Reduction of circulating microemboli in the subclavian vein of patients undergoing haemodialysis using pre-filled instead of dry dialysers

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Abstract

Background. Chronic microembolization that can be demonstrated by pulsed Doppler ultrasound may give rise to pulmonary side-effects during haemodialysis by direct vessel obstruction, increased complement activation or platelet aggregation. The objective of the present investigation was to study whether the use of pre-filled instead of dry dialysers would help to minimize the number of microemboli.

Methods. The study cohort consisted of 23 patients undergoing maintenance haemodialysis. Using a 2 MHz pulsed ultrasound device, the subclavian vein downstream to the dialysis fistula was investigated for 10 min during the dialysis session. The ultrasound examination was performed twice during two successive dialysis sessions, using a pre-filled or a dry dialyser in randomized order.

Results. In all patients investigated, numerous microembolic signals (MES) could be observed in the subclavian vein. Treatment with pre-filled dialysers was associated with significantly less MES (82 ± 94) as compared with dry dialysers (268 ± 296; \(P = 0.002\)).

Conclusions. In comparison to dry dialysers, the use of pre-filled dialysers leads to a significant reduction in microembolization, which may prevent repeated damage to the pulmonary vasculature and, thus, cause less pulmonary damage.

Keywords: dialysis; microemboli; ultrasonography
(mean: 57 years) were investigated after having given their informed consent. There were three females and 20 males. All of them suffered from end-stage renal disease and had been on haemodialysis for between 4 months and 14 years. Five patients suffered from diabetes mellitus and 19 from arterial hypertension. Reasons for renal insufficiency were glomerulonephritis in 12 patients, diabetic nephropathy in four, polycystic kidney disease in two, renal tumour in two and analgesic drug abuse in one. None of them had a mechanical prosthetic cardiac valve or was suffering from atrial fibrillation. All patients received heparin intravenously during dialysis. Each patient was studied during two haemodialysis sessions using in randomized order once a pre-filled dialyser and once a dry dialyser. During the two haemodialysis sessions the same needles and tubing systems were used.

**Haemodialysis**

Twenty out of the 23 patients underwent haemodialysis, while three patients were treated by online haemodiafiltration using different devices by Gambro Medizintechnik (München, Germany), Fresenius Medical Care (Bad Homburg, Germany), B. Braun Melsungen AG (Melsungen, Germany), Althion Medical Inc. (Stuttgart, Germany), or Nikkiso (Tokyo, Japan) (Table 1).

In all patients, the site of vascular access was on the upper extremity (forearm, elbow or upper arm). Only native arteriovenous fistulae were used and a double-needle access was possible in all patients. A bicarbonate-containing dialysis bath was used throughout the trial.

Prior to the start of dialysis, bloodlines and the hollow-fibre dialysers were filled and rinsed with 1000 ml normal saline at a flow velocity of 100–150 ml/min. Afterwards, the dialysate side was filled with dialysate and rinsed with 500 ml/min for at least 5 min. Access needles (15 gauge) were placed into the venous limb of the fistula and degassed by aspirating blood. Before connecting the bloodlines, a heparin bolus of 2000–6000 IU was injected intravenously. Then, the degassed arterial bloodline was connected to the distal needle pre-filled with blood and the tubing system was filled with blood. Finally, the venous line was connected to the proximal venous needle. Every effort was made to prevent the entry of air.

Mean blood flow was 247 ml/min (200–300 ml/min) and 1000–4000 IU/h heparin were continuously administered.

**Ultrasound investigations**

In all patients, the subclavian vein downstream to the arteriovenous fistula was investigated during dialysis in the infraclavicular fossa with a hand-held bigate 2 MHz probe. In order to avoid contamination from the connection period, recording was started 10 min after the onset of dialysis. All studies were performed by the same investigator (T.B.) using the same pulsed Doppler ultrasound device (Multidop X4; DWL, Sipplingen, Germany) and the corresponding software ‘TCD-8 for MDX’, version 8.11 for a duration of 10 min. 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. Figure 1 gives an example of a shower of microemboli passing in the subclavian vein.

The two isonation depths of the bigate probe were arranged over a length of 1 cm. Scale setting was −50 to +70 cm/s, the high-pass filter was set at 120 Hz. A 64-point fast Fourier transform yielded a colour-coded intensity distribution of the Doppler shift for time intervals of 12 ms each. The time window overlap was 67%. This setting was maintained unchanged throughout the recordings. A detection threshold of ≥12 dB was used for all studies. This threshold had been assessed prior to the study by investigating the subclavian veins of five patients on the site of the fistula during haemodialysis-free intervals for spontaneous fluctuations of the background spectrum, so-called ‘Doppler speckle background’. Two-hundred spontaneous fluctuations were followed in each of the five patients and their intensity distribution was plotted. Only 1.6% of the fluctuations were ≥12 dB (Figure 2). This concept takes into account that MES have a higher relative intensity increase than 98% of these spontaneous fluctuations to achieve a good inter-reader consistency. This procedure was in line with previous observations and recommendations based on an international consensus [1].

Therefore, the threshold of ≥12 dB was used for all Doppler studies. In addition to the relative intensity increase of the individual signals, the software gives the time delay in the occurrence of MES in the two sample volumes arranged in sequence as a criterion for a true MES, whereas an artefact signal would occur in both sample volumes simultaneously. The audio Doppler signal of the more proximally positioned channel was continuously recorded onto a digital audiotape deck recorder (DTC-690; Sony, Tokyo, Japan) with normal speed. Off-line analysis of the data (but not the recording) was done blinded in terms of the patient’s identity and dialyser used. The analysis comprised audiovisual evaluation of the Doppler signal by one investigator (T.B.) and comparison with the data pre-selected by the software applying recognized criteria [1]. The only signals taken into account were those above the pre-defined detection threshold.

