Comparison of classical and non-classical cardiovascular risk factors influencing the patency of native arteriovenous fistulas after percutaneous transluminal angioplasty therapy among haemodialysis patients

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Objective: To evaluate the classical and non-classical cardiovascular risk factors that effect patency of native arteriovenous fistulas (AVF) in end stage renal disease (ESRD) patients who are undergoing regular haemodialysis treatment and have a percutaneous transluminal angioplasty (PTA) procedure.

Methods: All PTAs performed between 1 October 2002 and 30 September 2004 were identified from case notes and the computerised database and follow up to 31 March 2005. The definition of patency of AVF after PTA was including primary or secondary patencies. Risks were analysed to assess the influence on survival following PTAs of age, sex, serum cholesterol, serum triglyceride, diabetes, use of aspirin, current smoking and hypertension, serum albumin, serum calcium-phosphate product, intact parathyroid hormone (I-PTH), and urea reduction ratio (URR).

Results: The patency rate of AVFs of all interventions was 65% at 6 months. Factors with poor patencies of AVFs after PTA procedures were higher serum calcium-phosphate product ($p=0.033$), higher URR ($p<0.001$), lower serum albumin ($p<0.001$), non-hypertension ($p=0.010$) and "non-smoker + ex-smoker group" ($p=0.033$). The hypertensive patients and current smokers had lower patency failure after PTAs ($p<0.01$ and $p<0.05$, respectively).

Conclusions: Unfavourable cumulative patency rates are observed in haemodialysis patients with higher URR, higher serum calcium-phosphate product and hypoalbuminaemia (lower serum albumin before the PTA procedure). Hypertension and current smoking were associated with better patency rates of AVF after PTA.

Construction and maintenance of a well-functioning vascular access remains one of the most important tasks for haemodialysis patients. Complications related to vascular access are the main cause of hospitalisations, being responsible for up to 25% of hospitalisations among dialysis patients.¹ Thrombosis (occlusion) and atherosclerosis (stenosis) are the leading cause of arteriovenous fistula (AVF) dysfunction among dialysis patients.² Percutaneous transluminal angioplasty (PTA) is an accepted therapeutic procedure for AVF dysfunction management.¹ Generally, the native AVF is considered the best access for chronic haemodialysis. Age, diabetes, increased serum lipoprotein Lp(a), increased serum fibronectin and synthetic grafts (polytetrafluoroethylene (PTFE)) have been associated with vascular access dysfunction and may influence the survival of AVFs in patients on haemodialysis.^{3–4}

A variety of factors are involved in the pathogenesis of vascular diseases associated with chronic renal failure. Classical cardiovascular risk factors such as age, male gender, smoking, hypertension, dyslipidaemia, and diabetes exist in the general population and in patients with chronic renal failure. Additional non-classical risk factors such as oxidative stress, dysparathyroidism, hyperhomocysteinaemia, dialytic inadequacy, malnutrition and disruption of calcium-phosphate homeostasis play more important roles in cardiovascular disease in chronic renal failure patients.^{5–6} In fact, classical cardiovascular risk factors alone have been reported to be inadequate predictors of cardiovascular disease in haemodialysis patients in a recent report.⁵ To our knowledge, the comparison of classical and non-classical cardiovascular risk factors influencing the patency of native AVF in ESRD patients

is rarely investigated. The first aim of our study is to identify possible cardiovascular risk factors influencing patency rate of native AVF after PTAs among haemodialysis patients. The second aim is to determine whether non-classical cardiovascular risk factors play more important roles in influencing the patency rate of AVF after PTAs.

MATERIALS AND METHODS

Design, patient selection and definition

This retrospective, observational study was performed in China Medical University Hospital in Taiwan. The haemodialysis centre provided chronic haemodialysis treatment to approximately 280 patients during the study period. The definition of patency of AVF after PTA was to include primary or secondary patencies according to the Society of Interventional Radiology reporting standard and quality improvement guidelines.⁷ Primary patency is defined as the uninterrupted patency after intervention until the next access thrombosis or reintervention. Secondary patency after intervention is defined as patency until the access is surgically declotted, revised, or abandoned by the surgeon, renal transplant, loss to follow-up, and so forth. Inclusion criteria of our patients were: ESRD treated with haemodialysis three times weekly and >4 h treatment in each haemodialysis session via a surgically created autologous AVF

