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Association of plasma homocysteine with restenosis after percutaneous coronary angioplasty

G. Schnyder, M. Roffi, Y. Flammer, R. Pin and O. M. Hess

Division of Cardiology, Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland

Aims Restenosis after percutaneous coronary angioplasty remains an important limitation of this procedure. This study evaluates whether elevated total plasma homocysteine levels contribute to the development of restenosis after coronary angioplasty.

Methods and Results Two hundred and five patients were recruited after successful angioplasty of at least one coronary stenosis ($\geq$50%). End-points were restenosis ($\geq$50%) and a composite of major adverse cardiac events. Of the 205 patients, 183 (89·3%) underwent 6 months angiographic follow-up. Patients with restenosis had significantly higher homocysteine levels than those without ($10{\cdot}9 \pm 3{\cdot}9$ µmol . l^{-1} vs $9{\cdot}3 \pm 3{\cdot}8$ µmol . l^{-1}, $P<0{\cdot}01$). Homocysteine levels were significantly correlated to follow-up diameter stenosis ($r=0{\cdot}24$, $P=0{\cdot}0001$), especially in small vessels (<3 mm) treated with balloon angioplasty only ($r=0{\cdot}40$, $P<0{\cdot}0005$). Late lumen loss at follow-up was significantly smaller with homocysteine levels below 9 µmol . l^{-1} ($0{\cdot}62 \pm 0{\cdot}82$ mm vs $0{\cdot}90 \pm 0{\cdot}77$ mm, $P<0{\cdot}01$). Restenosis rate (25·3% vs 50·0%, $P<0{\cdot}001$) and major adverse cardiac events (15·7% vs 28·4%, $P<0{\cdot}05$) were also significantly lower in patients with homocysteine levels below 9 µmol . l^{-1}. Multivariate analysis did not weaken these findings.

Conclusion Total plasma homocysteine is a strong predictor of restenosis and major adverse cardiac events after coronary angioplasty. Thus, plasma homocysteine appears to be an important cardiovascular risk factor influencing outcome after successful coronary angioplasty.
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Key Words: Angioplasty, death, homocysteine, myocardial infarction, restenosis.

Introduction

Restenosis after percutaneous coronary angioplasty remains an important limitation of this procedure[1]. Although many mediators appear to modulate neointima formation and vascular remodelling, the search for effective pharmacotherapy has been elusive[2–5]. The identification of novel risk factors would allow the development of new therapeutic strategies to improve outcome after coronary angioplasty. Thus the observation that total plasma homocysteine is an important cardiovascular risk factor[6,7] and correlates with the severity of coronary artery disease[8,9] has led to interest in its potential role in restenosis. The pathogenesis of homocysteine-induced vascular damage is still a subject of much research. Numerous studies have suggested adverse interaction with vascular smooth muscle cells[10–12], endothelium function[13,14] and plasma lipoproteins[15], which may contribute to homocysteine-induced atherogenesis as well as restenosis after coronary angioplasty. The controlled release of intracellular homocysteine provides an accurate index of plasma homocysteine status[16] and a potential marker for the extent of restenosis. Thus, the purpose of the present study was to test the hypothesis that elevated levels of total plasma homocysteine may contribute to the development of restenosis after successful coronary angioplasty.

Methods

This was a prospective study enrolling consecutive patients undergoing successful coronary angioplasty of at least one coronary stenosis ($\geq$50%). The study protocol was approved by the local ethics committee, and all patients gave written informed consent. Patients with recent myocardial infarction (<2 weeks), significant left main disease, renal dysfunction (serum creatinine

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Correspondence: Guido Schnyder, MD, UCSD Medical Center-MC 8784, Cardiology Division, 200 West Arbor Drive, San Diego, CA 92103, U.S.A.

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>160 μmol . l^{-1}), megaloblastic anaemia, taking multivitamins or undergoing angioplasty of a bypassed vessel with patent graft were excluded. Patients were asked to withhold from any multivitamin intake. Fasting homocysteine levels were measured between 0600 h and 0800 h the day following the procedure using the technique described by Ubbink *et al*., a sensitive and reproducible method with a variation coefficient of 6·6% and a 2 μmol . l^{-1} lower limit of detection[17].

