Arterial Indices and Serum Cystatin C Level in Individuals With Occupational Wide Band Noise Exposure

Ali R. Khoshdel1, Benyamin Mousavi-Asl2, Babak Shekarchi3, Kazem Amini4, Iraj Mirzaii-Dizgah5

1Department of Epidemiology, Faculty of Medicine, AJA University of Medical Sciences, 2Faculty of Medicine, Tehran University of Medical Sciences, 3Department of Radiology, Faculty of Medicine, AJA University of Medical Sciences, 4Department of Aerospace Medicine, School of Aerospace Medicine, AJA University of Medical Sciences, 5Department of Physiology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

Abstract

Background: Chronic exposure to noise is known to cause a wide range of health problems including extracellular matrix (ECM) proliferation and involvement of cardiovascular system. There are a few studies to investigate noise-induced vascular changes using noninvasive methods. In this study we used carotid artery intima-media thickness (CIMT) and aortic augmentation as indices of arterial properties and cystatin C as a serum biomarker relating to ECM metabolism.

Materials and Methods: Ninety-three male participants were included in this study from aeronautic technicians: 39 with and 54 without a history of wide band noise (WBN) exposure. For better discrimination, the participants were divided into the two age groups: <40 and ≥40 years old. Adjusted aortic augmentation index (AI) for a heart rate equal to 75 beats per minute (AIx@HR75) were calculated using pulse wave analysis (PWA). CIMT was measured in 54 participants who accepted to undergo Doppler ultrasonography. Serum cystatin C was also measured.

Results: Among younger individuals the mean CIMT was 0.85 ± 0.09 mm and 0.75 ± 0.22 mm in the exposed and the control groups respectively. Among older individuals CIMT had a mean of 1.04 ± 0.22 mm vs. 1.00 ± 0.25 mm for the exposed vs. the control group. However, in both age groups the difference was not significant at the 0.05 level. A comparison of AIx@HR75 between exposure group and control group both in younger age group (5.46 ± 11.22 vs. 8.56 ± 8.66) and older age group (17.55 ± 10.07 vs. 16.61 ± 5.77) revealed no significant difference. We did not find any significant correlation between CIMT and AIx@HR75 in exposed group (r = 0.314, P value = 0.145) but the correlation was significant in control group (r = 0.455, P value = 0.019).

Serum cystatin C level was significantly lower in individuals with WBN exposure compared to controls (441.10 ± 104.70 ng/L vs. 616.89 ± 136.14, P value < 0.001) both in younger and older groups.

Conclusion: We could not find any evidence for the association of WBN exposure with arterial properties, but cystatin C was significantly lower in the exposed group.

Keywords: Arterial stiffness, carotid intima-media thickness, cystatin C, noise, occupational

INTRODUCTION

Noise as characterized as unpleasant sound, can affect human health. Hearing loss is one of the most known consequences of chronic noise exposure. The audiologic profile is the presence of sensorineural hearing loss around the 4000-Hz region, but it has been shown that noise exposure can affect other physiological and psychological systems.[1] Then, hearing conservation programs are mandatory in most industrial occupations but extra-aural noise-induced problems have been ignored in most cases.[2]

Various factors including exposure duration, amplitude, and frequency are important in health problems caused by noise exposure. Recently it has been found that chronic exposure to large pressure amplitude of low frequency noise (≥90 dB, ≤500 Hz which includes infrasound ≤20 Hz) causes a whole-body pathology with a wide range of presentations including mild psychological problems to malignant tumors.[3] These presentations have been identified in aeronautical technicians, aircraft and helicopter pilots, cabin crewmembers and disc-jockeys.[2-4,7]

In 1980, late-onset epilepsy was diagnosed among 10% of aircraft technicians employed by the Portuguese Air Force,
at an aircraft maintenance, repair, and manufacturing plant, while the expected value was 0.2%.\[^7\] In 1987 first autopsy was performed on one of these patients who died of cardiac tamponade caused by a small infarct. Cardiac valves seemed swollen, and the pericardium surrounding the heart was greatly thickened. Coronary arteries were thickened not by the usual atherosclerotic plaques but continuous thickening of the intima lined all vessel walls.\[^7\]

