Plasma homocysteine levels are related to medium-term venous graft degeneration in coronary artery bypass graft patients

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Abstract

Objective: Saphenous venous grafts (SVGs) are established choices for coronary artery bypass grafting (CABG); however, their lumen patency is limited. Our goal was to investigate the risk factors of SVG degeneration.
Methods: Seventy-five patients (mean age, 57.5±10.4 years) with 133 SVG conduits who had cardiac catheterization ≥1 year after CABG were selected; follow-up period was 67.6±36.8 months. Patients were divided into 3 groups according to angiographic status at follow up [intact: <20% (n=23); narrowed: 20–99% (n=24); and occluded (n=28)]. Baseline clinical conditions were evaluated in relation to follow-up angiography. As onset date of chronic total occlusions is usually uncertain, they arise typically from thrombotic lesions; thus, their value in evaluation is limited.
Results: There were no significant differences between the 3 groups in clinical parameters. Linear correlation analysis found significant ($p<0.01$) positive connection of SVG disease (luminal diameter reduction 20–99%) with C-reactive protein (CRP) and homocysteine (Hcy), as well as between CRP and Hcy. Multiple regression analysis showed plasma Hcy level to be significantly related to graft diameter reduction normalized to time elapsed until angiography in narrowed grafts: 1 µmol/L increase of Hcy was associated with 0.053%/month decrease in lumen diameter ($p<0.01$; $R^2=0.428$); extrapolating: +10 µmol/L higher Hcy level during 5 years is associated with 32.1% lumen reduction.
Conclusion: Medium- to long-term SVG degeneration is related to elevated plasma total Hcy in patients with sub-occlusive graft stenosis, while in cases with intact SVGs, the beneficial local flow conditions may protect the grafts from degeneration. *(Anatol J Cardiol 2016; 16: 000-00)*
Keywords: homocysteine, saphenous vein graft disease

Introduction

Arterial and venous conduits have been used for coronary artery bypass grafting (CABG) to alleviate serious myocardial ischemia. Saphenous venous grafts (SVGs) have been verified to carry a higher risk of developing accelerated graft disease induced by hereditary, environmental, or systemic or local factors in complex interactions (1, 2). It is known that shear stress and local blood flow affect graft patency (3). Despite the improvement of surgical techniques and experiences, CABG still poses a challenge in secondary cardiovascular prevention. Holistic risk stratification is often unworkable or incompletely established, or managing comorbidities proves ineffective (2).

The aim of our investigation was to map the risk factors of chronic SVG disease in relation to the individual—on both per patient and per graft basis. Our investigation focused on homocysteine (Hcy), a sulfur-containing amino acid formed during the metabolism of methionine. Its association with atherosclerotic lesions of native vessels was published by McCully in the early 1960s (4). In the last half century, several clinical and experimental studies have clarified that elevated blood Hcy levels are related to atherosclerotic disease (5, 6). However, trials investigating the effect of the lowering of Hcy levels yielded controversial results concerning risk reduction in cardiovascular patients (7, 8). Furthermore, only very limited data are available regarding the effect of Hcy on medium- and long-term venous graft patency (9, 10).

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Table 1. Perioperative clinical characteristics of patients in subgroups per follow-up status (n=75)