Abbreviations: AVF, arteriovenous fistula; BCP, bromocresol purple; BUN, blood urea nitrogen; ESRD, end stage renal disease; I-PTH, intact parathyroid hormone; MIA, malnutrition, inflammation, and atherosclerosis; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene; PTH, parathyroid hormone; URR, urea reduction ratio

for >6 months; age >20 years; and absence of infection. Exclusion criteria were: haemodialysis less than three times weekly; haemodialysis via arteriovenous graft; significant evidence of infection of the AVF; autologous AVF construction <6 months prior; and patients with poor compliance for long term dialysis treatment.

Between 1 October 2002 and 30 September 2004 there were 148 PTAs for autologous AVF stenosis or occlusion in 85 patients in our centre. Each patient was included only once (for the first intervention) for PTA outcome evaluation during the follow up period. Three patients were excluded from this analysis; this was because of major infection with hospitalisation in two patients and age <20 years in one patient. Thus, a total of 82 PTAs were included in this study. Detection of fistula lesion was based on physical examination, flow rate measurements, venous pressure, and analytical determinations performed at dialysis by nephrologists. The effects of each PTA procedure were observed for 180 days, for primary patency loss, or secondary patency loss.

Risk factors

Serum biochemistries were studied monthly by standard laboratory methods. Also, we calculated the urea reduction ratio (URR) every 3 months throughout the period of observation. We calculated the URR (percentage reduction in blood urea nitrogen (BUN) concentration after a dialysis session) using the following formula: $[\text{predialysis BUN} - \text{postdialysis BUN}] / \text{predialysis BUN}$.⁸ Postdialysis BUN was measured 1 min after the end of haemodialysis. URR was used as the dialysis adequacy marker in our study. The URR was a proportionate measure of blood clearance during the dialysis treatment, and values of 65% and higher are associated with decreased mortality.⁸ Serum albumin was measured using bromocresol purple (BCP). Intact parathyroid hormone (PTH) levels were measured by immunoradiometric assay using the Allegro Intact PTH assay kit (Nichols Institute, San Juan Capistrano, California, USA) every 3 months. Serum calcium (total calcium) was determined with an automated clinical chemistry analyser.

The subgroup with hypertension included patients with a systolic blood pressure >145 mm Hg and diastolic blood pressure >95 mm Hg before the initiation of the haemodialysis session. Also, patients had to have been taking antihypertensive regimens (for example, β -blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, angiotensin II antagonists or direct-acting vasodilators) throughout the study period. The smoking subgroup was defined according to their pre-intervention smoking habits. If they had stopped smoking 2 months or more before the PTA procedure, they were considered to be an ex-smoker in our study. Individuals were classified as belonging to the "current smoker" group or the "ex-smoker + no smokers" group. The aspirin subgroup was defined as patients taking low dose aspirin (100 mg every day or every other day, orally) throughout the follow up period.

Interventions

Diagnostic fistulography of the AVF was performed using a blood pressure cuff, which temporarily occluded blood flow and caused reflux of contrast material across the arterial anastomosis of the fistula. When a stenotic or occlusive lesion of a fistula was detected, a balloon catheter was then advanced to the stenotic or occlusive lesion, and the balloon was inflated until the stenosis or occlusion was eliminated. Balloon diameters of 4–6 mm were generally used. Inflation was maintained for at least 30 s at a pressure of 12 atm or higher until full expansion of the balloon was achieved based on operator experience. Urokinase was administered intravenously

before the PTA intervention at the discretion of the operator in doses of up to 60 000–120 000 IU with total occlusion. Heparin was used with doses ranging between 0–10 000 IU before balloon dilation. All patients were monitored during the procedure with pulse oximetry, electrocardiography and blood pressure determination. Clinical success was defined as the ability to provide adequate dialysis for at least one session and was determined by a review of the dialysis chart. Only successful PTAs were included in the analysis in this study.

Statistical analysis

Data are expressed as mean (SD). Continuous data were compared by unpaired Student's *t* test. Categorical variables were compared by χ^2 or Fisher's exact test, as appropriate. Actuarial cumulative patency curves of PTAs were determined according to the Kaplan–Meier method and log rank tests to test for statistical differences in survival between different patient subpopulations (categorical variables). Predictors of patency loss after initial angioplasty were determined by using a Cox proportional hazards regression model with nine potential risk factors (continuous variables). All calculations were performed with SPSS version 10.0 for Windows (SPSS Institute, Chicago, Illinois, USA). A value of $p < 0.05$ was considered significant.

