Identification of microemboli during haemodialysis using Doppler ultrasound

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Abstract

Background. Doppler ultrasound methods were used during haemodialysis sessions for the detection of microemboli and determination of their origin. Methods. A 2-MHz ultrasound probe (Multidop X4 DWL®) was used to assess the number of microembolic signals (MES) in the subclavian vein downstream from the arteriovenous fistula before the dialysis session and over two periods of 15 min at the beginning and end of haemodialysis sessions in 25 patients without previous cardiovascular disease. A similar probe was used during in vitro studies to detect MES at different sites in the dialysis machine (before and downstream from the blood pump, and before and downstream from the air trap). Results. No MES were detected during in vivo studies before haemodialysis sessions. MES were registered in all patients (100%) at the beginning and end of the haemodialysis procedure at an average of 12.7 ± 9 and 16.7 ± 11.5 signals/min respectively. The average intensity of MES was 19.2 ± 5.0 dB and 19.4 ± 3.9 dB respectively. No MES were detected on the arterial line during in vitro studies. In contrast, 19 ± 6 MES/min were detected after the blood pump, 13 ± 4.2 before the air trap, and 16.5 ± 5.5 thereafter. Conclusions. In all patients, MES were recorded during haemodialysis sessions in the drainage vein from arteriovenous fistulae. The results of in vitro studies indicate that MES are formed by the blood pump of the haemodialysis machine. The intensity of the MES suggests that they correspond to synthetic particles or microbubbles, which are not detected by the air trap. The final destination of these microbubbles will be assessed in further studies.

Keywords: Doppler ultrasound; haemodialysis; microembolic signals; roller pump

Introduction

In 1990, Spencer et al. described a microembolic signal (MES) as a high-intensity transient signal during cerebral Doppler monitoring [1]. As established by the International Consensus Group on Microembolus Detection in 1998, MES is identified by the following characteristics [2]:

- a Doppler microembolic transient signal usually lasting less than 300 ms;
- an amplitude usually at least 3 dB greater than that of the background blood flow signal and which is dependent on the characteristics of the individual microembolus;
- a unidirectional signal within the Doppler velocity spectrum;
- a specific audible signal.

Artefacts are easily distinguishable from MES as they correspond to low-frequency and bi-directional signals and they usually occur during probe moves [3,4].

MES have been observed in numerous disease situations such as stroke, carotid stenosis, cardiac surgery with extracorporeal blood circulation, and in patients with mechanical prosthetic heart valves [3,5–7]. Recent studies have demonstrated their role in neuropsychological decline or in the prediction of a forthcoming stroke [8,9]. Haemodialysis procedures require an extracorporeal blood circulation using haemodialysis machines that could induce MES similar to those observed in cardiac surgery [10]. This procedure might induce the formation of particles that could be detected in the patient circulation. However, this issue has never been addressed before.

The aim of the present study was to determine whether MES were released into the circulation during haemodialysis sessions. In addition, in vitro studies were also performed to detect the origin of such MES.

Subjects and methods

In vivo studies

Patient selection Doppler monitoring was performed over a
period of 6 months in 25 patients (age 59.0±14.5 years, range 28–86, 14 women and 11 men) with a mean time on dialysis of 10±9 years (range 2 months to 21 years), after obtaining informed consent. Patients with a previous history of stroke or cardiovascular surgery within 6 months before recordings or a mechanical prosthetic heart valve were excluded. Echo-Doppler examinations of fistulae, transthoracic echocardiography, and ECG were performed. Haemodynamic fistula disturbances and embolic cardiovascular disease were ruled out. The mean fistula blood flow was 540±150 ml/min (range 250–750 ml/min).

**Doppler studies** Pulsed Doppler (Multidop X4 DWL, Sipplingen, Germany) with one 2-MHz ultrasound probe was used for monitoring. This probe was applied over the subclavian vein and secured with adhesive tape in order to record the blood flow downstream from the arteriovenous fistula. Three separate recordings were made at different times during one session for each patient: the first over 1 min before the dialysis session (period A), the second during the first 15 min of the dialysis session (period B), and the third during the last 15 min (period C).

**Haemodialysis procedures** Dialysis generators AK 100 Gambro (Hechingen, Germany) and 4008 E Fresenius (St Wendel, Germany) were used with the blood lines Haemodia 480 and 487 (Labègue, France) respectively. Two types of dialyser were used, each with polysulphone membranes: a low-permeability dialyser (Haemoflow Fresenius F6, ultrafiltration coefficient of 5.5 ml/h/mmHg) and a high-permeability dialyser (Haemoflow Fresenius F60, ultrafiltration coefficient of 40 ml/h/mmHg). The haemodialysis procedures were identical in all patients, including preparation set-up, rinsing procedure, discontinuation of the procedure, blood flow (300 ml/min), and blood temperature (37°C). Low-molecular-weight heparin (Dalteparin sodium, 5000 IU) was administered into the venous line after the membrane 5 min before initiation of the treatment session. At the end of the session, the arterial blood line was connected to a container with sterile physiological solution. The rinse-back blood pump flow rate was set at 150 ml/min in order to return as much blood as possible to the patient. No injections were given during recordings.