Coronary angioplasty was performed with standard guide wires and balloon catheters. Inflation pressure and duration, as well as the use of stents and adjunctive drug therapy (heparin, aspirin, ticlopidine or clopidogrel, glycoprotein IIb/IIIa inhibitors) were at the operator's discretion. Successful angioplasty was defined as residual percentage diameter stenosis <50% with normal flow pattern (TIMI III). Clinical and angiographic follow-up was performed at 6 months, or earlier if symptoms recurred. Follow-up angiographic data obtained less than 3 months after coronary angioplasty were included if restenosis was documented.

Quantitative coronary angiography

Baseline coronary angiograms were obtained from two orthogonal views after pre-dilatation with nitrates. Quantitative coronary angiography was performed using the automated edge-detection system Philips Integris-BH-3000 (version 2) if online or Philips View-Station-CDM-3500 (version 2) if offline. The tip of the diagnostic or guiding catheter (positioned at the coronary ostium) was used as a scaling device to obtain absolute arterial dimensions. The same views and calibration techniques were used at follow-up examination. End-diastolic frames in the two orthogonal views showing maximal stenosis severity were chosen for luminal diameter measurement. Reference diameter, minimal luminal diameter, percentage diameter stenosis and lesion length were calculated as the average value of the two views. Absolute lumen loss was defined as reference diameter minus minimal luminal diameter. Late lumen loss was defined as minimal luminal diameter immediately after coronary angioplasty minus minimal luminal diameter at follow-up. Angiograms were reviewed by an experienced interventional cardiologist blinded to homocysteine levels.

Study end-points

Restenosis was defined as percentage diameter stenosis ≥50% at follow-up examination. Patients who had more than one lesion treated were defined as having restenosis if at least one dilated artery fulfilled restenosis criteria. An additional analysis of restenosis rate per lesion dilated was performed. The primary end-point was the presence of restenosis at follow-up examination. Minimal luminal diameter before, immediately after and at follow-up was plotted for treated lesions split at the 50th percentile of our study population's homocysteine levels. The principal clinical end-points were death from any cause and a composite of major adverse cardiac events defined as the occurrence of cardiac death, non-fatal myocardial infarction and target lesion revascularization.

Statistical analysis

Plasma homocysteine was first considered as a continuous value and then as a dichotomous parameter split at the 50th percentile (9·0 μmol . l^{-1}) of our study population's homocysteine levels. A sample size of 91 patients in each homocysteine-distribution group was calculated to achieve a power of 0·80 to detect a 20% difference in absolute restenosis rate. To account for potential patients lost to follow-up, the planned sample size was 205 patients. Categorical variables are reported as counts (percentages) and continuous variables as mean ± SD. For categorical variables, a chi-square test was used to test differences between study groups. For the analysis of continuous data, a two-tailed t-test was employed. The Pearson correlation coefficient was used to estimate the correlation between homocysteine levels and follow-up percentage diameter stenosis. Freedom from restenosis was analysed by means of Kaplan–Meier curves, with differences between the two homocysteine distribution groups compared with the Mantel–Cox log-rank test. Multiple logistic regression analysis was used to evaluate the relation between angiographically identified restenosis and multiple clinical and angiographic variables, including age, creatinine, treatment of restenotic lesions, history of previous myocardial infarction, history of previous coronary angioplasty, use of stents, post-procedural vessel reference diameter and minimal luminal diameter. Creatinine was used as a covariate because plasma homocysteine is eliminated by the kidneys and indirectly related to creatinine levels. Patients with a history of renal failure (creatinine >160 μmol . l^{-1}) were excluded to avoid elevated creatinine values as confounders for increased homocysteine levels. A two-sided 5% level of significance was considered significant for all statistical tests. Data were prospectively collected and analysed using StatView Version 4.5 (SAS Institute, Cary, NC).

