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

Ph.D. thesis

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List of Abbreviations

ABPM	Ambulatory blood pressure monitoring
ALARA	As low as reasonably achievable
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ANS	Autonomic nervous system
AV	Arteriovenous
AVM	Arteriovenous malformation
BDI	Beck Depression Inventory
BMI	Body mass index
BP	Blood pressure
BPV	Blood pressure variability
CNR	Contrast-to-noise ratio
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DSA	Digital subtraction angiography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DVA	Digital variance angiography
FMD	Flow-mediated dilation
HR	Heart rate
HRV	Heart rate variability
IQR	Interquartile range
ISYA-D	Interview Schedule for Young Adults – Follow-up Diagnostic Version
N.A.	Not applicable
PWV	Pulse wave velocity
ROI	Region of interest
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
TACE	Transarterial chemoembolization
W	Kendall's coefficient of concordance

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for approximately 17.9 million deaths each year. [1] Early detection and diagnosis of cardiovascular (CV) conditions are vital for effective intervention and management, especially in vulnerable populations – such as children and young adults – because of the potentially lifelong implications. In recent years, technological advances 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 yet 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 (ANS) function – is altered in young adults with a history of childhood depression, offering potential insight into early predictors of CV risk.

1.1. Vascular anomalies and arteriovenous malformations

Vascular malformations represent a subset of congenital vascular anomalies that typically grow proportionately with the individual and are often first identified during adolescence. These anomalies are most frequently diagnosed within the first two decades of life and have an estimated prevalence of approximately 0.5% in North American and European populations. [2] Vascular malformations can manifest in any anatomic region and may present as isolated lesions or as part of multiplex anomalies. [3] The classification system most widely accepted for vascular anomalies is that of the International Society for the Study of Vascular Anomalies, last updated in 2018. According to this framework, AVMs are categorized as high-flow lesions based on their hemodynamic characteristics. High-flow vascular malformations, such as AVMs, are associated with an increased risk of complications – including hemorrhage – compared with their low-flow counterparts. [4]

1.1.1. Pediatric arteriovenous malformations

Although rare, pediatric AVMs are clinically important because they pose unique diagnostic and therapeutic challenges. Children are not only more susceptible to procedural risks but also have smaller anatomic structures and greater long-term vulnerability to radiation exposure.

1.1.1.1. Pathophysiology and clinical presentation

AVMs are vascular anomalies characterized by abnormal arteriovenous (AV) shunts, in which dysplastic, tortuous arteries bypass the capillary bed and connect directly to the venous system. [5] These abnormal vessels form a mesh-like, low-resistance structure known as the nidus. [6] Although the precise pathophysiological mechanisms underlying AVM development remain unclear, AVMs are generally believed to originate during the third week of embryogenesis, arising either from persistent primitive AV connections or from aberrant development of new vascular pathways. The absence of an intervening capillary bed leads to progressive hypertrophy of arterial and venous vessels, causing gradual enlargement of the lesion. [7]

The clinical presentation of AVMs varies widely and is largely determined by anatomic location. Clinically, AVMs are broadly classified as intracranial or extracranial; the latter typically involves the limbs, thorax, or abdomen. [6] Intracranial AVMs may present with headaches, recurrent seizures, or focal neurological deficits. In pediatric patients, hemorrhage is the most common initial presentation, occurring in approximately 80–85% of cases. [7–10] By contrast, extracranial AVMs often present with a pulsatile mass, pain, ulceration, bone marrow edema, or arterial ischemia – symptoms that vary with the affected region. [5, 11–13]

1.1.1.2. Diagnosis

The diagnosis of AVMs typically relies on a combination of detailed clinical assessment and advanced imaging techniques, including magnetic resonance imaging, computed tomography angiography, and catheter-based digital subtraction angiography (DSA). Superficial AVMs may be identified on physical examination by characteristic features – raised, well-circumscribed lesions that are warmer than surrounding tissue and purplish in hue – and may have a palpable thrill or audible bruit. [2] In such cases, ultrasound is

commonly used as a first-line imaging modality because it is effective at differentiating vascular from nonvascular lesions and assisting with classification. Doppler ultrasound is also valuable for tracking disease progression and assessing treatment response over time. [8]

In more complex cases – particularly when complications such as hemorrhage are suspected – computed tomography angiography and magnetic resonance imaging are essential for assessing lesion extent, identifying the source of bleeding, and guiding treatment decisions. Although noninvasive imaging is valuable, DSA remains the gold standard for evaluating AVMs. DSA provides superior spatial and temporal resolution, enabling precise visualization of lesion architecture, including location, size, feeding arteries, draining veins, and nidus characteristics, and offers real-time hemodynamic information by capturing contrast flow, which is essential for evaluating the dynamic behavior of AVMs and guiding appropriate treatment. [7, 8]

1.1.1.3. Treatment

The classification of lesions as intracranial or extracranial helps clinicians select the most appropriate treatment strategy. While intracranial AVMs are primarily managed by neurosurgeons and neurointerventionalists, extracranial malformations are typically treated by pediatric surgeons, vascular surgeons, or interventional radiologists. [8, 13] In all cases, the success of invasive therapy depends on lesion location, size, and hemodynamic profile; the patient's clinical condition; and the selected therapeutic approach. [8]

Treatment options for AVMs include conservative management, pharmacologic therapies, minimally invasive procedures (such as sclerotherapy or image-guided embolization), and surgical excision. Conservative management may include analgesics and compression therapy to reduce pain and swelling, particularly when venous pressure is elevated. [5, 13, 14] Although pharmacological therapies are largely off-label, several agents – such as sirolimus, alpelisib, bevacizumab, and dabrafenib – are under investigation for their ability to modulate aberrant signaling pathways and inhibit lesion growth. [13, 15] Invasive interventions – such as surgical resection, radiosurgery, microsurgery, endovascular embolization, or combinations thereof – are typically indicated when the risk of lesion progression or rupture is high. Surgical excision is

considered when there is a reasonable expectation of complete lesion removal. In clinical practice, embolization followed by surgical resection has become the preferred strategy to reduce recurrence and improve outcomes. [13, 16]

Embolization aims to devascularize the lesion by targeting the nidus and, when possible, the feeding arteries and draining veins. This usually requires multiple sessions, typically scheduled 6–8 weeks apart. [13, 17] Embolization can be performed via various access routes: trough the feeding arteries, retrograde via the draining veins, or by direct image-guided percutaneous puncture. The choice of approach depends on lesion accessibility, size, and vascular characteristics. For high-flow AVMs, cytotoxic embolic agents – such as ethanol, polyvinyl alcohol, or Onyx – are generally preferred to noncytotoxic alternatives. [5, 18–20]

1.1.1.4. Digital subtraction angiography

DSA is a widely used imaging technique in catheter-based angiography to evaluate CVDs. It involves the intravascular administration of an iodinated contrast agent followed by X-ray imaging to visualize vascular structures. The process generates two sets of images: a baseline (pre-contrast) set acquired before contrast injection and a second set acquired afterward. With digital post-processing, nonvascular anatomic structures – such as bone and soft tissue – are removed by subtracting the pre-contrast image from the post-contrast images. This subtraction provides high-resolution, contrast-enhanced visualization of the vascular system. DSA remains the gold standard in vascular imaging because of its superior spatial and temporal resolution. [21]

Despite its diagnostic value, DSA carries risks. Complications may arise from the procedure itself, the contrast agent, or radiation exposure. [22] Procedural risks related to vascular access or catheter manipulation include hemorrhage or hematoma at the puncture site, pseudoaneurysm formation, iatrogenic AV fistula, vessel wall perforation or dissection, and the development of local thrombosis or distal embolization. [22] Contrast agents can cause adverse reactions ranging from mild symptoms – such as a transient warm sensation, metallic taste, urge to urinate or defecate, dizziness, or nausea – to more severe effects, including allergic reactions, contrast-induced thyroid dysfunction, and contrast-induced nephropathy. [22–25]

1.1.1.5. Digital variance angiography

DVA is based on the concept of kinetic imaging, which involves statistical processing of pixel intensity fluctuations over time. [26–28] In this approach, rapid intensity changes – such as those caused by flowing contrast agent – are amplified to produce a strong signal, whereas slower changes result in weaker signals. The foundational study on kinetic imaging, published in 2014 by researchers in the Department of Biophysics and Radiation Biology at Semmelweis University, introduced a novel X-ray technique that captures a sequence of underexposed images instead of a single well-exposed image while maintaining the same overall dose and exposure time. [28] By statistically analyzing the image sequence together with measurement noise, the method generates two distinct outputs: an expected value image and a variance image. This variance – or kinetic – image reveals motion-related details that are otherwise invisible with static imaging. For example, in studies involving *Xenopus laevis* (African clawed frog), structures such as the heart, valves, and aorta – undetectable with standard imaging – became visible. [28] Compared to traditional DSA, DVA provides a superior contrast-to-noise ratio (CNR), enabling high-quality vascular imaging during endovascular procedures with significantly reduced contrast agent use and radiation exposure. [26, 29] While DVA's clinical benefits have been explored in adult populations, its application in pediatric catheter-based interventions has not yet been studied. Table I summarizes the two imaging techniques.

Table I. Comparison of digital subtraction angiography and digital variance angiography

Aspect	DSA	DVA
Image generation	Subtraction of pre-contrast (mask) images from post-contrast images	Variance calculation from temporal pixel intensity fluctuations
CNR	Standard	Improved CNR in most cases
Background suppression	Effective, but prone to motion-related misregistration	Strong; no subtraction mask required
Contrast agent volume	Full dose typically required	Potential for dose reduction (up to 50%)
Radiation dose	Standard exposure	Potential for dose reduction (up to 70%)
Sensitivity to motion	High (causes subtraction artifacts)	Moderate to high (manifests as increased background variance)

CNR, Contrast-to-noise ratio; DSA, digital subtraction angiography; DVA, digital variance angiography.

1.1.1.6. Radiation safety in pediatric imaging

Many diagnostic imaging techniques, including DSA, rely on ionizing radiation. The widespread adoption of these modalities has increased radiation exposure for patients and, to a lesser extent, health care personnel. [30, 31] A 2012 analysis reported that the average annual radiation dose per person in the United States nearly doubled from 3.6 mSv in 1980 to 6.2 mSv in 2006, largely because exposure from medical imaging rose from about 15% to become the largest single source, contributing approximately 3 mSv per year. [32] The guiding principle for medical radiation use is ALARA (as low as reasonably achievable), which emphasizes three practices: ensuring appropriate justification for imaging, minimizing the dose per examination, and avoiding unnecessary procedures. [31] This principle is particularly critical in pediatric imaging. A large retrospective cohort study in the United Kingdom found an association between childhood exposure to multiple computed tomography scans and increased cancer risk, particularly in the

developing brain and bone marrow. Cumulative doses of approximately 60 mGy were associated with a threefold increase in brain tumor risk, whereas approximately 50 mGy was associated with a similar increase in leukemia risk. [33] Accordingly, there is broad consensus that children are especially vulnerable to ionizing radiation and that any imaging study involving radiation must confer a clear benefit that outweighs potential risks. In pediatric care, radiation exposure should be kept as low as reasonably achievable.