**In vitro studies**

In *vitro* studies were subsequently performed to investigate the origin of MES. Recordings were made at four different sites of the haemodialysis machine (Figure 1) using the same dialysis machines and dialysers that were used during *in vivo* studies: on the arterial line before the blood pump (site A), after the blood pump (site B), between the dialyser and the air trap (site C), and after the air trap (site D). A special mixture of serum (87%) and glycerine (13%) was used to provide a volumetric mass (1.037 g/cm^3^) and viscosity (0.469 mPa·s) similar to those of human blood. The conditions of dialysis were those described during *in vivo* studies. Four 4-min recordings were made using the same 2 MHz probe that was used during the *in vivo* studies. Six different blood flows were tested with Doppler recording at site C (200, 250, 300, 350, 400 and 450 ml/min).

**Statistical analysis** Results are presented as the mean±standard deviation. The number of MES was expressed per minute. ANOVA with repeated measures was used to assess the effect of the dialysis session on the number and intensity of MES. Two-way ANOVA with repeated measures was used to assess the effects of the membranes (Fresenius F6 vs Fresenius F60) and generators (AK 10 Gambro vs 4008 E Fresenius) on the number and intensity of MES during haemodialysis and to assess the effects of the membranes and blood flows on the number of MES during *in vitro* studies. Statistical significance was set at P<0.05.

**Results**

In *vivo* studies

**Baseline characteristics** Fifteen patients (60%) were dialysed with low-permeability dialysers, 10 (40%) with high-permeability dialyser. Nineteen (76%) patients were dialysed using an AK 100 Gambro® generator, six (24%) using a 4008 E Fresenius® generator. The mean duration of dialysis sessions was 4 h (range 3.5–5 h). The mean weight loss during the haemodialysis session was 2.5±0.5 kg (range 1.5–4.5 kg). The average Doppler gate depth to monitor the subclavian vein flow downstream from the fistula was 32.5±6.0 mm.

**Detection of MES during haemodialysis sessions**

(Figure 2)

No MES were detected before the haemodialysis session. MES were detected in all patients (100%) in periods B and C during the haemodialysis session. No significant difference was noted concerning the number of MES during periods B and C (12.7±9 and 16.7±11.5 respectively) and the intensity of MES during periods B and C (19.2±5.0 and 19.4±3.9 dB respectively). No alarm signals were detected by the air detector in any case. As shown in Table 1, the intensity of MES was higher when using F60 than F6 (F=4.94; P=0.03). The number of MES was similar during the first 15 min of dialysis (period B) regardless of the membrane used (13±1.3 for F60 vs 12.2±3.7 for F6, NS). However, at the end of dialysis (period C)
The number of MES was greater in patients with F60 membranes (21.6 ± 4.7) than with F6 membranes (13.5 ± 1.8). The number and intensity of MES was not influenced by the type of generator or by the baseline fistula blood flow.

**In vitro studies**

No MES were detected on the arterial line before the blood pump during in vitro studies (Figure 3). In contrast, MES were recorded at all three sites after the blood pump. The number of MES was similar for each of the three sites: 19 ± 6 MES at site B (after the blood pump), 13 ± 4.2 at site C (after the dialyser), and 16.5 ± 5.5 at site D (after the air trap) (Table 2). The number of MES increased with the increase in blood flow with a significantly higher count for 400 and 450 ml/min than with lower blood flows ($P<0.01$) (Table 3).

**Discussion**

This is the first study to our knowledge to focus on the both detection and quantification of MES using Doppler methods during haemodialysis sessions. The in vivo studies demonstrated the absence of MES before the dialysis session and the presence of MES in the drainage vein from the arteriovenous fistula during the sessions in all patients. The air trap was unable to
Table 2. Number of MES/min (mean ± SD) recorded at sites A–D during in vitro procedures