Results

Two hundred and five patients were recruited after successful angioplasty of at least one coronary stenosis (≥50%), with a total of 277 successfully treated lesions. Of the 205 patients, 183 (89·3%) underwent 6 months reangiography, with a total of 240 lesions with angiographic follow-up. Of the 22 patients that did not come back for follow-up, 15 refused reangiography, one was excluded because of post-procedural renal insufficiency

Table 1 Clinical characteristics and laboratory findings

	Restenosis	
	No (n=112)	Yes (n=71)
Gender M/F (%)	79/21	73/27
Age (years)	61 ± 11	62 ± 11
Smoker (%)†	29	28
Diabetes mellitus (%)††	27	28
Arterial hypertension (%)‡	59	65
Hypercholesterolaemia (%)§	79	89
Previous myocardial infarction (%)	58	49
within the last 6 months (%)	33	28
Previous PTCA (%)	30	37
Previous CABG (%)	12	14
Treated lesions per patient	1·32 ± 0·62	1·32 ± 0·56
Laboratory findings Hb A_{1c} (%)	6·0 ± 1·0	5·9 ± 1·1
Creatinine (μmol . l^{-1})	92 ± 17	92 ± 18
Homocysteine (μmol . l^{-1})	9·3 ± 3·8	10·9 ± 3·9*
Cholesterol (mmol . l^{-1})	5·6 ± 1·2	5·5 ± 1·2
HDL-cholesterol (mmol . l^{-1})	1·2 ± 0·3	1·2 ± 0·4
Triglycerides (mmol . l^{-1})	2·2 ± 1·5	2·2 ± 1·5

†Smoking: current or discontinued during the last 6 months.
††Diabetes mellitus: Hb A_{1c} ≥6·2%, current insulin or oral hypoglycaemic therapy.
‡Hypertension: >140/90 mmHg or current antihypertensive therapy.
§Hypercholesterolaemia: cholesterol ≥5·2 mmol . l^{-1} or current lipid lowering drugs.
*P=0·008 vs no restenosis.
PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting.

and six died before reangiography. In terms of baseline clinical, laboratory and angiographic criteria, the 22 patients without follow-up angiography did not significantly differ from the remaining population.

Clinical characteristics and laboratory findings (Table 1)

Study subgroups with or without restenosis were similar in terms of gender, age and cardiovascular risk factors. About 1/4 of patients were women, mean age was 61 and cardiovascular risk factor distribution was typical of a central European population. In the subgroups with homocysteine levels below or above the 50th percentile (9 μmol . l^{-1}) a significant association of homocysteine with the severity of coronary artery disease as assessed by the prevalence of previous coronary angioplasty (24% vs 38%, P<0·05) was observed. The average number of dilated lesions per patient was similar in all subgroups. Baseline laboratory values did not show any association with restenosis after coronary angioplasty, the only exception being homocysteine levels (P<0·01). Homocysteine considered as a continuous value was also significantly associated with the severity of coronary artery disease (as measured by previous myocardial infarction and percutaneous revascularization). Patients with previous myocardial infarction had higher levels of homocysteine (10·4 ± 4·2 μmol . l^{-1} vs 9·1 ± 3·6 μmol . l^{-1}, P<0·05), as did patients with previous coronary angioplasty (11·0 ± 4·0 μmol . l^{-1} vs 9·5 ± 4·1 μmol . l^{-1}, P<0·05). There was a weak but significant correlation between homocysteine levels and age (r=0·14, P<0·05), and with serum creatinine (r=0·24, P<0·0005).

Angiographic analysis (Table 2)

Mean angiographic follow-up was 20 ± 13 weeks. Lesions distribution was similar between the different subgroups: about 48% were located in the left anterior descending coronary artery, 24% in the circumflex coronary artery and 28% in the right coronary artery. Lesion severity (lesion length, vessel size, minimal luminal diameter, absolute lumen loss and percentage diameter stenosis) before coronary angioplasty was also comparable between the different subgroups. There was a small but significant difference directly after coronary angioplasty with regard to vessel size (2·88 ± 0·61 mm vs 3·06 ± 0·65 mm, P<0·05) and minimal luminal diameter (2·18 ± 0·52 mm vs 2·35 ± 0·64 mm, P<0·05) between lesions with and those without restenosis, but with an identical absolute lumen loss (0·69 ± 0·34 mm vs 0·70 ± 0·36 mm, P=0·8). After multivariate analysis with homocysteine levels as independent variables, vessel size (P=0·6) and minimal luminal diameter (P=0·5) lost their significance for restenosis, but not homocysteine