The underlying mechanism of these presentations of chronic noise exposure is not completely understood but according to microscopic studies, includes abnormal proliferation of extracellular matrix (ECM) in the absence of an inflammatory process\[^8-10\] which could be presented as cardiovascular morphological and dynamic changes such as pericardial thickening, tracheal lung, and kidney changes. In 1999, Marciniak et al.\[^11\] performed an echocardiographic evaluation of 485 aircraft technicians which showed thickening of cardiac structures, mainly the pericardium and heart valves. Although these presentations were grouped together under a common syndrome, vibro-acoustic disease (VAD) by a Portuguese research group, the existence of VAD is still debated.\[^12\]

Noise exposure causes generalized cardiovascular system disease including arteries. There are few studies evaluating vascular changes including arterial wall thickening and stiffness in persons who exposed to low frequency noise. Carotid artery intima-media thickness (CIMT) measured by Doppler ultrasonography is a marker of structural vessel wall properties and is well-known to be a strong predictor of future vascular events and a marker of atherosclerosis.\[^13\] In 1991, Albuquerque et al. found that in severe cases of VAD, echo-Doppler imaging shows thickened carotid arteries.\[^14\]

Augmentation index (AI) of central blood pressure (BP) is used as a surrogate measure of arterial stiffness and is defined as the percentage of the central pulse pressure attributed to enhancement (augmentation) due to the reflected pulse wave.\[^15\] AI could be measured non-invasively by pulse wave analysis (PWA). PWA uses a high-fidelity tonometer to capture electronically the shape of a peripheral arterial pulse.\[^16\] The shape and dimensions of the central aortic pressure wave could be derived from shape of the peripheral pulse wave after calibrating with the brachial systolic and diastolic pressure. In this study, we measured CIMT and augmentation indices to assess vascular properties.

From other perspective, cystatin-C has been investigated in this study. Cystatin C is a cysteine protease inhibitor. Serum cystatin C level is affected in some diseases such as abdominal aortic aneurysm (AAA) which involve arterial wall ECM. Several previous studies demonstrated that serum cystatin C level is decreased in AAA.\[^17\] Here we measured this biomarker to find whether it has been affected in individuals exposed to large pressure amplitude of noise.

### Materials and Methods

#### Study subjects and study design

The participants were selected randomly from male aeronautic technicians who were employed in a helicopter repair and maintenance plant. All of them were asked about their past history of diagnosed diabetes, renal insufficiency, coronary artery diseases, collagen-vascular diseases, and hereditary diseases of connective tissue (such as Ehlers–Danlos syndrome and Marfan syndrome) for exclusion purposes. The participants were divided into two age groups: the younger age group was defined as individuals <40 years old and the older, ≥40 years old. Thirty-nine aeronautic technicians, who were exposed to wide band noise (WBN), were included in this study, 14 were below 40 years old and 25 were more than 40 years old. The control group was selected randomly from technicians who had the same work environment but without exposure to large pressure amplitude of WBN (≥90 dB). Our control group consists of 27 individuals who were below 40 years and 27 individuals who were more than 40 years old. PWA, blood sampling, and physical examinations were conducted in one session. Of 93 participants, eight were excluded from PWA measurements because of using antihypertensive drugs which is known to affect arterial stiffness parameters.\[^18\] The participants were scheduled to undergo Doppler ultrasonography for CIMT measurement, but 54 of them took part in this measurement (25 in the exposure group and 29 in the control group).

General data were collected through questionnaires. We assessed noise exposure in the working environment. Overall noise level of around 102 dB(L) was recorded in the working environment of the exposure group while individuals of control group were exposed to overall noise levels of between 60 and 70 dB(L). Spectral analysis of environmental noise in the exposure group is shown in Figure 1.

#### Anthropometric measurement

Body mass index (BMI) was calculated from the measured height and weight and according to the standard formula:

\[
\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}
\]

![Figure 1: Spectral analysis of noise in the working environment of the exposure group. Noise levels were around 90 dB or higher in the frequency bands ranging from 32 Hz to 4000 Hz.](image-url)
weight in kilograms divided by the square of the height in meters. The heights of subjects were measured using a stadiometer in standing position and were recorded to the nearest 5 mm. The weights of subjects wearing light clothes but no shoes were measured.