1.2. Cardiovascular function and mental health in young adults

The transition from adolescence to adulthood involves substantial physical, psychological, and neurobiological changes. [34] Emerging evidence suggests that early-life psychological well-being has enduring implications for somatic health, particularly in the regulation of CV function. [35] Psychiatric disorders, particularly depression, not only disrupt emotional and social development but also affect autonomic, inflammatory, and hemodynamic systems, thereby laying the groundwork for future CV risk. [36]

1.2.1. Psychiatric disorders in youth

Most psychiatric disorders emerge during adolescence or early adulthood, [37] making this period critical for early identification and intervention, given their profound impact on development and well-being. Globally, approximately one in seven individuals aged 10–19 experiences a mental disorder. [38] Anxiety disorders are the most common, with an estimated prevalence of 4.4% in early adolescence (10–14 years) and 5.5% in late adolescence (15–19 years). Behavioral disorders are also prevalent among youth. For instance, attention-deficit/hyperactivity disorder affects approximately 2.9% of those aged 10–14 and 2.2% of those aged 15–19. Conduct disorders occur in roughly 3.5% of early adolescents, decreasing to 1.9% in later adolescence. [39] Other common conditions in youth include neurodevelopmental disorders and substance use disorders, each contributing to the overall burden of pediatric mental health issues. These conditions often co-occur and may lead to significant functional impairments.

Among mood disorders in youth, depression is particularly prominent and concerning. Depression in adolescence (often presenting as major depressive disorder) has a point prevalence of approximately 1.4% in early adolescence, rising to about 3–4% by mid-to-late adolescence. [39] Notably, rates of depression increase sharply during

adolescence and are generally higher in females than in males by mid-adolescence. Depression in youth is clinically significant not only because of its acute impact but also because of its potential for persistence and recurrence. Adolescent-onset depression often predicts recurrent depressive episodes in adulthood and is associated with a host of adverse psychosocial outcomes, such as academic underachievement, interpersonal difficulties, and increased risk of substance abuse. [40] Depression also elevates the risk of suicidal behavior; suicide is among the leading causes of death in older adolescents and young adults with depression. [41]

1.2.2. Depression and its impact on somatic health

Beyond its psychological toll, depression is increasingly recognized as a disorder that significantly affects physical health and is now considered an independent risk factor for numerous adverse medical outcomes, particularly in CV health. [42] Epidemiologic studies show that, even after adjustment for conventional risk factors, a history of depression is associated with a higher incidence of hypertension, coronary heart disease, and increased all-cause mortality. [43, 44] It often coexists with unhealthy behaviors (e.g., physical inactivity, poor diet, and smoking), which further amplify somatic risk. [45, 46]

The adverse effects of depression on long-term health are evident even in young populations. Adolescents with depression are at increased risk of developing obesity, insulin resistance, and other components of metabolic syndrome during the transition to adulthood. [47] Moreover, depression in youth is linked to the early presence of CVD risk factors: one study reported that more than half of adolescents with major depressive disorder exhibited at least two CVD risk factors, such as elevated body mass index (BMI) or blood pressure (BP). [48] The mechanisms underlying the link between depression and poor somatic health are multifactorial, involving both direct biological pathways and indirect behavioral routes. Chronic stress and autonomic dysregulation are key proposed mechanisms. Depression is often accompanied by alterations in ANS function characterized by increased sympathetic activity and blunted parasympathetic (vagal) tone. [49] Individuals with depression frequently exhibit reduced heart rate variability (HRV), reflecting diminished vagal modulation of heart rate (HR). [50] This autonomic imbalance – marked by a heightened fight-or-flight response and vagal withdrawal – may contribute to elevated resting HR, BP irregularities, and increased arrhythmogenic

potential. Such ANS dysfunction has been posited as a central biological link between depression and a range of physical illnesses. [50] For example, reduced HRV and heightened sympathetic output can promote myocardial ischemia, endothelial shear stress, and proarrhythmic conditions, thereby increasing CV strain over time. Depression is also associated with chronic low-grade inflammation, evidenced by elevated circulating levels of inflammatory markers such as C-reactive protein and interleukin-6, even when controlling for confounders such as BMI. [51] Inflammation linked to depression may accelerate atherosclerosis, induce endothelial dysfunction, and promote a prothrombotic state, thereby increasing CV risk. This relationship appears to be bidirectional: while depression may promote inflammation, inflammatory states can likewise contribute to the onset or exacerbation of depressive symptoms in vulnerable individuals. [52]

1.2.3. Characterization and assessment of cardiovascular function

CV function can be assessed using various physiologic parameters and tests, which capture distinct aspects of CV health – even in young, asymptomatic individuals. Among the most informative indicators are HRV, arterial stiffness, endothelial function, and BPV. Each metric offers complementary insight into CV regulatory mechanisms and vascular integrity.

HRV refers to beat-to-beat fluctuations in HR and serves as a proxy for ANS balance, particularly reflecting vagal (parasympathetic) modulation of cardiac activity. [50, 53] Higher resting HRV generally indicates a greater capacity of the heart to adapt to physiologic demands and is associated with better CV health. Conversely, reduced HRV reflects autonomic dysregulation, often characterized by increased sympathetic dominance. [53] HRV is typically derived from electrocardiographic recordings and quantified using time-domain metrics (e.g., the standard deviation [SD] of normal-to-normal intervals) or frequency-domain metrics (e.g., spectral power within high- and low-frequency bands). [54] Low HRV has been associated with an elevated risk of arrhythmias, adverse cardiac events, and mortality in cardiac populations. In young adults, HRV can serve as a sensitive marker of psychological stress and mental health; for instance, individuals with a history of childhood depression have been shown to exhibit altered HRV responses to acute stress. [55, 56]

Arterial stiffness reflects the elasticity of the arterial walls, especially in large conduit arteries such as the aorta. With advancing age and exposure to CV risk factors – such as hypertension, obesity, or dyslipidemia – arteries progressively lose their elastic properties. This stiffening increases left ventricular afterload, contributes to elevated systolic blood pressure (SBP) and pulse pressure, and accelerates vascular aging. [57] The gold standard for assessing arterial stiffness is pulse wave velocity (PWV), which measures the speed at which the pressure wave propagates through the arterial system. Higher PWV values indicate greater arterial stiffness and have been independently associated with increased risk of CV events and all-cause mortality. [58, 59] Arterial stiffness is influenced by several modifiable and nonmodifiable factors, including physical fitness, adiposity, metabolic status, and family history of CVD. Noninvasive techniques, such as carotid–femoral PWV, are widely used in clinical and research settings because of their high reproducibility and prognostic utility. [60] Notably, increased arterial stiffness in youth or young adulthood may serve as an early biomarker of future hypertension, atherosclerosis, or other adverse CV outcomes. [58, 61]

Endothelial function is most commonly assessed using flow-mediated dilation (FMD), which evaluates the ability of a conduit artery – typically the brachial artery – to dilate in response to increased shear stress. [62] During the FMD procedure, a BP cuff is inflated above systolic pressure to induce transient ischemia by occluding the artery, usually for 5 minutes. Upon cuff release, the resultant reactive hyperemia leads to an increase in blood flow, which stimulates endothelial nitric oxide release and subsequent vasodilation. The change in arterial diameter is expressed as a percentage (FMD%). Reduced FMD indicates endothelial dysfunction, a key early marker of atherosclerosis that can precede structural vascular changes. [63] Impaired endothelial responses have been prospectively associated with increased risk of CV events in both adult and pediatric populations. In adolescents and young adults, adverse factors such as dyslipidemia, smoking, obesity, and chronic psychosocial stress have been shown to negatively influence endothelial function. [64]

BP is a fundamental CV parameter; beyond its mean levels, the variability in BP over time is increasingly recognized as meaningful. [43] BPV refers to fluctuations in an individual's BP measurements across various time scales. [65, 66] It can be measured

over seconds or minutes, 24-hour periods, day-to-day, or visit-to-visit across months (see section 1.2.4).

1.2.4. Blood pressure and its variability

BP is among the most critical vital signs and a well-established determinant of CV risk. BP is typically measured with a pneumatic cuff placed on the upper arm at heart level. Readings are obtained either by manual auscultation of Korotkoff sounds with a stethoscope or by automated oscillometric devices. To ensure accuracy, the patient should be seated comfortably with the back supported and legs uncrossed, after at least five minutes of rest. Physical exertion, caffeine intake, and smoking should be avoided for at least 30 minutes before measurement. The measured arm must be supported at heart level to avoid isometric muscle tension, and an appropriately sized cuff must be used to prevent systematic error. The cuff is placed approximately 2–3 cm above the antecubital fossa. SBP corresponds to the maximum arterial pressure during ventricular contraction, whereas diastolic blood pressure (DBP) reflects the lowest pressure during cardiac relaxation. Both are expressed in millimeters of mercury (mmHg). According to the European Society of Cardiology, hypertension in adults is defined as a sustained office SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. [67] Elevated BP (hypertension) is strongly associated with adverse outcomes such as stroke, myocardial infarction, heart failure, and kidney disease. [68] Beyond absolute BP levels, there is growing interest in the significance of BPV – the degree to which BP fluctuates over time. BPV provides additional prognostic information: numerous studies have shown that increased BPV is associated with target-organ damage and a higher risk of CV events. [65, 66, 69, 70] Two individuals with the same mean BP may have different risk profiles if one has highly variable BP while the other's BP is more stable. Thus, both BP and BPV are important considerations in evaluating CV health.

BPV can be conceptualized across multiple time scales, each capturing different physiologic processes with distinct clinical implications. [71, 72]

Ultra-short-term BPV refers to beat-to-beat fluctuations in BP. This rapid variability is driven primarily by baroreflex activity, respiratory cycles, and other immediate CV reflexes. It can be captured using continuous beat-to-beat BP monitoring (e.g., a finger arterial pressure device or an intra-arterial catheter). Ultra-short-term BPV

reflects ANS modulation of the CV system on a moment-to-moment basis and is used less often in routine clinical practice because it requires specialized equipment. [71, 72]

Short-term BPV generally denotes fluctuations over minutes up to 24 hours. This is most commonly assessed with ambulatory blood pressure monitoring (ABPM), in which a portable device measures BP at regular intervals (e.g., every 15–30 minutes) over a full day and night, providing a detailed profile of BP and short-term BPV across consecutive readings. [71, 72] Short-term BPV is clinically relevant; higher short-term BPV has been linked to hypertensive organ damage (e.g., left ventricular hypertrophy, microvascular damage in the eye and kidney) and worse CV prognosis. [73–75] Short-term BPV monitoring is increasingly used to confirm hypertension and assess BP control; patients with high short-term variability may require closer monitoring or tailored therapy.