Table 2 Lesion characteristics and treatment options in 240 lesions with angiographic follow-up stratified according to the 50th percentile of homocysteine distribution

	Homocysteine		*P* value
	<9·0 μmol . l^{-1} (n=111)	≥9·0 μmol . l^{-1} (n=129)	
Lesion location (%)			
LAD	46	50	ns
Circumflex	22	26	ns
RCA	32	25	ns
Restenotic lesions (%)*	6	8	ns
Treatment options			
Stents	48	62	0·03
GP IIb/IIIa inhibitors	12	13	ns
Lesion length (mm)	12·4 ± 5·3	11·9 ± 4·6	ns
Vessel size (mm)			
Before angioplasty	2·81 ± 0·65	2·85 ± 0·67	ns
After angioplasty	3·02 ± 0·69	2·98 ± 0·59	ns
At follow-up	2·82 ± 0·59	2·73 ± 0·65	ns
Minimal luminal diameter (mm)			
Before angioplasty	0·93 ± 0·52	0·89 ± 0·46	ns
After angioplasty	2·31 ± 0·64	2·28 ± 0·57	ns
At follow-up	1·69 ± 0·83	1·39 ± 0·85	0·007
Percent diameter stenosis (%)			
Before angioplasty	67·4 ± 15·9	68·1 ± 14·9	ns
After angioplasty	23·4 ± 10·5	23·5 ± 10·1	ns
At follow-up	41·2 ± 24·0	49·7 ± 27·1	0·01

*Restenotic lesions=lesions previously treated for restenosis.
LAD=left anterior descending coronary artery; RCA=right coronary artery.

levels ($P<0·05$). Those variables did not differ between lesions with homocysteine levels below and above 9·0 μmol . l^{-1}. The use of stents was similar between lesions with and those without restenosis and slightly lower in lesions with homocysteine levels below as opposed to above 9·0 μmol . l^{-1} (48% vs 62%, $P<0·05$). The use of glycoprotein IIb/IIIa inhibitors was similar in the different subgroups.

Plasma homocysteine as a continuous value was significantly associated with restenosis. Lesions with restenosis had higher homocysteine levels (10·7 ± 3·8 μmol . l^{-1} vs 9·4 ± 3·8 μmol . l^{-1}, $P<0·05$). Homocysteine levels were also directly correlated to percentage diameter stenosis at follow-up (r=0·24, $P=0·0001$). The highest correlation was found in small vessels with reference diameter <3 mm (r=0·31, $P<0·0001$), in lesions treated with balloon angioplasty only (r=0·38, $P<0·0001$) or a combination of the two (r=0·40, $P<0·0005$). This correlation disappeared when larger vessels (≥3 mm) were stented (r=0·10, $P=0·44$).

Angiographic restenosis differed markedly according to the dichotomous homocysteine-distribution split at the 50th percentile (9·0 μmol . l^{-1}) of our study population's homocysteine levels. At reangiography, lesions with baseline homocysteine levels <9·0 μmol . l^{-1} compared to those ≥9·0 μmol . l^{-1} had larger minimal luminal diameter (1·69 ± 0·83 mm vs 1·39 ± 0·85 mm, $P<0·01$), smaller absolute lumen loss (1·13 ± 0·67 mm vs 1·33 ± 0·82 mm, $P<0·05$), smaller late lumen loss (0·62 ± 0·82 mm vs 0·90 ± 0·77 mm, $P<0·01$) and less severe percentage diameter stenosis (41·2 ± 24·0% vs 49·7 ± 27·1%, $P=0·01$). In Fig. 1, minimal luminal diameter before and immediately after coronary angioplasty demonstrated the similarity of the two homocysteine-distribution groups at baseline and the similar angiographic results after angioplasty. However at follow-up, a higher rate of late lumen loss can be seen in the group with higher homocysteine levels. A multivariate analysis including several variables independently associated with homocysteine levels (age, creatinine, treatment of restenotic lesions, history of previous myocardial infarction and history of previous coronary angioplasty) did not weaken the association between homocysteine levels and restenosis after coronary angioplasty (univariate: $P=0·008$, multivariate: $P=0·01$). After multivariate analysis, the only other variable significantly associated with restenosis was the restenotic nature of previously treated lesions (univariate: $P=0·01$, multivariate: $P=0·01$).