<table>
<thead>
<tr>
<th>Dialysis Generators</th>
<th>Dialyser</th>
<th>Site A</th>
<th>Site B</th>
<th>Site C</th>
<th>Site D</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK 100</td>
<td>F6</td>
<td>17.5 ± 4.7</td>
<td>11.2 ± 4.3</td>
<td>14 ± 3.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F60</td>
<td>11.2 ± 3.6</td>
<td>8 ± 3.5</td>
<td>12 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>4008 E</td>
<td>F6</td>
<td>21.2 ± 5.7</td>
<td>17.5 ± 4.7</td>
<td>16.2 ± 4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F60</td>
<td>25.5 ± 7.4</td>
<td>15 ± 3.9</td>
<td>19.5 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>19 ± 6</td>
<td>13 ± 4.2</td>
<td>16.5 ± 5.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Number of MES/min (mean ± SD) recorded at site (C) with the changes in flow during in vitro experiments

<table>
<thead>
<tr>
<th>Dialysis Generators</th>
<th>Dialyser</th>
<th>Flow (ml/min)</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
<th>450</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK 100</td>
<td>F6</td>
<td>3 ± 2</td>
<td>2.5 ± 2</td>
<td>5 ± 2</td>
<td>8 ± 3</td>
<td>5 ± 2</td>
<td>58 ± 22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F60</td>
<td>2.5 ± 2</td>
<td>4.3 ± 3</td>
<td>5 ± 2</td>
<td>12 ± 6</td>
<td>76 ± 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4008 E</td>
<td>F6</td>
<td>4.2 ± 3</td>
<td>11 ± 4</td>
<td>6 ± 3</td>
<td>13 ± 8</td>
<td>32 ± 14</td>
<td>72 ± 31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F60</td>
<td>4 ± 3</td>
<td>3 ± 2</td>
<td>4.3 ± 3</td>
<td>12 ± 7</td>
<td>22 ± 12</td>
<td>83 ± 33</td>
<td></td>
</tr>
</tbody>
</table>

The exact nature of these MES remains unclear. The intensity and location of signals were inconsistent with artefacts that could easily be eliminated from Doppler recordings. It has previously been reported that the intensity of MES is related to the nature and the size of microemboli [4,11]. Among the different types of microemboli, the intensity of gaseous embolism and synthetic particles (usually greater than 10 dB) are higher than microthrombi or calcified materials (usually less than 9 dB) [4,11]. Haemorheological and/or haematological perturbations such as complement or coagulation activation, influenced by the type of the dialyser, have been demonstrated during haemodialysis sessions [12–14]. These abnormalities could induce the formation of thrombi or platelet aggregates [12–14] that could migrate into the arteriovenous fistula, but the intensity of the MES detected in the present study is inconsistent with this hypothesis. The intensity of MES related to synthetic particles is similar to that of microbubbles [2,4]. Some studies [15–19] have suggested that synthetic particles sizes ranging from 5 to 200 μm might be shed into the extracorporeal circuit from tubing damage induced by repeated flexion and compression of tubing by the roller pump. There are some discrepancies between these studies regarding the number and the size of these particles that aggregate causing a decrease in the particle counts. Haemodynamic turbulence due to the roller pump could induce the formation of air microbubbles by cavitation phenomenon from gas dissolved in the blood, as in mechanical prosthetic heart valves [20]. The increase in MES with the changes in blood flow during the in vitro experiment might be connected to an increase in microbubbles related to the increase in cavitation phenomenon as well as the increase in migration of synthetic particles from the tubing damage. As the detection of MES signals is based on Doppler intensity, which is the same for microbubbles as for synthetic particles, this study did not allow differentiation between the two possible particles. The passage of particles with higher intensity when using high permeability membranes might be related to the facilitated passage of larger particles across these membranes.

Although this study was not designed to investigate the final destination of such MES, the normal destination would be the lung capillaries in the absence of a right-to-left cardiac shunt. The precise consequence of the presence of these particles remains unknown. We can, however, speculate on their possible role in lung vascular permeability observed in chronic haemodialysed patients [21,22]. Indeed, animal experiments have demonstrated that chronic gaseous microbubble injection into the veins can induce arterial structural and functional pulmonary changes, mainly chronic arterial pulmonary hypertension [23,24]. Similarly, many subjects have undiagnosed right-to-left shunt, allowing particles to migrate into the systemic circulation. The implication of such migration into the brain circulation in neuropsychological impairment observed in haemodialysed patients among other well-known factors remains speculative.

Conclusion

The results of the present study prove the capability of Doppler methods to demonstrate that microemboli occur during dialysis. These microemboli can migrate into the drainage vein from an arteriovenous fistula, despite the presence of an air trap. Our results suggest that the roller pump might induce the formation of the detected particles. Further studies including different dialysis membranes and machines are required to confirm these preliminary results. According to previous studies of extracorporeal circulation, the pathogenic implications could be numerous, in particular for pulmonary and cerebral areas, and must be investigated further.

References


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