Prognostic value of infection and inflammation markers for late cardiac events in an Iranian sample

N. Sarrafzadegan,[1] P. Rezaporian,[1] M. Kaypour,[1] M. Mohseni,[1] M. Sadeghi,[1] S. Asgary[1] and B. Sabet[1]

القيم الإنذارية للعدوى والواسمات الالتهابية في الأحداث القلبية المتأخرة في عيِّنة من الإيرانيِّين

نضال صراف زادكان، بريسا رضا بوريان، مريم كي بور، مسعود محسني، معصومة صادقي، صديقة عسكري، بابك ثابت

الخلاصة: أجرى الباحثون في هذه الدراسة تقييماً للمستويات المصلية لأضداد الغلوبولين المناعي G لكل من الملوية البوابية، والمتدثرة الرئوية، والفيروسة المضخمة للخلايا، وكذلك لمستوى الواسمَيْن الالتهابيَـيْن: البروتين المتفاعل C، والفبرينوجين، لدى 57 مريضاً يعانون من متلازمة تاجية حادة، و65 مريضاً يعانون من ذبحة لا مستقرة، و60 من ذبحة مستقرة، و44 من الشواهد الأصحاء. كما قيّمت الدراسة ما إذا كانت هذه الواسمات مرتبطة بعدم استقرار حالة القلب بعد مضي 6 أشهر من الدخول إلى المستشفى. وقد ازداد اختطار الإصابات التاجية المتأخرة (الوفاة القلبية أو معاودة الدخول إلى المستشفى بسبب الإصابات القلبية الحادة) المصحوبة بإيجابية المصل للمتدثرة الرئوية (نسبة الأرجحية المعدَّلة OR= 2.12؛ **متـراوحة** بين 1.16 و4.08 بفاصل ثقة 95٪). في حين لم تترابط المتثابتات الأخرى مع الأحداث القلبية المتأخرة بشكل يعتد به إحصائياً بعد تعديلها بحسب السن، والجنس، والإصابة بالسكري، وفرط ضغط الدم، وفرط شحميات الدم، والتدخين.

ABSTRACT We evaluated the serum levels of IgG antibodies to ***Helicobacter pylori***, ***Chlamydia pneumoniae*** and cytomegalovirus and the level of the inflammatory markers C-reactive protein and fibrinogen in 57 patients with acute coronary syndrome, 65 with unstable angina, 60 with stable angina and 44 healthy controls, and whether these markers were associated with cardiac instability 6 months after admission. There was a significant increased risk of late coronary events (cardiac death or readmission with acute coronary events) associated with seropositivity to ***C. pneumoniae*** (adjusted odds ratio 2.12; 95% confidence interval: 1.16–4.08). Other parameters were not significantly associated with late cardiac events after adjustment for age, sex, diabetes mellitus, hypertension, hyperlipidaemia and smoking behaviour.

Valeur pronostique des marqueurs d'infection et d'inflammation quant aux complications cardiaques dans un échantillon de sujets iraniens

RÉSUMÉ Cette étude a évalué les niveaux sériques des anticorps anti-***Helicobacter pylori***, ***Chlamydia pneumoniae*** et cytomégalovirus de type IgG et le niveau des marqueurs inflammatoires de la protéine C réactive (PRC) et du fibrinogène chez 57 patients présentant un syndrome coronaire aigu, 65 présentant un angor instable, 60 présentant un angor stable et 44 sujets sains, et a déterminé si ces marqueurs étaient associés à une instabilité cardiaque six mois après l'hospitalisation. On a constaté une augmentation significative du risque de complications coronaires (mort d'origine cardiaque ou réadmission avec événements coronaires aigus) associée à la séropositivité à ***C. pneumoniae*** (OR ajusté 2,12 ; IC 95 % : 1,16-4,08). Les autres paramètres n'étaient pas significativement associés aux complications cardiaques après ajustement en fonction de l'âge, du sexe, du diabète sucré, de l'hypertension, de l'hyperlipidémie et du tabagisme.