Mid-term BPV refers to BP fluctuations occurring over days to weeks. It can be evaluated using home BP monitoring or repeated office measurements over several days. Mid-term BPV reflects BP instability under routine conditions, influenced by factors such as day-to-day stressors, sleep quality, or medication timing. [71, 72] It has been associated with cognitive impairment and vascular stiffness in older adults and may also indicate challenges in achieving consistent BP control. [76]

Long-term BPV refers to fluctuations in BP measured over months to years, typically assessed across serial outpatient visits – often termed visit-to-visit BPV – and influenced by factors such as disease progression, medication adherence, seasonal variation, and age-related BP drift. High visit-to-visit BPV is a strong predictor of stroke, coronary events, kidney disease progression, and mortality. [71, 72] Long-term BPV has been incorporated into risk prediction frameworks (e.g., the QRISK3 score) because it provides prognostic information beyond mean BP. [77] Clinically, patients with highly variable BP between visits may be at greater risk and could benefit from treatment adjustments, such as the use of longer-acting antihypertensives to help stabilize BP.

Terminology for “short-” versus “long-term” BPV varies across sources. Some authors classify within-24-hour variability as short-term, day-to-day fluctuations over weeks as mid-term, and visit-to-visit variability over months or years as long-term BPV. Others simplify the classification to just short-term (within 24 hours) and long-term (between visits). [65, 78] Regardless of terminology, the underlying principle is the same:

BP exhibits inherent variability across time scales, each with potential health implications.

Methods of measuring BPV depend on the time scale of interest. Beat-to-beat monitoring requires continuous intra-arterial lines or noninvasive finger cuffs and is used mainly in research to assess ultra-short-term BPV. ABPM provides numerous readings over a 24-hour period, allowing calculation of various variability indices. In home BP monitoring, patients measure BP over several days or weeks, supporting BP management and enabling assessment of day-to-day variability. Clinic- or office-based measurements compare BP across multiple visits – preferably using standardized protocols – to estimate visit-to-visit variability. [79] Each method has its own clinical applications. ABPM is recommended to confirm a diagnosis of hypertension and to detect patterns such as white-coat or masked hypertension. Long-term BPV analysis can help identify patients who may benefit from specific antihypertensive regimens or closer follow-up. [65, 80] Calcium channel blockers and diuretics have been reported to reduce long-term BPV and are sometimes preferred in patients with high variability. [81] Exploring BPV is particularly relevant in young adults with early-life risk factors or conditions such as childhood-onset depression: if depression and associated stress exposures affect autonomic regulation, this may manifest as altered BP dynamics (e.g., subtle changes in BP), even in otherwise healthy individuals. A recent systematic review found that people with mental illnesses tend to have increased BPV. [82] A concise summary of BPV types by time scale, physiologic mechanisms, measurement techniques, and clinical implications is provided in Table II.

Table II. Summary of blood pressure variability types

BPV type	Time scale	Primary mechanisms	Measurement	Clinical relevance
Ultra-short-term BPV	Beat-to-beat (seconds)	Baroreflex, respiration, immediate autonomic reflexes	Intra-arterial line or continuous noninvasive monitoring	Reflects moment-to-moment autonomic regulation
Short-term BPV	Minutes to 24 hours	Autonomic tone, physical activity, circadian rhythms	ABPM; repeated in-clinic readings	Target-organ damage; worse CV prognosis
Mid-term BPV	Days to weeks	Behavioral factors, medication timing, stress	Home BP monitoring; repeated office visits	Cognitive impairment; increased vascular stiffness (older adults)
Long-term BPV	Months to years (visit-to-visit)	Medication adherence, aging, disease progression	Serial outpatient visits	Predictor of stroke, CV events, and mortality

ABPM, Ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CV, cardiovascular.

Despite robust evidence linking BPV to adverse outcomes, it is not yet routinely assessed as a vital sign in clinical practice. One key barrier is the lack of standardization: different studies use varying protocols (e.g., office, home, or ambulatory measurements) and metrics, making it difficult to establish clear clinical cutoffs. [65] Measuring BPV can also be resource-intensive, often requiring 24-hour monitoring or multiple outpatient visits. Ongoing research aims to develop more feasible methods for assessing BPV. For example, a practical approach is to obtain a small number of BP readings in a controlled setting (analogous to an office visit) and calculate their range or variability to estimate

short-term BPV. [72] If such simplified measures reliably reflect an individual's BP stability, they could be implemented in primary care or youth mental health settings as early screening tools for CV risk.

2. Objectives

2.1. Study I (Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study – Semmelweis University Institutional Review Board approval No. 182/2022)

Minimizing radiation exposure for both patients and health care personnel during X-ray-based diagnostic and interventional procedures is critically important. One potential means of achieving this is the use of DVA. In recent years, several national and international retrospective and prospective studies have explored the clinical utility of DVA in adult populations. [26, 29, 83–86] However, the clinical value and applicability of this technique in pediatric patients remain unverified; to date, no studies have examined its role in children. Therefore, we aimed to retrospectively compare imaging parameters between DVA and conventional DSA in children with extracranial AVMs undergoing endovascular treatment.

2.2. Study II (Short-term blood pressure variability among young adults at high or low risk for depression – University of Pittsburgh Institutional Review Board approval No. PRO15020542; Hungarian National Ethical Committee approval No. 44352–3/2016/EKU)

Depression adversely affects CV regulation, autonomic balance, and BP control. However, most studies on this topic have focused on middle-aged or older adults. We sought to determine whether these physiologic perturbations are evident in young adults in their twenties, particularly those with a history of early-onset depression or elevated familial risk. The primary objectives were to: (1) test whether young adults with a history of childhood-onset major depressive disorder exhibit greater short-term BPV than never-depressed high-risk siblings and emotionally healthy controls; (2) evaluate whether clinical features of depression – such as the number of lifetime episodes – predict elevated BPV; and (3) determine whether familial risk alone (in the absence of clinical depression) is associated with BP dysregulation.

3. Methods

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

3.1.1. Patient selection

This retrospective, observational, single-center study included data from 10 patients younger than 18 years with extracranial AVMs who underwent a total of 15 endovascular procedures at the Heart and Vascular Center, Department of Interventional Radiology, Semmelweis University, between December 2022 and December 2024. All examinations were conducted in full compliance with ethical standards, in accordance with the 1964 Declaration of Helsinki (and its later amendments) and national research ethics committee regulations. Patient data were processed and analyzed only after complete anonymization.

3.1.2. Generation of digital variance angiography and digital subtraction angiography images

Endovascular procedures were performed by two interventional radiologists, each with more than 20 years of professional experience. For each intervention, the contrast agent volume and injection rate were tailored to patient-specific characteristics and lesion-specific parameters. The choice and amount of contrast agent – ranging from 15 to 147 mL per procedure – were determined at the discretion of the performing radiologist. Intra-arterial contrast media included Ultravist (Bayer AG, Leverkusen, Germany), Iomeron (Bracco Imaging SpA, Milan, Italy), and Omnipaque (GE HealthCare Technologies Inc., Chicago, IL, USA). Raw angiographic images were acquired at 2 or 4 frames per second using a Siemens Artis Zee angiography system equipped with a 30 × 40 cm detector (Siemens Healthineers AG, Forchheim, Germany). The same raw image series was used to generate both DSA and DVA images. DSA images were produced on a Syngo workstation (Siemens Healthineers AG), whereas DVA images were created with the Kinepict Medical Imaging Tool, version 5.3 (Kinepict Health Ltd., Budapest, Hungary). Post-processing steps – including motion correction (pixel shift) and brightness/contrast adjustments – were identical for both modalities and were performed

by a designated interventional radiologist. The resulting images were archived in Tagged Image File Format and organized into matched pairs by anatomic region for CNR analysis and web-based visual quality assessment.

3.1.3. Objective comparison: contrast-to-noise ratio

For CNR calculation, regions of interest (ROIs) were manually placed in pairs for each AVM: one ROI over a vascular structure and a corresponding ROI in an adjacent extravascular background area. At least 25 ROI pairs were identified per image. Figure 1 illustrates the comparison of CNR values between DSA and DVA images based on these ROI pairs.

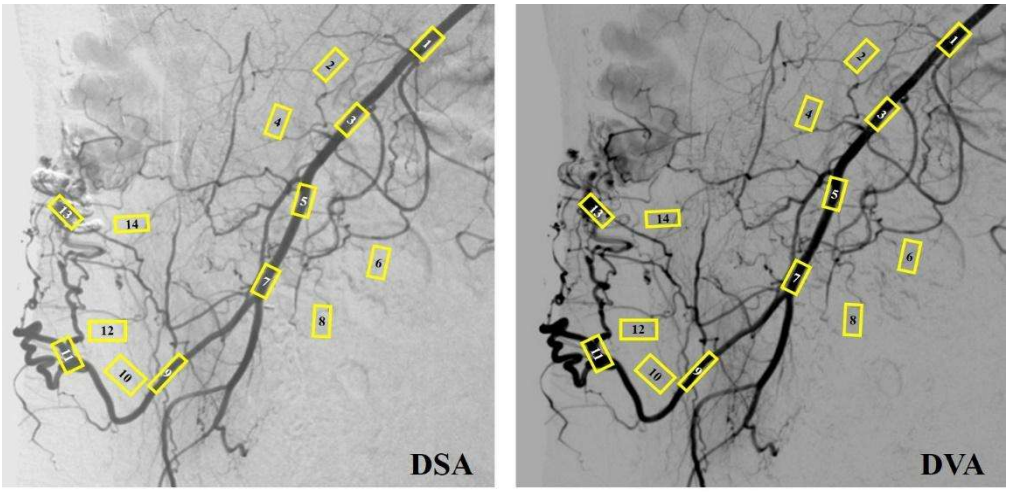

Figure 1. Comparison of contrast-to-noise ratios between digital subtraction angiography and digital variance angiography images

(Images from the archive of the Heart and Vascular Center, Semmelweis University; acquired by Edit Dósa.)

When geometric discrepancies between DSA and DVA images occurred (e.g., due to pixel shift differences), ROIs on the DVA images were manually realigned to match their corresponding ROIs on the DSA images. The CNR for each ROI pair was calculated as:

$$\mathbf{CNR = (Mean_v - Mean_b) / SD_b}$$

Where $Mean_v$ denotes the mean pixel intensity within the vascular ROI, $Mean_b$ the mean pixel intensity within the background ROI, and SD_b the standard deviation of pixel intensities in the background ROI. CNR values were computed separately for each ROI pair on both the DSA and DVA images. In addition, a CNR ratio (CNR_{DVA} / CNR_{DSA}) was calculated for each pair. ROI placement and measurements were performed using Fiji (ImageJ; version 2.0.0-rc-68/1.52e; National Institutes of Health, Bethesda, MD, USA).

