The high incidence of left atrial appendage thrombosis in patients on maintenance haemodialysis

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Abstract

Background. The incidence of intracardiac thrombosis in haemodialysis patients has not been studied. Here we determined the incidence in end-stage renal disease patients on maintenance haemodialysis.

Methods. Transoesophageal echocardiography was performed in 215 patients (125 males, 90 females; mean age 60 ± 9 years). Any potential candidate with current or past chronic or intermittent atrial fibrillation or with cardiovascular diseases was excluded from the study.

Results. Thrombi were found in the left atrial appendages in 71 out of 215 subjects (33%). Based on multiple logistic regression analyses, the probability of finding a thrombus was found to be increased in patients on chronic antiplatelet therapy (odds ratio 4.268) and in those with diabetes mellitus and a low haematocrit (<0.3; odds ratio 7.173). Other clinical parameters, including gender, age, duration of haemodialysis, blood pressure, left ventricular dimension, smoking habit or type of anticoagulation during dialysis, were not associated with the incidence of left atrial appendage thrombosis.

Conclusions. Maintenance haemodialysis patients have a high incidence of left atrial appendage thrombosis. Either chronic use of antiplatelet drugs or the background conditions requiring antiplatelet therapy, and the concomitant presence of diabetes mellitus and a low haematocrit may be involved in left atrial appendage thrombosis.

Keywords: antiplatelet therapy; diabetes mellitus; haematocrit; haemodialysis; left atrial appendage; thrombosis

Introduction

Intracardiac sources of cerebrovascular ischaemic events reportedly account for 15–20% of strokes in the general population [1]. Thrombi in the left atrium, which are often most associated with atrial fibrillation, or rheumatic mitral valve stenosis, account for >45% of cardiogenic thromboemboli [2,3]. Left atrial thrombi are present in 14–27% of patients with atrial fibrillation of >3 days duration [4]. Thrombi in the left atrium have a predisposition to form in the atrial appendage (LAA) because of its shape and the presence of trabeculations. The LAA lies within the pericardium close to the free wall of the left ventricle. In contrast to the limited ability of transthoracic echocardiography to identify or exclude left atrial or LAA thrombi, transoesophageal echocardiography (TEE) can accurately diagnose the presence of thrombi in the LAA. In fact, the sensitivity and specificity of TEE for LAA thrombi are 93–100 and 99–100%, respectively [5].

The incidence of cerebrovascular accidents is high in Japanese patients on maintenance haemodialysis: 17.2–17.6 per 1000 haemodialysis patients per year [6]. However, the contribution of cardiogenic thromboemboli to cerebrovascular accidents as well as the incidence of intracardiac thrombus in patients with end-stage renal disease (ESRD) on maintenance haemodialysis has never been reported. In this study, we determined the incidence of intracardiac thrombi using TEE in maintenance haemodialysis patients with no cardiac disease (including atrial fibrillation), and...
evaluated the association of clinical factors with the presence of intracardiac thrombi.

Subjects and methods

Study population

Of 646 ESRD patients who had been on maintenance haemodialysis for >6 months in Toujinkai Hospital, 215 patients were enrolled in this study (mean age 60 ± 0.6 years; 125 males and 90 females; mean dialysis duration 111 ± 6 months) (Table 1). In addition, 13 ESRD patients receiving continuous ambulatory peritoneal dialysis (CAPD) were included in this study (mean age 59 ± 1.3 years; nine males and four females; mean dialysis duration 39 ± 8 months). Of 646 potential subjects, 431 were excluded because of: (i) current or past atrial fibrillation documented by either routine electrocardiograms performed every 3 months or by 24 h ambulatory electrocardiography (n = 56); (ii) current or past coronary or valvular heart diseases including the presence of either 201Tl or 123I-BMIPP myocardial perfusion defects (n = 214); or (iii) refusal of TEE examination (n = 161). Of the 215 patients enrolled, 152 had neither presently nor a past history of diabetes mellitus (65 females, 87 males), while the remaining 63 patients had diabetes mellitus either presently or in the past (25 females, 38 males). Of the 63 diabetic patients, 28 used insulin and 18 other anti-diabetic drugs. The remaining 17 diabetic patients used no medications, because their serum haemoglobin A1c levels were stable below 5.8%. Histories of smoking or alcohol use were ascertainment by administering a questionnaire to the participants. This study was approved by the Ethical Committee for Human Research of Kyoto Prefectural University of Medicine, and all patients provided informed consent prior to participation.