[1]Isfahan Cardiovascular Research Centre, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran (Correspondence to N. Sarrafzadegan: nizal.sarrafzadegan@gmail.com).
Received: 13/04/06; accepted: 06/11/06

Introduction

It is generally accepted that inflammation plays an important role in the pathogenesis of atherosclerosis. It has been reported that an elevated level of fibrinogen—a readily measurable acute-phase protein—at the time of hospital admission is a determinant factor for future coronary events in patients with acute coronary syndrome (ACS) [*1*] and is an indicator of the extent of coronary atherosclerosis [*2*]. It has also been suggested that elevated levels of C-reactive protein (CRP), a nonspecific but sensitive marker of inflammation, has prognostic value unrelated to myocardial ischaemia or damage [*3,4*].

On the other hand, several studies have reported that seropositivity to *Chlamydia pneumoniae* [*5,6*], *Helicobacter pylori* [*6,7*] and cytomegalovirus (CMV) [*8*] are associated with ACS. It is not clear whether the infectious burden could explain the role of inflammation in cardiac instability and atherosclerosis or not. However, the role of these infectious agents is controversial because of some negative data [*9–11*] and the scarcity of studies with long-term follow-up. Another source of ambiguity is that it is not known whether the role of infection and inflammatory markers for future attacks of ACS is the same in patients with chronic coronary heart disease (CHD) and ACS including subjects with and without myocardial necrosis.

In our previous survey in an Iranian sample, the overall prevalence of CHD based on the World Health Organization (WHO) standard Rose questionnaire and/or ECG was as high as 19.4% [*12*]. Regarding the overall trend towards establishing the role of infection and inflammation in the development of atherosclerosis and ACS, it is important to evaluate their role in cardiovascular instability in combination with other prevalent cardiovascular risk factors in our study population [*13*]. We conducted this study to evaluate: (a) whether the concentrations of antibodies to *H. pylori*, *C. pneumonia* and CMV and the level of CRP and fibrinogen are different in patients with ACS, stable angina pectoris and healthy controls; and (b) whether serum concentrations of infection and inflammatory markers on admission, after adjustment for classic risk factors for CHD, could predict late cardiac outcomes.

Methods

Sample

The study group was 226 consecutive patients (134 men, 92 women) who had been hospitalized in coronary care units affiliated to Isfahan University of Medical Sciences or referred for diagnostic angiography. The patients were divided into 4 groups: acute myocardial infarction, unstable angina pectoris, stable angina pectoris and healthy controls.

The diagnosis of acute myocardial infarction was based on WHO criteria as a combination of typical acute symptoms, serial ECG changes and elevation of cardiac enzymes [*14*].

Unstable angina pectoris was defined as angina at rest lasting at least 10 minutes and occurring in the 48 hours preceding hospital admission, associated with transient ST-segment depression and/or T-wave inversion.

The remaining 2 groups were enrolled from patients who were suspected of having CHD but not ACS, and therefore underwent diagnostic coronary angiography. The patients with angiographic evidence of atherosclerosis in their epicardial coronary tree were classified as stable angina pectoris and those without as healthy controls. Two

cardiologists reviewed the coronary angiograms independently. A significant lesion was defined as ≥ 50% stenosis of at least 1 coronary vessel. Of 104 coronary angiograms performed, cardiologists agreed in 96 cases (kappa = 0.84).

Patients were not included if they had cardiogenic shock, known thrombotic disorders, a known systemic inflammatory condition or malignancy, significant valvular heart disease, surgery or major trauma in the previous month or marked renal failure. Written informed consent was obtained from each patient. The study was approved by the ethics committee of Isfahan Cardiovascular Research Centre, which is a member of the Office for Human Research Protections, United States Department of Health and Human Services (assurance number: FWA00008578).

Study protocol

The patients were evaluated for a history of CHD risk factors including diabetes mellitus, hypertension, hyperlipidaemia and smoking habits.