3.1.4. Subjective comparison: quality assessment

To subjectively compare the quality of DSA–DVA image pairs, we developed a randomized, web-based evaluation questionnaire that enabled anonymized, side-by-side comparisons while blinding evaluators to image modality. Four interventional radiologists and one vascular surgeon, each with ≥ 5 years of clinical experience in diagnosing vascular pathologies, participated in the assessment. Using a four-point Likert scale, the experts rated the visibility and diagnostic value of large vessels, small vessels, tissue blush (when applicable), and the venous phase (when applicable). The image pairs covered four anatomic regions: upper extremity (n = 14), lower extremity (n = 56), head and neck (n = 23), and chest (n = 39). The scoring system was defined as follows: 0 = no difference in image quality; 1 = one image slightly better; 2 = one image clearly better; 3 = one image superior in all respects. Image pairs were presented in random order via the web interface without disclosing the modality (DSA or DVA), ensuring a fully blinded evaluation. Each pair was assessed once by each expert, and evaluations were performed independently. Figure 2 illustrates the layout of the web-based interface using a representative lower limb AVM image pair; for illustration, DSA is shown on the left and the corresponding DVA image on the right.

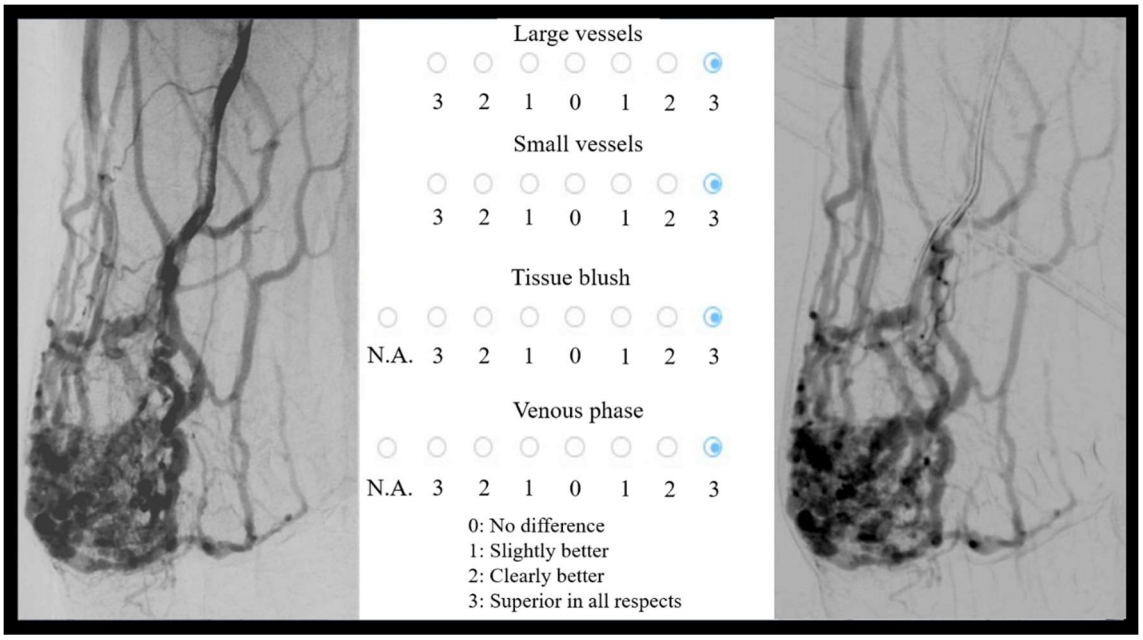

Figure 2. Visual layout of the web-based interface for side-by-side comparison of digital subtraction angiography and digital variance angiography images, illustrated with a representative lower limb arteriovenous malformation

(Images from the archive of the Heart and Vascular Center, Semmelweis University; acquired by Edit Dósa.)

DSA, Digital subtraction angiography; DVA, digital variance angiography.

3.1.5. Statistical analysis

Statistical analyses were performed using Stata 15.0 (StataCorp LLC, College Station, TX, USA) and GraphPad Prism 8.4.2 (GraphPad Software Inc., La Jolla, CA, USA). Continuous variables were reported as mean ± standard error of the mean (SEM) or as median (interquartile range [IQR]), as appropriate; categorical variables were presented as counts and percentages. CNR values were compared using the Wilcoxon signed-rank test. For the qualitative comparison of paired DSA–DVA images, either a one-sample *t*-test or a one-sample Wilcoxon signed-rank test was applied, depending on data normality. To assess interobserver agreement among evaluators, Kendall's coefficient of concordance (W) was calculated and interpreted as follows: $0 \leq W < 0.1$, no agreement; $0.1 \leq W < 0.3$, weak; $0.3 \leq W < 0.6$, moderate; $0.6 \leq W < 1.0$, strong; $W = 1.0$, perfect agreement. A p-value < 0.05 was considered statistically significant.

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

3.2.1. Participant selection

Participants for this cross-sectional study were recruited from a previously established cohort assembled for a genetic and clinical investigation of juvenile-onset depression conducted in Hungary between 1999 and 2006. [87] The original longitudinal study enrolled probands and their siblings from 23 child and adolescent mental health services spanning urban and rural regions. Inclusion criteria for probands in the original study were: a current or recent episode of major depressive disorder or dysthymia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); [88] age 7–14 years at recruitment; absence of intellectual disability or severe medical conditions; and availability of at least one biological parent and a sibling aged 7–18 years. Control participants were recruited contemporaneously from local schools within the catchment areas of the clinical sites. These controls were selected to match the proband group demographically and were screened to ensure the absence of major psychiatric disorders. For detailed information regarding recruitment methodology and diagnostic procedures, see references. [89, 90]

All individuals from the original cohort who were aged ≥ 18 years and had consented to be recontacted for future research were invited to participate in the current study. 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) (Figure 3).

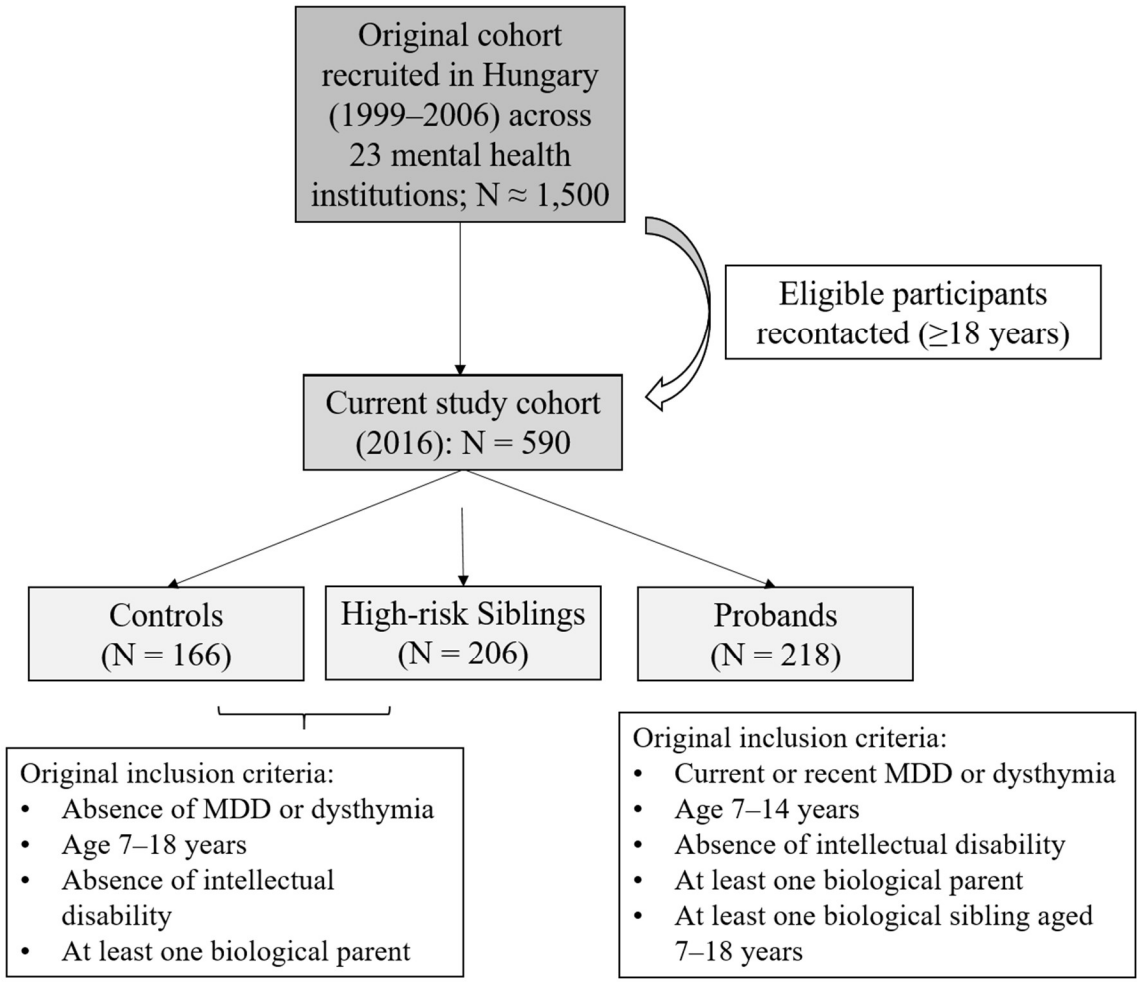

Figure 3. Study II flowchart

MDD, Major depressive disorder.

Written informed consent was obtained from all participants prior to enrollment. The study protocol was approved by the Hungarian National Research Ethics Committee, the Institutional Review Board of the University of Pittsburgh, and affiliated Hungarian research sites.

3.2.2. Psychological assessment

All participants were enrolled as part of a larger longitudinal research project incorporating both psychiatric and CV evaluations, including BP assessments. Psychiatric diagnoses were determined according to 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), a semi-

structured tool adapted to the developmental stage of the sample. Standardized operational criteria were applied to determine the onset and duration of psychiatric episodes. The identification and quantification of specific disorders, as well as the number of lifetime episodes, were verified during consensus diagnostic meetings led by senior clinicians to ensure high diagnostic reliability. In addition to the clinical interview, participants completed the Beck Depression Inventory-II (BDI-II), a validated self-report measure of current depressive symptom severity over the preceding two weeks.

