The risk factor profile of patients undergoing cardiovascular surgery and their relatives*

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Introduction: Pro-inflammatory status measured as elevated levels of high-sensitive C–reactive protein (hsCRP) has been shown to be a risk factor for atherosclerosis progression, but the mechanisms contributing to its elevation are not clearly elucidated yet. In order to prove our theory that there is a strong genetic background regulating hsCRP concentration, we studied potential genetic and environmental effects in patients undergoing elective coronary revascularization (coronary artery bypass grafting, CABG), their spouses and offspring.
Method: All consecutive male patients (n = 200) under 65 years of age admitted to the Cardiac Surgery Department of České Budějovice Hospital for CABG between April 2003 and October 2005 were included in the study. The day prior to surgery, blood was taken for biochemical analysis, a health questionnaire completed and anthropological parameters measured. The same examinations were performed also in their spouses (n = 193) and offspring (n = 192). Age–matched controls were selected from a 1% representative population sample of adult men and women.
Results: In patients, hsCRP levels were significantly higher than in their population controls (2.69 ± 2.30 vs. 1.70 ± 1.79 mg/L, $p < 0.001$); in lipoprotein parameters, total, LDL-and HDL-cholesterol were significantly lower in patients than in controls. Ninety-two percent of patients were on statin treatment. hsCRP levels did not differ significantly between spouses and their population controls. In offspring, hsCRP levels were significantly higher than in their population controls ($p = 0.0018$ for male, $p = 0.0201$ for female offspring), suggesting an effect of genetic background on hsCRP concentration.
Conclusion: Genetic background influencing hsCRP levels is very probable. In the future, genetic screening may be a useful tool for identifying individuals who are most at risk.
Key words: Atherosclerosis – CABG – Coronary artery disease – hsCRP – Pro-inflammatory status – Risk factors

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Úvod: Zjistilo se, že prozánětlivý stav stanovený na základě zvýšených koncentrací hsCRP (high-sensitive C–reactive protein) je rizikovým faktorem progrese aterosklerózy; mechanismy přispívající ke zvýšení hodnot hsCRP však zatím nebyly objasněny. Ve snaze prokázat naši teorii, že koncentrace hsCRP jsou ve velké míře regulovány geneticky, jsme hodnotili potenciální genetické a externí vlivy u pacientů podstupujících plánovanou revaskularizaci koronárních tepen (koronární bypass; CABG), jejich partnerek a potomků.
Metody: Do studie byli zařazeni všichni po sobě jdoucí pacienti (muži) (n = 200) ve věku do 65 let, kteří byli v době od dubna 2003 do října 2005 přijati na Kliniku kardiochirurgie Nemocnice České Budějovice k provedení CABG. Den před operací byla pacientům odebrána krev pro biochemickou analýzu, byl vyplněn zdravotnický dotazník a byly změřeny antropologické parametry. Stejná vyšetření byla provedena u partnerek (n = 193) i u potomků pacientů (n = 192). Věkově odpovídající kontrolní osoby byly vybrány z 1% reprezentativního populačního vzorku dospělých mužů a žen.

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Výsledky: U pacientů byly koncentrace hsCRP statisticky významně vyšší než u jejich populačních kontrol (2,69 ± 2,30 oproti 1,70 ± 1,79 mg/l; $p < 0,001$). Z lipoproteinových parametrů byly hodnoty celkového, LDL- a HDL-cholesterolu u pacientů statisticky významně nižší než u kontrolních osob. Devadesát dva procent pacientů užívalo statiny. Hodnoty hsCRP u partnerek a jejich populačních kontrol se významně nelišily. U potomků byly hodnoty hsCRP statisticky významně vyšší než u jejich populačních kontrol ($p = 0,0018$ u mužských, $p = 0,0201$ u ženských potomků), což ukazuje na genetický vliv na koncentraci hsCRP.
Závěr: Působení genetických vlivů na koncentraci hsCRP je velmi pravděpodobné. V budoucnu může genetický screening představovat užitečný nástroj k identifikaci jedinců s nejvyšším rizikem.
Klíčová slova: Ateroskleróza – CABG – Ischemická choroba srdeční – hsCRP – Prozánětlivý stav – Rizikové faktory