	Per patient*			
Variable	**Intact[a]**	**Narrowed[b]**	**Occluded[c]**	***P***
Total no. of patients n=75;	23	24	28	–
Age, years, (mean±SD)	59.4±10.2	53.5±8.8	59.1±10.1	NS
Male, n, (%)	13 (56.5)	22 (91.7)	19 (67.8)	NS
Diabetes†, n, (%)	9 (39.1)	3 (12.5)	14 (50.0)	NS
Hypertension††, n, (%)	16 (69.5)	16 (66.7)	21 (75.0)	NS
Hyperlipidemia‡, n, (%)	17 (73.9)	19 (79.2)	26 (92.8)	NS
Myocardial infarction, n, (%)	14 (60.8)	15 (62.5)	20 (71.4)	NS
Stroke, n, (%)	2 (8.7)	2 (8.3)	3 (10.7)	NS
Peripheral vascular disease, n, (%)	7 (30.4)	3 (12.5)	9 (32.1)	NS
Smoking#, n, (%)	3 (13.0)	5 (20.8)	7 (25.0)	NS
EF, (%, mean±SD)	52.6±9.5	48.6±10.0	48.0±10.7	NS
Systolic blood pressure, mm Hg, (mean±SD)	136.1±16.8	136.7±14.9	133.8±13.0	NS
Diastolic blood pressure, mm Hg, (mean±SD)	80.9±12.5	83.1±10.8	79.6±5.9	NS
Creatinine, µmol/L, mean±SD)	85.7±15.3	88.4±20.4	87.7±17.3	NS
HDL, mmol/L, (mean±SD)	1.1±0.2	1.0±0.2	1.1±0.3	NS
LDL, mmol/L, (mean±SD)	3.1±0.6	3.4±0.9	3.3±0.6	NS
Total-cholesterol, mmol/L, (mean±SD)	5.1±0.7	5.3±1.0	5.4±0.8	NS
TG, mmol/L, (mean±SD)	1.9±0.7	2.0±1.6	2.2±1.4	NS
Lipoprotein(a), nmol/L, (mean±SD)	421.4±590.4	494.6±514.7	521.9±593.1	NS
CRP, mg/L, (mean±SD)	5.1±4.7	5.5±5.0	4.5±3.6	NS
Homocysteine, µmol/L, (mean±SD)	15.9±7.6	16.0±15.2	15.1±4.7	NS
Folate, nmol/L, (mean±SD)	13.9±7.6	11.0±4.3	12.2±3.6	NS
Vitamin B_{12}, pmol/L, (mean±SD)	232.6±129.0	251.1±111.2	248.2±103.4	NS
Follow up time, month, (mean±SD)	70.1±33.5	74,6±39.1	64.1±38.9	NS
Affected grafts, n, (%)	–	–	–	NS
to LAD	7 (30.4)	7 (29.2)	8 (28.6)	NS
to CX	9 (39.2)	16 (66.6)	14 (50.0)	NS
to RCA	7 (30.4)	1 (4.2)	6 (21.4)	NS
Indication of post CABG coronary angiography	–	–	–	NS
Stable angina, n, (%)	15 (65.2)	15 (62.5)	20 (71.5)	NS
Unstable angina, n, (%)	4 (17.4)	8 (33.3)	5 (17.8)	NS
Acute coronary syndrome, n, (%)	1 (4.3)	1 (4.2)	0 (0.0)	NS
Others, n, (%)	3 (13.0)	0 (0.0)	3 (10.7)	NS

*Ranking: patients with >1 SVG were classified according to their most severe graft's status. Definitions: Intact: <20% SVG lumen diameter reduction; Narrowed: Between 20% and 99% SVG lumen diameter reduction; and Occluded: SVG with closed lumen. CABG - coronary artery bypass grafting; Chol - cholesterol; CRP-C - reactive protein; CX - circumflex coronary artery; EF - ejection fraction; Hcy - homocysteine; HDL - high-density lipoprotein; LAD - left anterior descending coronary artery; LDL - low-density lipoprotein; NS - not significant; RCA - right coronary artery; SVG - saphenous venous graft; TG - triglyceride

Methods

The present study was based on retrospective data collected from our clinical database between 2001 and 2013. The scientific plan had previously been submitted to and approved by the Institutional Ethics Committee. All details potentially revealing the identity of the subjects were handled according to the ICH GCP guidelines and authority regulations. Data were collected from 75 SVG recipients (aged ≥30 years) who had ≥1 cardiac catheterization because of symptoms of coronary artery disease (CAD) at least 1 year after CABG. Patients <1 year after CABG were excluded to avoid considering technical failure

Table 2. Relationship of known or potential risk factors of SVG disease in "intact" and "narrowed" SVG patient group (n=47)