3.2.3. Measurement of short-term blood pressure variability

Short-term BPV served as the primary CV parameter. BP measurements followed a standardized study protocol aligned with established international guidelines to ensure consistency and minimize external influences. [67, 91] Participants were instructed to abstain from caffeine, alcohol, and tobacco for at least 1 hour before assessment. All measurements were obtained by trained research staff using a detailed written protocol that included verification of correct cuff size, a quiet environment, and consistent posture and timing. After a brief initial rest, participants remained seated upright with both feet flat on the floor and the right arm supported at heart level. BP was recorded using a validated automated oscillometric device (Omron M6; Omron Corporation, Kyoto, Japan), widely recognized for clinical reliability and accuracy. [92] Three consecutive brachial BP measurements were taken at 5-minute intervals. This approach provides a simple, practical index of intra-individual variability over a short observational window and has been used in population-based and clinical studies assessing autonomic regulation. [93, 94]

3.2.4. Statistical analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Before hypothesis testing, all variables were screened for distributional assumptions and outliers. Initial group comparisons of demographic, psychological, and CV variables were performed using one-way analysis of variance (ANOVA) for continuous variables and chi-square (χ^2) tests for categorical variables. When distributional assumptions were not met, appropriate nonparametric methods (e.g., Mann–Whitney *U* tests) were applied. To examine group differences in average BP and short-term BPV, we used analysis of

covariance (ANCOVA), adjusting sequentially for covariates known to influence CV parameters, including age, sex, BMI, and smoking status (yes/no). Current depressive symptom severity, measured by the BDI-II, was also included as a covariate where relevant. All ANCOVA models were estimated via linear mixed-effects models with random intercepts to account for the potential nonindependence of observations among family members (e.g., probands and their biological siblings). Short-term BPV, the primary outcome, was operationalized as the range (maximum minus minimum) of three consecutive brachial BP readings and was analyzed separately for systolic and diastolic values. Estimated marginal means (least-squares means) were used for post hoc pairwise comparisons among groups (probands, high-risk siblings, controls).

A power analysis for the one-way ANOVA indicated that, given the sample size, the study had 80% power to detect an overall F test corresponding to a pairwise group mean difference of approximately 0.29 SD – about 1.7 mmHg for systolic BPV and 1.6 mmHg for diastolic BPV – representing a medium effect size.

A secondary set of regression analyses focused exclusively on the proband group. In these models, short-term BPV was regressed on key clinical features of depression history, including number of depressive episodes, age at onset of the first episode, and the percentage of life spent in depression. All models controlled for sex, age, BMI, and smoking status. Predictive strength was evaluated using partial R^2 values from the mixed-effects models, and effect sizes for individual predictors were reported as partial eta squared (η^2). A p-value < 0.05 was considered statistically significant.

4. Results

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

4.1.1. Patient characteristics

The study included 10 patients (mean age, 12 years; range, 7–17 years), comprising six females and four males. None had known comorbidities, and none were taking regular medications. Each patient had a single AVM (total n = 10). By anatomic region, AVMs were distributed as follows: upper extremity (n = 2), lower extremity (n = 4), head and neck (n = 2), and chest wall (n = 2). Collectively, patients underwent 15 endovascular procedures (three diagnostic and 12 therapeutic).

Figures 4 and 5 present representative DSA–DVA image pairs from two of the four anatomic regions: Figure 4 shows an upper limb AVM, and Figure 5 illustrates a head and neck AVM. A representative chest wall image pair was shown previously in the CNR comparison (Figure 1), and a lower extremity image pair appeared earlier in the description of the web-based evaluation (Figure 2).

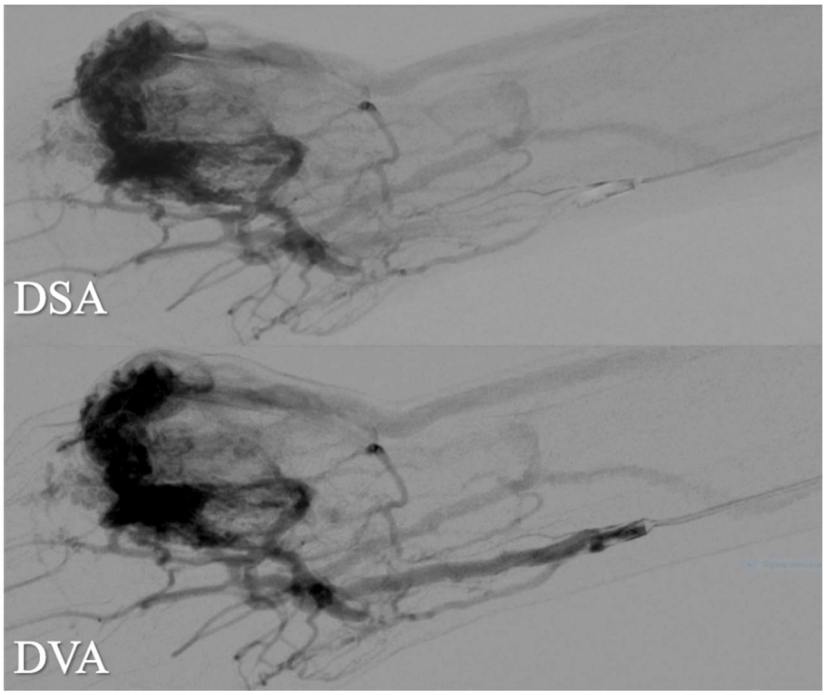

Figure 4. Representative digital subtraction angiography–digital variance angiography image pair of an upper limb arteriovenous malformation

(Images from the archive of the Heart and Vascular Center, Semmelweis University; acquired by Edit Dósa.)

DSA, Digital subtraction angiography; DVA, digital variance angiography.

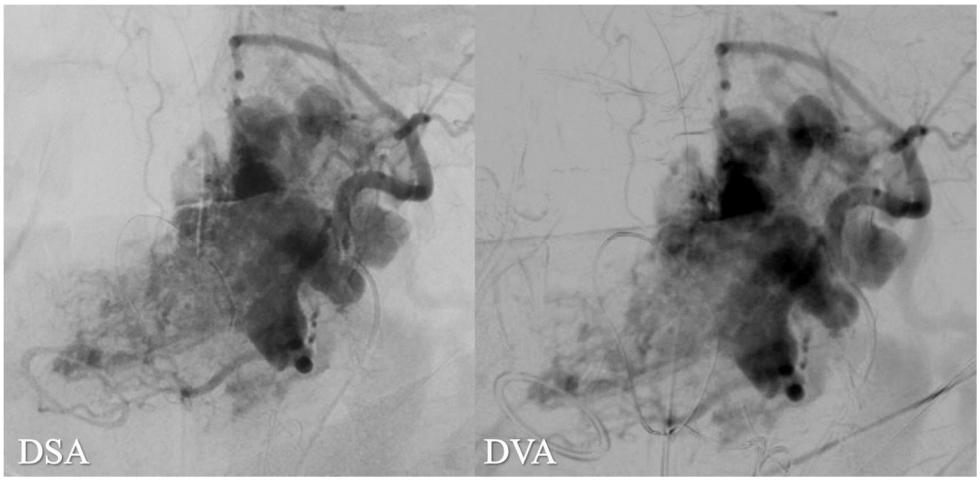

Figure 5. Representative digital subtraction angiography–digital variance angiography image pair of a head and neck arteriovenous malformation

(Images from the archive of the Heart and Vascular Center, Semmelweis University; acquired by Edit Dósa.)

DSA, Digital subtraction angiography; DVA, digital variance angiography.

4.1.2. Objective comparison: contrast-to-noise ratio results

We analyzed 132 paired DSA–DVA images. In total, 3,318 ROI pairs were manually placed for CNR analysis. By anatomic region, the distribution of ROI pairs was: upper extremity (n = 501), lower extremity (n = 1,659), head and neck (n = 472), and chest (n = 686).

CNR values for DVA images were significantly higher than those for conventional DSA across all comparisons (all $p < 0.001$), as shown in Figure 6 and Table III. The highest median CNR ratio (DVA/DSA) was observed in upper extremity AVMs, with a median of 2.23 (IQR, 1.18–4.19).

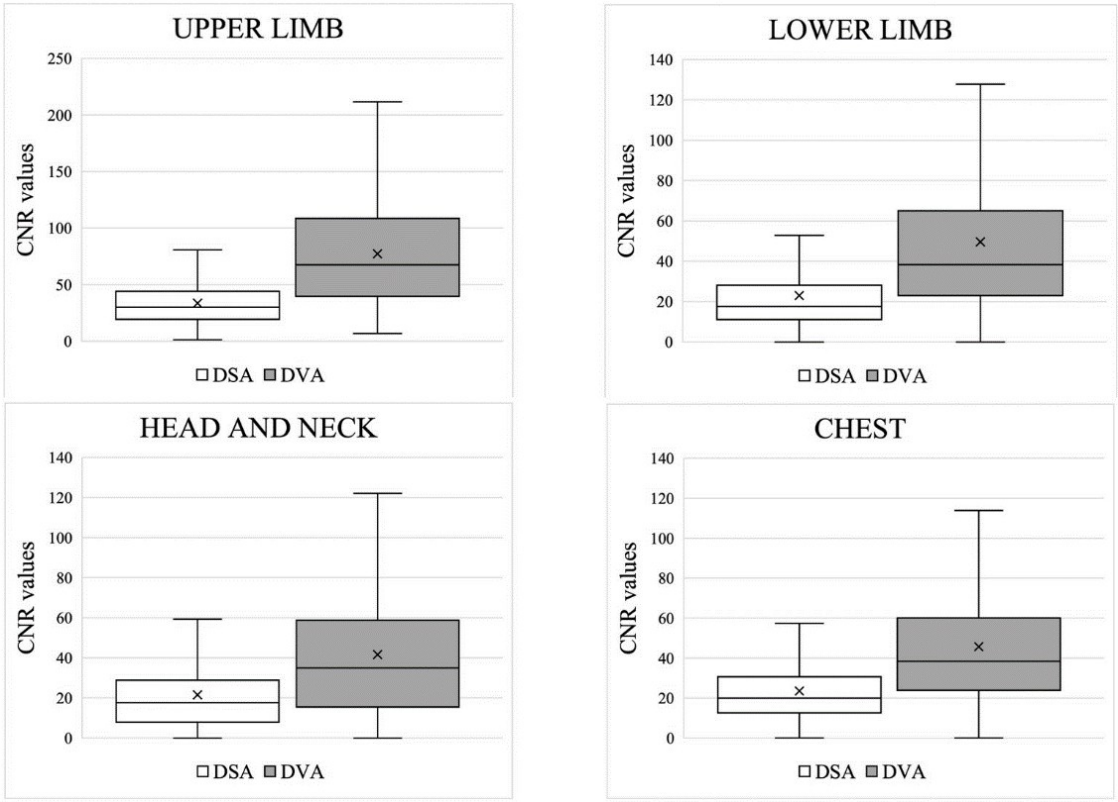

Figure 6. Comparison of contrast-to-noise ratio values between digital subtraction angiography and digital variance angiography image pairs

(Each panel shows the mean, median, interquartile range, minimum, and maximum values.)

