

CARDIOVASCULAR DIAGNOSTICS: DIGITAL VARIANCE ANGIOGRAPHY IN CHILDREN AND BLOOD PRESSURE VARIABILITY IN YOUNG ADULTS DIAGNOSED WITH CHILDHOOD DEPRESSION

Ph.D. thesis (short version)

Balázs Bence Nyárády, M.D.

Semmelweis University Doctoral School
Cardiovascular Medicine and Research Division



Supervisor:

Edit Dósa, M.D., Ph.D.

Official Reviewers:

Ádám Farkas Zoltán, M.D., Ph.D.

Csaba Balázs Nagy, M.D., Ph.D.

Head of the Complex Examination Committee:

György Wéber, M.D., D.Sc.

Members of the Complex Examination Committee:

Pál Ákos Deák, M.D., Ph.D.

Rudolf Ménesi, M.D., Ph.D.

Budapest
2025

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for approximately 17.9 million deaths each year. Early detection and diagnosis of cardiovascular (CV) conditions are vital for effective intervention and management, especially among vulnerable populations – such as children and young adults – given the potentially lifelong implications. In recent years, technological advancements and a growing understanding of pathophysiological mechanisms have enabled researchers and clinicians to assess CV health with greater precision and sensitivity. This thesis focuses on two distinct but interconnected domains within CV diagnostics. The first part evaluates the clinical utility of digital variance angiography (DVA), an emerging imaging modality, in children undergoing diagnostic and/or therapeutic imaging for arteriovenous malformations (AVMs). The second part examines whether short-term blood pressure variability (BPV) – a sensitive marker of autonomic nervous system function – is altered in young adults with a history of childhood depression, offering potential insights into early predictors of CV risk.

2. Objectives

2.1. Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study

Our aim was to retrospectively compare the imaging parameters of DVA with those of conventional digital subtraction angiography (DSA) in children diagnosed with

extracranial AVMs who underwent endovascular treatment.

2.2. Short-term blood pressure variability among young adults at high or low risk for depression

Our aim was to assess whether young adults with a history of childhood-onset major depressive disorder exhibit greater short-term BPV compared with never-depressed high-risk siblings and emotionally healthy controls; to evaluate whether clinical features of depression predict elevated BPV; and to determine whether familial risk is associated with blood pressure (BP) dysregulation.

3. Methods

3.1. Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study

This retrospective, observational, single-center study included ten patients under 18 years of age who were diagnosed with extracranial AVMs and underwent a total of 15 endovascular procedures at the Heart and Vascular Center, Semmelweis University, between December 2022 and December 2024. All examinations were conducted in accordance with ethical standards. Patient data were processed and analyzed only after complete anonymization.

For each intervention, the volume and administration rate of the contrast agent were tailored to patient-specific characteristics and lesion parameters. Raw angiographic images were acquired using a Siemens Artis Zee angiography system (Siemens Healthineers AG,

Forchheim, Germany). The same raw angiographic series was used to generate both DSA and DVA images. DSA images were produced on the Syngo workstation (Siemens Healthineers AG), whereas DVA images were created with the Kinect Medical Imaging Tool v5.3 (Kinect Health Ltd., Budapest, Hungary). Both image types underwent identical post-processing steps (pixel shift and brightness/contrast adjustments).

For the calculation of the contrast-to-noise ratio (CNR), regions of interest (ROIs) were manually placed in pairs for each AVM, with one ROI positioned over a vascular structure and the corresponding ROI placed on an adjacent extravascular background area. At least 25 ROI pairs were identified per image. The CNR was calculated using the following formula: $CNR = (Mean_v - Mean_b) / SD_b$, where $Mean_v$ refers to the mean pixel intensity within the vascular ROI, $Mean_b$ denotes the mean pixel intensity within the background ROI, and SD_b represents the standard deviation of the background ROI pixel intensities. CNR values were calculated for both DSA and DVA images, and the CNR_{DVA}/CNR_{DSA} ratio was determined for each pair. ROI placement and measurement were performed using Fiji software (version 2.0.0-rc-68/1.52e; National Institutes of Health, Bethesda, MD, USA).