	SVG narrowing (%)/month	Age	Creatinine	**HDL**	LDL	TG	**CRP**	Hcy	**Folic acid**	Vit B_{12}	EF
SVG narrowing (%)/month											
Age	0.148 0.320										
Creatinine	0.231 0.118	-0.017 0.907									
HDL	0.252 0.091	-0.082 0.586	-0.009 0.951								
LDL	-0.028 0.850	-0.053 0.721	0.098 0.514	-0.157 0.297							
TG	-0.002 0.989	-0.132 0.377	0.091 0.543	-0.336* 0.022	-0.092 0.538						
CRP	0.483** 0.0001	0.122 0.437	0.159 0.310	0.002 0.988	0.214 0.168	0.036 0.816					
Hcy	0.752** 0.0001	0.248 0.093	0.268 0.068	0.248 0.096	-0.092 0.539	0.015 0.923	0.509** 0.0001				
Folic acid	-0.052 0.730	-0.117 0.438	0.166 0.270	0.188 0.216	-0.187 0.213	-0.205 0.171	-0.109 0.492	-0.012 0.935			
Vit B_{12}	-0.254 0.730	-0.235 0.117	-0.074 0.627	0.083 0.586	-0.191 0.204	-0.128 0.398	-0.167 0.289	-0.253 0.090	0.443** 0.0002		
EF	-0.055 0.713	0.134 0.371	-0.279 0.057	0.073 0.628	-0.163 0.273	-0.056 0.709	-0.048 0.762	0.020 0.895	-0.075 0.621	-0.70 0.645	

Method of analysis: Pearson correlation analysis. The r-value is shown above; P-value is shown below in the cells. Significance is marked by bold letter and asterisk (*): *P<0.05; **P<0.01. SVGs were classified as according to their luminal diameter status at repeat coronary angiography as intact with ≤20% and narrowed with a luminal diameter narrowing between >20% and 99%. CRP-C - reactive protein; EF - ejection fraction; Hcy - homocysteine; HDL - high-density lipoprotein; LDL - low-density lipoprotein; SVG - saphenous venous graft; TG - triglyceride; vit B_{12} - vitamin B_{12}

and premature thrombosis as a different manifestation of SVG disease. Patients with renal dysfunction (serum creatinine >160 μmol/L), known history of diabetic ketoacidosis, left ventricular ejection fraction ≤35%, or intervened SVGs were also excluded.

The following peri-CABG clinical parameters were collected: demographic characteristics; medical history (e.g., onset of CAD, previous MI, stroke) and history of cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia); smoking history and smoking status; CAD-related drug therapy; systolic and diastolic blood pressure; left ventricular ejection fraction (EF); and levels of plasma Hcy, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, apo-AI, apo-B, creatinine, high-sensitivity C-reactive protein, folate, and vitamin B_{12}. Blood parameters were determined by standard laboratory techniques using validated methods. As regards CABG, the number of venous conduits, location, host coronary parameters, previous coronary interventions, and data of repeat cardiac catheterization were documented.

Coronary angiographies were performed using the standard technique according to the accepted guidelines with Philips Integris X-ray equipment (Inturis Suite ViewerLite v1.0; Philips, The Netherlands). Baseline SVG status at CABG was deemed as intact. Follow-up coronary angiograms were indicated in the case of clinical symptoms. The diagnosis of SVG disease was based on independent judgement of repeat coronary angiographies by 2 expert cardiologists; SVGs were classified according to their lumen status (diameter stenosis; %) at repeat coronary angiography. By excluding coronary angiographies within 12 months after CABG, it was possible to clearly distinguish technical failure or premature thrombosis caused short-term SVG degenerations. Our approach ensured time proportional evaluation of grafts by normalizing the change of diameter according to the time elapsed during follow-up. In this way, the selection bias could not affect the observed relations and reflected the "real-life" complexity of graft degeneration where the same pathophysiological conditions may result in different manifestations of SVG disease in different grafts of the same patient. Grafts were graded as intact with a <20% lumen diameter reduction similar to large vascular trials (11, 12); narrowed, between 20% and 99%; or occluded (closed lumen). Based on previous observations that chronic occlusions often arise from thrombotic lesions (13, 14) with undefined onset date, occluded SVGs were not used for comparison.