Study end-points (Table 3)

Fewer patients reached the primary end-point of restenosis in the subgroup with homocysteine levels below

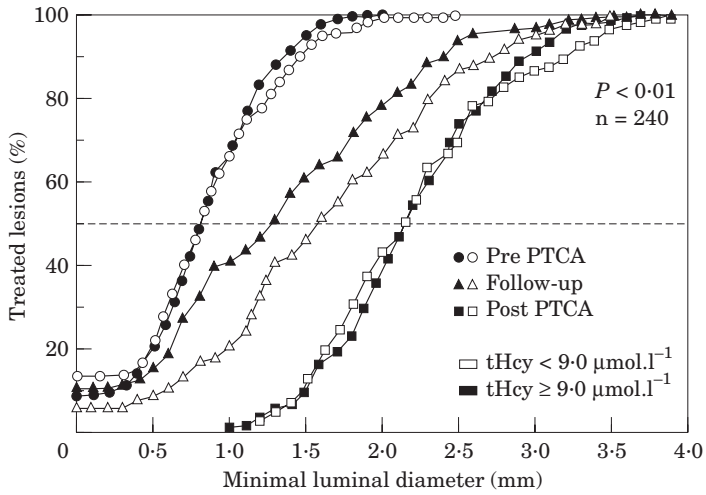

Figure 1 **The cumulative distribution curve for minimal luminal diameter before and immediately after coronary angioplasty demonstrates the similarity of the two homocysteine distribution groups at baseline and the similar angiographic results after angioplasty. However at follow-up, a higher rate of late lumen loss can be seen in the group with higher homocysteine levels. PTCA=percutaneous transluminal coronary angioplasty; tHcy=total plasma homocysteine.**

Table 3 Events at follow-up stratified according to the 50th percentile of homocysteine distribution

	Homocysteine		*P* value
	<9·0 μmol . l^{-1}	≥9·0 μmol . l^{-1}	
Restenosis of ≥50% (%)*	25·3	50·0	0·0006
Target lesion restenosis of ≥50% (%)†	20·9	44·6	0·0001
Death (from any cause) (%)‡	0·0	6·9	0·01
MACE (%)‡			
Target lesion revascularization	15·7	25·9	0·08
Non-fatal myocardial infarction	1·1	5·2	0·11
Cardiac death	0·0	3·3	0·08
Any event	15·7	28·4	0·03

*Restenosis rate in 183 patients with angiographic follow-up.
†Restenosis rate in 240 treated lesions with angiographic follow-up.
‡Death from any cause and MACE in baseline study population (205 patients). MACE=major adverse cardiac events.

as opposed to above 9·0 μmol . l^{-1} (25·3% vs 50·0%, $P<0·001$), a restenosis rate reduction of 49% (Fig. 2). When individual lesions were considered, there was a 53% reduction in restenosis rate (20·9% vs 44·6%, $P=0·0001$). Death from any cause was significantly associated with homocysteine levels ≥9·0 μmol . l^{-1} (6·9% vs 0·0%, $P=0·01$). Six patients died before follow-up, four of unknown cause (no autopsy) (3, 22, 28 and 28 weeks after inclusion) and two of cardiac death (sudden death and myocardial infarction) (8 and 30 weeks after inclusion). An additional two patients died during rescue angioplasty for stent thrombosis (1 and 5 weeks after inclusion). Patients who died had significantly higher homocysteine levels than those who survived (13·5 ± 1·3 μmol . l^{-1} vs 9·8 ± 3·8 μmol . l^{-1}, $P<0·05$). The cumulative incidence of major adverse cardiac events was significantly smaller with homocysteine levels <9 μmol . l^{-1} (15·7% vs 28·4%, $P<0·05$). Similarly, there was a trend towards less cardiac death ($P=0·08$), non-fatal myocardial infarction ($P=0·11$) and target lesion revascularization ($P=0·08$) with homocysteine levels <9 μmol . l^{-1}.

