Detection of microemboli in the subclavian vein of patients undergoing haemodialysis and haemodiafiltration using pulsed Doppler ultrasound

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Abstract

Background. The pathophysiology leading to pulmonary side effects during haemodialysis and haemodiafiltration is not yet fully understood. Chronic microembolization, which can be demonstrated by pulsed Doppler ultrasound, may be one cause.

Methods. The study cohort consisted of 24 long-term dialysis patients undergoing haemodialysis (n = 21) and online-haemodiafiltration (n = 3), respectively. The subclavian vein downstream to the venous access was investigated during different phases of the procedure using a 2-MHz pulsed ultrasound device.

Results. In all periods investigated (connection, dialysis, disconnection), numerous microembolic signals (MES) were found in the subclavian vein. The numbers of MES detected during haemodiafiltration (314–709 MES per 10 min) were higher than during haemodialysis (0–81 MES per 10 min).

Conclusions. The composition (gaseous or solid) and origin (pump, tubing system or shunt) of the microemboli detected remains unclear. Chronic microembolization may be one cause of pulmonary complications of haemodialysis and haemodiafiltration. The detection method described in this article will help us to better understand this process and to determine what role microemboli might play in pulmonary and central nervous system disorders. It may also help to optimize the devices and techniques used.

Keywords: dialysis; microemboli; ultrasonography

Introduction

Haemodialysis and haemodiafiltration are beneficial achievements in the field of renal replacement therapy for patients with end-stage renal disease. However, these procedures also bear risks such as pulmonary disease and cognitive deficits [1–3]. The pathophysiology leading to these side effects may be multifactorial and is not yet fully understood. Ongoing microembolization in the pulmonary vasculature may be one cause and has been suggested by reduced arterial oxygenation following dialysis and especially with inadequate filtering [4,5]. In patients with a right-to-left shunt, microemboli may also reach the cerebral vasculature and contribute to cognitive deficits. Using 2-MHz pulsed ultrasound, it is possible to detect clinically silent circulating microemboli [6]. Oxygen inhalation can distinguish solid from gaseous microemboli [7,8]. To our knowledge F. Tranquart et al. [9] and F. Rollé et al. [10] were the first to publish a preliminary report on microembolization occurring during haemodialysis. Another recent case report described microembolic signals (MES) on ultrasound B-mode and spectral mode in a dialysis graft and a dialysis fistula, respectively [11]. The present study was conducted to provide further evidence for the occurrence of microemboli during different phases of extracorporeal treatment and to delineate in a small patient group whether such microemboli may even reach the cerebral circulation.

Subjects and methods

Twenty-five randomly selected, long-term dialysis patients, aged from 31 to 75 years (mean, 53 years) were investigated after having given their informed consent. There were 12 women and 13 men. All of them suffered from end-stage renal disease and had been on haemodialysis for between 2 months and 13 years. Six patients had a history of previous cerebral ischaemic events. All patients were on intravenous heparin during the dialysis. Eight patients were on aspirin (patients 1, 3, 11, 12, 15, 17, 20 and 22), three on ticlopidine (patients 18, 23 and 24), and two on the oral anticoagulation, phenprocoumon (patients 3 and 25). No patient had a mechanical cardiac valve or was in atrial fibrillation during the recording. Each patient was studied in only one haemodialysis or haemodiafiltration session.
**Haemodialysis and haemodiafiltration**