Blood samples were taken on admission and tested for serum immunoglobulin G (IgG) antibodies to *H. pylori*, *C. pneumoniae* and CMV as well as quantitative CRP level and plasma fibrinogen concentration. Serum IgG titres were measured using commercial enzyme-linked immunoassay (ELISA) kits (Trinity Biotech, Wicklow, Ireland). CRP was measured by immunonephelometric assay and fibrinogen by the Clauss method [*15*].

All patients were followed up for 6 months, looking for the occurrence of clinical endpoints, described as cardiac death or readmission with ACS.

Statistical analysis

Continuous variables were evaluated for normality of distribution. Variables with normal distribution are presented as mean and standard deviation (SD); otherwise data are presented as median and range. Serum concentrations of IgG antibody against *H. pylori*, *C. pneumoniae* and CMV infections, CRP level and plasma concentration of fibrinogen were compared among the 4 study groups using ANOVA or Kruskal–Wallis tests as appropriate. In cases of significant differences, *post hoc* analysis with the Tukey test was done to detect the sources of observed differences.

In order to assess the predictive value of infection and inflammatory markers for late cardiac events, logistic regression analysis was used. The model was adjusted for age, sex, diabetes mellitus, hypertension, hyperlipidaemia and smoking habits. *P*-value < 0.05 was considered statistically significant. Statistical analysis was performed with *SPSS*, version 11.0 software.

Results

Of 226 patients, 57 were classified as acute myocardial infarction, 65 as unstable angina pectoris, 60 as stable angina pectoris and 44 were controls. The baseline characteristics of patients are presented in Table 1. None of the patients died during the first admission period.

Among the total group of patients, the seroprevalence of antibodies to *H. pylori* was 92%, to *C. pneumoniae* was 27% and to CMV was 96%. The median IgG antibody to *H. pylori* was significantly higher in the patients with unstable angina than in other groups: median 140 IU/mL (range 1–301 IU/mL) versus 65 IU/mL (range 2–350 IU/mL) in acute myocardial infarction, 46 IU/mL (range 1–306 IU/mL) in stable angina pectoris and 39 IU/mL (range 2–227 IU/mL) in controls (Table 2). However, the proportion of cases with positive antibody

Table 1 **Baseline characteristics in the 4 groups of patients**

Variable	Acute myocardial infarction (*n* = 57)	Unstable angina pectoris (*n* = 65)	Stable angina pectoris (*n* = 60)	Controls (*n* = 44)	*P*-value
Mean age (SD) (years)	58 (12)	61 (11)	65 (11)	53 (8)	0.003
Male sex (% of patients)	75.4	47.7	70.0	40.9	< 0.001
Diabetes mellitus (% of patients)	21.1	33.8	28.3	25.0	0.44
Hypertension (% of patients)	40.4	56.9	38.3	40.9	0.13
Hyperlipidaemia (% of patients)	31.6	35.4	45.0	38.6	0.48
Smoking (% of patients)	42.1	24.6	35.0	18.2	0.03

n = ***number of patients; SD = standard deviation.***

titres was not statistically different between the 4 groups (90.5% in unstable angina, 94.7% in stable angina, 90.2% in acute myocardial infarction and 92.7% in the controls). Neither quantitative nor binary analysis showed a statistical difference among the 4 groups in *C. pneumoniae* or CMV levels (Table 2). Although the median CRP level was not statistically different between the 4 groups, positive CRP concentrations in healthy controls, stable angina pectoris, unstable angina and acute myocardial infarction were 0%, 2.2%, 8.6% and 19.1%, suggesting a trend for positive CRP levels to be associated with cardiovascular instability (Table 2). The median fibrinogen level in control patients was less than patients with CHD, but not significantly so.

Positive clinical endpoints in the 6-month follow-up period and the corresponding mean levels of the 5 markers are shown in Table 3.

