Activation of platelets and coagulation during haemodialysis

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Changes in platelet volume, morphology and RNA content in subjects treated with haemodialysis

M. SCHOORL, M. SCHOORL & P. C. M. BARTELS

ABSTRACT

During haemodialysis treatment, blood flows from the body to the extracorporeal circuit and vice versa. In this study, pathophysiological defects in platelets indicated by alterations in RNA content and aberrations in platelet volume and morphology are detected before and during haemodialysis treatment. In subjects receiving haemodialysis treatment, qualitative interpretation of platelet characteristics with application of light microscopic evaluation reveals only 19 ± 11 % of platelets with appropriate staining density of the granule containing cytoplasm. On the contrary, a reference group of apparently healthy subjects shows 70 ± 12 % platelets with appropriate staining density of the granule-containing cytoplasm. During haemodialysis treatment, mean values for platelet volume, platelet distribution width and platelet large cell ratio demonstrate a tendency to decrease by 10 %, 11 % and 6 %, respectively, from the mean initial value to the value at $t=150$ min. Reduction of the platelet volume parameters just mentioned is hypothesized to be due to platelet degranulation as a result of platelet activation.
INTRODUCTION

Activation of coagulation occurs in subjects treated with haemodialysis (HD) as a consequence of extracorporeal blood circulation. Important factors inducing thrombogenicity include reduction of blood flow, modifications in the blood vessel wall, changes in blood composition and bioincompatibility of artificial membranes [1–3]. Acute phase reactants and concomitantly increased degree of hypercoagulability are demonstrated to be initiated by surface characteristics of the dialyser membrane; for instance, permeability and chemical composition.

Platelets (PLTs) are activated due to contact with artificial membranes during treatment with HD. PLT activation is related to composition of the protein layer coated on a dialyser membrane and heparin suppletion at the start of a dialysis session [1]. Activation of PLTs can be evaluated with application of flow cytometric detection of PLT markers. CD62p (140 kD) is an alpha and dense granule labelling membrane protein exposed on the outside of the PLT membrane after activation. The process of PLT activation results in release of granule content. The amount of Platelet Factor 4 (PF4) released from alpha granules and serotonin from dense granules in plasma is indicative of activation of PLTs [4–6]. In peripheral blood smears, the degree of PLT degranulation can be scored by microscopic evaluation.

A PLT population is considered to be a heterogeneous mixture of particles consisting of intact PLTs, shape-changed PLTs, activated PLTs and PLTs that are already more or less degranulated due to damage as a result of previous activation. During extracorporeal circulation, blood flows from the body to the extracorporeal circuit and vice versa. As a consequence of activation, a heterogeneous population with young, reticulated PLTs, and old, smaller PLTs is present [7]. Shape anomalies occur when PLTs lose their discoid form upon reorganization of the cytoskeleton. A reversible shape modification is likely to be associated with changes in cellular forward and right-angle light scatter intensity [8]. Shedding of thrombogenic microparticles from PLT membranes is thought to be indicative of PLT activation. Microparticles expose an attractive surface for adhesion of activated plasma coagulation factors that can promote thrombin generation [9].

Levels of PLT counts in peripheral blood reflect the result of a balance between output of thrombopoiesis and rate of PLT removal. In the case of disorders such as inflammation, discrimination between bone marrow suppression and enhanced rate of PLT destruction is difficult. By applying flow cytometric analysis, the population of immature PLTs (IPF) or so-called reticulated PLTs is discriminated on the basis of increased PLT RNA content. Morphologically, immature reticulated PLTs are characterized by similar volumes, but increased granule density compared with mature PLTs [10]. IPF is expressed as a percentage of the total optical PLT count, or may be quantified as the absolute reticulated PLT count. Conclusive studies concerning disturbances of the thrombopoietic status of subjects with uraemia are not yet available. A result of previous studies in the case of HD patients is that activation of PLTs does not coincide with statistically significant changes in mean platelet volume (MPV) and platelet distribution width (PDW) [1,11,12].