**Arterial stiffness**

Pulse wave analysis was evaluated using the radial artery pressure waveform. We used a validated tonometer (Millar SPC-301B, Huston, USA) to obtain the peripheral (radial) artery waveform and then was processed with dedicated software (SphygmoCor, version 7.1, AtCor Medical, Sydney, Australia) which converts the peripheral waveform to a central waveform using a proprietary algorithm. Augmentation indices were measured. Adjusted AI for a heart rate equal to 75 beats per minute (AIx@HR75) was estimated based on an internal normogram in the software.\(^1\)

**Doppler ultrasonography**

All measurements were performed by a single expert sonographer who was blind to the study groups, using Doppler sonography machine – VolusonE8. High resolution B-mode gray scale and color Doppler ultrasound with a 12 MHz transducer was used for the determination of intima-media thickness (IMT). The study was performed while keeping the patients in supine position. Longitudinal B-mode color Doppler images were obtained of the walls of the carotid artery. The IMT of common and internal carotid artery was assessed. The internal carotid artery was assessed in the 10 mm distal to the tip of the flow divider. All ultrasound scans were obtained with single ultrasound exam Voluson E-8 system by General Electric. The image boundaries were marked manually. For CIMT measurements, trailing edges were traced on the near wall boundaries and leading edges on the far wall boundaries. Measurements were calculated with different angle and mean measurements calculated.

**Cystatin C and other laboratory measurements**

A 10 mL venous blood sample was taken from each patient after 10h fasting. The blood samples were allowed to form clot in clot activator vacuum tube with gel separator for about 4 h at room temperature. Then they were centrifuged at 1000 \( \times \) g for 15 min. The serum was separated and stored in micro-tube at \(-70^\circ C\).

Serum cystatin C was measured using Abcam’s Human Cystatin C in vitro Enzyme-Linked Immunosorbent Assay (ELISA) kit with detection range of 312–20,000 pg/mL, which is designed for the accurate quantitative measurement of human cystatin C. The working dilution was 1:100. Triglyceride, total cholesterol, fasting blood glucose, and creatinine were measured using Pars azmoon biochemical kits.

**Statistical analysis**

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20. Data were presented as mean ± SD. The normal distribution of variables was checked by Kolmogorov–Smirnov test. Mean values in exposure group and control group were compared using independent \( T \) test. The relationship between CIMT and aortic augmentation indices were assessed calculating bivariate correlations. For all data analysis, \( P \)-value less than 0.05 were considered significant.

**Results**

General characteristics of the study subgroups are summarized in Table 1.

**Carotid artery intima-media thickness**

In the younger age group, CIMT had a mean value of 0.85 mm (SD, 0.09) among individuals of the exposure group vs. 0.75 mm (SD, 0.22) in the control group, but the difference was not statistically significant (\( P \) value = 0.30). In the older age group mean value of CIMT was 1.04 mm (SD, 0.22) among members of the exposure group vs. 1.00 mm (SD, 0.25) among the control group and there was no significant difference (\( P \) value = 0.61) comparing these groups.

**Arterial stiffness**

The indices of arterial stiffness were universally greater in the older group compared to the younger group, both in the exposed and the control group. However, among individuals below 40 years old, the mean value of A11 (AP/PP) was lower in the exposure group in comparison with the control group (1.53 ± 9 vs. 7.59 ± 8.62) and the difference was significant (\( P \) value = 0.047). The same results were found comparing A12 (P1/P2), mean value was significantly (\( P \) value = 0.037) higher in the control group (10.07 ± 9.90 vs. 10.18 ± 9.56 in the exposure group). In the older age group, difference between mean values of A11 in the exposure group (16.27 ± 9.11) and the control group (14.50 ± 8.68) was not significant (\( P \) value = 0.51). The difference was not significant (\( P \) value = 0.50) comparing mean values of A12 in the exposure group (120.81 ± 12.73) and the control group (118.22 ± 12.61). In the younger age group AIx@HR75 mean value was 5.46 ± 11.22 in the exposure group and 8.56 ± 8.66 in the control group, the difference was not significant (\( P \) value = 0.343). Among older individuals, difference between mean value of AIx@HR75 in the exposure group (17.55 ± 10.07) and the control group (16.61 ± 5.77) was not significant (\( P \) value = 0.706).

**Correlation between intima-media thickness and arterial stiffness**

There was no significant correlation between CIMT and neither of A11 (\( r = 0.266, \ P \) value = 0.220) nor A12 (\( r = 0.252, \ P \) value = 0.245) in exposure group. In control group mean CIMT shows moderate correlation with both A11 (\( r = 0.431, \ P \) value = 0.032) and A1 (\( r = 0.454, \ P \) value = 0.023). Correlation between CIMT and AIx@HR75 was not
significant in the exposure group ($r = 0.314$, $P$ value = 0.145) but it was significant in the control group ($r = 0.455$, $P$ value = 0.019).