To subjectively compare the quality of DSA–DVA image pairs, we developed a web-based, randomized evaluation questionnaire that enabled anonymized, side-by-side comparisons blinded to image type. Four interventional radiologists and one vascular surgeon participated in the assessment. Using a four-point Likert scale, the experts evaluated the visibility and diagnostic

value of large vessels, small vessels, and – when applicable – tissue blush and the venous phase. The image pairs covered four anatomical regions: upper extremity, lower extremity, head and neck, and chest. The scoring system was defined as follows: 0 = no difference in image quality; 1 = one image is slightly better; 2 = one image is clearly better; 3 = one image is superior in all respects.

For statistical analysis, we used Stata 15.0 (StataCorp LLC, College Station, TX, USA) and GraphPad Prism 8.4.2 (GraphPad Software Inc., La Jolla, CA, USA).

3.2. Short-term blood pressure variability among young adults at high or low risk for depression

Participants in this cross-sectional study were recruited from a previously established cohort assembled in Hungary between 2000 and 2006. All individuals in the original cohort who were 18 years or older and had consented to be recontacted for future research were invited to participate. Eligible participants comprised three groups: (1) individuals with a documented history of childhood-onset major depressive disorder ('probands'; $n = 218$); (2) their full biological siblings with no lifetime history of depressive disorders ('high-risk siblings'; $n = 206$); and (3) school-based controls who remained free of major psychiatric diagnoses during follow-up assessments ('controls'; $n = 166$). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with ethical standards.

Psychiatric diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, based on structured clinical evaluations. Trained mental health professionals

conducted direct interviews using the Interview Schedule for Young Adults – Follow-up Diagnostic Version (ISYA-D) to determine the onset and duration of psychiatric episodes. Participants also completed the Beck Depression Inventory-II (BDI-II) to assess the severity of current depressive symptoms over the preceding two weeks.

BP measurements were conducted according to a standardized protocol. Participants were instructed to abstain from caffeine, alcohol, and tobacco for at least one hour prior to assessment. After a brief initial rest period, three consecutive brachial BP measurements were obtained at five-minute intervals using a validated digital oscillometric device (Omron M6; Omron Corporation, Kyoto, Japan).

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study

Patient characteristics

The study included ten patients with a mean age of 12 years (range: 7–17 years), comprising six females and four males. None of the participants had known comorbidities, and none were on regular medication. Each patient had a single AVM, yielding a total of ten AVMs assessed. Based on anatomical location, the AVMs were classified into four groups: two in the upper extremities, four in the lower extremities, two in the head and neck region, and two on the chest wall. Collectively, these patients underwent 15

endovascular procedures (three diagnostic and twelve therapeutic).

Objective comparison: contrast-to-noise ratio

A total of 132 paired DSA–DVA images were analyzed, yielding 3,318 ROI pairs. The distribution of ROI pairs by anatomical region was as follows: 501 in the upper extremities, 1,659 in the lower extremities, 472 in the head and neck region, and 686 in the chest region.

The CNR values of images generated using DVA were significantly higher than those obtained with conventional DSA across all comparisons (all $p < 0.001$), as shown in Table I. The highest median CNR ratio (DVA/DSA) was observed in AVMs located in the upper extremities, with a median of 2.23 (IQR, 1.18–4.19).

Table I. Contrast-to-noise ratio by arteriovenous malformation location

AVM location	<i>p</i>-value	CNR_{DVA}/CNR_{DSA} median (IQR)
Overall	< 0.001	2.00 (0.74–4.49)
Upper limb	< 0.001	2.23 (1.18–4.19)
Lower limb	< 0.001	2.06 (0.78–4.63)
Head and neck	< 0.001	1.72 (0.33–4.33)
Chest	< 0.001	1.84 (0.78–4.41)

Subjective comparison: visual image quality

A total of 132 anonymized DSA–DVA image pairs were evaluated on a web-based platform by five experienced clinicians. The pairs were distributed across anatomical regions as follows: 14 from the upper extremities, 56 from the lower extremities, 23 from the head and neck region,

and 39 from the chest wall. For upper extremity AVMs, there no statistically significant difference was observed between DSA and DVA images. In the lower extremities and the head and neck region, DSA images were rated significantly higher for the visibility of large vessels, small vessels, and tissue blush. For chest wall AVMs, visibility of large and small vessels also favored DSA. However, these differences were clinically negligible, with scores falling between the “same” (0) and “slightly better” (1) categories on the four-point Likert scale (Figure 1).