We hypothesize that decreases in MPV and PDW will occur during HD treatment as a result of disturbance of the ratio of reticulated and degranulated PLTs in peripheral blood. Before the start of HD treatment, flow cytometric results (IPF, PLT-x), in conjunction with
PLT counts, together with MPV, PDW and PLT large cell ratio (p-LCR), are compared with a reference group of apparently healthy subjects. In this study, longitudinal investigations during HD treatment are performed with regard to deviations in PLT volume and RNA content in order to elucidate the relationship between PLT morphology and PLT activation.

PATIENTS AND METHODS

A group of 20 subjects (age 28–82 years) with chronic renal failure and who are treated with HD three times a week participated in the study. The aetiology of renal insufficiency includes hypertensive nephrosclerosis, chronic pyelonephritis and membranous nephropathy. Subjects with active inflammation, thrombocytopenia, autoimmune disease or malignancy, and/or using specific categories of drugs (immunosuppressives, calcium antagonists, serotonin receptor antagonists, coumarin derivatives or salicylates), were excluded from participation.

For treatment with HD, a low flux polysulphone® F8 membrane (Fresenius, Bad Homburg, Germany) is used with anticoagulant Fragmin® (intravenously 2000–5000 U bolus injection).

The patients received 10–150 µg/week erythropoietin-α (Amgen Europe b.v., Breda, The Netherlands) subcutaneously. According to the guidelines of the Dutch Dialysis Society, patients receive intravenously 0–100 mg/2 weeks iron sucrose (Venofer®; American Reagent Inc. Shirley, N.Y. 11967, USA).

Bicarbonate dialysate (Fresenius Medical Care, Bad Homburg, Germany) was applied with a dialysate flow of 500 mL/min. Depending on individual need and efficacy of treatment, ultrafiltration flow rates varied between 300 and 1000 mL/min. Blood flow rates were kept constant at 250–300 mL/min, resulting in HD sessions of 3–4 h. Blood samples were collected from the arterial line before starting HD (t=0) and subsequently from the efferent line after 1, (t=1), 5 (t=5), 30 (t=30), 60 (t=60) and 150 (t=150) min.

Reference group

A reference group of 20 healthy subjects (laboratory technicians, aged between 20 and 50 years) was selected in order to establish reference ranges for parameters reflecting morphological aspects of PLTs. The subjects were not using any medication that would interfere with PLT activation.

Analytical methods

Blood samples were drawn into K₂EDTA tubes (Vacutainer®, Becton Dickinson, Plymouth, UK) and analysed within 2 h after collection.

1. PLT, PDW, MPV, p-LCR, IPF and PLT-x

PLT counts, PDW, MPV, p-LCR and IPF are measured using a Sysmex XE-2100 haematology analyser with a dedicated IPF-Master software package (Sysmex Corporation, Kobe, Japan). A fluorescent dye reagent containing polymethine and oxazine is used with the flow cytometric IPF test methodology. After injecting the dye through the cell membrane,
RNA in reticulated red blood cells and reticulated PLTs is stained. The stained cells pass through a semiconductor diode laser beam and the resulting forward scatter light intensity (measure for cell volume) and fluorescence intensity (measure for RNA content) are measured. IPF count is calculated from the combination of intensity of the fluorescence signal and the forward scattered light signal from the XE-2100 reticulocyte measurement channel by application of a Sysmex algorithm. PLT-x indicates the amount of RNA present in reticulated PLTs. The mean value of fluorescence intensity corresponding with the mean RNA content is expressed by channel numbers.