SVG conduits were evaluated both per patient and per graft level. Patients having >1 SVG with different luminal diameter status at follow-up were graded according to the more severe

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Table 3. Predictors of SVG progression (dependent variable) in narrowed graft group (n=37)

Variable	Coefficient	*P*
Age	0.036	0.813
LDL	0.250	0.073
HDL	0.066	0.686
Tg	0.027	0.851
Chol	0.206	0.138
Creatinine	0.158	0.276
EF	-0.157	0.272
CRP	0.098	0.537
HCy	**0.053**	***p*<0.01**
Vit B_{12}	0.075	0.632

R^2=0.428; Adjusted R^2=0.409
Method: multiple regression analysis; R^2=0.428; Adjusted R^2=0.409; Progression=SVG diameter lumen reduction (%) at follow-up per elapsed time (months). SVG was classified as narrowed showing 20–99% lumen diameter reduction at follow-up; Chol - cholesterin; CRP - c-reactive protein; EF - ejection fraction; Hcy - homocysteine; HDL - high-density lipoprotein; LDL - low-density lipoprotein; SVG - saphenous venous graft; Tg - triglyceride; vit B_{12} - vitamin B_{12}

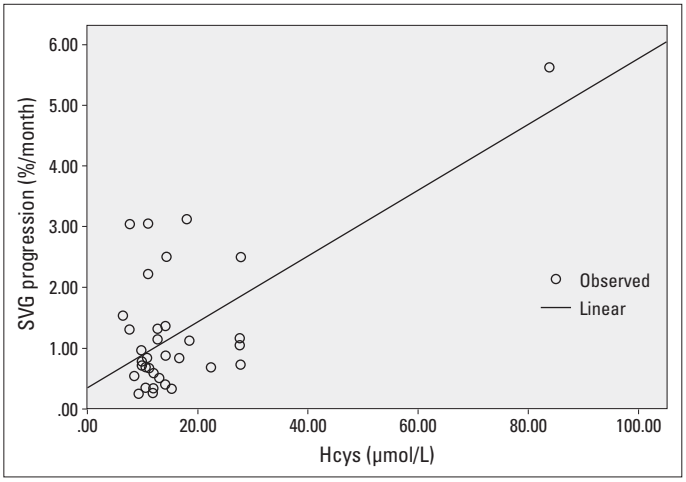

Figure 1. ??

graft's status classifying them into 1 of the 3 above-mentioned patient groups, and absolute values of luminal diameter reduction were averaged. Conduits with any kind of intervention were excluded. We complemented evaluation at per graft level as well. This way, by having an increased item of data about SVGs, stronger confidence of the statistical analysis was achieved.

Categorical variables are reported as percentages, while continuous variables are reported as mean±standard deviation (SD). The Kolmogorov–Smirnov test was used to test the normality of parameters. The equality of data of patient groups was tested by analysis of variance (ANOVA). The effect of elevated Hcy on the risk of SVG degeneration was analyzed by stepwise forward linear regression analysis, with a p value significance level of <0.05. Analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics software v20.0.0), USA.

Results

Mean follow up time was ≥5 years (67.6±36.8 months). The elapsed time until follow-up coronary angiography did not differ between the 3 groups. Clinical characteristics and laboratory findings regarding different patient groups are listed in Table 1. Mean patient age was 57.5±10.4 years, reason of post-CABG repeat coronary angiography was primarily stable angina, and more than two-thirds of patients showed vascular signs of SVG disease (stenosis/occlusion). Demographics, medical history, indication of repeat coronary angiography, clinical parameters, and risk factors did not differ significantly between the groups according to ANOVA.