**Statistics**

Data are presented as means ± SD. Besides descriptive statistics, the numbers of MES and the MES’ relative intensity increase with the two types of dialysers were compared using the non-parametric Wilcoxon test (signed rank test). The comparisons of relative intensity were done with the mean value of all MES in a 10 min period for an individual patient to avoid repeated measurements. Statistical significance was accepted at the 0.05 level.

**Results**

Haemodialysis was well tolerated, except for patient 14 who suffered from a hypotensive episode with vertigo and nausea. In this case, dialysis had to be stopped and the patient was not willing to undergo the investigation with this particular dialyser for a second time.

In all periods investigated, except for one period using a pre-filled dialyser in patient 2, MES were found in the subclavian vein varying from 6 to 1018 per 10 min. As can be seen in Table 1, the mean number of MES was 82 ± 94 (median: 46) using a pre-filled dialyser and 268 ± 296 (median: 181) with a conventional dialyser. This difference was highly
Table 1. The patients' demographics, devices and dialysers used in the study as well as the numbers of MES in the subclavian vein. In patient 14, the dialysis session had to be stopped because of a hypotensive reaction.

<table>
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<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Procedure</th>
<th>Device</th>
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<th>Dialyser (pre-filled)</th>
<th>MES (dry)</th>
<th>MES (pre-filled)</th>
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HD, haemodialysis; HDF, haemodiafiltration.
significant ($P = 0.002$). The individual results are given in Figure 3.

The relative intensity increase of MES using a pre-filled dialyser was 18.6 ± 3.8 (range: 13.5–28.1 dB; median: 17.2) and 20.4 ± 3.8 (range: 13.7–28.0 dB; median: 21.1). This difference did not reach significance ($P = 0.057$).

**Discussion**

Our study corroborates previously reported observations that haemodialysis is associated with a large number of circulating microemboli in the drainage vein of the arteriovenous fistula [10,11,13]. Woltmann et al. [12] described the occurrence of MES ex vivo on ultrasound B-mode and spectral mode, respectively, in a synthetic dialysis access graft and in a dialysis fistula. These microemboli are eventually trapped in the pulmonary vasculature and may account at least partly for the pulmonary morbidity in haemodialysis patients. Up to now, however, it has not been realized that the use of pre-filled dialysers would reduce the number of microemboli. The relative intensity increase of the signals as a possible marker of their size, however, was not significantly different between the two types of dialysers.

The limitations of our study are that only one investigator performed the recordings and the off-line analysis. Also, there might be concern about the blinding. However, we took care that the characteristics of the recording (patient, dialyser used) were not obvious from the label and off-line analysis was done at the end of the examination. On the other hand, the use of a single reader has the advantage of consistency over the whole study.

The size of microemboli is estimated to be in the μm range. The composition of these microemboli is not yet resolved. Their high relative intensity increase suggests a gaseous composition (i.e. microbubbles) [14]. However, a strong signal could either be due to a gaseous microembolus or to a large solid embolus, both backscattering a large amount of ultrasound. Therefore, it is hardly possible to distinguish solid from gaseous microemboli and to assess the size of the microemboli by their pattern or intensity characteristics. Both gaseous and solid microemboli may coexist. The origin of these microemboli is also not yet completely understood. They most likely represent air bubbles trapped in the dialyser during filling of the extracorporeal circuit or entering the blood system during connection and disconnection of the tubing system. Formation of gas bubbles may also be caused by cavitation due to the pressure gradients inside the filter or the fistula. MES may also represent particles originating from the bloodlines, especially from the pump segment of the tubing system. A further possibility would be microthrombi formed in the dialyser or in the tubing system, which are too small to be held back by the venous line microemboli filter [15].

Rapp et al. [2] clearly demonstrated that microemboli of μm size could cause cerebral damage in a rat model.
Technical refinements led to a decrease of MES caused by the extracorporeal circulation and of neuropsychological deficits [3,4]. These are strong arguments to suggest that microemboli are not always clinically silent. A similar effect is supposed for cognitive deficits of patients with mechanical cardiac valves [16,17] and for patients undergoing intra-arterial angiography [18]. Pulmonary damage, such as pulmonary fibrosis, advanced arteriosclerosis of the pulmonary vasculature and calcification is a well-known phenomenon in haemodialysis patients [5–7]. Furthermore, there are reports on hypoxaemia and activation of complement, coagulation and platelet aggregation during dialysis [19–21]. It would be interesting to compare arterial pO2 during dialysis with pre-filled and dry dialysers. Continuous microembolization into the pulmonary arteries may explain, at least partly, pulmonary morbidity in long-term dialysis patients by direct obstruction of pulmonary capillaries and indirect changes, such as activation of complement and aggregation/coagulation [22]. Reduction of microemboli during haemodialysis might, therefore, be a valid strategy to minimize pulmonary injury. However, we cannot correlate these paraclinical findings with clinical findings yet. Here, we could show that the use of pre-filled dialysers leads to a significant reduction in microembolization. This difference may in part be explained by more gas bubbles still being present in the dry dialysers due to the late filling. It would be interesting to compare the effect of different rising procedures on the formation of microemboli. Further studies need to be performed to show that the use of pre-filled dialysers also entails less pulmonary damage. This study does not yet give enough evidence to generally recommend the use of pre-filled dialysers, taking into account that they are considerably more expensive than dry dialysers.

Conflict of interest statement. None declared.

References

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