CNR, Contrast-to-noise ratio; DSA, digital subtraction angiography; DVA, digital variance angiography.

Table III. Contrast-to-noise ratio values and digital variance angiography-to-digital subtraction angiography contrast-to-noise ratios by anatomic location

AVM location	CNR – DSA median (IQR)	CNR – DVA median (IQR)	*p*-value	CNR_{DVA}/CNR_{DSA} median (IQR)
Overall	19.71 (2.52–61.27)	41.29 (1.90–137.02)	< 0.001	2.00 (0.74–4.49)
Upper limb	29.98 (9.51–72.51)	67.41 (19.90–162.19)	< 0.001	2.23 (1.18–4.19)
Lower limb	17.64 (3.54–60.93)	38.32 (4.63–129.24)	< 0.001	2.06 (0.78–4.63)
Head and neck	17.65 (0.72–57.40)	34.99 (0.30–109.68)	< 0.001	1.72 (0.33–4.33)
Chest	20.01 (5.31–53.30)	38.41 (5.11–107.78)	< 0.001	1.84 (0.78–4.41)

AVM, Arteriovenous malformation; CNR, contrast-to-noise ratio; DSA, digital subtraction angiography; DVA, digital variance angiography; IQR, interquartile range.

4.1.3. Subjective comparison: pairwise visual assessment of image quality

The source angiographic series used to generate the corresponding DSA and DVA images contained a mean of 15 frames per series (range, 5–53). A total of 132 anonymized DSA–DVA image pairs were evaluated on a web-based platform by five experienced clinicians. By anatomic region, image pairs were distributed as follows: upper extremity (n = 14), lower extremity (n = 56), head and neck (n = 23), and chest wall (n = 39). Figure 7 and Table IV summarize the Likert scale quality scores by region and diagnostic feature. In upper extremity AVMs, there were no statistically significant differences between DSA and DVA in the visualization of large vessels, small vessels, tissue blush, or venous phase. For lower extremity and head and neck AVMs, DSA received significantly higher ratings for large vessel, small vessel, and tissue blush visibility. In chest wall AVMs, visibility of large and small vessels also favored DSA. However, these differences were clinically negligible: mean scores fell between “same” (0) and “slightly better” (1), with averages ranging from 0 to 0.4 and no regional mean exceeding 0.55 (Figure 7 and Table IV).

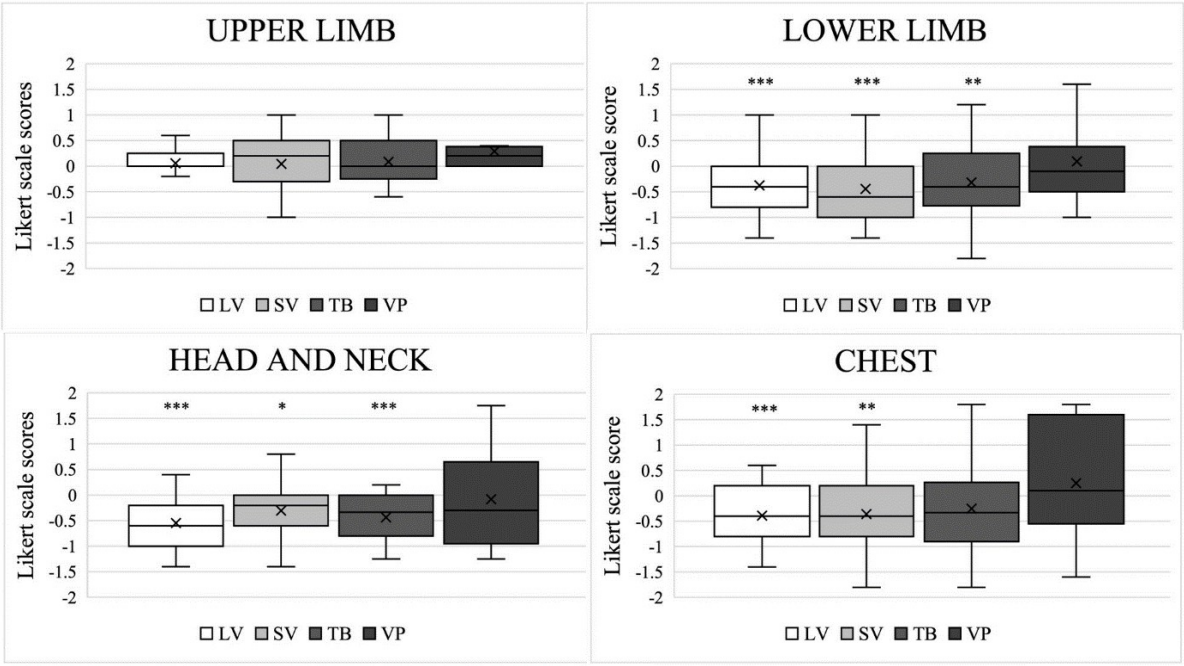

Figure 7. Results of the subjective comparison of digital subtraction angiography–digital variance angiography image pairs based on Likert scale ratings

(Each panel shows the mean, median, interquartile range, minimum, and maximum values.)

*LV, Large vessel; SV, small vessel; TB, tissue blush; VP, venous phase. Negative values indicate an advantage of digital subtraction angiography. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$*

Table IV. Likert scale comparison of digital subtraction angiography and digital variance angiography image pairs by anatomic region and diagnostic criterion

Region	Large vessels	Small vessels	Tissue blush	Venous phase
Overall	–0.36 ± 0.05	–0.34 ± 0.06	–0.25 ± 0.07	–0.06 ± 0.09
Upper limb	0.06 ± 0.09	0.04 ± 0.19	0.09 ± 0.18	–0.29 ± 0.14
Lower limb	–0.38 ± 0.07	–0.44 ± 0.09	–0.32 ± 0.12	0.09 ± 0.21
Head and neck	–0.55 ± 0.11	–0.30 ± 0.12	–0.44 ± 0.11	–0.08 ± 0.36
Chest	–0.39 ± 0.09	–0.36 ± 0.12	–0.25 ± 0.19	0.25 ± 0.36

Values are mean ± standard error of the mean.

Interobserver agreement among the five evaluators was moderate for the assessment of large and small vessels across all regions (Kendall's coefficient of

concordance W between 0.3 and 0.6). Agreement was lower for tissue blush and venous phase visibility, with W values ranging from 0.1 to 0.3 (see Table V).

Table V. Interobserver agreement (Kendall's W) for Likert scale ratings during the subjective evaluation of digital subtraction angiography–digital variance angiography image pairs

Region	Large vessels	Small vessels	Tissue blush	Venous phase
Overall	0.368 (< 0.001)	0.317 (< 0.001)	0.288 (< 0.001)	0.200 (< 0.001)
Upper limb	0.463 (< 0.001)	0.387 (< 0.001)	0.402 (< 0.001)	0.561 (< 0.001)
Lower limb	0.364 (< 0.001)	0.339 (< 0.001)	0.312 (< 0.001)	0.216 (< 0.001)
Head and neck	0.423 (< 0.001)	0.421 (< 0.001)	0.359 (< 0.001)	0.182 (0.050)
Chest	0.363 (< 0.001)	0.303 (< 0.001)	0.204 (< 0.001)	0.145 (0.108)

Values are W (Kendall's coefficient of concordance) with *p*-value in parentheses.

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

4.2.1. Participant characteristics

The final sample comprised three groups: young adult probands with a history of childhood-onset depression (n = 218), their full biological siblings with no history of depression (n = 206), and controls with no personal or family history of major psychiatric disorders (n = 166). Table VI summarizes the demographic and clinical characteristics of these groups. 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 common in both the proband and sibling groups, consistent with established sex differences in depression prevalence. Antihypertensive medication use did not differ across groups, whereas probands and siblings had higher 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 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, with the remainder 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 during BP assessment, whereas none of the controls were ($\chi^2 = 8.59$, $p = 0.014$).

Table VI. Demographic, clinical, and blood pressure characteristics across groups (probands, siblings, and controls)

Parameter	**Probands (n = 218)**	**Siblings (n = 206)**	**Controls (n = 166)**	**F or χ^2**
Female, n (%)	103 (47.2)[a]	108 (52.4)[a]	62 (37.3)[b]	8.54*
Age at assessment (years), mean (SD)	25.1 (2.5)[a]	24.3 (3.7)[b]	21.7 (1.5)[c]	73.61***
Body mass index (kg/m²), mean (SD)	24.65 (5.36)[a]	24.83 (5.61)[a]	23.16 (3.49)[b]	6.02**
Current smokers, n (%)	116 (53.5)[a]	87 (42.4)[b]	41 (24.7)[c]	31.15***
Current BP medication, n (%)	2 (0.9)	3 (1.5)	2 (1.2)	0.26
Systolic BP (mmHg)				
Average (SD)	112.2 (12.1)	111.8 (10.7)	111.4 (11.5)	0.24
Range (SD)	8.6 (6.0)	9.0 (5.6)	9.2 (6.1)	0.41
Diastolic BP (mmHg)				

Average (SD)	73.0 (8.2)[a]	73.4 (8.1)[a]	70.4 (7.8)[b]	7.29**
Range (SD)	7.0 (7.0)	6.9 (4.4)	7.2 (5.4)	0.14
BDI-II score, mean (SD)	7.08 (8.15)[a]	4.66 (5.61)[b]	3.56 (4.22)[b]	15.75***
Age at onset of first depressive episode (years), mean (SD)	10.4 (2.4)	N.A.	N.A.	N.A.
Number of depressive episodes, n (%)				
1	94 (43.1)	N.A.	N.A.	N.A.
2	80 (36.7)	N.A.	N.A.	N.A.
3 or more	44 (20.2)	N.A.	N.A.	N.A.
% of lifetime spent in depressive episodes, mean (SD)	12.24 (11.99)	N.A.	N.A.	N.A.

BDI-II, Beck Depression Inventory-II; BP, blood pressure; SD, standard deviation.

BP average and BP range were computed, respectively, as the mean and the largest within-visit difference among the three seated assessments. All statistics are unadjusted. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Superscript letters (a, b, c) denote significant pairwise contrasts at $p < 0.05$.

4.2.2. Blood pressure characteristics and variability

Short-term BPV was calculated as the within-visit range (maximum minus minimum) of three consecutive brachial BP measurements obtained during a 15-minute seated rest period. As shown in Table VI, there were no significant group differences in mean SBP or systolic BPV, either in unadjusted models ($F [2, 586] < 0.5$, $p > 0.60$) or after adjustment for age, sex, BMI, and family clustering (random intercept for family; $F [2, 440] = 0.70$, $p = 0.50$). Similarly, although mean DBP initially differed across groups ($F [2, 586] = 7.29$, $p < 0.001$), this effect was no longer significant when age was included as a covariate. No significant differences in diastolic BPV were found across groups in

either unadjusted (F [2, 586] = 0.14, $p > 0.80$) or adjusted models (F [2, 587] = 0.62, $p = 0.54$).

