A Case Study of Supernormal Vascular Aging in Leningrad Siege Survivors

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Phenotyping information

Anthropometry was performed on both visits: measurement of height and body weight with the calculation of body mass index (BMI) according to the Quetelet formula, measurement of waist circumference. Blood pressure (BP) and pulse rate were measured using the OMRON device (Japan) on the right hand after 5 minutes of rest in a sitting position three times with the calculation of the average value of the last two measurements. After obtaining the mean values of systolic and diastolic blood pressure (SBP and DBP), pulse pressure (PP) was calculated as the difference between SBP and DBP.

A fasting blood sample was taken with the determination of the lipid profile (total cholesterol, high density lipoproteins, low density lipoproteins, triglycerides), glucose level. At the second visit the creatinine level was additionally determined with the calculation of the glomerular filtration rate (GFR) according to the CKD-EPI formula. The morning urine sample was collected to determine the concentration of albumin and creatinine, followed by the calculation of the albumin-creatinine ratio. The analysis of blood and urine parameters was performed on an Abbot Architect c8000 biochemical analyzer (USA).

At both visits electrocardiogram (ECG) was registered using PADSY computerized complex ("Medset Medizintechnik GmbH", Germany), interpretation was carried out according to a standard protocol. At the first visit the following was performed:

- carotid ultrasonography: assessment of the morphology of the carotid arteries, detection of signs of atherosclerotic damage and calculation of TIM (thickness of intima-media). We used a Vivid 7 (Samsung, Korea (General Electric, USA), 7 MHz high-resolution transducer.

- echocardiography. The study was carried out on a Vivid 7 (GE, USA), a 3.25 MHz transducer in M-modal, two-dimensional and Doppler modes in standard echocardiographic positions along the short and long axes. At the second visit, the cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) were determined on the right and left using the VaSera VS-1500 device (FukudaDenshi, Japan).

At both visits, the carotid-femoral pulse wave velocity (PWV) was assessed using a SphygmoCor device (AtCor, Australia) by applanation tonometry. Reference PWV values by age group were taken from the paper "The Reference Values for Arterial Stiffness Collaboration", based on data from a large European study. For people over 60 years of age, the following PWV indicators (median, 10th and 90th percentiles): 60-69 years - 9.7 (7.9-13.1) and -70 years - 10.6 (8.0-14.6). Based on these values, we conditionally isolated the phenotype (or phenomenon) of supernormal vascular aging (SUPERNOVA) - the PWV value less than the 10th percentile for this age group.

Cognitive functioning was assessed by the Mini Mental State Examination (MMSE) – a brief (11 tasks) quantitative screening measure of cognitive status in adults. The cut-off point for cognitive impairment was 26 points and lower.

Anxiety and depression were assessed using a Russian validated version of the Hospital Anxiety and Depression Scale (HADS). Cut-offs for increased level of anxiety and depression were 8 points and higher.
Two general instruments for assessing health-related quality of life were used: EQ-5D (3-level version) and 36-Item Short Form Survey (SF-36).

The sense of meaningfulness and purpose in life was assessed by the Purpose in Life Orientation Test (PLO). The short version (K-22) of the Social Support Questionnaire F-SozU (Fragebogen zur Sozialen Unterstützung) was used to assess perceived functional social support.

At the second visit, the patients completed the EFPQ (European Food Propensity Questionnaire), which includes 116 questions regarding the consumption of various food and beverage groups.
Patients clinical presentation