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INTRODUCTION

Coronary artery disease (CAD) and its risk factors are currently one of the most widely discussed topics. As obesity spreads across Western populations, the prevalence of CAD and metabolic syndrome (MS) has increased, together with morbidity and mortality as consequence of these two conditions.[1] Considerable attention has been paid to the underlying pathophysiological mechanisms, i.e., external and genetic factors. Effective prevention and risk assessing algorithms should focus on the causes of the disease.

Together with conventional risk factors such as hypertension and dyslipidemia, more attention has recently been paid to pro-inflammatory status measured as elevated C-reactive protein (CRP) levels. For cardiovascular risk assessment, CRP measured by an ultrasensitive method that distinguishes values within the physiological range is used; this is usually designated as hsCRP. hsCRP has been shown to be a marker of a higher risk of CAD,[2] peripheral artery disease,[3] stroke[4] and it has also been shown to correlate with the extent of atherosclerotic injury to the vessels.[5] Still, the exact mechanisms of hsCRP level elevations remain to be elucidated. Both genetic and environmental factors are currently believed to play a role in atherosclerotic disease progression.[6]

Several candidate genes have been suggested,[7] with the 174 G/C polymorphism in the IL-6 gene as one of the first polymorphisms to have been related to pro-inflammatory status and atherogenesis. It was found to be associated with indicators of preclinical atherosclerosis (carotid artery intima-media thickness) and the risk of CAD.[8] A polymorphism in the promotor of the CRP gene[9] has been shown to affect hsCRP concentrations; this, however, without an association to cardiovascular risk. Other genetic polymorphisms (e.g. TNF–α, TGF-β, IL-10, CD14) have also been investigated in relation to cardiovascular disease, but with controversial results.[7]

Assessment of a single gene effect on hsCRP concentration is a problematic approach—there are interactions of genes and their transcripts, and the effects of many of these are probably modulating rather than determining.[8] The exact extent of the effect of genetics and environment on the whole has not been yet determined. It is important to assess and distinguish these two underlying effects—to give an answer to the question of whether our attention should be focused on modulating environmental factors and lifestyle, or whether genetic screening could also play a role.

The hypothesis tested in this study was that genetic factors affect hsCRP levels more than environmental factors. Therefore, not only patients but, also, their offspring living in a different environment, should show elevated hsCRP levels. We conducted a cross-sectional study aimed at assessing the CAD profile risk factors in a group of patients indicated for elective coronary revascularization (coronary artery bypass grafting, CABG). The risk factors were also measured in spouses and offspring of patients to assess the ratio of genetic and environmental factors.

METHOD

A total of 200 consecutive male patients under 65 years of age admitted to the Department of Cardiac Surgery of České Budějovice Hospital for CABG between April 2003 and October 2005 were involved in the study. The day prior to surgery, blood was taken for lipoprotein and hsCRP determination. Anthropologic data were also measured and a health questionnaire completed. The same measurements were performed with relatives of the patients' spouses and offspring.

Controls were selected as age–matched individuals, two for every patient and spouse, from a 1% representative population sample of adult men and women, selected in 9 Czech districts according to the protocol of the WHO MONICA study. It was not possible to select similarly age-matched controls for offspring. Accordingly, the 100 youngest men and 100 youngest women from the population sample were chosen as controls, which was the closest age–matching group.

Plasma glyceride levels of total, HDL- and LDL-cholesterol were measured enzymatically using a standardized procedure (CDC external quality control system /Centers of Disease Control/), using a Cobas Mira analyser (Hoffman-LaRoche, Switzerland). hsCRP levels were measured using an ultrasensitive assay from Orion-Diagnostica, Finland.