2. PLT morphology
Two peripheral blood slide smears are prepared for evaluation of PLT morphology aberrations and are stained according to May-Grünwald-Giemsa methodology on a Sysmex SP-100 analyzer (Sysmex Corporation, Kobe, Japan). The slides are microscopically screened for qualitative evaluation of morphological aspects of PLTs with application of a Cellavision™ DM96 analyzer (Cellavision AB, Lund, Sweden). Using the Cellavision™ DM96 analyzer it is possible to reduce deviations between observations of biomedical scientists. Granule-containing cytoplasm, indicated as the granulomere, is stained light purple or pink. PLTs contain several kinds of granules, of which α-granules correspond with azurophilic granules viewed in light microscopy. After discharge of granule content, activated PLTs are grey [13]. Modifications of qualitative aspects of PLTs are evaluated by classification of the PLT content in four categories corresponding with staining density of granule-containing cytoplasm amounting to <25 %, 25–50 %, 50–75 % or >75 %, respectively. Staining density of >75 % of the granule-containing cytoplasm in >50 % of PLTs is considered to be appropriate.

Statistical evaluation
Statistical evaluation of data is performed with application of SPSS software v. 14.0 for Windows. Data are expressed as mean values±SD. Statistical significance of deviations between mean values during HD treatment is evaluated using Student’s t-test for paired data. The statistical significance of differences between mean values of the group of HD subjects and the reference group is calculated by applying Student’s t-test two-tailed for unpaired data. A p-value<0.05 is considered to be statistically significant.

Results for PLT counts, PDW, MPV and IPF counts at t=1, t=5, t=30, t=60 and t=150 min are corrected for changes in haematocrit (Ht). For example: corrected value $t=30 = \left( \frac{Ht_{t=0}}{Ht_{t=30}} \right) \times value_{t=30}$.
TABLE I. Evaluation of platelet (PLT) parameters, including mean value, standard deviation (SD), minimum-maximum values established in 20 subjects at several stages of haemodialysis (HD). This longitudinal study concerns results before HD (t=0) and at t=1, t=30 and t=150 min, respectively, after starting HD treatment.

<table>
<thead>
<tr>
<th>Time after starting HD (min)</th>
<th>Mean value</th>
<th>SD</th>
<th>Minimum-maximum</th>
<th>Statistical significance (1)</th>
<th>Statistical significance (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT ($10^9$/L)</td>
<td>0</td>
<td>198</td>
<td>43</td>
<td>117–229</td>
<td>p = 0.006</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>173</td>
<td>36</td>
<td>125–230</td>
<td>p = 0.013</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>185</td>
<td>45</td>
<td>82–285</td>
<td>p = 0.000</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>182</td>
<td>42</td>
<td>73–264</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>0</td>
<td>10.5</td>
<td>0.8</td>
<td>9.1–11.8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10.2</td>
<td>1.4</td>
<td>7.9–13.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>10.2</td>
<td>1.0</td>
<td>8.6–12.4</td>
<td>p = 0.015</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>9.5</td>
<td>0.9</td>
<td>7.7–11.4</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>PDW (fL)</td>
<td>0</td>
<td>12.3</td>
<td>1.9</td>
<td>9.2–15.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>11.9</td>
<td>2.2</td>
<td>8.3–15.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>12.0</td>
<td>1.8</td>
<td>9.2–15.1</td>
<td>p = 0.041</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>11.0</td>
<td>1.6</td>
<td>8.3–14.1</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>p-LCR (%)</td>
<td>0</td>
<td>29.0</td>
<td>7.4</td>
<td>16.9–40.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>27.4</td>
<td>8.1</td>
<td>17.2–40.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>29.2</td>
<td>8.3</td>
<td>15.7–41.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>27.2</td>
<td>7.8</td>
<td>13.8–36.7</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>IPF ($10^9$/L)</td>
<td>0</td>
<td>6.7</td>
<td>2.8</td>
<td>1.8–12.3</td>
<td>p = 0.006</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5.2</td>
<td>2.6</td>
<td>1.9–9.9</td>
<td>p = 0.019</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>6.3</td>
<td>3.5</td>
<td>2.4–15.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>6.1</td>
<td>3.1</td>
<td>1.8–14.7</td>
<td>p = 0.031</td>
</tr>
<tr>
<td>PLT-x (ch)</td>
<td>0</td>
<td>18.0</td>
<td>1.8</td>
<td>14.4–20.9</td>
<td>p = 0.005</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>18.2</td>
<td>1.9</td>
<td>14.2–21.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>18.8</td>
<td>1.8</td>
<td>16.0–21.8</td>
<td>p = 0.000</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>18.4</td>
<td>1.6</td>
<td>14.9–21.3</td>
<td>p = 0.013</td>
</tr>
<tr>
<td>PLTs with &gt;75 % staining intensity</td>
<td>0</td>
<td>19</td>
<td>11</td>
<td>4–41</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>of granule containing cytoplasm (%)</td>
<td>30</td>
<td>18</td>
<td>14</td>
<td>4–62</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>29</td>
<td>16</td>
<td>8–62</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