Table S1
Lifestyle factors

| Parameter                              | Patient No. 1                                      | Patient No. 2                                      |
|----------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Breastfeeding after birth              | Delivered                                         | Delivered                                         |
| Living conditions during the blockade  | Room in a communal (shared) apartment              | Room in a communal (shared) apartment              |
| Number of people in a communal apartment | 3                                                 | 5                                                 |
| Diseases during the blockade           | Acute respiratory diseases                         | Childhood infections Cachexia                     |
| Gynecological anamnesis                | Pregnancy – 1. Childbirth - 1                      | Pregnancy – 3. Childbirth – 1, Abortion - 2       |
| Menopause start                        | 47 years                                          | 55 years                                          |
| Education                              | Higher education                                  | Secondary education                               |
| Family status                          | Widow                                             | Widow                                             |
| Heredity: mother                       | Death at 89 years old, was overweight and hypertensive | Death at 79 years old, was overweight.             |
| Heredity: father                       | Death at 40 years old (during the war), diseases are unknown | Death at 94, diseases are unknown                  |
| What part of income is spent on food?  | 1/3                                               | 1/3                                               |
| Alcohol consumption                    | Once a month, 3 doses (spirits)                    | Several times a week ½ dose (wine)                |
| Smoking                                | Never smoked                                      | Never smoked                                      |
| Physical activity                      | Daily walk 60 min.                                | Daily walk 60 min.                                |
|                                        | Rare moderate physical activity for 20-30 minutes | Rare moderate physical activity for 20-30 minutes |
| Sleep duration, hours                  | 7                                                 | 8                                                 |
| Sitting time, hours                    | 5                                                 | 10                                                |
| Snoring                                | Snoring - unknown.                                | Snoring - yes.                                    |
|                                        | Sleep apnea - no                                   | Sleep apnea – unknown                             |
| Pet                                    | No                                                | Has a cat                                         |
### Table S2

**Results of laboratory and instrumental investigation**

| Parameter                                              | Target value | Patient No. 1 | Patient No. 2 |
|--------------------------------------------------------|---------------|---------------|---------------|
|                                                        |               | Visit 1 | Visit 2 | Visit 1 | Visit 2 |
| Date of examination                                    |               | 14.04.2010 | 20.12.2013 | 13.04.2010 | 12.12.2013 |
| Age, years                                             | -             | 69      | 73  | 68   | 71  |
| Height, cm                                             | -             | 158     | 153 | 154  | 148 |
| Weight, kg                                             | -             | 67,0    | 66,4 | 58   | 62  |
| BMI, kg/m²                                             | < 25          | 26,9    | 28,2 | 24,4 | 28,3 |
| Waist circumference, cm                                | < 80 (f)      | 90      | 89  | 75   | 83  |
| SBP sitting mean, mm Hg                                | < 140         | 122     | 110 | 133  | 148 |
| DBP sitting mean, mm Hg                                | < 80          | 80      | 68  | 76   | 81  |
| SBP standing mean, mm Hg                               | -             | -      | 115 | -    | 144 |
| DBP standing mean, mm Hg                               | -             | -      | 78  | -    | 90  |
| PP sitting mean, mm Hg                                 | < 60          | 42      | 42  | 57   | 67  |
| Pulse, beats / min                                     | ≤ 80          | 64      | 64  | 60   | 65  |
| Hypertension diagnosis                                  | No            | No      | No  | No   | Yes |
| Antihypertensive therapy                               | No            | No      | No  | No   | No  |
| Glucose, mmol / l                                      | < 5,6         | 5,3     | 4,9 | 4,9  | 5,0 |
| TC, mmol / l                                           | ≤ 4,9         | 5,4     | 5,4 | 4,8  | 4,2 |
| HDL, mmol / l                                          | ≥ 1,2         | 1,3     | 1,1 | 1,6  | 1,4 |
| LDL, mmol / l                                          | < 2,6         | -       | 3,8 | -    | 2,5 |
| TG, mmol / l                                           | < 1,7         | 1,1     | 0,9 | 0,58 | 0,6 |
| Lipid-lowering therapy                                 | No            | No      | No  | No   | No  |
| GFR ml/min/1.73 m²                                      | ≥ 60          | -       | 78,3 | -    | 88,9 |
| ACR in a single portion of urine, mg / mmol            | < 3,4         | -       | 0,5 | -    | 1,4 |
| Duplex ultrasound of the carotid arteries               | IMT <0.9 mm   | IMT 1.1 mm bilaterally | - | IMT 1.1 mm bilaterally | - |
| LVMI, g/m²                                             | ≤ 95 (f)      | 130     | -   | 83   | -   |
| LVDd/LVSd, mm (f)                                      | ≤ 52,2/34,8   | 44/27   | -   | 44/28 | -   |
| Zone of left ventricle myocardial contractility disorder| No            | No      | -   | No   | -   |
| EF, according to Simpson, %                            | > 55          | 71      | -   | 72   | -   |
| LV diastolic dysfunction | No | No | - | No | - |
|-------------------------|----|----|---|----|---|
| ECG                     |    |    |   |    |   |
| Sinus rhythm, HR 65 bpm |    |    |   |    |   |
| Sinus rhythm, HR 57 bpm |    |    |   |    |   |
| Sinus rhythm, HR 61 bpm |    |    |   |    |   |
| Sinus rhythm, HR 81 bpm |    |    |   |    |   |
| PWV, m / s               | ≤ 10 | 6,1 | 7,6 | no data | 5,7 |
| CAVI right               | < 9,0 | - | 7,7 | - | 8,4 |
| CAVI left                | < 9,0 | - | 8,1 | - | 8,3 |
| Estimated age of arteries (according to CAVI) | 65-69 years | 65-69 years |
| ABI right                | > 0,9 | - | 1,15 | - | 1,05 |
| ABI left                 | > 0,9 | - | 1,03 | - | 1,09 |
| MMSE, points             | 29-30 | 28 | 29 | 25 | 26 |