Twenty-two of the 25 patients underwent haemodialysis, while five patients were treated by online-haemodiafiltration using different devices by Gambro Medizintechnik (München, Germany), Fresenius Medical Care (Bad Homburg, Germany), or B. Braun Melsungen AG (Melsungen, Germany) (Table 1). In the 22 haemodialysis patients, a low-flux hollow fibre dialyser (Hemoflow F6HPS, Fresenius Medical Care) was used, while haemodiafiltration was performed with a high-flux hollow fibre dialyser (Hemoflow F60 Highflux, Fresenius Medical Care, Bad Homburg, Germany) for patients 11, 19 and 24. The dialyser membrane material for the filters was polysulphone. In 20 of the 25 cases (patients 1, 3–9, 11–14, 16–20, 22 and 23), two needles were used for vascular access (Diacan V17G/A17G, diameter and length of the cannula 1.5 and 20 mm, respectively; B. Braun Melsungen AG), while five patients (patients 2, 10, 15, 21 and 24) were on single needle dialysis (Bionic 632T 1.6 mm, Bionic Medizintechnik, Friederichsdorf, Germany). In all but one patient, the site of vascular access was the forearm, elbow, or upper arm. Only native fistulas were used. Patient 25 was dialysed using a Sheldon catheter (Duality-Cath 32/11, Vygon, Aachen, Germany) placed in the right jugular vein. In all 22 patients on dialysis, a bicarbonate-containing dialysis bath was used.

Prior to the start of the extracorporeal treatment, the bloodlines and the hollow-fibre dialyser were filled and rinsed with normal saline. Access needles were placed into the venous limb of the fistula and degassed by aspirating blood into a syringe. Before connecting the bloodlines, a heparin bolus of 1000–5000 I.U. was injected intravenously. Then the arterial bloodline was connected to the distal needle and the tubing system was filled with blood. Finally, the venous line was connected to the proximal venous access needle. Every effort was made to prevent air entry.

Blood flow was set at a mean of 213 ml/min (200–280 ml/min) and 2000–8000 I.U./h of heparin were constantly infused. The haemodialysis and haemodiafiltration was well tolerated, although two patients had minor hypotensive events with vertigo and dizziness and one patient suffered from nausea.

**Ultrasound investigations**

In patients 1–24, the subclavian vein downstream to the arteriovenous fistula was investigated during dialysis in the infracavicular fossa with a hand-held multidepth-2-MHz probe. All studies were performed by the same investigator (K.K.) using the same pulsed Doppler ultrasound device (TC4040, Nicolet-EME, Kleinostheim, Germany). An axial width of the small sample volume of 4 mm in length and a low gain provided a setting guaranteeing optimal embolus discrimination from the background spectrum [12]. Power was 10 mW/cm². The insonation depths of the 4-gate probe were arranged over a length of 1 cm according to the following sequence: channel 1 (deep), channel 2 (4 mm more distally), channel 3 (8 mm more distally), and channel 4 (10 mm more distally). This setting was maintained unchanged throughout the recordings. A detection threshold of ≥ 5 dB was used for all studies. The audio Doppler signal of all the four channels was continuously recorded onto an 8-channel digital audio tape-deck recorder (TA-88, TEAC Corporation, Tokyo, Japan) with normal speed. Further details of the technique have been described previously [13].

Ultrasound recordings during extracorporeal therapy were done as follows: (i) Due to a scheduling problem, in 14 patients it was only possible to record during the period of connecting the tubes to the patients and starting the dialysis. This period lasted from 7 to 13 min in the individual patients. (ii) After a treatment period of 10 min, we recorded the 24 patients for 10 min. (iii) After a second break, we performed another 10 min ultrasound recording. In a randomized way, oxygen was applied at a dose of 6 l/min by a loosely-fitted facial mask either during the first 10 min or during the second 10 min of the recording times previously mentioned [7]. This second break was used as a washout period after instances of oxygen application. In the remaining one of these two 10-min periods and during the rest of the haemodialysis or haemodiafiltration period the patients breathed normal air. (iv) In all 24 patients, it was possible to record for the period of tube disconnection from the patients (3.5–12 min in the individual patients). (v) After disconnection, we waited for 10 min, and then investigated the subclavian vein for another 10 min. In patients 2 and 9, these investigations were not performed immediately following dialysis, but on the following day.

For intensity quantification of the MES, each recording period was separated into five sections. At the end of each section, the MES was measured automatically by the software yielding four relative intensity values for each period. The mean of these four values was entered into the statistical analysis for each patient to avoid repeated measures.