Results of statistical evaluation are indicated: (1) Statistical significance of deviations between results at t=0 and t=1, t=30 and t=150 min after starting HD. (2) Statistical significance of deviations between results at t=0 and the group of reference subjects (n=20). NS=deviation not statistically significant.
RESULTS

Investigations in the selected subjects’ group before and during HD treatment are performed for monitoring kinetics along with intra-individual variations due to activation of PLTs during HD treatment. Results for parameters reflecting PLT characteristics (mean value ± SD) are presented in Table I. For purposes of comparison, PLT parameters established in a reference group of apparently healthy subjects are listed in Table II.

PLT, PDW, MPV and p-LCR
As demonstrated in Table I, PLT counts in subjects with HD treatment are in the lower range of the reference interval. If compared with initial values, during HD treatment a statistically significant decrease in PLT count amounting to 8 % at $t=150$ min occurs ($p=0.000$). Changes in PLT volumes are estimated by monitoring MPV, PDW and p-LCR (Figure 2). Longitudinal evaluation of MPV and PDW yielded markedly decreased results during HD treatment. MPV values decreased from $10.5 \pm 0.8$ fL at $t=0$ to $9.5 \pm 0.9$ fL at $t=150$ min, a reduction of approximately 10 %. PDW results decreased from $12.3 \pm 1.9$ fL at $t=0$ to $11.0 \pm 1.6$ fL at $t=150$ min, a reduction of 11 %.

Results for p-LCR showed a decrease amounting to 6 % from $29.0 \pm 7.4$ % at $t=0$ to $27.2 \pm 7.8$ % at $t=150$ min ($p=0.000$). When results of the group of HD subjects before starting HD treatment are compared with results of the reference group of apparently healthy subjects, no statistically significant deviations for MPV, PDW and p-LCR are established.

IPF
IPF counts in subjects with HD treatment are situated in the lower range of the reference interval (Figure 3). At $t=1$ min after starting HD treatment, 250–300 mL of blood has already passed along the dialysis membrane. Immediately after starting extracorporeal

### TABLE II. Platelet (PLT) parameters concerning mean value, standard deviation (SD), minimum-maximum values established in a group of healthy subjects ($n=20$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value</th>
<th>SD</th>
<th>Minimum-maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT (10^9/L)</td>
<td>238</td>
<td>47</td>
<td>150–337</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>10.1</td>
<td>0.6</td>
<td>8.9–11.6</td>
</tr>
<tr>
<td>PDW (fL)</td>
<td>11.7</td>
<td>1.3</td>
<td>9.5–14.1</td>
</tr>
<tr>
<td>p-LCR (%)</td>
<td>25.5</td>
<td>5.4</td>
<td>15.2–37.3</td>
</tr>
<tr>
<td>IPF (10^9/L)</td>
<td>10.6</td>
<td>5.5</td>
<td>4.0–23.3</td>
</tr>
<tr>
<td>PLT-x (ch)</td>
<td>19.7</td>
<td>2.0</td>
<td>17.3–23.4</td>
</tr>
<tr>
<td>PLTs with &gt;75 %</td>
<td>70</td>
<td>12</td>
<td>44–86</td>
</tr>
</tbody>
</table>
blood circulation, a statistically significant decrease of IPF counts is observed from 6.7 ± 2.8 $10^9/L$ at $t=0$ to 5.2 ± 2.6 $10^9/L$. The decrease in IPF counts amounts to 22 %, whereas total PLT counts reveal a smaller decrease of 13 % within the first minute. Afterwards, a steadily ongoing increase is detected. At $t=150$ min, a statistically significant decrease in IPF count of 9 % from the initial level is demonstrated. Mean fluorescence intensity of PLTs expressed as PLT-x in the group of subjects with HD treatment is statistically significantly decreased compared with the reference group of apparently healthy subjects (Table II).