BMI - body mass index, f – female, SBP - systolic blood pressure, DBP - diastolic blood pressure, PP - pulse pressure, TC - total cholesterol, LDL - low density lipoproteins, HDL - high density lipoproteins, TG - triglycerides, GFR - glomerular filtration rate, ACR - albumin / creatinine ratio, IMC - Intima-media complex, LVMI - left ventricular myocardial mass index, LVDd/ LVSd - left ventricular end-diastolic dimension / left ventricular end-systolic dimension, EF - ejection fraction, ECG – electrocardiogram, HR – heart rate, PWV - pulse wave velocity, CAVI - cardio-ankle vascular index, ABI - ankle-brachial index, MMSE - Mini-Mental State Examination
### Table S3

**Results of psychological assessment**

| Instrument | Subscales           | Patient 1 | Patient 2 |
|------------|---------------------|-----------|-----------|
| **HADS**   | Anxiety             | 11        | 11        |
|            | Depression          | 2         | 7         |
| **EQ-5D**  |                     | 11122     | 21112     |
| **SF-36**  | Physical Activity   | 60        | 40        |
|            | Role Physical       | 25        | 50        |
|            | Bodily Pain         | 51        | 62        |
|            | General Health      | 62        | 50        |
|            | Vitality            | 55        | 55        |
|            | Social Functioning  | 75        | 50        |
|            | Mental Health       | 0         | 100       |
|            | Role Emotional      | 52        | 76        |
| **PLO**    | life goals,         | 31        | 28        |
|            | life process,       | 26        | 36        |
|            | life efficiency     | 27        | 22        |
|            | locus of control – Self | 21    | 17        |
|            | locus of control – Life | 25     | 36        |
|            | total score         | 97        | 104       |
| **F-SozU 22** | emotional support, | 40        | 45        |
|            | instrumental support, | 18    | 20        |
|            | social integration  | 30        | 29        |
|            | satisfaction with social support | 2  | 6        |
|            | total score of social support | 90 | 100     |

HADS – Hospital Anxiety and Depression Scale, SF-36 - The 36-Item Short Form Survey, PLO - Purpose in Life Orientation Test.
Figure S1.
Polygenic risk score distribution for (A) diastolic blood pressure (DBP), (B) systolic blood pressure (SBP), (C) light-density protein (LDL), (D) total cholesterol (TC) level, (E) triglycerides (TG) level, (F) waist circumference, (G) hip circumference, (H) body mass index (BMI), (I) weight, (J) glucose level.
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