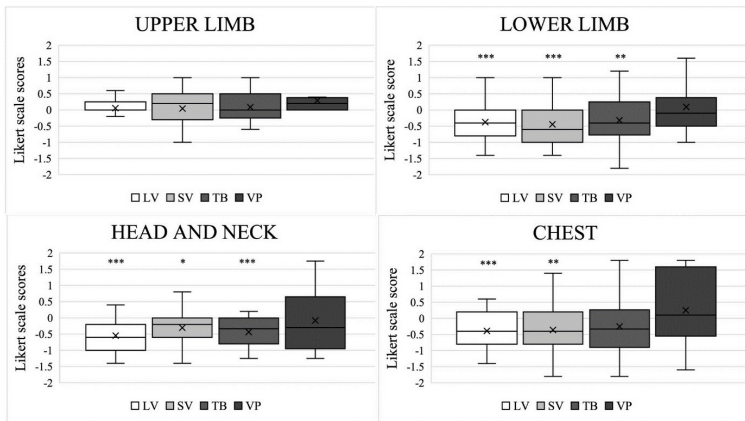


Figure 1. Results of the subjective comparison based on Likert scale ratings

Interobserver agreement was moderate among the five evaluators for the assessment of large and small vessels across all anatomical regions (Kendall’s coefficient of concordance, $W = 0.3\text{--}0.6$). Agreement was lower for tissue blush and venous phase visibility ($W = 0.1\text{--}0.3$).

4.2. Short-term blood pressure variability among young adults at high or low risk for depression

Participant characteristics

The sample comprised three groups: young adult probands ($n = 218$), their high-risk siblings ($n = 206$), and controls ($n = 166$). Probands were older than both siblings and controls ($p < 0.001$), and siblings were also significantly older than controls ($p = 0.01$). Female participants were more prevalent in the proband and sibling groups than in controls. Although the three groups did not differ in the use of antihypertensive medication, probands and siblings had a higher body mass index (BMI) and were more likely to smoke than controls. As expected, BDI-II scores were highest among probands. Both probands and siblings showed elevated resting diastolic blood pressure (DBP) relative to controls; however, these differences did not remain significant after adjustment for age, sex, and BMI. At the time of assessment, 9.2% of probands were experiencing a current depressive episode, while the remainder were in remission; none of the siblings or controls met criteria for current depression ($\chi^2 = 35.33$, $p < 0.001$). Additionally, a small proportion of probands (4.1%) and siblings (1.5%) were taking psychotropic medication at the time of BP assessment, whereas none of the controls were ($\chi^2 = 8.59$, $p = 0.014$).

Blood pressure characteristics and variability

Short-term BPV was calculated as the range (maximum minus minimum) across three consecutive measurements obtained during a 15-minute seated rest period. There were no significant group differences in mean systolic BP or systolic BPV, either in unadjusted models ($F[2, 586] < 0.5$,

$p > 0.60$) or after adjusting for age, sex, BMI, and family clusters ($F[2, 440] = 0.70, p = 0.50$). Similarly, although mean DBP initially differed across groups ($F[2, 586] = 7.29, p < 0.001$), this effect was no longer significant after adjusting for age. No significant differences in diastolic BPV were observed in either unadjusted ($F[2, 586] = 0.14, p > 0.80$) or adjusted models ($F[2, 587] = 0.62, p = 0.54$).

Association between depressive history and blood pressure variability in probands

To examine whether depression-related features were associated with short-term BPV, we conducted a set of regression analyses within the proband group. The models tested whether the number of lifetime depressive episodes, age at onset of the first episode, or the percentage of life spent depressed predicted systolic or diastolic BPV, adjusting for sex, age, BMI, smoking status, and family clustering.