In the stable angina pectoris group, logistic regression analysis showed that the unadjusted odds ratios (ORs) were significant for *C. pneumonia*, CMV and CRP levels. However, when adjusted for age, sex, diabetes mellitus, hypertension, hyperlipidaemia and smoking behaviour, only serum concentration of IgG antibodies to *C. pneumoniae* were significantly associated with late cardiac events (cardiac death or readmission with acute coronary events in the 6-month follow-up period) [adjusted OR = 2.12; 95% confidence interval (CI): 1.16–4.08; $P = 0.02$] (Table 4). CMV (adjusted OR = 1.56; 95% CI: 0.96–2.64; $P = 0.07$), *H. pylori* (adjusted OR = 1.02; 95% CI: 0.52–1.78; $P = 0.46$), serum CRP (adjusted OR = 1.42; 95% CI: 0.88–2.59; $P = 0.09$) and fibrinogen (adjusted OR = 0.97; 95% CI: 0.52–1.89; $P = 0.89$) were no longer significant (Table 4). In the 3 other groups—acute myocardial infarction, unstable angina pectoris and controls—infection and inflammatory markers did not show predictive value (data not shown).

Discussion

In the present study no association was found between serum markers of infection and inflammation and late cardiac events

Table 2 **Comparison of infection and inflammation markers among the 4 groups of patients**

Variable	Acute myocardial infarction (*n* = 57)	Unstable angina pectoris (*n* = 65)	Stable angina pectoris (*n* = 60)	Controls (*n* = 44)	*P*-value
Helicobacter pylori					
Median level (range) (IU/mL)	65 (2–350)	140 (1–301)	46 (1–306)	39 (2–227)	0.05
Seropositive rate (% of patients)	90.2	90.5	94.7	92.7	0.79
Chlamydia pneumoniae					
Median level (range) (IU/mL)	0.62 (0.12–3.46)	0.46 (0.12–3.64)	0.65 (0.13–2.75)	0.65 (0.22–3.14)	0.28
Seropositive rate (% of patients)	29.4	20.3	33.3	26.8	0.43
Cytomegalovirus					
Median level (range) (IU/mL)	2.2 (1.0–4.2)	2.7 (0.3–6.0)	2.2 (2.0–17.8)	2.4 (0.4–4.3)	0.57
Seropositive rate (% of patients)	98.0	93.8	98.2	95.1	0.50
C-reactive protein					
Median level (range) (IU/mL)	4.5 (2.1–29.8)	4.4 (1.2–21.7)	4.3 (2.0–17.8)	4.6 (2.5–8.3)	0.69
Seropositive rate (% of patients)	19.1	8.6	2.2	0.0	0.004
Fibrinogen					
Median level (range) (IU/mL)	304 (189–461)	301 (116–461)	304 (149–556)	284 (140–461)	0.54
Seropositive rate (% of patients)	7.1	3.2	6.8	2.4	0.58

n = ***number of patients.***

Table 3 **Comparison of positive (yes) and negative (no) clinical endpoints in the 6-month follow-up period and inflammation markers among the 4 groups of patients**

Variable	Acute myocardial infarction (*n* = 57)		Unstable angina pectoris (*n* = 65)		Stable angina pectoris (*n* = 60)		Controls (*n* = 44)	
	Yes (*n* = 35)	No (*n* = 22)	Yes (*n* = 23)	No (*n* = 42)	Yes (*n* = 28)	No (*n* = 32)	Yes (*n* = 4)	No (*n* = 40)
Mean (SD) ***Helicobacter pylori*** level (IU/mL)	93 (89)	87 (87)	120 (93)	124 (97)	64 (71)	87 (88)	86 (93)	71 (71)
Mean (SD) ***Chlamydia pneumoniae*** level (IU/mL)	0.82 (0.68)	0.88 (0.94)	0.65 (0.56)	0.81 (0.85)	0.97 (0.74)	0.74 (0.47)	0.33 (.12)	0.86 (0.65)
Mean (SD) cytomegalovirus level (IU/mL)	2.3 (0.8)	2.6 (0.8)	2.7 (0.9)	2.5 (1.0)	2.66 (0.9)	2.19 (0.9)	3.0 (0.9)	2.4 (0.9)
Mean (SD) C-reactive protein level (IU/mL)	6.6 (5.9)	6.2 (3.1)	5.3 (4.3)	5.6 (4.0)	5.7 (3.3)	4.2 (1.4)	5.4 (2.4)	4.6 (1.4)
Mean (SD) fibrinogen level (IU/mL)	312 62)	294 (70)	298 (55)	293 (88)	320 (80)	301 (70)	299 (77)	280 (84)

n = ***number of patients; SD = standard deviation.***

in patients with ACS, while in patients with stable angina pectoris, the CMV and *C. pneumoniae* antibody titres as well as CRP level were associated with instability. Although there is a general trend towards establishing the role of inflammation and some particular infectious agents in the development of CHD, the pathogenesis in chronic CHD may be different from that of ACS.