Discussion

Homocysteine levels are modulated through a series of steps in the pyridoxal phosphate-dependent

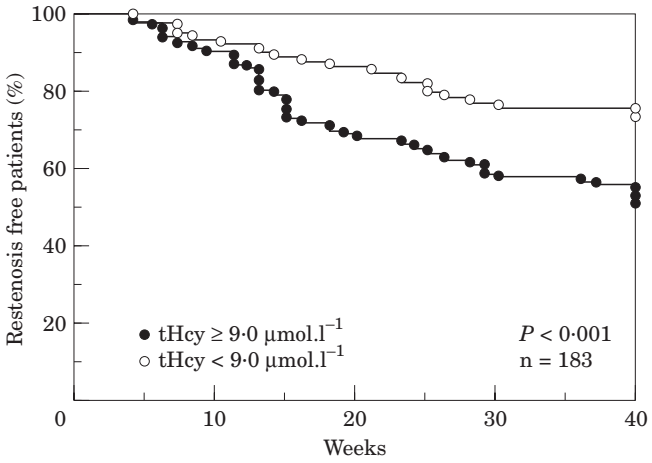

Figure 2 **Kaplan–Meier curves for freedom from restenosis according to homocysteine levels. There is a higher rate of freedom from restenosis of 74·7% with homocysteine levels <9·0 µmol . l^{-1}, as opposed to 50·0% with levels ≥9·0 µmol . l^{-1}. tHcy = total plasma homocysteine.**

cystathionine *β*-synthase pathway, or through vitamin B12- and folate-dependent re-methylation to methionine. It has been suggested that partial deficiencies of cystathionine *β*-synthase, or 5′,10′-methylenetetrahydrofolate reductase are associated with mild to moderate elevations of plasma homocysteine levels and lead to vascular disease[18]. Elevated homocysteine levels may either reflect genetic defects (up to 14%)[18,19] or acquired conditions such as folate-, pyridoxine- and vitamin B12-deficiencies or renal failure.

Plasma homocysteine in coronary artery disease

This study provides the first prospective evidence that homocysteine levels predict restenosis after coronary angioplasty, particularly in small vessels and lesions treated with balloon angioplasty only. Plasma homocysteine is also a significant predictor of mortality from any cause and of major adverse cardiac events. These results contradict the findings of a prospective study by Miner *et al.*[20]. This group was unable to correlate homocysteine levels with restenosis after coronary angioplasty. The smaller sample size, the use of follow-up angiographic data obtained less than 6 months after coronary angioplasty even in the absence of restenosis and the lack of subgroup analyses (small vessels and stent use) raises the possibility of a false negative result or type II error. On the other hand a type I error cannot be excluded as a possible explanation for our results. However, the presence of a statistically significant association between homocysteine levels and restenosis, a follow-up stenosis severity directly proportional to homocysteine levels, as well as the stronger correlation of homocysteine levels with stenosis severity in smaller vessels and unstented lesions favour a true association. Our results are also consistent with those of a recent case-control study by Morita *et al.*[21]. Nevertheless, the final conclusion will be drawn by interventional studies eventually showing reduced restenosis rate with lowering of plasma homocysteine levels.

Pathophysiological mechanisms

The pathogenesis of homocysteine-induced vascular damage and its possible role in restenosis are not clearly understood. Nevertheless, several hypotheses have been suggested. Elevated homocysteine levels stimulate proliferation of vascular smooth muscle cells[10,11], increase collagen deposition[12], impair endothelium-dependent vasodilation[13], promote intimal thickening[14] and increase production of extracellular superoxide dismutase[15]. There is also a clear association between elevated plasma homocysteine levels and increased thrombogenicity through interaction with coagulation factor V[22], protein C[23], tissue plasminogen[24] and tissue factor procoagulant activity[25].