4.2.3. Association between depressive history and blood pressure variability in probands

To examine whether aspects of depression were associated with short-term BPV, we conducted regression analyses within the proband group. Models tested whether number of lifetime depressive episodes, age at onset of the first episode, or percentage of life spent in depression 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 more episodes exhibited higher diastolic BPV ($\beta = 1.76$, t [210] = 2.87, $p = 0.005$, $\eta^2_p = 0.039$). For example, the diastolic BP range was 5.86 mmHg (SD = 4.8) in probands with a single episode and 9.53 mmHg (SD = 12.0) in those with three or more episodes. This pattern is consistent with a dose-response relationship between depression recurrence and autonomic dysregulation (see Figure 8).

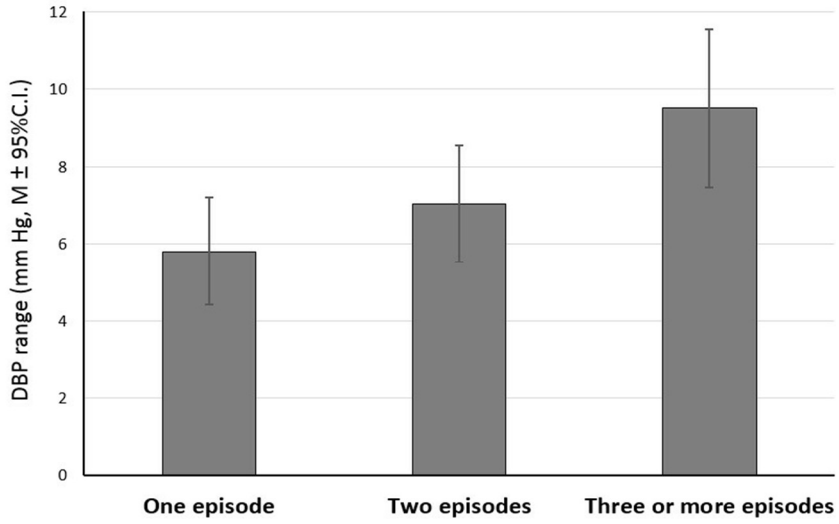

Figure 8. Number of lifetime depressive episodes and diastolic blood pressure range among probands (adjusted for sex, age, body mass index, and smoking status)

CI, Confidence interval; DBP, diastolic blood pressure; M, mean.

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 (β = 0.98, t [210] = 1.82, p = 0.071), suggesting a possible, albeit weaker, relationship.

By contrast, neither age at onset of depression nor percentage of life spent in depression significantly predicted systolic or diastolic BPV (all $p > 0.23$). Furthermore, psychotropic medication use at the time of assessment 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. Discussion

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

In this retrospective, observational study, we evaluated the reliability and clinical applicability of DVA compared with conventional DSA in pediatric patients with extracranial AVMs. To the best of our knowledge, this is the first evaluation of DVA in pediatric endovascular interventions. Our findings show that, although DVA yielded a significantly superior CNR – with a median CNR_{DVA}/CNR_{DSA} ratio of 2.00 – the subjective image quality assessment did not demonstrate a substantial advantage for DVA. In terms of visual quality, DVA images were rated as equivalent to or slightly inferior to their DSA counterparts. Importantly, these differences were not clinically meaningful and did not compromise the overall diagnostic utility of DVA. The absence of clear visual superiority does not detract from DVA's clinical value; its enhanced CNR provides a "quality reserve" that can be leveraged to achieve the ALARA (as low as reasonably achievable) principle in vulnerable pediatric patients.

The CNR values observed in our study align with previously reported trends in adult endovascular interventions, where DVA consistently outperformed DSA in terms of CNR. [29, 84, 86, 95] Historically, DVA research has focused primarily on lower extremity arterial interventions – a common site of atherosclerotic disease – where CNR_{DVA}/CNR_{DSA} ratios ranged from 1.84 to 2.80 with iodinated contrast agents. [29, 84, 86, 95] Our findings in pediatric AVMs corroborate these results, with CNR_{DVA}/CNR_{DSA} ratios of 2.23 for the upper limbs and 2.06 for the lower limbs. These regions benefit from reduced tissue attenuation and minimal motion artifacts, allowing DVA's kinetic imaging algorithm to perform optimally – potentially explaining the enhanced image quality and DVA performance. Similar benefits have been reported in adult carotid imaging, where CNR ratios of approximately 2.1–2.3 favor DVA. [85] The consistency of results across studies and vascular territories supports the generalizability of DVA-related CNR enhancement across age groups. DVA appears to extract more signal from angiographic

series than DSA, owing to its variance-based processing, thereby enhancing vessel conspicuity in a variety of settings.

At the same time, our data also highlight that DVA's relative benefits are context dependent, particularly with respect to motion and anatomic factors. In regions prone to motion artifacts, DVA's CNR advantage can be attenuated. Compared with adult populations, pediatric head and neck imaging is more challenging, yielding a lower CNR_{DVA}/CNR_{DSA} ratio of 1.72 in this region (versus 2.1–2.3 reported in adults). [85] This is likely attributable to the practical challenges of pediatric craniofacial angiography: children's involuntary movements – irregular breathing, swallowing, crying, and spontaneous motion – induce image blur that disproportionately affects DVA processing. Because DVA amplifies temporal intensity fluctuations, motion can be emphasized, reducing the net gain in image CNR. A similar pattern is observed in other regions affected by organ motion (e.g., the liver), where DVA's advantage diminishes. For example, in transarterial chemoembolization (TACE) – a procedure highly susceptible to respiratory and cardiac motion – studies have reported only a modest median CNR ratio (DVA/DSA) of approximately 1.24-fold over DSA. [96] Our chest wall results (thoracic AVMs) outperformed TACE-specific outcomes, showing an intermediate benefit with a CNR ratio of 1.84 – better than in TACE interventions but still less pronounced than in the extremities. We suspect this reflects fewer confounding factors: respiratory motion in the chest, while present, was likely less severe than intra-abdominal organ motion, and our chest wall lesions were not subject to additional image degradation from bowel gas or diaphragmatic movement. These observations reinforce that DVA's performance is optimal when patient or organ motion is minimal. In a nearly static anatomic context, the advantages of DVA can be substantial. For instance, in prostatic artery embolization (a procedure with minimal motion) DVA yielded a > 4-fold improvement in CNR relative to DSA (CNR ratio 4.11). [97] Collectively, these findings illustrate how technical factors – especially motion and tissue attenuation – mediate DVA's efficacy: DVA excels in settings with less motion and attenuation, whereas its edge narrows in more challenging environments such as the head and neck of an awake child or a moving visceral field.

Despite DVA's clear superiority in CNR, we found no consistent improvement in subjective image quality over DSA. In our study, blinded experts often rated DVA image quality as equivalent to that of DSA and, in certain domains, slightly lower; however,

these differences were small and clinically negligible – findings that contrast with prior reports of superior subjective quality for DVA. [26, 29, 95] Several pediatric-specific factors may explain this discrepancy. First, smaller anatomic structures and reduced compliance increase susceptibility to motion artifacts, which can be amplified by DVA's sensitivity to temporal intensity fluctuations, thereby degrading perceived sharpness. Second, at our center, interventional radiologists routinely perform superselective catheterization and angiography in children to minimize contrast use, producing already high-quality DSA images and effectively creating a ceiling effect that DVA may not readily surpass. Third, the smaller body size in pediatric patients, with less tissue and smaller fields, reduces radiation scatter and X-ray attenuation, yielding inherently better image quality even with low-dose DSA. Taken together, pediatric angiography benefits from favorable conditions (small body size, short source-to-object distance, and optimized protocols), so DVA's potential visual advantage may be less apparent – especially under standard pediatric imaging that uses lower contrast volumes and reduced radiation doses. Accordingly, the lack of subjective quality improvement with DVA does not imply a flaw in the technique; rather, it reflects the exceptional baseline quality of modern DSA and the unique challenges inherent to imaging children.

The clinical implications of our findings are significant: the substantial improvement in CNR achieved with DVA represents a potential quality reserve that can be redirected toward patient safety. This enhanced CNR ratio can be leveraged to reduce radiation dose or contrast agent volume while preserving diagnostic utility. Recent studies support this concept; for example, in carotid interventions DVA permitted approximately a 50% reduction in iodinated contrast without loss of image information. [85] Likewise, applying DVA in lower extremity angiography enabled about a 70% decrease in radiation exposure compared with standard DSA protocols. [98] A 2023 randomized controlled trial confirmed that DVA's quality reserve can be used in routine practice to substantially lower radiation doses in lower extremity angiography without compromising image quality or diagnostic yield. [86] These advantages likely extend to pediatrics: if DVA images are inherently less noisy, diagnostically acceptable clarity can be achieved with a fraction of the usual X-ray dose or contrast volume. This is particularly crucial for children, who stand to benefit most from dose-sparing techniques. Our results therefore

reinforce the view that DVA could be a valuable tool for advancing pediatric imaging safety.

This study has several limitations. Despite the extended study period, the sample size remains limited, a reflection of the rarity of pediatric AVM interventions, which reduces statistical power and generalizability. In addition, the retrospective, observational design at a single high-volume center restricts control over confounding variables and may introduce selection bias, thereby limiting external validity. Although image presentation was anonymized and randomized, inherent visual cues may still have introduced bias during the subjective evaluation; this bias could act in either direction (novelty preference vs. familiarity with the conventional appearance) and was not fully controllable. Furthermore, our analyses focused on immediate image quality metrics; we did not directly assess clinical outcomes or diagnostic accuracy, which are the ultimate indicators of effectiveness. These limitations underscore the need for prospective studies to confirm DVA's potential advantages. In particular, a randomized controlled trial that acquires angiographic series at systematically reduced doses (or with diluted contrast) using DVA would allow determination of how far exposure can be lowered while maintaining diagnostic sufficiency. Because pediatric physiology demands tailored approaches, future protocols should also incorporate strategies to minimize motion – e.g., age-appropriate sedation or distraction techniques – during image acquisition. Such studies could establish concrete dose–image quality thresholds and help formulate pediatric-specific guidelines for the clinical use of DVA.

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

We examined whether young adults with a history of early-onset depression or a familial risk of depression exhibit altered short-term BPV, and whether depression characteristics (e.g., recurrence, age at onset, duration) relate to BPV. The main findings indicate that, at the group level, there were no significant differences in systolic or diastolic BPV among participants. However, within the proband group, those who had experienced a greater number of depressive episodes showed significantly higher short-term BPV – specifically in DBP. The DBP range increased from approximately 5.9 mmHg in probands with a

single lifetime episode to about 9.5 mmHg in those with three or more episodes. This association persisted after adjustment for age, sex, BMI, and smoking. High-risk individuals who had never been depressed (siblings) did not exhibit elevated BPV relative to controls, implying that familial predisposition alone is insufficient to produce BP dysregulation by this age. Taken together, cumulative depression burden shows a measurable, though modest, association with BPV even in young adults, whereas being at risk or having a history of a single early episode, by itself, does not confer detectably aberrant BPV.