Angiographic studies show that the extension and severity of coronary atherosclerosis are significantly less in patients who first present with infarction or unstable angina than in those who first present with chronic stable angina [*16,17*]. Moreover, because inflammatory cell infiltrates are very common in chronic stable CHD and present on average only quantitative differences [*18,19*] they may not explain rare, short-lasting episodes of instability. Thus, it would appear reasonable to conclude that the acute inflammatory stimuli that suddenly trigger instability may not necessarily be the same as those most commonly involved in atherogenesis. Our results are comparable to some prior studies that indicate the association of infectious burden and serum CRP concentration with atherosclerosis but not instability of angina [*20,21*].

In the present study, CRP but not fibrinogen was associated with chronic CHD. Today, a growing body of evidence supports the independent prognostic role of CRP in CHD [*22,23*]. However, the low utility of inflammatory markers during times of infection or trauma, and among individuals with known systemic inflammatory conditions, limits their clinical utility. Moreover, several major lifestyle and physical characteristics, including cigarette smoking [*24*], diabetes mellitus [*25*] and raised blood

Table 4 **Relative risk for late cardiac events associated with infection and inflammation markers in patients with stable angina pectoris**

Variable	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	*P*-value
Helicobacter pylori level	1.12 (0.58–1.88)	1.02 (0.52–1.78)	0.46
Chlamydia pneumoniae level	2.32 (1.33–4.26)	2.12 (1.16–4.08)	0.02
Cytomegalovirus level	1.89 (1.13–2.96)	1.56 (0.96–2.64)	0.07
C-reactive protein level	1.68 (1.04–2.84)	1.42 (0.88–2.59)	0.09
Fibrinogen level	1.06 (0.55–2.03)	0.97 (0.52–1.89)	0.89

[a]Adjusted for age, sex, diabetes mellitus, hypertension, hyperlipidaemia and smoking.
OR = odds ratio, CI = confidence interval.

pressure [*26*], all influence the plasma level of inflammatory markers. In support of this hypothesis, it has been shown that the predictive value of inflammatory markers becomes remarkable when the level of other determinants of risk is low [*27*].

The association of some particular infectious agents and CHD remains controversial. A major limitation in interpreting any association between *H. pylori* and CMV infections and CHD is the confounding role of socioeconomic circumstances [*28,29*]. Although no association was found for *H. pylori* infection in our study, it has the limitation that information concerning socioeconomic status was not obtained. Our finding is in accordance with prior studies that reported the predictive value of CMV seropositivity for CHD in patients with chronic CHD [*8,30*]. Despite increasing volumes of data, it is still not clear whether the reported associations for *H. pylori*, *C. pneumoniae* and CMV may simply reflect their role as "innocent bystanders" or as a consequence rather than a cause of atheroma. Some authors voice the opinion that stress, which accompanies ACS, is one of the factors predisposing to the reactivation or flaring of some particular infectious agents, specifically latent CMV infection [*31*]. Moreover, due to the widespread prevalence of CMV and *H. pylori* infections in the general population, as in our subjects, the presence of IgG antibodies precludes proper evaluation of the relationship between active infection and cardiac events.

The role of *C. pneumoniae* in atherosclerosis and cardiovascular instability has been investigated in several studies with different methodologies. The results of studies aimed at the detection of *C. pneumoniae* in atherosclerotic lesions by electron microscopy [*32,33*], culture [*34,35*], *in situ* hybridization [*36,32*] and even PCR [*33,34*] are controversial. Assessment of the relationship between *C. pneumoniae* in peripheral blood monocytes and CHD has also yielded conflicting results [*35*]. Danesh proposed that prospective seroepidemiological studies should help to better assess the causal association of *C. pneumoniae* and atherosclerosis [*37*].