The *t*-test was used to calculate statistical significance for the differences between the groups. All the results shown are non-adjusted, but age- and BMI-adjusted averages did not differ in statistical significance. Values of hsCRP levels above 10 mg/L were excluded from statistical analysis because of possible acute illness at the time of the blood check (22 patients and 8 spouses, 4 individuals in the female offspring group, 6 in the control group for patients, 3 in the control group for female offspring were excluded).

Table I

Characteristics of patients and their age-matched controls. *P* for the difference between the groups was calculated using Student's *t*-test. Values are shown as mean ± SD.

	Patients	Controls	*p*
N	200	400	
Age	58.43 ± 4.84	58.62 ± 5.04	0.84
BMI	29.27 ± 3.86	28.94 ± 3.99	0.69
Total cholesterol (mmol/L)	4.91 ± 1.08	5.89 ± 1.02	< 0.001
Triglycerides (mmol/L)	2.20 ± 1.18	2.08 ± 1.33	0.67
LDL-cholesterol (mmol/L)	2.86 ± 0.83	3.81 ± 0.91	< 0.001
HDL-cholesterol (mmol/L)	1.02 ± 0.24	1.19 ± 0.36	< 0.001
hsCRP (mg/L)	2.69 ± 2.30	1.66 ± 1.86	< 0.001

Table II

Characteristics of spouses and their age-matched controls. *P* for the difference between the groups was calculated using Student's *t*-test. Values are shown as mean ± SD.

	Spouses	Controls	*p*
N	193	386	
Age	55.05 ± 7.01	54.92 ± 6.59	0.841
BMI	27.92 ± 5.71	28.70 ± 5.01	0.110
Total cholesterol (mmol/L)	6.00 ± 1.10	6.19 ± 1.05	0.076
Triglycerides (mmol/L)	1.84 ± 1.06	1.64 ± 0.86	0.047
LDL-cholesterol (mmol/L)	3.67 ± 0.95	3.99 ± 0.97	0.0007
HDL-cholesterol (mmol/L)	1.41 ± 0.38	1.46 ± 0.38	0.215
hsCRP (mg/L)	1.83 ± 1.80	1.95 ± 2.07	0.54

RESULTS

In the patient group, there was no statistically significant difference in BMI between the patients and their controls ($p = 0.69$). As could have been expected, the average total and LDL-cholesterol levels in patients were significantly lower than in their control group ($p < 0.001$ for both cases). Ninety-two percent of patients were treated by statins. HDL-cholesterol was also significantly lower in patients than in controls ($p < 0.001$). The least difference in triglyceride levels did not reach statistical significance ($p = 0.67$) *(Table I)*.

Differences between patients and controls in other risk factors were also found. While only 24.3% of the controls smoked, 34.0% were ex-smokers and 41.7% never smoked, the figures for patients were 33.8% of smokers, 47.1% of ex-smokers, with only 19.1% of never-smokers ($p < 0.001$). The situation was similar with the occurrence of hypertension—while 70.6% of patients had hypertensive disease, the figure was only 53.3% in controls ($p = 0.005$). The difference for diabetes was also statistically significant, with 45.6% of patients having diabetes while the disease was present in only 10.6% of controls ($p < 0.001$).

The levels of hsCRP in patients (2.69 ± 2.30 mg/L, 95% CI 2.37–3.01) were significantly higher compared with their population controls (1.70 ± 1.79 mg/L, 95% CI 1.53-1.88); the difference reached 58% ($p < 0.001$) *(Table I)*. The medians were 1.91 (interquartile range 0.91/3.85) in patients and 0.98 (interquartile range 0.46/2.13) in controls.