RESULTS

Demographic, clinical and laboratory data according to the timing of PTA treatments are shown in table 1. A total 342 haemodialysis patients were observed during the study period. Eighty-two (23.98%) of them received PTAs and were enrolled in the study. Most patients were female (60.91%) with an average age of 61.93 years (range 36–79 years): 45.12% of the patients had diabetes mellitus; 90.24% of AVFs were located on the forearm; 23.17% of patients were taking aspirin for prevention of specific diseases; 53.66% had hypertension; and 24.39% of patients were current smokers. The main cardiovascular risk factors of the two groups of patients, with and without patency failure of fistula after PTAs, are summarised in table 2. Age, gender distribution, and incidence of diabetes and aspirin use were not significantly different between the two groups. Also, no significant difference in serum cholesterol values was observed.

We first investigated the presence of classical cardiovascular risk factors for vascular disease in our patient population to elucidate their potential influence on fistula patency. Hypertension and smoking habit are two well-known factors for atherosclerosis. However, the number of patients with a documented smoking habit (current smokers) and hypertension were notably higher in the group without episodes of AVF dysfunction (table 2). Interestingly, the cumulative patency

Table 1 Demographic and baseline characteristics of 82 study subjects

Characteristic	Value
Age (years)	61.93 (10.62)
Gender (male/female)	32/50
Diabetes	37
Fistula in forearm	74
Aspirin use	19
Hypertension	44
Primary intervention*	52
Current smoker	20
Haemodialysis duration (months)	56.53 (42.62)
Age of fistula (months)	40.63 (38.37)

Data are shown as number or mean (SD), as appropriate.

*Primary intervention is defined as the first intervention of the newly created fistula.

Table 2 Main clinical cardiovascular risk factors of patients with or without patency failure of percutaneous transluminal angioplasty

	With failure (n = 29)	Without failure (n = 53)	p Value
Age (years)	61.45 (10.08)	62.19 (10.99)	0.765
Gender (male/female)	10/19	22/31	0.533
Hypertension	10	34	0.010
Diabetes	14	23	0.671
Cholesterol (mg/l)	170.72 (34.02)	177.26 (41.27)	0.469
	4.41 (0.89)	4.58 (1.07)	
Aspirin use	6	13	0.694
Current smoker	3	17	0.033
I-PTH (pg/ml)	197.50 (219.39)	173.28 (187.16)	0.600
Ca-P	53.03 (16.45)	44.95 (15.95)	0.033
URR (%)	78.08 (7.04)	72.81 (5.60)	<0.001
Albumin (g/dl)	3.02 (0.21)	3.43 (0.37)	<0.001

Ca-P, calcium-phosphate product; I-PTH, intact parathyroid hormone; URR, urea reduction ratio.

Data are shown as number or mean (SD), as appropriate.

The Student's *t* test is used for continuous data analysis, and χ^2 test or Fisher's exact test for categorical data analysis as appropriate.

rate was statistically higher in patients with current smoking habit ($p < 0.05$) (fig 1) and in patients with hypertension ($p < 0.01$) (fig 2).

We investigated the potential association between serum I-PTH and calcium-phosphate product and the incidence of patency failure. The levels of serum I-PTH in patients with patency failure after PTA did not differ significantly from the group without patency failure. However, the patients with patency failure had a mean serum calcium-phosphate product concentration significantly higher than the ones without patency failure during the study period (table 2).

The patients with patency failure had a mean URR significantly higher than the ones without failure. On the other hand, mean serum albumin levels were significantly lower in patients with patency failure of PTAs than in those patients without failure (table 2).

To identify the potential risks independently associated with fistula patency failure, we applied a Cox proportional hazards regression model by using the following factors (continuous variables): age, I-PTH, serum cholesterol, serum triglyceride, URR, total serum calcium, serum phosphate, serum calcium-phosphate product, and serum albumin. A statistically significant association with increased risk of patency failure was observed for URR and serum calcium-phosphate product (table 3). The relative risks of patency loss were estimated at 1.056 ($p = 0.009$) for URR and at 1.217 ($p = 0.042$) for serum

calcium-phosphate production. The relative risk for 180 day patency failure after PTA for each increase in serum albumin levels was associated with a 0.317 decrease in the risk ($p = 0.001$). This implied that hypoalbuminaemia was associated with a poor patency outcome after PTA procedure.