Comparable to our results, some recent seroepidemiological studies support the association of *C. pneumoniae* with atherosclerosis and cardiac instability [*5,6*], while others do not [*10,11,38*]. However, previous studies have demonstrated that the serological method chosen to measure *C. pneumoniae* antibodies has a strong impact

on the association between *C. pneumoniae* and atherosclerosis [*39,40*]. Collectively, further large-scale prospective epidemiological studies which validate serological methods are needed to fully disclose the association of *C. pneumoniae* and atherosclerosis.

Another approach to test the hypothesis would be evaluating the effectiveness of secondary prevention with antibiotics in patients with CHD. Some earlier studies showed beneficial effects of antibiotic therapy [*41,42*], whereas some recent trials did not [*43–45*]. Higgins in his review states that short-term antibiotic treatment does not significantly reduce cardiovascular events [*46*], but a robust study should determine whether long-term treatment is required to decrease cardiovascular instability. Nevertheless, in interpreting the results we should know that, if negative, these trials would tell us only that certain antibiotic regimens do not alter the prognosis of CHD patients, and it does not necessarily mean the loss of association between *C. pneumoniae* and atherosclerosis. It is noteworthy that atherosclerosis develops progressively from an early age and the use of antibiotics late in the inflammatory process is unlikely to have a beneficial effect. A substitute approach might be the use of antibiotics or vaccination to eliminate carriage of infectious agents in peripheral blood cells in young people without established atherosclerosis [*47*]. Conducting clinical trials to evaluate the effectiveness of this approach, though difficult, would give valuable guidelines.

If confirmed in a larger series of patients, our findings may point the way to a cost-effective and easily available method for identifying patients at high risk of future cardiac instability. In order to obtain acceptable clinical outcomes, inexpensive commercial assays for the above-mentioned markers need to be available. Clinicians will need also to gain knowledge regarding the population distribution of seropositivity to markers of inflammation and infection, and develop health prevention measures that address the identified risks.

Acknowledgements

This study was supported by grant No. 3130930 from the Isfahan Cardiovascular Research Centre as well as the School of Medicine; both are affiliated to Isfahan University of Medical Sciences.

The authors would like to acknowledge the contribution of the laboratory staff for their assistance with data laboratory tests as well as that of Dr Afshan Akhavan and Mrs Sonia Zarfeshani for their technical assistance.

References

1. Becker RC et al. Prognostic value of plasma fibrinogen concentration in patients with unstable angina and non-Q-wave myocardial infarction (TIMI IIIB Trial). ***American journal of cardiology***, 1996, 78:142–7.

2. ECAT Angina Pectoris Study Group. ECAT angina pectoris study: baseline associations of haemostatic factors with extent of coronary arteriosclerosis and other coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. ***European heart journal***, 1993, 14:8–17.

3. Liuzzo G et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. ***New England journal of medicine***, 1994, 331:417–24.

4. Liuzzo G et al. Plasma protein acute phase response in unstable angina is not

induced by ischemic injury. ***Circulation***, 1996, 94:2374–80.

5. Adiloglu AK et al. Infection with ***Chlamydia pneumoniae*** but not ***Helicobacter pylori*** is related to elevated apolipoprotein B levels. ***Acta cardiologica***, 2005, 60:599–604.

6. Fraser AG et al. ***Helicobacter pylori***, ***Chlamydia pneumoniae*** and myocardial infection. ***Internal medicine journal***, 2003, 33:267–72.

7. Kinjo K et al. Prevalence of ***Helicobacter pylori*** infection and its link to coronary risk factors in Japanese patients with acute myocardial infarction. ***Circulation journal***, 2002, 66:805–10.

8. Gabrylewicz B et al. Cytomegalovirus infection in acute myocardial infarction. Is there a causative relationship? ***Kardiologia polska***, 2003, 69:283–92.