Haemodialysis was performed three times weekly using a dialysate containing Na+(140 mEq/l), K+(2.0 mEq/l), Cl− (110 mEq/l), Ca2+(3.0 mEq/l), Mg2+(1.0 mEq/l), HCO3− (30 mEq/l) and CH3COO− (10–15 mEq/l), and using either synthetic or semisynthetic membranes (dialysis filter surface area 1.8–2.1 m2). Blood pressure was measured every hour during dialysis using a mercury sphygmomanometer. Blood pressure and pulse pressure were taken as the mean of the measurements obtained during three different midweek haemodialysis sessions in which patients had the same increase in body weight. Haematocrit was measured every 2 weeks in each patient, and the dose of recombinant erythropoietin (Eposin S, Chugai Pharmaceutical Co., Tokyo, Japan) was adjusted to maintain the haematocrit at >0.3.

Echocardiographic measurements

TEE was performed with a 5 MHz biplane transducer attached to a commercially available echocardiograph (UF-8800, Fukuda Denshi Co., Tokyo, Japan). Each patient was studied in the fasting state on a non-haemodialysis day. Attention was paid to imaging the left atrial cavity and LAA to look for thrombi. Particular attention was paid to differentiating an LAA thrombus from normal cardiac structures, such as the pectinate muscles. The TEE images were checked by two independent inspectors (a cardiologist and a sonographer), and the presence of an LAA thrombus was accepted only when the diagnoses of both observers were concordant. Two-dimensionally guided M-mode and Doppler transthoracic echocardiographies were performed on each patient using the same echocardiography system just before the midweek dialysis, on the day before the TEE examination. Measurements for M-mode-guided calculation of left ventricular mass (LVM), left ventricular internal end-diastolic and end-systolic dimensions (LVIDd and LVIDs), interventricular septal wall thickness (IVST) and left ventricular posterior wall thickness (PWT) were performed according to the guidelines of the American Society of Echocardiography. Relative left ventricular wall thickness (rLWWT) was calculated as 2 × PWT/LVIDd. LVM was calculated according to the formula devised by Devereux et al. [7]

\[
LVM (g) = 1.04 [(LVIDd + IVST + PWT)^3 – LVIDd^3] – 13.6 g
\]

LVM was normalized to body surface area and expressed as the LVM index (LVMI). The ratio of the transmural pulse Doppler flow E velocity and A velocity (the E/A ratio) was calculated and taken as an index of left ventricular diastolic function.

Biochemical measurements

Blood samples (5 ml) were obtained just before the start of a midweek haemodialysis session, on the day before the TEE examination, after the patients had been supine for at least 10 min. Plasma intact parathyroid hormone (iPTH) was measured using a chemiluminescent assay (Chemiluminescence Intact PTH 100T kit, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The intra- and inter-assay variations were 3.15 and 3.52%, respectively. Haematocrit and serum haemoglobin and albumin were determined as the mean of four different measurements over a 2 month period, which included the echocardiographic examination.

Twenty-four hour ambulatory electrocardiography

To reconfirm the absence of intermittent atrial fibrillation, 24 h ambulatory electrocardiograms were recorded (FM-100, Fukuda Denshi Co.), between dialysis sessions, and analysed (SCM-6000, Fukuda Denshi Co.) in 71 haemodialysis patients with LAA thrombi. The analyses were performed by cardiology experts (Fukuda Denshi Co.) who were unaware of the purpose of this study.

Evaluation of past cerebral ischaemic events

The occurrence of past cerebral ischaemic events, such as infarction (which does not include cerebral lacunae), was explored by computed X-ray tomography (CT) (HISPEED ADVANTAGE, GE Medical Systems, Waukesha, WI, USA) in the 215 patients in this study. Brain CT images were interpreted by consensus by two experienced radiologists who were unaware of the diagnoses and of the results of the TEE examinations.