The number of depressive episodes emerged as a significant predictor of diastolic BPV: probands with a greater number of episodes showed significantly higher diastolic BPV ($\beta = 1.76, t[210] = 2.87, p = 0.005, \eta^2_p = 0.039$). This pattern is consistent with a dose-response relationship between depression recurrence and autonomic dysregulation (Figure 2).

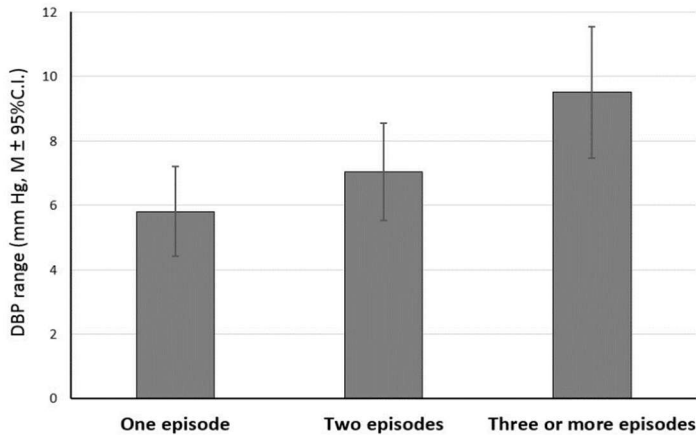


Figure 2. Number of lifetime depressive episodes and diastolic blood pressure variability among probands

A similar trend was observed for systolic BPV, although the overall model did not reach statistical significance ($F[5, 210] = 1.13, p = 0.34$). The number of depressive episodes was marginally associated with greater systolic BPV ($\beta = 0.98, t[210] = 1.82, p = 0.071$), suggesting a possible, albeit weaker, relationship.

Neither age at onset of depression nor the percentage of life spent depressed was a significant predictor of systolic or diastolic BPV (all $p > 0.23$). The use of psychotropic medication did not significantly influence BPV outcomes ($F < 1.77, p > 0.19$), indicating that medication status was not a confounding factor in these associations.

5. Conclusions

5.1. Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study

DVA provides a significant CNR advantage over conventional DSA in pediatric AVM imaging, although its visual quality does not surpass that of DSA. The demonstrated diagnostic reserve suggests an opportunity to reduce radiation dose in children.

5.2. Short-term blood pressure variability among young adults at high or low risk for depression

While group-level differences in BPV were not statistically significant, a higher number of depressive episodes among probands was associated with increased diastolic BPV, indicating that the cumulative burden of depression may affect CV regulation even in early adulthood.

6. Bibliography of the candidate's publications

6.1. Peer-reviewed articles relevant to the current work

1. **Nyárády BB**, Vértés M, Dósa E, Yang X, George CJ, Kiss E, Baji I, Kapornai K, Kovacs M. (2024) Short-term blood pressure variability among young adults at high or low risk for depression. *J Clin Med*. 13(16):4640. **IF: 2.9**

2. **Nyárády BB**, Gubán R, Pataki Á, Bibok A, Mihály Z, Korda D, Horváthy D, Nagy AI, Kiss JP, Dósa E. (2025) Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study. *Eur Radiol Exp*. 9(1):74. **IF: 3.6**

6.2. Other peer-reviewed articles

1. Bérczi Á, Nguyen DT, Sarkadi H, **Nyárádi BB**, Beneda P, Szőnyi Á, Philippovich M, Szeberin Z, Dósa E. (2022) Amputation and mortality rates of patients undergoing upper or lower limb surgical embolectomy and their predictors. *PLoS One*. 17: e0279095. **IF: 3.7**

2. Nguyen DT, Bérczi Á, **Nyárády BB**, Szőnyi Á, Philippovich M, Dósa E. (2022) Short- and Mid-Term Outcomes of Stenting in Patients with Isolated Distal Internal Carotid Artery Stenosis or Post-Surgical Restenosis. *J Clin Med*. 11:5640. **IF: 3.9**

3. Nguyen DT, Vokó B, **Nyárádi BB**, Munkácsi T, Bérczi Á, Vokó Z, Dósa E. (2022) Restenosis rates in patients with ipsilateral carotid endarterectomy and contralateral carotid artery stenting. *PLoS One*. 17: e0262735. **IF: 3.7**