**PLT morphology**

In subjects with chronic HD treatment, staining density of the granule-containing cytoplasm is reduced to a minimum score compared to that of the group of reference subjects (Figure 4). In HD subjects, only 19 ± 10 % of the PLTs yield an appropriate staining density. In the group of apparently healthy subjects, 70 ± 12 % of the PLTs reveal appropriate staining.

During HD treatment, after $t=1$ min an ongoing decrease of PLTs with an appropriate staining density is detected until $t=30$ min. From $t=60$ min an increase of PLTs with an appropriate staining density is observed amounting to 29 ± 16 % at $t=150$ min ($p=0.001$) (Figure 4).
PLT activation in subjects with HD treatment may result in increased amounts of less densely granulated PLTs in the blood circulation. Activation of PLTs and activation of coagulation in an extracorporeal circuit is known to be a multifactorial process. If not effectively managed, thrombogenicity may result in HD inefficacy, because the membrane area does not function appropriately. It has been demonstrated that cuprophan and polyacrylonitrile membranes induce a higher degree of intradialytic PLT activation compared

DISCUSSION

Figure 2. Results (mean±SD) for MPV (fL), PDW (fL) and p-LCR (%) established in subjects before the start of haemodialysis (HD) treatment and subsequently at t=1, t=5, t=30, t=60 and t=150 min after starting HD (n=20). If compared with results at t=0 for MPV and PDW, statistically significant decreased values are demonstrated at t=30 and t=150, respectively. For p-LCR, a statistically significant reduction is detected only at t=150. For comparison, results for a group of 20 apparently healthy subjects (REF) are detected. At t=0 no statistically significant deviations are demonstrated. The horizontal dashed lines indicate the upper and lower level of the reference range for apparently healthy subjects.
with polysulphone and cellulose-triacetate membranes [3,14–16]. In addition, the anticoagulation mode has an important role in the efficacy of HD treatment [5,17,18]. Results of the present study with application of low-flux polysulphon F8 membranes demonstrate similar deviations in activation of PLTs when compared with high-flux polysulphon F60 membranes [5,6].

PLT adhesion is induced by interaction between PLTs, adhesive proteins and dialyser membrane. PLT aggregation is enhanced by increased plasma levels of fibrinogen and Von Willebrand factor [9]. The results in our study, concerning decreased PLT counts in patients on chronic HD treatment compared with apparently healthy controls, concur with those of other studies [19,20]. An obvious further decrease in PLT count is detected amounting to 13 % after the first passage of blood along the dialysis membrane at t=1 min after the start of HD treatment. Afterwards, a steady state occurs with decreased levels of PLT counts with a reduction of 8 % from the initial value at t=0.
Establishment of IPF count is a useful tool for elucidating aberrations in respect of PLT pathophysiology [10]. The amount of reticulated PLTs is considered to be a marker of marrow megakaryopoiesis activity [21,22]. As a result of the present study, IPF counts have been demonstrated to be statistically significantly decreased in patients receiving chronic HD treatment compared with apparently healthy subjects.