Magnetic resonance (MR) imaging

In addition to the 215 subjects, 10 ESRD patients on maintenance haemodialysis in Toujinkai Hospital (61 ± 0.8
Intracardiac thrombosis in ESRD patients

Table 1. Clinical characteristics of maintenance haemodialysis patients with or without left atrial appendage thrombus

<table>
<thead>
<tr>
<th>Thrombus (-)</th>
<th>Thrombus (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>144</td>
<td>71</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 0.8</td>
<td>61 ± 1.1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>80/64</td>
<td>45/26</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35/144 (24.3%)</td>
<td>28/71 (39.4%)</td>
</tr>
<tr>
<td>Duration of HD (months)</td>
<td>114 ± 7.3</td>
<td>104 ± 10.4</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>10/144 (6.9%)</td>
<td>19/71 (26.8%)</td>
</tr>
<tr>
<td>Dialysis membranes</td>
<td>Synthetic</td>
<td>Semisynthetic</td>
</tr>
<tr>
<td>Cardiothoracic ratio (%)</td>
<td>52 ± 0.4</td>
<td>52 ± 0.4</td>
</tr>
<tr>
<td>MBP pre-HD (mmHg)</td>
<td>99 ± 0.9</td>
<td>99 ± 1.4</td>
</tr>
<tr>
<td>MBP post-HD (mmHg)</td>
<td>87 ± 0.9</td>
<td>87 ± 1.7</td>
</tr>
<tr>
<td>PP pre-HD (mmHg)</td>
<td>65 ± 1.1</td>
<td>67 ± 1.8</td>
</tr>
<tr>
<td>PP post-HD (mmHg)</td>
<td>66 ± 1.1</td>
<td>67 ± 1.9</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>40.9 ± 0.58</td>
<td>43.1 ± 0.81</td>
</tr>
<tr>
<td>LVIdD (mm)</td>
<td>49 ± 0.7</td>
<td>50 ± 1.0</td>
</tr>
<tr>
<td>LVIds (mm)</td>
<td>32 ± 0.8</td>
<td>32 ± 1.1</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>37 ± 0.8</td>
<td>37 ± 1.4</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>139 ± 5.6</td>
<td>154 ± 8.4</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.73 ± 0.023</td>
<td>0.70 ± 0.037</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.32 ± 0.003</td>
<td>0.31 ± 0.004</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>4.1 ± 0.32</td>
<td>4.1 ± 0.35</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>152 ± 2.4</td>
<td>149 ± 3.4</td>
</tr>
<tr>
<td>Serum LP (a) (mg/dl)</td>
<td>38 ± 0.7</td>
<td>36 ± 0.8</td>
</tr>
<tr>
<td>Plasma AT III activity (%)</td>
<td>104 ± 6.5</td>
<td>95 ± 1.5</td>
</tr>
<tr>
<td>Plasma protein C (%)</td>
<td>98 ± 1.2</td>
<td>98 ± 1.5</td>
</tr>
<tr>
<td>Plasma protein S (%)</td>
<td>103 ± 2.4</td>
<td>101 ± 1.8</td>
</tr>
<tr>
<td>Plasma fibrinogen (mg/dl)</td>
<td>349 ± 6.6</td>
<td>352 ± 9.7</td>
</tr>
<tr>
<td>Ca×P (mg/dl)²</td>
<td>48 ± 0.8</td>
<td>46 ± 1.5</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>264 ± 18.4</td>
<td>226 ± 25.8</td>
</tr>
<tr>
<td>Smoking habit*</td>
<td>0, no smoking; +1, &lt;10 cigarettes/week; +2, ≥10 cigarettes/week and &lt;20 cigarettes/day; +3, 20–39 cigarettes/day; +4, ≥40 cigarettes/day.</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption*</td>
<td>0, no alcohol consumption; +1, &lt;20 g/week; +2, ≥20 g/week and &lt;30 g/day; +3, 30–49 g/day; +4, ≥50 g/day.</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Ca blockers</td>
<td>Ras inhibitors</td>
</tr>
<tr>
<td></td>
<td>35.4%</td>
<td>45.1%</td>
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<tr>
<td></td>
<td>+1</td>
<td>+2</td>
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<tr>
<td></td>
<td>42.4%</td>
<td>42.4%</td>
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<tr>
<td></td>
<td>44.4%</td>
<td>44.4%</td>
</tr>
<tr>
<td></td>
<td>7.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td></td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Recombinant erythropoietin (IU/week)</td>
<td>4260 ± 191</td>
<td>4711 ± 278</td>
</tr>
</tbody>
</table>

MBP, mean blood pressure; PP, pulse pressure; HD, haemodialysis; LAD, left atrial diameter; LVIdD, left ventricular internal end-diastolic dimension; LVIds, left ventricular internal end-systolic dimension; LVFS, left ventricular fractional shortening; LVMI, left ventricular mass index; E/A ratio, transmitral flow velocity E/A ratio; LP (a), lipoprotein (a); AT III, antithrombin III; PTH, parathyroid hormone; RAS, renin-angiotensin system. NS, not significant, P > 0.05.