In patient 25, and during a second haemodialysis procedure in patients 10 and 14, both middle cerebral artery main stems were simultaneously investigated for 30 min through the temporal window using an elastic head ribbon with a probe holder. Two sample volumes were placed in each middle cerebral artery separated by 1 cm. Instrumentation settings and the microembolus detection procedure were as described above except for the instrument’s power, which was adjusted to achieve an adequate skull penetration. In these three patients that were investigated transtemporally, a test for the presence of cardiac or pulmonary right-to-left shunting was performed following the microembolus detection [14]. Microcavitation saline contrast was generated by agitating a mixture of 10 ml of normal saline and 1 ml of air between two 12 ml syringes connected by a three-way stopcock. Once the contrast fluid was prepared, 10 ml were immediately injected as a bolus into one of the access needles. The Valsalva manoeuvre started 5 s after the beginning of the injection with deep inspiration followed by pressing against the closed glottis and expiration 10 s after the beginning of the injection.

**Statistics**

Besides descriptive statistics, the numbers of MES with and without oxygen inhalation were compared using the non-parametric Wilcoxon test. Statistical significance was declared at the 0.05 level. Using the same test, the relative intensity increases of MES were compared across the following periods: (i) connection period vs the haemodialysis/haemodiafiltration period without oxygen application, (ii) disconnection period vs haemodialysis/haemodiafiltration period without oxygen application, and (iii) the period following haemodialysis/haemodiafiltration vs the haemodialysis/haemodiafiltration period without oxygen application. Because not all patients had measurements made during all phases of the study, for each single comparison only the
patients with data were considered. Statistical significance was declared at the 0.0125 level, having corrected for multiple comparisons.

Results

In all periods investigated, MES were found in the subclavian vein. Figure 1 gives an example of an MES with a characteristic time delay in occurrence in the four channels.

Table 1 summarizes the results in the individual patients. MES were detected in none of the recordings from the middle cerebral arteries. The tests for right-to-left shunting were all negative.

The relative intensity increase of MES during connection was 19.1 ± 3.0 dB (mean ± SD; range 14.8–24.0), during haemodialysis/haemodiafiltration without the application of oxygen 14.0 ± 9.2 dB (range 5.0–48.7), during haemodialysis/haemodiafiltration with the application of oxygen 10.7 ± 4.3 dB (range 5.5–19.5), during disconnection 16.0 ± 5.1 dB (range 7.8–29.5), and following the procedure 8.4 ± 3.6 dB (range 5.0–15.88). Only the difference in relative intensity increase between the connection and the haemodialysis/haemodiafiltration period without application of oxygen was significant ($P = 0.003$).

Discussion

Our study demonstrates that both haemodialysis and haemodiafiltration are associated with a large number of microemboli, which will eventually be trapped in the pulmonary vasculature and do not reach the cerebral circulation. The highest numbers of MES were detected during haemodiafiltration. These observations are in concordance with those published by Tranquart et al. [9] and Rollé et al. [10] who found means of 190 and 251 MES/15 min in the subclavian vein at the beginning and the end of dialysis, respectively. In contrast to our observations, they found a low number of MES in the middle cerebral artery. However, they did not report on right-to-left shunt testing. It may well be that by chance their population consisted of more patients with a cardiac or extracardiac right-to-left shunt allowing the microemboli to enter the cerebral circulation. These shunts are present in about 40–50% of the population [14]. In our study, there were no right-to-left shunts detected. The dB values of MES in our study (8.4–19.1 dB) are comparable to those found by Rollé et al. [10] (average 12.7–19.4 dB) using the same device. This suggests a similar composition and size of the microemboli in the two studies. Woltmann et al. [11] described the occurrence of MES on ultrasound B-mode and spectral mode, respectively, in a synthetic dialysis access graft and in a dialysis fistula, but not in the proximal human vasculature.