4. **Nyárády BB**, Kiss LZ, Bagyura Z, Merkely B, Dósa E, Láng O, Kőhidai L, Pállinger É. (2024) Growth and differentiation factor-15: A link between inflammaging and cardiovascular disease. *Biomed Pharmacother.* 174:116475. **IF: 6.9**

5. **Nyárády BB**, Dósa E, Kőhidai L, Pállinger É, Gubán R, Szőnyi Á, Kiss LZ, Bagyura Z. (2024) Associations between various inflammatory markers and carotid findings in a voluntary asymptomatic population sample. *Int J Mol Sci.* 25(17):9656. **IF: 4.9**

6. Szőnyi Á, **Nyárády BB**, Philippovich M, Dobai A, Sari EA, Szőnyi A, Nagy AI, Dósa E. (2024) The effect of arterial elongation on isolated common iliac artery pathologies. *Life (Basel).* 14(11):1440. **IF: 3.4**

7. Szőnyi Á, Balázs G, **Nyárády BB**, Philippovich M, Horváth T, Dósa E. (2024) Effect of sex, age, and cardiovascular risk factors on aortoiliac segment geometry. *J Clin Med.* 13(6):1705. **IF: 2.9**

8. Kiss LZ, **Nyárády BB**, Pállinger É, Lux Á, Jermendy ÁL, Csobay-Novák C, Soós P, Szelid Z, Láng O, Kőhidai L, Dinya E, Dósa E, Merkely B, Bagyura Z. (2024) Association of growth and differentiation factor-15 with coronary artery calcium score and ankle-brachial index in a middle-aged and elderly Caucasian population sample free of manifest cardiovascular disease. *Geroscience.* 46(1):1343–1350. **IF: 5.4**

9. Szőnyi Á, **Nyárády BB**, Mezzetto L, Dósa E. (2025) The evolution of vascular interventional radiology and endovascular surgery: an overview of recent advances. J Clin Med. 4(3):939. **IF: 2.9**

6.3. Published abstracts

1. **Nyárády BB**, Szőnyi Á, Nguyen DT, Philippovich M, Dósa E. (2022) Occurrence and characteristics of carotid filter debris – preliminary results. CIRSE Book of Abstracts. Cardiovasc Intervent Radiol. 45 (Suppl 4), page: 502. **IF: –**

2. Szőnyi Á, Dósa E, **Nyárády BB**, Vértés M, Philippovich M. (2022) Configurational variations of the aorto-iliac (AI) segment. CIRSE Book of Abstracts. Cardiovasc Intervent Radiol. 45 (Suppl 4), page: 647. **IF: –**

3. Bérczi Á, **Nyárády BB**, Szeberin Z, Dósa E. (2022) A felső vagy alsó végtagi sebészi embolectomián átesett betegek amputációs és mortalitási rátái, valamint azok prediktív faktorai. Érbetegségek. Suppl. 2, page: 79. **IF: –**

4. Philippovich M, **Nyárády BB**, Szőnyi Á, Nguyen TD, Dósa E. (2023) The significance of femoral plaque characteristics in restenosis after carotid artery stenting (CAS). ECR Book of Abstracts. Insights Imaging. 14 (Suppl 4), page: 160. **IF: –**

5. **Nyárády BB**, Kiss LZs, Bagyura Zs, Dósa E. (2024) A növekedési és differenciálódási faktor-15 (GDF-15) kapcsolata a koronária kalcium score-ral és a boka-kar

indexszel olyan középkorú és idős egyéneknél, akiknek nincs manifeszt kardiovaszkuláris betegsége. Érbetegségek. Suppl. 2, page: 31. **IF:** –

6. **Nyárády BB**, Szőnyi Á, Philippovich M, Nguyen D, Góg I, Pataki Á, Mihály Z, Korda D, Horvathy D, Bibók A, Dósa E. (2024) Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study. CIRSE Book of Abstracts. Cardiovasc Intervent Radiol. 47 (Suppl 7), page: 1538. **IF:** –