*Smoking habit: 0, no smoking; +1, < 10 cigarettes/week; +2, ≥10 cigarettes/week and < 20 cigarettes/day; +3, 20–39 cigarettes/day; +4, ≥ 40 cigarettes/day.

*Alcohol consumption: 0, no alcohol consumption; +1, < 20 g/week; +2, ≥ 20 g/week and < 30 g/day; +3, 30–49 g/day; +4, ≥ 50 g/day.

years, six males and four females, mean dialysis duration 116 ± 10 months), who had LAA thrombus-like echoes diagnosed by TEE examination, had MR studies to ascertain the presence of LAA thrombi. A 1.5 T scanner (EXELART XG Spin Edition, Version 5.3, Toshiba Medical Systems, Tokyo, Japan) was used for MR imaging. The MR imaging protocol included an electrocardiogram-triggered, dark blood-prepared, fast advanced spin echo (FASE) sequence (repetition time (TR) 1600 ms, echo time (TE) 32 ms; flip angle 90°) covering the entire heart in the axial orientation. Thereafter, four-chamber and two-chamber views as well as contiguous short-axis images of the entire heart were acquired with a steady-state free precession (true SSFP) cine sequence (TR 5 ms, TE 2.7 ms, flip angle 70°). Images in the oblique orientation were obtained to investigate suspicious areas further. All MR images were interpreted by consensus by two radiologists who were unaware of the diagnoses and of the results of TEE examinations.
Statistical analysis

Data are expressed as mean ± SEM. The association of LAA thrombi with other continuous or categorical data was analysed with a logistic regression model, with a dichotomous response variable for the presence/absence of LAA thrombus and using a backward elimination procedure. Interaction terms between selected covariates were also examined in the model. As a measure of the relative risk for the presence of an LAA thrombus, odds ratio (OR) and 95% confidence intervals (CIs) are calculated in order to summarize the effects of each covariate. All statistical tests were two-sided, with a value for $P < 0.05$ considered significant.

Results

Intracardiac thrombi were detected by TEE in 71 of 215 (33%) ESRD patients undergoing maintenance haemodialysis (Table 1). All intracardiac thrombi detected in this study were in the LAA. The size of the major axis of the thrombi ranged from 5 to 11 mm in TEE (Figure 1). The incidence of old cerebral infarctions was higher in patients with LAA thrombi than in those without (Table 1). Patients with LAA thrombi were more likely to have diabetes mellitus and an enlarged left atrium, and to use antiplatelet drugs, than those without. Furthermore, haematocrit tended to be lower in patients with LAA thrombi than in those without. Other clinical parameters, including age, gender, mean blood pressure, pulse pressure, cardiothoracic ratio, left ventricular dimension or function, and serum concentrations of albumin, total cholesterol or lipoprotein (a) did not differ between the patients with or without LAA thrombi (Table 1). Likewise, plasma fibrinogen concentrations and the activities of plasma antithrombin III, protein C and protein S did not differ between the two groups (Table 1). The frequencies of the use of synthetic or semisynthetic dialysis membranes were similar between the patients with or without LAA thrombi (Table 1). Heparin sodium, low molecular weight deltaheparin and the antithrombin agent nafamostat mesilate were used as anticoagulants during haemodialysis in 112 (77.8%), 29 (20.2%) and three (2%) of the 144 patients without LAA thrombus, and in 56 (78.9%), 14 (19.7%) and one (1.4%) of the 71 patients with LAA thrombi, respectively. Of 74 patients receiving antiplatelet agents, aspirin (81–162 mg/day) was used in 70 patients, ticlopidine hydrochloride (100 mg/day) in two patients, cilostazol (200 mg/day) in one patient, and ethyl icosapentate (900 mg/day) in one patient. Antiplatelet drugs were administered to 60 haemodialysis patients with histories of a thrombosis of arteriovenous shunt [31/71 patients with LAA thrombi (43.7%), 29/144 patients without LAA thrombus (20.1%)] and were administered to eight haemodialysis patients to prevent clotting in the dialyser [4/71 patients with LAA thrombi (5.6%) and 4/144 patients without (2.8%)]. The reason for the antiplatelet therapy was unknown in the remaining six patients.