The spouses represent individuals genetically different from patients, but living in the same environment. The control group was selected as age-matched individuals and, therefore, there was no difference in age between spouses and their controls. The BMI in spouses did not differ significantly from their controls ($p = 0.110$). The differences in total and HDL-cholesterol levels did not reach statistical significance ($p = 0.076$ and 0.215, respectively) whilst that of triglycerides levels was of borderline significance ($p = 0.047$). LDL-cholesterol levels were lower in spouses than in their population controls ($p = 0.0007$). hsCRP levels did not differ significantly between spouses (1.83 ± 1.80 mg/L, 95% CI 1.58–2.08) and their population controls (1.95 ± 2.07, 95% CI 1.74–2.16), $p = 0.54$ *(Table II)*. The medians were 1.39 (inter-quartile range 0.66/2.80) in spouses and 1.24 (inter-quartile range 0.49/2.44) in controls.

Offspring were defined as individuals genetically related to their parents, but living in a different environment. Both groups (male and female offspring) showed no statistically significant differences in BMI from their controls ($p = 0.465$ and 0.979, respectively). The average BMI in males was in the range of overweight while, in females, it was within the normal range. Also, LDL-cholesterol and HDL-cholesterol showed no significant difference between offspring and their control groups. The average triglyceride levels in male offspring extended over the physiological range (2.41 ± 1.81 mmol/L) and differed significantly from their controls (1.52 ± 0.87 mmol/L), $p = 0.0035$. In female offspring, triglycerides levels were within the physiological range (1.43 ± 0.80 mmol/L), but significantly higher than those of their population controls (1.05 ± 0.61 mmol/L), $p = 0.0034$ *(Table III)*.

The differences in pro-inflammatory status measured as hsCRP concentration were significantly higher in both male and female offspring than in their population controls. In male offspring, average hsCRP

Table III

Characteristics of the offspring and their age-matched controls. *P* for the difference between the groups was calculated using Student's *t*-test. Values are shown as mean ± SD.

	Male offspring	Controls	*p*	Female offspring	Controls	*p*
N	106	100		86	100	
Age	30.04 ± 6.60	29.6 ± 1.61	0.572	29.56 ± 6.58	28.8 ± 1.26	0.280
BMI	26.13 ± 3.70	26.49 ± 3.48	0.465	23.69 ± 4.50	23.67 ± 4.14	0.979
Total cholesterol (mmol/L)	5.41 ± 1.02	5.20 ± 0.91	0.177	5.07 ± 0.97	4.89 ± 1.07	0.249
Triglycerides (mmol/L)	2.24 ± 1.81	1.52 ± 0.87	0.0035	1.43 ± 0.80	1.05 ± 0.61	0.0034
LDL-cholesterol (mmol/L)	3.17 ± 0.81	3.25 ± 0.81	0.708	2.85 ± 0.86	2.85 ± 0.91	0.989
HDL-cholesterol (mmol/L)	1.22 ± 0.30	1.27 ± 0.36	0.942	1.47 ± 0.37	1.57 ± 0.36	0.891
hsCRP (mg/L)	1.49 ± 1.74	0.75 ± 0.83	0.0018	2.13 ± 2.33	1.38 ± 1.67	0.0201

levels were 1.49 ± 1.74 ml/L, with a median of 0.83 (inter-quartile range 0.41/1.71), while average hsCRP levels in controls were 0.75 ± 0.83, with the median being 0.37 (inter-quartile range 0.31/0.84), $p = 0.0018$. In female offspring, average hsCRP levels were 2.13 ± 2.33 mg/L, with a median of 1.00 (inter-quartile range 0.59/2.99), whilst average hsCRP levels in controls were 1.38 ± 1.67 mg/L, with the median of 0.50 (inter-quartile range 0.31/1.77), $p = 0.0201$.