PLT interaction with the dialysis membrane will result in adhesion of PLTs on the membrane surface and release of PLT-derived factors. Adherence of PLTs and leukocytes to the dialysis membrane probably occurs during the first minutes of HD treatment. In the present study, IPF counts reveal an immediate decrease of 22 % at \( t=1 \) min. Subsequently, a slight recovery of IPF count is demonstrated. Finally, at \( t=150 \) min a decrease in IPF count amounting to 9 % from the initial level is observed. We hypothesize that young reticulated PLTs, because of a high quality of viability during the first passage of blood through sterile lines of the extracorporeal circuit, readily adhere to the dialysis membrane. The slight decrease in p-LCR results at \( t=1 \) min, as well as the observation of steadily decreasing MPV and PDW results during HD treatment, also supports the hypothesis just mentioned.

A decrease in serotonin concentration in PLTs and an increase in plasma serotonin concentrations revealed an indication for increasing PLT activation during HD treatment [4,6]. Reticulated PLTs are considered to be more viable compared with degranulated PLTs [23]. A rapid decrease in RNA-rich IPF count during HD treatment is hypothesized to be due to elimination of young, viable PLTs. Preferred removal of young active PLTs is presumed to exaggerate thrombocytopenia, which may be present in uraemic patients [24].

When PLT turnover is increased, increasing amounts of young PLTs with fairly large volumes are produced. The absence of large PLTs in the case of subjects with HD treatment is indicative of a qualitative defect of PLT production. PLTs contain azurophilic granules that are finely dispersed throughout the cytoplasm or are concentrated near the centre. PLTs contain various species of granules. The azurophilic granules are equivalent to \( \alpha \)-granules and may be visualized by light microscopy [13]. When PLTs are being activated, CD62p is expressed at the outside of the PLT surface membrane. Various products are released from PLT granules; among others, PF4 from alpha granules and serotonin from dense granules. Cytoplasm of PLTs that lack \( \alpha \)-granules appear grey or pale blue, implying that PLTs contain few stained azurophilic granules [13]. Degranulated PLTs still demonstrate increased exposition of p-selectin and procoagulant phospholipids on their surface and continue to circulate [13, 25].

As a result of our study, PLTs with rather small volumes in the case of subjects with HD treatment are detected. With respect to a 10-day life-span of PLTs and HD treatment three times a week, the pale blue stained granule containing cytoplasm and decreased mean fluorescence intensity reflecting RNA content elucidate that peripheral PLT populations of HD subjects consist of about 30 % of PLTs which remained briefly in the extracorporeal circuit. Secondary, increased urea concentrations in HD patients may yield an additional factor exaggerating the pale blue aspect of cytoplasm. A group of 20 uraemic subjects with a glomerular filtration rate ranging from 3 to 74 mL/min demonstrated 49 ± 14 % of PLTs with appropriate staining, whereas the reference group of apparently healthy subjects reveal a score of 70 ± 12 % (pers. comm.). The degranulation phenomenon may result from exhaustion due to exposition of PLTs to increased urea concentrations over a short period of time.
As a result of adherence of PLTs to the dialysis membrane at $t=1$ min and simultaneously increased degree of activation of PLTs till $t=30$ min of HD treatment, native and not yet activated PLTs are released into the circulation [5, 6, 26]. As a consequence, an increased number of PLTs with appropriate staining density or modal fluorescence intensity is demonstrated to be present. Young PLTs are characterized with a high content of azurophilic granules or RNA content. We hypothesize that a balance arises between adherence and retention of PLTs to the dialysis membrane and release of PLTs into peripheral blood while the HD treatment process continues.

**CONCLUSIONS**

Reduced PLT and IPF counts are indicative of suppressed activity of megakaryopoiesis or destruction as a result of chronic HD treatment. Results of this study demonstrate an obvious decrease in MPV, PDW and p-LCR during HD treatment. Predominantly, adherence of young reticulated PLTs to the dialyser membrane is hypothesized to occur. As a consequence of repeated PLT activation in HD subjects, increased amounts of degranulated PLTs with smaller volumes are detected in the blood circulation. Increased urea concentrations may reveal an additional cause for occurrence of PLTs with reduced density of granules in the cytoplasm. In subjects with HD treatment, suppressed activity of megakaryopoiesis is accompanied by PLT volume reduction as a result of activation.
REFERENCES