9. Zhu J et al. Lack of association of ***Helicobacter pylori*** infection and frequency of acute myocardial infarction or death. ***American journal of cardiology***, 2002, 15:155–8.

10. Zibaeenezhad MJ et al. Relation of ***Chlamydia pneumoniae*** infection to documented coronary artery disease in Shiraz, Southern Iran. ***Angiology***, 2005, 56(1):43–8.

11. Bermejo Garcia J et al. Inflamacion e infeccion en la enfermedad coronaria estable y en el sindrome coronario agudo [Inflammation and infection in stable coronary disease and acute coronary syndrome]. ***Revista española de cardiología***, 2001, 54:453–9.

12. Sarraf-Zadegan N et al. The prevalence of coronary artery disease in an urban population in Isfahan, Iran. ***Acta cardiologica***, 1999, 54:257–63.

13. Sarraf-Zadegan N, Boshtam M, Rafiei M. Risk factors for coronary artery disease in Isfahan, Iran. ***European journal of public health***, 1999, 9(1):20–5.

14. Rose G, Blackburn H, Gillum R, eds. ***Cardiovascular survey methods***, 2nd ed. Geneva, World Health Organization, 1982.

15. Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. [Rapid physiological coagulation method in determination of fibrinogen]. ***Acta haematologica***, 1957, 17:237–46.

16. Bogaty P et al. Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease. ***Circulation***, 1993, 87:1938–46.

17. Cianflone D et al. Comparison of coronary angiographic narrowing in stable angina pectoris, unstable angina pectoris, and in acute myocardial infarction. ***American journal of cardiology***, 1995, 76:215–9.

18. Arbustini E et al. Comparison of coronary lesions obtained by directional coronary atherectomy in unstable angina, stable angina, and restenosis after either atherectomy or angioplasty. ***American journal of cardiology***, 1995, 75:675–82.

19. Van der Wal AC et al. Clinically stable angina pectoris is not necessarily associated with histologically stable atherosclerotic plaques. ***Heart***, 1996, 76:312–6.

20. Belomo G et al. Inflammation, infection and cardiovascular events in chronic hemodialysis patients: a prospective study. ***Journal of nephrology***, 2003, 16:245–51.

21. Liuzzo G et al. ***Helicobacter pylori*** and ***Cytomegalovirus*** infections are strongly associated with atherosclerosis but not responsible for instability of angina. ***Journal of the American College of Cardiology***, 1997, 29(Suppl. A):217A.

22. Biasucci LM et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. ***Circulation***, 1999, 99:855–60.

23. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk

assessment in the primary prevention of cardiovascular disease. ***Circulation***, 2001, 103(13):1813–8.

24. Krobot K et al. Determinants of plasma fibrinogen: relation to body weight, waist-to-hip ratio, smoking, alcohol, age, and sex. Results from the second MONICA Augsburg survey 1989–1990. ***Arteriosclerosis and thrombosis***, 1992, 12:780–8.

25. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. ***Diabetes care***, 1999, 22:1971–7.

26. Liu Y et al. Evidence for activation of endothelium and monocytes in hypertensive rats. ***American journal of physiology***, 1996, 270(6Pt. 2):H2125–31.

27. Eriksson M et al. Relationship between plasma fibrinogen and coronary heart disease in women. ***Arteriosclerosis, thrombosis, and vascular biology***, 1999, 19:67–72.

28. Patel P et al. Association of ***Helicobacter pylori*** and ***Chlamydia pneumoniae*** infections with coronary heart disease and cardiovascular risk factors. ***British medical journal***, 1995, 311:711–14.

29. Sarraf-Zadegan N, Amiri M, Maghsoudloo S. ***Helicobacter pylori*** relation to acute myocardial infarction in an Iranian sample. ***Coronary health care***, 2001, 5:202–7.

30. Eryol NK et al. Are the high levels of cytomegalovirus antibodies a determinant in the development of coronary artery disease? ***International heart journal***, 2005, 46:205–9.

31. Prosch S et al. A novel link between stress and human cytomegalovirus (HCMV) hyperactivity infection: sympathetic hyperactivity stimulates HCMV activation. ***Virology***, 2000, 5:357–65.