DISCUSSION

The most prominent result were the significantly higher hsCRP levels in patients than in controls despite statin treatment (statins were shown to significantly lower CRP levels).[9] There could be several reasons for the hsCRP elevation in our patients. Firstly, hsCRP levels correlate with body weight and are elevated in obese individuals, as cytokines produced by adipose tissue (especially visceral) induce CRP synthesis in the liver. However, our patients did not differ in BMI from their controls, so other explanatory reasons must be investigated. Secondly, in this stage of disease—advanced atherosclerosis—hsCRP levels may also serve as an indicator of the extent of the disease,[5] though any exact evaluation is difficult when statins are involved. It has been shown in some studies[9] that hsCRP lowering by statins is dose independent. In the stage of advanced atherosclerotic disease, hsCRP elevation may represent the mechanisms participating in disease development (indicating elevated risk of atherosclerotic disease progression) or it may be the marker of the extent to which the disease has already progressed.

The levels of hsCRP in offspring were higher in both males and females than in their population controls, although there was no difference in BMI. hsCRP has been shown to be associated with weight and body fat in other studies,[10] an effect on hsCRP is most likely to be played by factors other than body weight in offspring. Unfortunately, waist and hip circumference values were not measured in offspring so we do not know whether the type of obesity was the same in offspring and their controls, or whether there was a difference in fat distribution that could play a role.

Our patients lived in both rural and urban environments. Most of the offspring lived in households different from those of their parents, though we did not specify data whether they relocated from a rural to an urban environment (or vice versa) or stayed in the same area. Additionally, the subject of so-called "social heritability" is rather difficult—descendants often tend to share the same habits as their parents, dietary habits including. Therefore, we cannot conclude whether the elevated triglycerides levels in offspring are due to their genetic background or to their dietary habits. Elevated triglycerides in the spouses of our patients suggest they probably have the same dietary habits as their husbands, but their pro-inflammatory reaction was different—their hsCRP levels were not elevated. Even if the offspring had the same dietary habits, the fact that spouses living in the same environment as the patients who do not have elevated hsCRP levels (while their offspring do), strongly suggests the of genetic background. The fact that spouses do not differ—but offspring do—from their population controls, is essential here. An interventional study focused on assessing pro-inflammatory reaction in response to changes in lifestyle (in the general population and in descendants of patients with atherosclerosis) would be needed to prove this theory.

While, in female offspring, triglyceride levels were significantly higher than in controls (but still within the physiological limits), in male offspring, the average value of triglycerides was well above the upper range of the physiological limit. This could suggest both a genetic background and an effect of lifestyle on lipoprotein metabolism, as already suggested. Also, the effect of elevated triglycerides on hsCRP elevation cannot be excluded—metabolic regulation of hsCRP levels via triglycerides has been shown to exist.[11]

Some polymorphisms have been shown to affect hsCRP levels[12,13] but the differences in levels, as affected by a single polymorphism, were rather small. The heritability may be of a polygenic type, but the strong effects by polymorphisms other than those mentioned above cannot be excluded (e.g., polymorphisms in genes affecting other pro-inflammatory molecules).

Compared with their population controls, the patients had significantly lower total and LDL-cholesterol levels. This result is due to statin treatment, with 92% of patients treated with statins (recommended treatment according to the current guidelines for management of coronary heart disease). Statins are a powerful lipid-lowering treatment, therefore their effect was seen in patients with total cholesterol levels being about 1.0 mmol/L lower than in the con-

trol population group; the same lowering was observed in patients undergoing LDL-cholesterol levels.

It is possible that HDL-cholesterol levels were lower than the population average even before statin administration, as low HDL-cholesterol is currently recognized as one of the most prominent risk factors for CAD.[14]

Surprisingly, the levels of LDL-cholesterol, as in the spouses of our patients, was significantly lower than in their population controls. The reason for this difference is unclear, and it can only be speculated that changes in diet, often introduced to patients by their spouses after CAD has been diagnosed, has also had some impact on the spouses themselves.

CONCLUSION

An effect of a genetic background on hsCRP levels is most likely. In the future, genetic screening may be a useful tool for identifying individuals who are most at risk. It is important to investigate for polymorphisms affecting regulation of the pro-inflammatory response.

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