**Cystatin C**

Serum cystatin C level was significantly lower in the exposure group in comparison with the control group (441.10 ± 104.70 ng/L vs. 616.89 ± 136.14 ng/L, $P$ value < 0.001). The same results were found when comparison was made in two age groups separately. In the younger age groups, serum cystatin C mean value was 463.81 ng/L (SD, 84.72) in the exposure group vs. 638.89 (SD, 155.70) in the control group and the difference was significant ($P$ value = 0.001). In older age group, serum cystatin C had a mean value of 428.71 ng/L (SD, 114.06) among members of the exposure group vs. 594.90 ng/L (SD, 112.51) in the control group and the difference was statistically significant ($P$ value < 0.001). Results are shown in Figure 2.

**DISCUSSION**

There are a few studies to evaluate usability of Doppler ultrasonography as a diagnostic tool for noise-induced cardiovascular diseases. Doppler ultrasonographic findings have been described in severe cases. In this study although

![Figure 2: Serum cystatin C level was significantly lower in the exposure group both in individuals below 40 years old and more than 40 years old. Error bars show 95% CI for mean values](image)

**Table 1: Characteristics of study subgroups**

|                      | Exposure group | Control group | $P$ value |
|----------------------|----------------|---------------|-----------|
| Below 40 years old   |                |               |           |
| Age                  | 33 ± 2         | 33 ± 2        | 0.40      |
| BMI (kg/m²)          | 28 ± 4         | 26 ± 3        | 0.05*     |
| Waist circumference  | 99.2 ± 12.3    | 99.9 ± 8.0    | 0.86      |
| Systolic blood       | 107 ± 12       | 119 ± 11      | <0.01*    |
| Diastolic blood       | 72 ± 12        | 76 ± 7        | 0.26      |
| pressure (mmHg)      |                |               |           |
| Fasting blood         | 85 ± 8         | 87 ± 11       | 0.62      |
| glucose              |                |               |           |
| Triglyceride          | 105 ± 47       | 161 ± 175     | 0.25      |
| Total cholesterol     | 176 ± 41       | 171 ± 38      | 0.68      |
| Creatinine            | 0.86 ± 0.17    | 0.81 ± 1.7    | 0.29      |
| More than 40 years old|                |               |           |
| Age                  | 50 ± 4         | 51 ± 4        | 0.59      |
| BMI (kg/m²)          | 26 ± 4         | 27 ± 3        | 0.60      |
| Waist circumference  | 100.5 ± 9.9    | 101.8 ± 5.9   | 0.55      |
| Systolic blood        | 116 ± 13       | 121 ± 15      | 0.15      |
| Diastolic blood       | 75 ± 10        | 80 ± 8        | 0.04*     |
| pressure (mmHg)      |                |               |           |
| Fasting blood         | 89 ± 20        | 88 ± 7        | 0.92      |
| glucose              |                |               |           |
| Triglyceride          | 180 ± 136      | 126 ± 49      | 0.12      |
| Total cholesterol     | 193 ± 39       | 180 ± 23      | 0.21      |
| Creatinine            | 0.97 ± 0.20    | 0.85 ± 0.21   | 0.06      |

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FBS = fasting blood glucose. Data are given as mean ± SD, *$P$ < 0.05.

According to our review of literature, there is no study yet to investigate arterial stiffness in individuals exposed to noise. According to our findings, aortic augmentation indices not adjusted for heart rate (AP/PP, P1/P2) were higher in control group in comparison with exposure group among individuals below 40 years old, but there was no significant difference between the exposure group and the control group among individuals older than 40 years old. After adjustment for heart rate, there was no significant difference in both age groups. To better understand the pattern of vascular changes among individuals exposed to WBN, we studied the relation between CIMT and arterial stiffness.

There are several previous studies which have found significant correlation between IMT and aortic AI.[20-22] Our study confirmed their findings in the control group which have not been exposed to WBN. We have found significant positive correlations between CIMT and aortic augmentation indices (AP/PP, P1/P2, and AIx@HR75) in this group. However, there was no significant correlation between
CIMT and aortic augmentation indices in exposure group which suggests another pattern of vascular changes in individuals exposed to WBN.