32. Jantos CA et al. Low prevalence of ***Chlamydia pneumoniae*** in atherectomy specimens from patients with coronary heart disease. ***Clinical infectious diseases***, 1999, 28:988–92.

33. Hoymans VY et al. Immunohistostaining assays for detection of ***Chlamydia pneumonia*** in atherosclerotic arteries indicate cross-reactions with nonchlamydial plaque constituents. ***Journal of clinical microbiology***, 2004, 42:3219–24.

34. Mahara B et al. Is there perceived association between ***Chlamydia pneumoniae*** and vascular disease biased by methodology? ***Journal of clinical microbiology***, 2004, 42:3937–41.

35. Meijer A et al. ***Chlamydia pneumoniae*** antigens, rather than viable bacteria, persist in atherosclerotic lesions. ***Journal of clinical pathology***, 2000, 53:911–6.

36. Gaydos CA et al. Diagnostic utility of PCR-enzyme immunoassay, culture, and serology for detection ***Chlamydia pneumoniae*** in symptomatic and asymptomatic patients. ***Journal of clinical microbiology***, 1994, 32:903–5.

37. Danesh J, Whincup P, Walker M. ***Chlamydia pneumoniae*** IgA titres and coronary heart disease: prospective study and meta-analysis. ***European heart journal***, 2003, 24:881.

38. Romano S et al. ***Chlamydia pneumoniae*** infection in patients with acute coronary syndrome: a clinical and serological 1-year follow-up. ***International journal of immunopathology and pharmacology***, 2004, 17:209–18.

39. Hoymans VY et al. Importance of methodology in determination of ***Chlamydia pneumoniae*** seropositivity in healthy subjects and in patients with coronary atherosclerosis ***Journal of clinical microbiology***, 2003, 41:4049–53.

40. Maraha B et al. Impact of serological methodology on assessment of the link between ***Chlamydia pneumoniae*** and vascular diseases. ***Clinical and diagnostic laboratory immunology***, 2004, 11:789–91.

41. Gupta S et al. Elevated ***Chlamydia pneumoniae*** antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. ***Circulation***, 1997, 96:404–7.

42. Gurfinkel E et al. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. ROXIS Study Group. ***Lancet***, 1997, 350:404–7.

43. Grayston JT et al. Azithromycin for the secondary prevention of coronary events. ***New England journal of medicine***, 2005, 352:1637–45.

44. Cannon CP et al. Antibiotic treatment of ***Chlamydia pneumoniae*** after acute coronary syndrome. ***New England journal of medicine***, 2005, 352:1646–54.

45. Muhlestein JB et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical results of the ACADEMIC study. ***Circulation***, 2000, 102:1755–60.

46. Higgins JP. ***Chlamydia pneumoniae*** and coronary artery disease: the antibiotic trials. ***Mayo Clinic proceedings***, 2003, 78:321–32.

47. Taylor-Robinson D, Boman J. The failure of antibiotics to prevent heart attacks. ***British medical journal***, 2005, 331:361–2.

International Day of Persons with Disabilities, 3 December

"Dignity and justice for all of us" is the theme of this year's International Day for Persons with Disabilities as well as for the 60th anniversary of the Universal Declaration of Human Rights.

2008 is a significant year in the international human rights movement given the entry into force on 3 May of the Convention on the Rights of Persons with Disabilities. However, all over the world, persons with disabilities, around 10% of the world's population, 650 million people, continue to face barriers to their participation in society and are often forced to live on the margins of society. There is a strong link between disability and poverty: 80% of persons with disabilities, more than 400 million people, live in poor countries. The statistics on employment for persons with disabilities are staggering: in developing countries, 80–90% of persons with disabilities of working age are unemployed compared to an estimated to be 50–70% in industrialized countries. The rights to education and health are also routinely denied: according to UNESCO, 90% of children with disabilities in developing countries do not attend school.

All human beings are not only entitled to rights, but also have the responsibility of making universal human rights a reality for all of us.