In analogy to the potent antioxidant probucol[3], the oxidant properties[15] of homocysteine may further influence the occurrence of restenosis even though other antioxidants, i.e. *β*-carotene, vitamin E and C, have failed to reduce the restenosis rate after coronary angioplasty[3]. The homocysteine-induced activation of the coagulation system may also trigger acute or late thromboses[22–25]. This hypothesis is supported by our findings with a surprising difference in mortality among patients with homocysteine levels above and below 9 µmol . l^{-1}. Finally, since restenosis rates in the balloon-only treated lesions were strongly correlated to homocysteine levels, it appears reasonable to postulate both a positive effect on vascular remodelling and an antiproliferative effect of lower homocysteine levels.

However, since treatment modalities (stent vs balloon only) were at the operator's discretion, these two subgroups cannot be compared readily. Furthermore, because intravascular ultrasound was not performed, the issue of the pathophysiologic mechanism cannot be addressed definitively.

Limitations

A critical question is whether the association of plasma homocysteine with restenosis rate reflects causality. Homocysteine levels were significantly correlated to age and serum creatinine, as well as associated with the restenotic nature of previously treated lesions, previous myocardial infarction and previous coronary angioplasty. Adjustment for these factors did not weaken the predictive power of homocysteine levels, suggesting an independent association with restenosis. Because patients with renal failure were not included, increased creatinine values ($>160\,\mu mol\,.\,l^{-1}$) can be excluded as confounders for increased homocysteine levels. Angiographic criteria such as balloon inflation pressure, balloon size and inflation time have been shown to influence restenosis[26]. The current study confirms the presence of such differences. Patients with restenosis have slightly smaller vessel size and smaller minimal luminal diameter after coronary angioplasty than patients without restenosis. Nevertheless, adjustment for these factors did not change the predictive power of homocysteine levels. The use of stents and glycoprotein IIb/IIIa inhibitors is known to reduce restenosis rate after coronary angioplasty[27,28]. However, these treatment modalities were similar in all study subgroups and are, therefore, unlikely to have affected our results. The slight overuse of stents in the group with higher homocysteine levels only adds to the strength of our results.

The overall high restenosis rate of this study is related to the study's inclusion criteria. Lesions in small vessels (<3·0 mm), which independent of stent use are at a higher risk of restenosis of about 40%[29], were also included. Furthermore, patients with lesions previously treated for restenosis, which are at a 50% increased risk of restenosis[30], were not excluded. Nevertheless, the proportion of patients with these types of lesions was similar in all study subgroups and therefore did not influence our final findings.

Potential other limitations merit consideration. Fasting plasma homocysteine levels were measured between 0600 h and 0800 h the day following the procedure and, thus, may have been influenced by the procedure itself. Even though absolute homocysteine levels at baseline may have been slightly altered, this should not have influenced our final results, given that blood samples for homocysteine determination were drawn in a similar fashion for all study patients. Finally, the inclusion of patients with a history of myocardial infarction within the last 6 months may have increased homocysteine levels[31]. Even though this may have had an influence on absolute homocysteine levels, this should not have affected our final results, given that all study subgroups had similar rates of prior infarction.

Clinical implications

This study shows that homocysteine levels predict restenosis rate, death rate and the cumulative incidence of major adverse cardiac events after coronary angioplasty. These results provide the rationale for randomized controlled interventional trials with homocysteine-lowering therapy. Homocysteine levels can be lowered by 25–30% with a daily dose of at least 500 µg of folic acid in combination with vitamin B12 and B6[6,32]. Thus, there is an urgent need for intervention trials because lowering homocysteine levels may possibly prevent restenosis and improve outcome after coronary angioplasty. This could be an inexpensive treatment with almost no side effects and a large saving potential for health care costs.

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