Cystatin C is known as one of the most abundant and potent extracellular inhibitors of cysteine proteases which prevents breakdown of proteins outside the cell by a specific type of protein degrading enzymes. Some studies have found that increased levels of cystatin C are associated with cardiovascular disease prevalence in individuals without renal impairment. Some other studies have demonstrated that cystatin C predicts mortality risk in subjects with established heart failure. On the other hand, there are several studies that have investigated cystatin C in pathogenesis of atherosclerosis or some other diseases which involve ECM remodeling in vascular system (such as AAA). Decreased levels of cystatin C are found in atherosclerotic and aneurysmal aortic lesions. Some other studies demonstrated that serum cystatin C level is negatively correlated with AAA size and progression. As mentioned before, ECM remodeling is one of the most known pathophysiological mechanisms of chronic noise exposure cardiovascular effects, so we were curious to find out whether serum cystatin C level is affected in individuals exposed to WBN. According to our findings, serum cystatin C is significantly decreased in individuals exposed to WBN both in younger and older age groups. Further studies are needed to investigate the mechanism of noise-induced ECM proliferation and proteins involved.

Cystatin C is known as a sensitive marker of renal function which can identify a preclinical stage of kidney disease and previous studies have shown that in comparison with creatinine, cystatin C is less influenced by age, gender, race, muscle mass, drug administration, physical activity, and diet. Our findings in this study suggest that WBN exposure might be a factor which influences serum cystatin C level.

**Conclusion**

Although we did not find any significant difference between WBN-exposed individuals and members of control groups in terms of CIMT and AIx@HR75, we found that, in contrast with our control group and normal population, there is no correlation between CIMT and AIx@HR75 in exposure group. In other words, no increase in CIMT was accompanied with any increase in arterial stiffness, which suggests another mechanism for WBN induced arterial thickening. We found that serum cystatin C level, a serum marker which is known to be influenced by ECM metabolism, is significantly decreased in WBN-exposed individuals. Further studies are needed to reveal the mechanism in which cystatin C is affected. The mechanism could be used as a target to treat or prevent health problems caused by chronic noise exposure.

**Acknowledgements**

We would like to thank AJA University of Medical Sciences for funding this study. The authors are also grateful to the Dr. Mohammad Athari MRI Center for providing facilities for sonographic measurements.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Basner M, Babish W, Davis A, Brink M, Clark C, Janssen S, *et al.* Auditory and non-auditory effects of noise on health. Lancet 2014;383:1325-32.
2. Alves-Pereira M, Castelo Branco N. Vibroacoustic Disease: The Need for a New Attitude Towards Noise. Lisbon: CITIDEP & DCEA-FCT-UNL, 2000.
3. Castelo Branco NA. The clinical stages of vibroacoustic disease. Aviat Space Environ Med 1999;70:A32-9.
4. Branco NC, Monteiro E, Alves-Pereira M, Águas AP, Pereira AS, Grande NR. Morphological changes in the pericardia of military helicopter pilots. Proc. Microscopy Barcelona, 2001. p. 318-9.
5. Araújo A, Pais F, Tuna JL, Alves-Pereira M, Branco NC. Echocardiography in noise-exposed flight crew. Proceedings of the International Congress and Exhibition on Noise Control Engineering, 2001.
6. Mendes A, Graça A, Jorge A, Alves-Pereira M, Castelo Branco NA, Freitas A, *et al.* The effects of ILFN-exposure on voice acoustic parameters of commercial cabin crewmembers. J Laryngol Voice 2012;2:70-80.
7. Branco NA, Alves-Pereira M. Vibroacoustic disease. Noise Health 2004;6:3-20.
8. Castelo Branco NA, Águas AP, Sousa Pereira AS, Monteiro E, Fragata JL, Tavares F, *et al.* The human pericardium in vibroacoustic disease. Aviat Space Environ Med 1999;70:A54-62.
9. Castelo Branco NA, Rodrigues E, Alves-Pereira M, Jones DR. Vibroacoustic disease: Some forensic aspects. Aviat Space Environ Med 1999;70:A145-51.
10. Alves-Pereira M. Noise-induced extra-aural pathology: A review and commentary. Aviat Space Environ Med 1999;70:A7-21.
11. Marciniak W, Rodrigues E, Olszowska K, Atkov O, Botvin I, Araujo A, *et al.* Echocardiographic evaluation in 485 aeronautical workers exposed to different noise environments. Aviat Space Environ Med 1999;70:A46-53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10189156. [Last accessed on 2015 Sep 17].
12. Jensen A, Lund SP, Lücke TH, Clausen OV, Svensden JN. Non-auditory health effects among air force crew chiefs exposed to high level sound. Noise Health 2009;11:176-81.
13. Balta S, Aparici M, Ortutx C, Unlu M, Celik T, Carotid intima media thickness can predict coronary artery disease. Int J Cardiol 2015;201:331
14. Albuquerque e Sousa J, Dinis da Gama A, Macedo MV, Cáciu I, Pimenta FM, Carotid angiodynographic studies in individuals with the whole-body noise and vibration disease. Rev Port Med Mil 1991;39:63-5.
15. Hayashi S, Yamada H, Bando M, Hotchi J, Ise T, Yamaguchi K, *et al.* Augmentation index does not reflect risk of coronary artery disease in elderly patients. Circ J 2014;78:1176-82.
16. Crilly M, Coch C, Bruce M, Clark H, Williams D. Repeatability of central aortic blood pressures measured non-invasively using radial artery application tonometry and peripheral pulse wave analysis. Blood Press 2007;16:262-9.
17. Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence? J Cardiol 2013;62:331-5.
18. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ. Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension 2001;37:1429-33.