The composition of these microemboli remains unclear. Their high relative intensity increase makes a gaseous composition very likely [13]. However, a strong signal can be due to a gaseous microembolus or to a large solid embolus. On the other hand, their number was not significantly reduced by oxygen inhalation. In patients with a mechanical cardiac valve, oxygen inhalation reduced the number of MES originating from cavitation bubbles by replacing the blood’s physically dissolved nitrogen with oxygen, which has a lower tendency to form gaseous bubbles [7]. Unfortunately, it is not yet possible to distinguish solid from gaseous microemboli and to assess the size of the microemboli by their pattern or intensity characteristics. In the present study, either the microemboli were large gas bubbles that needed some time to dissolve into blood, or they were of solid composition. There may even be a coexistence of gaseous and solid microemboli. These microemboli may correspond to air bubbles already in the haemodialysis/haemodiafiltration device before the procedure, or those entering the blood system during connection and disconnection of the device. The formation of gas bubbles may also be caused by cavitation due to the pressure gradients inside the device or the shunt. In addition there may be solid particles such as plastic or rubber originating from the device, especially from the pump segment of the tubing system. A third possibility would be microthrombi previously formed in the machine or the tubing system [15]. The persistence of a low number of MES even after haemodialysis/haemodiafiltration raises additional questions. Some microemboli from the procedure may still remain in the veins and appear in the subclavian vein later on. There may also be ongoing thrombus formation within the fistula. In patient 14, four MES were detected even on the day following haemodialysis, favouring the latter hypothesis.

In the literature, there are reports on pulmonary damage such as pulmonary fibrosis and calcification.
Table 1. The machines and filters used in the study as well as the numbers of MES in the subclavian vein during the different periods

<table>
<thead>
<tr>
<th>Patient</th>
<th>Machine</th>
<th>Capillary dialyser</th>
<th>Filtration mode</th>
<th>Blood flow (ml/min)</th>
<th>MES connection</th>
<th>MES 10 min, dialysis, no O₂</th>
<th>MES 10 min, dialysis, O₂</th>
<th>MES disconnection</th>
<th>MES 10 min, post-dialysis</th>
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The numbers of MES refer to single embolic events. The patients are organized in order of investigation.
in patients undergoing chronic haemodialysis [16,17]. In an autopsy study, the most common acute diseases were pulmonary infections (pneumonia, lung abscess, empyema) and fluid overload. The most common chronic process was interstitial pulmonary fibrosis. Other relatively common chronic diseases included pleural fibrosis and/or pleuritis as well as pulmonary arteriosclerosis, haemorrhage, thromboembolism and calcification [1]. In a recent study atelectasis, cardiomegaly, pleural effusion, vascular congestion, parenchymal consolidation, parenchymal scarring/fibrosis, and lymphadenopathy were the most common CT findings in long-term haemodialysis patients [18]. The authors attributed these findings mainly to infectious diseases. Microembolization with overt pulmonary embolism may occur, especially from thrombi generated at the surface of the in-dwelling catheter [19–21]. Ongoing massive microembolization into the pulmonary vasculature as described in this report may be another possible explanation for the high pulmonary morbidity in long-term dialysis patients.

The brain is particularly vulnerable to embolization. The three patients in our study who also underwent transcranial Doppler monitoring did not show any MES, and they did not have a right-to-left shunt. This may be different in patients with such a shunt, especially with a large atrial septal defect [22,23]. Paradoxical embolism may not only cause acute stroke, but may also result in slowly evolving cognitive deficits, which are common in patients on long-term haemodialysis. Similar to patients with mechanical cardiac valves or those undergoing cardiothoracic surgery with cardiopulmonary bypasses, chronic microembolization in the cerebral vasculature in dialysis patients with a right-to-left shunt may cause occlusion of cerebral capillaries, thereby giving rise to cognitive deficits [24,25].

In conclusion, the detection method described in this article may help to optimize the devices and techniques used in haemodialysis and haemodiafiltration to avoid chronic massive microembolization in the lungs or the brain.

References

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