The potential connection among clinical and angiography parameters were evaluated in intact and narrowed groups by univariate correlation analysis (Table 2). A significant positive correlation was found between the following parameters: CRP and SVG disease (luminal diameter reduction; %/month; p<0.01), Hcy and SVG disease (p<0.01), CRP and Hcy (p<0.01), as well as vitamin B_{12} and folic acid (p<0.01); while a significant (p<0.05) but negative correlation was seen between triglycerides and HDL-cholesterol. As patients with renal failure were not included, elevated creatinine values (>160 mmol/L) could be excluded as confounders of increased Hcy levels.

By stepwise forward multivariate linear regression analysis (Table 3, Fig. 1), only Hcy was associated independently and significantly with SVG disease; a 1 µmol/L increase in Hcy level was associated with a 0.053% increase in lumen diameter reduction/month (R^2=0.428; p<0.01), based on the corresponding patient coronary angiograms. Theoretically, this means that +10 µmol/L increase of Hcy level could be responsible for +32.1% luminal reduction in SVG within 5 years. A representative case of a CABG patient with venous graft degeneration is shown in Figure 2 (a-c).

Discussion

In this study, the patency rate was observed throughout the 5.6-year follow-up to be 74.4%, which was similar to previously published results but higher than that reported by Sabik (15) (65%) and less than that recorded by Hayward (16) (86%) and Collins (17) (86.4%). Harris (18) has found an association between plasma Hcy and LDL levels in 77 CAD patients 2 years after CABG. Our results could not confirm this, although we highlight the potential role of certain factors in medium-term SVG degeneration in contrast with short-term graft occlusions. Our results for lipid parameters were in line with previous clinical observations that a remarkable proportion of high-risk CAD patients do not achieve their therapeutic goals (19). Despite the fact that our patient population received standard statin therapy, the total-cholesterol levels did not differ significantly between patient groups. Statin treatment may slow down the atherosclerotic process in SVGs independently from the achieved total-cholesterol level, which can be explained by the pleiotropic effect of statins (20).