19. Khoshdel AR, Carney SL, Trevillian P, Gillies A. Evaluation of arterial stiffness and pulse wave reflection for cardiovascular risk assessment in diabetic and nondiabetic kidney transplant recipients. Iran J Kidney Dis 2010;4:237-43.

20. Qureshi G, Brown R, Salciccioli L, Qureshi M, Rizvi S, Farhan S, et al. Relationship between aortic atherosclerosis and non-invasive measures of arterial stiffness. Atherosclerosis 2007;195:e190-4.

21. Gómez-Marcos MA, Recio-Rodríguez JJ, Patino-Alonso MC, Agudo-Conde C, Gómez-Sánchez L, Rodríguez-Sánchez E, et al. Relationship between intima-media thickness of the common carotid artery and arterial stiffness in subjects with and without type 2 diabetes: A case-series report. Cardiovasc Diabetol 2011;10:3.

22. Westerbacka J, Leinonen E, Salonen JT, Salonen R, Hiakka A, Yki-Järvinen H, et al. Increased augmentation of central blood pressure is associated with increases in carotid intima-media thickness in type 2 diabetic patients. Diabetologia 2005;48:1654-62.

23. Cepeda J, Tranche-Iparraguirre S, Marín-Iranzo R, Fernández-Rodríguez E, Riesgo-García A, García-Casas J, et al. Cystatin C and cardiovascular risk in the general population. Rev Esp Cardiol 2010;63:415-22.

24. Koc M, Batur MK, Karaarslan O, Ahali G. Clinical utility of serum cystatin C in predicting coronary artery disease. Cardiol J 2010;17:374-80.

25. Shi GP, Sukhova GK, Grubb A, Ducharme A, Rhode LH, Lee RT, et al. Cystatin C deficiency in human atherosclerosis and aortic aneurysms. J Clin Invest 1999;104:1191-7.

26. Schulte S, Sun J, Libby P, Macfarlane L, Sun C, Lopez-Illasaca M, et al. Cystatin C deficiency promotes inflammation in angiotensin II-induced abdominal aortic aneurisms in atherosclerotic mice. Am J Pathol 2010;177:456-63.

27. Sukhova GK, Wang B, Libby P, Pan JH, Zhang Y, Grubb A, et al. Cystatin C deficiency increases elastic lamina degradation and aortic dilatation in apolipoprotein E-null mice. Circ Res 2005;96:368-75.

28. Lindholt JS, Erlandsen EJ, Henneberg EW. Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms. Br J Surg 2001;88:1472-5.

29. Eriksson P, Jones KG, Brown LC, Greenhalgh RM, Hamsten A, Powell JT. Genetic approach to the role of cysteine proteases in the expansion of abdominal aortic aneurysms. Br J Surg 2004;91:86-9.

30. Hellenthal FA, Buurman WA, Wodzig WK, Schurink GW. Biomarkers of AAA progression. Part I: Extracellular matrix degeneration. Nat Rev Cardiol 2009;6:464-74.