unable to collect autopsy data from patients who died without having been exposed to healthcare without injection or intravenous therapies before death. Since we were unable to get complete data from patient medical records, resuscitation efforts may have been missed in some patients. The extent of infusions, parenteral nutrition and injections could not be calculated. Another limitation was that the myocardial tissue was cut cross-sectionally towards the direction of the myocytes and vessels. Thus the area of the visible vessel was much smaller than for longitudinal sections. Therefore the extent of myocardial ME findings may be underestimated.

In summary, microbubbles can be verified at autopsy as ME in lung, heart and brain tissue from patients exposed to dialysis and more cannulation and infusions. More ME were present in HD patients compared with those who suffered from ALS. Minimizing air exposure from syringes, infusions and bloodlines may decrease the risk of ME and subsequent tissue injury.

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AUTHORS' CONTRIBUTIONS

U.F., B.S. and P.J. were responsible for the concept and design, data analysis and interpretation and manuscript preparation. U.F. and B.S. drafted the article and were responsible for data collection and statistics. U.F. secured funding. All authors approved the final article.

DATA AVAILABILITY STATEMENT

The data underlying this research will be made available upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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