Contribution of clinical factors to the presence of an LAA thrombus

The association of the incidence of LAA thrombi with clinical characteristics, presented in Table 1, was investigated by using a logistic regression model. As shown in Table 2, gender, age, concomitant antiplatelet drugs and a composite factor for the presence or absence of diabetes mellitus and the level of haematocrit ($>0.3$) eventually were included in the model. The composite factor defined by diabetes mellitus and the haematocrit level was made in order to interpret the effects of both diabetes mellitus and haematocrit, since a significant two-way interaction was found. The analysed results indicate that the use of antiplatelet drugs significantly increased the risk of having an LAA thrombus ($P < 0.001$), with an OR of 4.28 (95% CI 2.18–8.35); and the risk in patients who had diabetes mellitus and a haematocrit level of $<0.3$ was much higher, their OR being 7.17 (95% CI 2.11–24.36) when compared with patients who were not diabetic and had haematocrits $>0.3$. The relative risks of LAA thrombosis in the subgroups defined by the clinical characteristics used in the analysis are shown in Figure 2. For further analysis, the relative risk

Fig. 1. Intracardiac thrombi in the left atrial appendage (LAA) in two haemodialysis patients detected by transoesophageal echocardiography. (A) A 63-year-old male. (B) A 61-year-old female.
of LAA thrombosis was evaluated in stratified patient populations according to the presence or absence of diabetes mellitus or haematocrit levels.

Relative risk of LAA thrombosis in patients with or without diabetes mellitus (Figure 3)

In the patients without diabetes mellitus \( (n = 147) \), the OR for the use of antplatelet drugs was increased \( (P < 0.001) \). In patients with diabetes mellitus \( (n = 60) \), the OR for the use of antplatelet drugs also was increased \( (P = 0.011) \), and was similar to that in non-diabetic patients. The OR for the haematocrit \( (Ht>0.3) \) was 0.108 \( (CI 0.021–0.542; P = 0.007) \) in diabetic patients.

Relative risk of LAA thrombosis in patients based on their haematocrit (Figure 4)

In the patients with a haematocrit \( >0.3 \) \( (n = 159) \), the OR was high in those receiving antiplatelet therapy. In general, the relative risk of LAA thrombosis in patients receiving chronic antiplatelet therapy is increased.

Recombinant erythropoietin therapy and LAA thrombosis

The weekly dose of recombinant erythropoietin administered to haemodialysis patients did not differ between the patients with or without LAA thrombi (Table 1). However, the weekly dose of erythropoietin was greater \( (P<0.01) \) in the subgroups of patients with haematocrits \( \leq 0.3 \) than in those with haematocrits \( >0.3 \): non-diabetic patients with haematocrits \( >0.3 \), \( 3521 \pm 168 \) IU/week; patients with diabetes mellitus and haematocrits \( >0.3 \), \( 3954 \pm 219 \) IU/week; non-diabetic patients with haematocrits \( \leq 0.3 \), \( 6703 \pm 452 \) IU/week; patients with diabetes mellitus and haematocrits \( \leq 0.3 \), \( 7500 \pm 474 \) IU/week. The dose of erythropoietin also was greater in patients with LAA thrombi than in those without if the patients had diabetes mellitus and haematocrits \( \leq 0.3 \) \( [8182 \pm 422 \) IU/week \( (n = 11) \) vs \( 6000 \pm 949 \) IU/week \( (n = 5) \), \( P < 0.05 \), but not in other subgroups.
**CAPD patients**

An intracardiac thrombus was recognized in one of 13 CAPD patients, but in the right atrium. This CAPD patient with right atrial thrombus did not have diabetes mellitus or a haematocrit $\geq 0.3$.

**Warfarin therapy**

Warfarin was administered to 69 of 71 patients with LAA thrombi beginning on the day after the detection of the LAA thrombus in TEE examination. Warfarin therapy was started at 1 mg/day and increased gradually up to 5 mg/day based on the international normalized ratio (INR) for the prothrombin time, which was checked weekly. The INR was maintained between 1.5 and 2.5 for at least 4 weeks. The mean duration of warfarin administration was 62 $\pm$ 5 days. A repeat TEE was performed in 65 of 69 patients after warfarin therapy, and the resolution of the LAA thrombi was confirmed in 62 of the 65 patients (95%). The LAA thrombi in the remaining three patients showed evidence of severe calcification. Warfarin therapy was stopped in two patients because of intracerebral haemorrhage, although the INR was $< 1.5$ in both patients.