DISCUSSION

For haemodialysis, native AVFs have been considered to be the better choice rather than synthetic grafts. PTA is a common technique to prevent future occlusion/stenosis of AVFs. Few studies had compared the classical and non-classical cardiovascular risk factors influencing the patency rate of native AVF after PTA treatment among haemodialysis patients. Our study sought to identify potential cardiovascular risk factors influencing patency rates of AVFs in haemodialysis patients undergoing PTAs.

We identified the following non-classical cardiovascular risks influencing AVF patency: high serum calcium-phosphate product, high URR, and hypoalbuminaemia. Classical risk factors we identified included not smoking and not having hypertension as being associated with poorer patency outcomes of native AVFs after PTA.

In spite of the well-known effect of aspirin on blood coagulation, we found that regular administration of aspirin did not have a significant effect on patency of AVFs after PTAs. At the same time, our analysis could not demonstrate any significant association between diabetes and patency of AVFs after PTAs, although diabetes is a powerful fibrogenic stimulus that induces, directly or through the formation of advanced glycation end products, a variety of types of micro- and macrovascular damage.

Smoking is a major risk factor for the development of peripheral disease and patients who smoke have more frequent complications of their atherosclerotic disease at other vessel sites.⁹ Cohen *et al* documented that the rate of angiographic restenosis after initial intervention in coronary vessels was not different between smokers and non-smokers.¹⁰ Schillinger *et al* showed that smoking was associated with a reduced rate of intermediate-term restenosis after lower limb endovascular interventions.¹¹ To our knowledge, the effect of smoking on native AVF survival after PTA in ESRD patients has remained unanswered until now. Our data suggest that the "current smoker group" is associated with a reduced rate of restenosis after PTA of the native AVF in haemodialysis patients. This protective effect of smoking may be mediated by the influences of vascular remodelling and neointimal hyperplasia after PTA therapy. Two mechanisms that may account for the effect of smoking on vascular remodelling and neointimal hyperplasia of native AVF in ESRD patients could be postulated. First, elevated concentrations of carboxyhaemoglobin and increased carbon monoxide blood levels in smokers could play an inhibitory role in inflammation and in vascular smooth muscle proliferation.^{12,13} Second, various chemicals (nicotine, acetaldehyde, acrolein, etc) contained in cigarettes have been shown to cause necrosis of vascular smooth muscle cells and thus reduced neointima formation.¹⁴ In our study, current smokers had better patency outcome of AVFs than the non-current smokers after PTA therapy. This finding, however, does not imply that we recommend patients smoke after PTA treatment. Smoking has other documented adverse effects on long-term health. The risks and benefits of cigarette smoking must be weighed carefully.

Access blood flow is an identified positive predictive factor for AVF stenosis. The reduced access blood flow during haemodialysis treatment is associated with a higher risk of subclinical stenosis in native AVF.¹⁵ Systolic blood pressure is the major determinant of access blood flow in haemodialysis

Figure 1 Kaplan-Meier curves showing cumulative patency rate between "current smoker" (broken line, $n = 20$) and "ex-smoker + no smoker" (solid line, $n = 62$).

Figure 2 Kaplan-Meier curves showing cumulative patency rate between patients with (broken line, $n = 44$) and without (solid line, $n = 38$) hypertension.

patients with AVF.¹⁶ Also, access flow is well correlated with mean arterial pressure.¹⁷ Our study showed that haemodialysis patients with hypertension had a better cumulative patency rate of AVF than those without hypertension. The mechanism may be associated with the relation between higher blood pressure and higher access blood flow. However, high blood pressure can lead to the damage of many organs. The question of which blood pressure target do we aim at in order to benefit from the effect between hypertension and AVF blood flow remains to be answered.