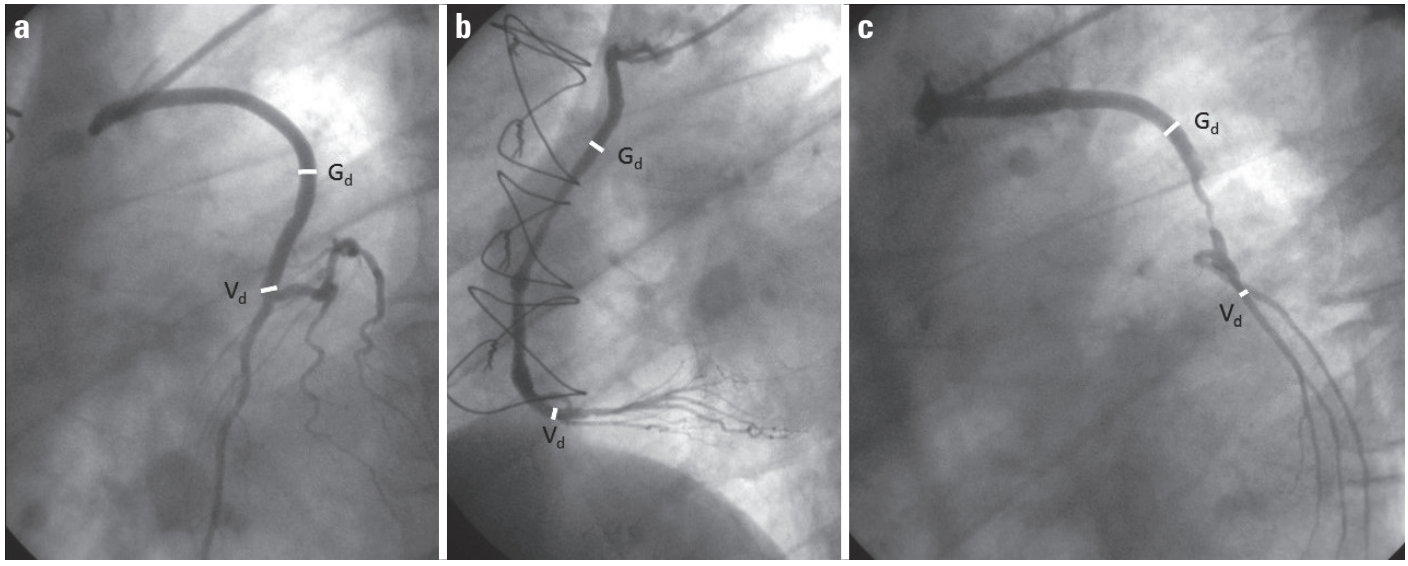

Figure 2. ??
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It is to be noted that the lack of general folic acid/vitamin B supplementation in grain products for cardiovascular prevention in Hungary can be a potential cause of the relatively elevated plasma Hcy and low folic acid and vitamin B_{12} levels in the study population. Results of the univariate correlation analysis suggested a correlation between CRP and the time proportional extent of SVG disease ($r=0.483$; $p<0.01$) as well as between CRP and Hcy ($r=0.509$; $p<0.01$) in SVG disease. The CRP–Hcy connection has been recently investigated in an animal model by Pang et al. (21). They found that Hcy can initiate an inflammatory response by stimulating CRP production. In line with our findings, human and experimental data were published about the role of CRP in the in the pathogenesis of SVG disease (22, 23). However, other results of Auer (24) or Friso and colleagues (25) in CAD patients did not find association between the elevated hs-CRP level and total plasma Hcy.

Our conclusion was similar to Shammas's (26) observations in 77 patients after 2 years that plasma Hcy is an independent prognostic factor of medium-term post-CABG graft degeneration. Among the known risk factors of CAD, clinical and experimental studies have confirmed a positive impact of Hcy on CAD (6, 27), but only few on SVG degeneration (26). Contrary to Rodionov's (28) observation that Hcy is only a bystander in CAD, our results support the opinion that Hcy plays an active role in SVG progression. Girelli et al. (29) observed similar results in 350 CAD patients after a mean follow-up of 4.8 years; Hcy was an important and independent prognostic factor of mortality after CABG. Furthermore, fasting Hcy level correlated positively with CRP. It was previously published by researchers, e.g., by Chong et al (3) that shear stress in vessels induces compensatory mechanisms in endothelial cells, thus causing local vasodilatory release of nitric oxide and prostaglandins and inhibition of constricting factors (e.g., endothelin). This can beneficially affect neutrophil adhesion and smooth muscle cell proliferation.

Study limitations

Limitations of the study include its retrospective and observational nature. Ideally, the question of how systemic and local risk factors (e.g., Hcy) affect medium- and long-term SVG progression should be addressed optimally in prospective randomized trials. The number of patients enrolled in this study was relatively low. We acknowledge that lack of baseline SVG angiography is a major limitation of this study. Status was recorded by coronary angiography, but the reasonable assumption was made that the grafts were intact at the time of CABG. Repeat coronary angiograms were indicated by clinical symptoms; therefore, the frequency of SVG disease might have been overestimated as compared to prospective angiography studies.

Where a single patient had ≥2 SVG conduits with different lumen status at follow-up, they were ranked according to the more severe graft's status for classification into the group with intact or narrowed or occluded SVG grafts. Our per patient approach required the averaging of the stenosis of the grafts in the narrowed group. Exclusion of follow-up coronary angiographies within 12 months post-CABG reduced the study population but allowed the differentiation between short-term and chronic SVG disease development. The possibility of residual confounding factors in manifestation is presumable.

Conclusion

This study revealed further details regarding factors of graft disease in CABG patients. The long-term SVG degeneration shows correlation with the elevated plasma total Hcy in patients with sub-occlusive graft stenosis, while in cases with intact SVGs, the beneficial local flow conditions may protect the grafts from degeneration. Thereby intensity of elements can change by individuals making assessment of their real involvement difficult.

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Elevated plasma total Hcy level should deserve attention in SVG patients regarding medium-term progression as Hcy seems to be associated with chronic SVG stenosis. Our data can be a promoter for further research to optimize prevention. We conclude that wide-scope risk management is an important objective of CABG patients for long-term success of their surgical treatment in CAD.

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