**Continuous ambulatory electrocardiography**

In 71 haemodialysis patients with LAA thrombi, absence of either intermittent atrial fibrillation or frequent supraventricular dysrhythmia, which may be associated with LAA thrombosis, was reconfirmed by 24 h ambulatory electrocardiography.

**Confirmation of LAA thrombi by MR imaging**

Of 10 thrombus-like echoes in the LAA of 10 haemodialysis patients, six were diagnosed as thrombi by MR imaging, but the other four thrombus-like echoes did not correlate with MR findings. The thrombi appeared isointense or slightly hyperintense relative to myocardium on dark blood-prepared FASE images (Figure 5), and showed low signal intensity on true SSFP images. The major axes of the six LAA thrombus-like echoes confirmed by MR images measured $> 10$ mm (12–18 mm) in TEE examination, whereas the major axes of the other four LAA thrombus-like echoes unconfirmed by MR imaging were between 5 and 8 mm. The disappearance of all 10 LAA thrombus-like echoes after warfarin administration was confirmed by TEE.
Intracardiac thrombi were present in the LAA of 71 of 215 ESRD patients in our study who were on maintenance haemodialysis. The incidence of LAA thrombosis in haemodialysis patients without atrial fibrillation or other cardiac disease (33%) is likely to be higher than that in patients with chronic atrial fibrillation (14–27%) [4], which is the leading cause of intracardiac thrombosis in the general population. The higher incidence of old cerebral infarction in patients with LAA thrombi compared with those without thrombi indicates the possible contribution of the thrombus to cerebrovascular events in haemodialysis patients, although direct evidence to show the association between the thrombi and cerebrovascular embolic events was not obtained from this study. In multivariate analyses using logistic regression models, the relative risk of LAA thrombosis was increased in patients receiving antiplatelet agents and in diabetic patients with a haematocrit ≤0.3. Other clinical parameters, including age, gender, haemodialysis duration, blood pressure, pulse pressure, left ventricular dimension or function, smoking, alcohol consumption and medications other than antiplatelet agents, were not associated with LAA thrombosis in haemodialysis patients.

Aspirin was the antiplatelet drug most patients in our study were using. Recent meta-analyses of randomized trials have shown that low dose administration of aspirin prevents a wide range of occlusive cardiovascular events, including acute myocardial infarction, unstable angina pectoris and stroke [8,9]. However, it has been reported that aspirin therapy is associated with an increase in the development of fistula thrombosis in haemodialysis patients who have new arteriovenous grafts [10]. Recent studies have suggested that aspirin does not inhibit the interaction of platelets with monocytes and polymorphonuclear cells, platelet expression of P-selectin, or the ability of platelets to release α-granules containing platelet-derived growth factor [11]. Aspirin may block the production of prostacyclin by endothelial cells, abrogating the antiaggregatory effects of prostacyclin [12]. In addition, salicylate reportedly is associated with decreased 13-hydroxoyctadecadienoic acid synthesis and increased platelet adhesion [13]. In uraemic patients, aspirin may have effects that differ from the effects in healthy individuals.

Of 74 haemodialysis patients receiving antiplatelet therapy, 60 (81%) had histories of thrombosis of arteriovenous shunts, and eight (11%) of blood clotting in the dialyser. The background conditions that necessitated the prescription of antiplatelet drugs—such as arteriovenous shunt thrombosis or blood clotting in the dialyser—may be associated with intracardiac thrombosis in haemodialysis patients, because the incidences of these events were higher in the past histories of patients with LAA thrombi than of those without. Further research is needed to clarify the relationship between antiplatelet therapy and LAA thrombosis in maintenance haemodialysis patients.