The relationship between PTH and accelerated atherosclerosis is often mediated through several pathways, including alterations in lipid metabolism, impaired carbohydrate tolerance, hypertension, and the deposition of calcium phosphate salt.¹⁸ Elevated plasma PTH level was associated with significantly increased risk of AVF dysfunction in Grandaliano's study.¹⁹ In recent years, it has become apparent that hyperphosphataemia and hypercalcaemia are commonly observed in association with adynamic bone disease as well as with hyperparathyroidism, and the same is true for the occurrence of soft tissue calcifications.²⁰ Our study revealed that the plasma calcium-phosphate product might play a more important role than plasma PTH levels in influencing patency rate of AVFs. We assumed that the pathogenesis of AVF dysfunction as well as atherosclerotic lesions was through increased calcium-phosphate product in ESRD patients, regardless of hyperparathyroidism or adynamic bone disease.¹⁸

URR provides a measure of haemodialysis adequacy. Arteriovenous access stenosis accompanied by insufficient blood flow rates during haemodialysis is a main risk factor that may result in inadequate dialysis and low URR. Interestingly, we found that better URR before PTA treatment is associated with poorer patency rate of AVFs. The hypothesis that small atherosclerotic plaques are most likely to rupture, with resulting occlusive thrombosis in coronary artery disease, has been reported in some studies.^{21–22} The higher prevalence of milder stenoses account for most myocardial infarcts; inflammation may play a role in destabilising the fibrous cap tissue, thus enhancing the risk of coronary thrombosis.^{23–25} In our hypothesis, we assumed that non-stenotic, haemodynamically insignificant small plaques may rupture, precipitating occlusive thrombosis in AVFs as in coronary artery disease, resulting in the observed relation between reverse URR and the further AVF patency rate in our study.

Serum albumin levels may not be a valid nutritional marker as it is affected by inflammation and external losses, but low serum albumin levels are generally accepted as an indicator of inflammation in ESRD patients.²⁶ Strong associations between malnutrition, inflammation and atherosclerosis in ESRD

Table 3 Independent predictors of patency failure risk after 180 day follow up using the Cox regression model with 82 patients after percutaneous transluminal angioplasty

Variable	p Value	RR	95% CI	
			Lower	Upper
Age	0.638	1.006	0.983	1.029
I-PTH	0.450	0.999	0.998	1.001
Cholesterol	0.802	0.999	0.994	1.005
URR*	0.009	1.056	1.014	1.100
Calcium	0.123	0.396	0.122	1.285
Phosphate	0.060	0.197	0.036	1.069
Ca-P*	0.042	1.217	1.007	1.471
Albumin*	0.001	0.317	0.162	0.620
Triglyceride	0.101	0.946	0.885	1.011

Ca-P, serum calcium-phosphate product; CI, confidence interval; I-PTH, intact parathyroid hormone; RR, relative risk; URR, urea reduction ratio. * $p < 0.05$.

populations suggested the presence of a syndrome we have called the malnutrition, inflammation, and atherosclerosis (MIA) syndrome.²⁷ Unlike the results of a UK study,²⁸ where serum albumin >3.5 g/dl was associated with poorer long-term patency of AVFs, our results showed that lower serum albumin levels were associated with a significantly poor patency rate of AVFs. We had no direct evidence to link hypoalbuminaemia and the inflammatory process in our patients, but we believe that inflammation might play a key role in the patency rate of AVFs.

Our study has several important limitations. First, it was an observational study. Thus, we could not exclude the possibility that unmeasured confounding factors may affect the results of our findings. Second, some identified cardiovascular risk factors such as inflammatory parameters and serum homocysteine levels were unavailable in our study. Finally, the chemical content of different brands of cigarettes was not measured; smoking status was not routinely assessed during follow-up and it is possible that some patients who were classified as smokers quit during follow up. In spite of these limitations, we believe that the results of this study are worth investigating further, with modifications to minimise bias.

In summary, our results suggest that classical risk factors for cardiovascular disease such as age, male gender, smoking, hypertension, dyslipidaemia, and diabetes do not worsen the patency failure of AVFs among haemodialysis patients after PTA procedures. Moreover, patients with hypertension and who are currently smoking have a better cumulative patency rate than those without hypertension and a smoking habit. Other non-classical risk factors (hypoalbuminaemia and higher calcium-phosphate product) may play more important roles in the fistula patency rate after PTA. The parameters of cardiovascular risks (classical and non-classical) show a variety of results influencing the patency of native AVFs among haemodialysis patients after PTAs.

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