Diabetes mellitus has a number of effects on platelet function that may enhance thrombosis. Primary platelet aggregation in response to ADP, and secondary platelet aggregation in response to ADP, collagen, arachidonic acid, platelet-activating factor and thrombin are enhanced in patients with diabetes mellitus. The release of the contents of α-granules, which include thromboglobulin and platelet factor IV, is increased in the platelets of diabetic patients. Serum concentrations of thromboxane B₂ are increased in diabetic patients with poor glycaemic control or vascular complications. In addition to causing abnormalities in platelet function, diabetes mellitus may cause abnormalities in coagulation, haemostasis and fibrinolysis. Circulating tissue-type plasminogen activator concentrations are normal or increased in diabetic patients, but its activity is decreased because of increased plasma concentrations of, and enhanced binding to, plasminogen activator inhibitor (PAI)-1 [14]. Elevated concentrations of PAI-1 are present in atheroma specimens obtained from type 2 diabetic patients [15]. Glycation of plasminogen decreases its susceptibility to activation.
Although the plasma concentration of fibrinogen and the activities of plasma antithrombin III, protein C and protein S did not differ between the patients with or without intracardiac thrombosis, these abnormalities in platelet function, coagulation and fibrinolysis in the setting of diabetes mellitus are likely to be involved in the formation of LAA thrombi in diabetic haemodialysis patients.

It is not clear if the administration of recombinant erythropoietin increases the clotting tendency of ESRD patients. Long-term administration of recombinant erythropoietin reportedly does not increase the risk of progressive stenosis of native arteriovenous fistulas of haemodialysis patients [16]. In a recent study, however, a significant increase in the thrombosis of both native fistulas and synthetic arteriovenous grafts was seen in haemodialysis patients with heart disease and normal haematocrits [17]. In our present study, the dose of recombinant erythropoietin did not differ between patients with or without LAA thrombi and was not associated with the incidence of LAA thrombosis, according to multivariate analysis. However, in the subgroup with both diabetes mellitus and a haematocrit <0.3, the dose of erythropoietin was greater in patients with LAA thrombi than in those without. One study reported that the administration of erythropoietin increased the incidence of peripheral vascular disease and the risk of serious limb or digit ischaemia in diabetic patients on peritoneal dialysis [18]. Therefore, long-term administration of high dose recombinant erythropoietin may play a role in the development of LAA thrombi only in diabetic haemodialysis patients.

An intracardiac thrombus was detected in one of 13 CAPD patients, but in the right atrium. Therefore, the incidence of intracardiac thrombosis in CAPD patients was 7.7%, but the incidence of LAA thrombosis was 0%. The difference between the incidences of intracardiac thrombosis in haemodialysis and CAPD patients might be due to differences in the number of the patients included in our study and in the duration of dialysis. However, the process of haemodialysis itself may be more strongly associated with LAA thrombosis than the state of chronic renal failure. Neutrophils, monocytes and platelets are activated by contact with haemodialysis membranes. Activation of monocytes leads to the production of monokines, such as tumour necrosis factor-α and interleukin-1, and activation of platelets leads to the release of thromboxanes [19]. Concentrations of proinflammatory cytokines, such as tumour necrosis factor-α and interleukin-1, reportedly increase in haemodialysis patients [20]. These cytokines partially regulate the expression of tissue factor on both endothelial cells and monocytes, which initiates the extrinsic coagulation cascade [21]. It is not the state of chronic renal failure but the process of maintenance haemodialysis which is likely to be involved in the formation of LAA thrombi in ESRD patients.

MR studies could not confirm the presence of LAA thrombi in four of 10 haemodialysis patients. However, four LAA thrombus-like echoes unconfirmed by MR imaging as well as another six thrombus-like echoes confirmed by MR disappeared after warfarin therapy. Therefore, the thrombus-like echoes identified by TEE are believed to be true thrombi, although we do not have direct evidence to prove it. The sizes of the LAA thrombi unidentified by MR imaging were smaller than those identified by MR in TEE examination. Although MR is a useful, non-invasive method to detect intracardiac thrombi, the sensitivity of TEE to detect LAA thrombi in haemodialysis patients may be higher than that of MR.

The results of this study indicate that maintenance haemodialysis patients have an increased risk of LAA thrombosis. Either the chronic use of antiplatelet agents or background clinical conditions requiring antiplatelet therapy may be involved in the formation of LAA thrombi in haemodialysis patients. In addition, the presence of both diabetes mellitus and haematocrit ≤0.3 is a risk factor for LAA thrombosis in these patients. It would be useful to keep the possibility of LAA thrombosis in mind in the management of maintenance haemodialysis patients, particularly those who are receiving antiplatelet therapy or have diabetes mellitus and a low haematocrit.

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