The absence of between-group differences in BPV suggests that the physiologic impact of depression on short-term BP dynamics may require a threshold of exposure to manifest. Depression is recognized as an independent risk factor for CVD and is thought to affect CV regulation via autonomic and endocrine pathways. [99] Prior studies have largely examined middle-aged or older adults and often report greater short-term BPV among clinically depressed individuals. A recent systematic review by Shahimi et al. concluded that mental illness is associated with increased BPV "regardless of age", with depressed individuals showing higher ambulatory and home monitor BPV on average. [82] Our findings suggest that, in the twenties, such BPV differences may not yet be evident – young adults may not have accumulated sufficient long-term CV alterations for BP regulation to be chronically disrupted. In our sample, probands were on average ~25 years old, and most were in full or partial remission at assessment. It is plausible that current depressive state exerts a more immediate influence on BPV than remitted disease. Although underpowered, our post hoc comparison hinted that the small subset of currently depressed probands (n = 20) had higher mean diastolic (M = 9.0, SD = 15.3) and systolic BPV (M = 12.2, SD = 11.5) than those in remission (n = 197; diastolic: M = 6.8, SD = 5.5; systolic: M = 8.3, SD = 5.1). Thus, a reasonable interpretation is that depression's impact on BPV is conditional – more apparent during active illness or following substantial recurrence, but not a blanket effect in all young people with past depression.

The finding that the number of depressive episodes predicted higher BPV supports a cumulative burden hypothesis: each episode may act as a significant psychosocial and physiologic stressor, accompanied by changes in ANS balance, inflammation, and health behaviors that can acutely affect CV function. Repeated episodes could therefore lead to

more persistent alterations in vascular tone or baroreflex sensitivity, manifesting as greater variability in BP readings. Moreover, depression-related differences in BPV were specific to DBP, whereas the effect on systolic BPV was weaker and not statistically significant (only a nonsignificant trend toward higher systolic BPV with more episodes). This pattern aligns with other reports: for example, Sible et al. found that subthreshold depressive symptoms in older adults correlated with greater visit-to-visit variability in DBP, but not in SBP. [100] Mechanistically, SBP, especially in young, healthy individuals, is strongly influenced by stroke volume and large artery compliance, whereas DBP more closely reflects peripheral vascular resistance and arteriolar tone. Short-term fluctuations in vascular resistance (e.g., transient stress-induced surges in sympathetic outflow) would be expected to influence diastolic pressure most. Depression is well known to be accompanied by autonomic dysregulation, particularly a shift toward sympathetic dominance and reduced parasympathetic (vagal) tone. [49, 50] Meta-analyses of HRV, for instance, consistently show decreased vagal cardiac control in depressed individuals, indicating ANS imbalance, which could plausibly contribute to greater variability in vascular tone and thus DBP. [101, 102]

The percentage of life spent depressed did not correlate with BPV, suggesting that BPV may be particularly sensitive to disruptions or discontinuities in functioning associated with the on–off nature of depressive episodes, whereas prolonged continuous exposure to depression exerts only a minimal effect. This interpretation is consistent with epidemiologic evidence: Nabi et al. reported that individuals with multiple depressive episodes over a 24-year period had higher odds of developing hypertension compared with those with infrequent or no episodes. [103] Age at depression onset also showed no relationship with BPV. By design, all probands had childhood-onset depression (mean onset ≈10 years; restricted range), limiting the ability to detect any effect of earlier versus later onset within this group. It remains possible that later-onset depression (e.g., midlife onset) might relate differently to BPV, perhaps because late-onset depression is often linked with vascular disease (the “vascular depression” hypothesis). [104] By contrast, early-onset depression is more often tied to genetic and developmental factors and tends to run a more recurrent course. [105]

Depression is often accompanied by behaviors such as smoking and reduced physical activity, which were more common in our probands and could contribute to

higher BPV or elevated BP levels. Although we adjusted statistically for smoking and BMI, residual confounding by lifestyle or unmeasured metabolic factors may partially account for the link between recurrent depression and BPV. An earlier study in this cohort found that early-onset depressed probands exhibit more components of metabolic syndrome (e.g., higher triglycerides, lower high-density lipoprotein cholesterol) than controls. [106] Metabolic syndrome and insulin resistance can lead to endothelial dysfunction and greater BP lability. Thus, it is conceivable that metabolic dysregulation mediates part of the BPV elevation observed in those with multiple depressive episodes.

The observation that high-risk siblings did not differ from controls in BPV provides additional insight. Despite sharing familial/genetic backgrounds with probands, these young adults with no personal history of depression showed normal BPV ranges, suggesting that depression itself – rather than genetic risk alone – is a key driver of any BPV changes. Siblings and probands resembled each other (and differed from controls) on certain CV risk factors, such as higher BMI and smoking rates, implying that a familial predisposition to depression may cluster with health behaviors or traits (e.g., obesity, smoking, subtle BP elevation) that raise baseline CV risk. In this sense, siblings serve as a natural "control" for shared familial factors (genetic or environmental), helping to isolate the effect of the illness itself. Our data therefore suggest that any substantial impact of depression on short-term BPV emerges only in the presence of a clinical depression history; genetic/familial risk without depression did not manifest as abnormal BPV in this age group.

Our finding that young adults with a heavier depression burden exhibit elevated BPV raises the possibility that BPV could serve as an early biomarker of CV risk in psychiatric populations. Accumulating evidence indicates that depression facilitates unhealthy behaviors and physiologic dysregulation (hyperactivation of stress pathways, inflammation, autonomic imbalance). [50–52] If short-term BPV reflects this dysregulation, it could be incorporated into clinical monitoring: BPV assessment is simple to implement and may flag young patients whose CV systems are under higher strain, prompting preventive interventions.

While this study leverages a large, well-characterized sample with standardized psychiatric evaluations by trained clinicians, several limitations warrant consideration. (1) BP was measured on a single day using three "office-style" readings, providing only

a limited snapshot of short-term variability. (2) Protocol adherence may have varied slightly; despite standardization, small differences in cuff placement, timing, or rest periods can introduce noise. (3) The cross-sectional design limits causal inference. (4) Controls and siblings were not perfectly age-matched (controls were, on average, slightly younger); we adjusted for age, but residual confounding by age or other demographics remains possible. (5) Only 20 probands were in a current depressive episode at assessment, which severely limited power to compare them with remitted probands on BPV.

6. Conclusions

6.1. Study I (Comparison of the performance of digital variance angiography and digital subtraction angiography in children with arteriovenous malformations: a retrospective observational study)

DVA offers a significant CNR advantage over conventional DSA in pediatric AVM imaging. Although subjective visual quality does not surpass that of DSA, the demonstrated quality reserve provides a compelling opportunity to reduce radiation dose and/or contrast agent volume in children while preserving diagnostic utility.

6.2. Study II (Short-term blood pressure variability among young adults at high or low risk for depression)

While group level differences in BPV were not significant, a higher number of depressive episodes among probands was associated with increased diastolic BPV, suggesting that the cumulative burden of depression may impact CV regulation even in early adulthood. These findings highlight BPV as a potential early marker of autonomic change linked to recurrent depression and underscore the importance of long-term monitoring in at-risk populations.

7. Summary

This thesis examines two complementary aspects of CV diagnostics in youth and young adults: the performance of DVA in pediatric endovascular imaging and the role of short-term BPV as a potential early biomarker of CV risk in individuals with a history of childhood-onset depression.

Study I. We assessed the diagnostic utility of DVA versus conventional DSA in 132 angiographic image pairs from pediatric patients with extracranial AVMs. DVA yielded consistently higher CNRs, with a median CNR_{DVA}/CNR_{DSA} ratio of 2.00, most notably in upper limb AVMs (2.23). Subjective image quality showed no significant advantage for DVA over DSA; while DSA was slightly preferred in certain vascular territories, the differences were minor and clinically negligible. These findings support the potential of DVA to maintain diagnostic quality while enabling reductions in radiation and contrast dose.

Study II. We examined the relationship between depression burden and short-term BPV in a sample of 218 young adult probands with childhood-onset major depression, 206 high-risk siblings, and 166 low-risk controls. The number of lifetime depressive episodes significantly predicted increased diastolic BPV, suggesting that recurrent depression may exert an early cumulative physiologic burden on vascular function and highlighting the importance of early CV monitoring.

Together, these studies underscore the significance of both technological innovation and psychosocial context in CV diagnostics. DVA offers a promising avenue for dose reduction in children, whereas short-term BPV may serve as a sensitive, accessible marker of long-term CV risk in psychologically vulnerable populations. Both approaches emphasize the need for individualized CV assessment strategies across the lifespan.

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9.1. Peer-reviewed articles with relevance to the current work

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

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Abstract

Background Reducing contrast agent and radiation exposure is paramount for pediatric patients. Digital variance angiography (DVA) might address this need by increasing the contrast-to-noise ratio (CNR).

Materials and methods A total of 132 raw iodinated contrast angiograms of 10 children (mean age: 12 years) who had endovascular procedures for arteriovenous malformations were retrospectively processed for DVA analysis. The CNR of the DVA and digital subtraction angiography (DSA) images was calculated. The visual image quality was assessed using a four-point Likert scale. Statistical analyses were based on the Wilcoxon signed-rank test and one-sample *t*-test.

Results The CNR was determined and compared for 3,318 regions of interest in 132 image pairs in four anatomical regions (upper limb (UL), lower limb (LL), head and neck (HN), and chest (CH)). DVA outperformed DSA, with a median overall CNR_{DVA}/CNR_{DSA} ratio of 2.00 (UL, 1.83; LL, 1.71; HN, 2.06; CH, 2.23; all $p < 0.001$). The paired Likert scale scores were significantly different from zero in 50% of the comparisons (in all large vessel and small vessel groups, except in the UL region, and the tissue blush group in the LL and HN regions), indicating a superiority of DSA, but the difference was clinically negligible.

Conclusion Although DVA improved CNR, it did not surpass DSA in subjective image quality, possibly due to motion artifacts and the high baseline quality of DSA images.

Relevance statement The enhanced CNR seen with DVA indicates a potential quality reserve that could be exploited to safely reduce contrast agent dose and radiation risks in pediatric patients, who are more susceptible to the long-term effects of radiation.

Key points

- In previous studies, DVA was superior to DSA due to a higher CNR and better image quality. However, no evidence was available regarding pediatric endovascular procedures.

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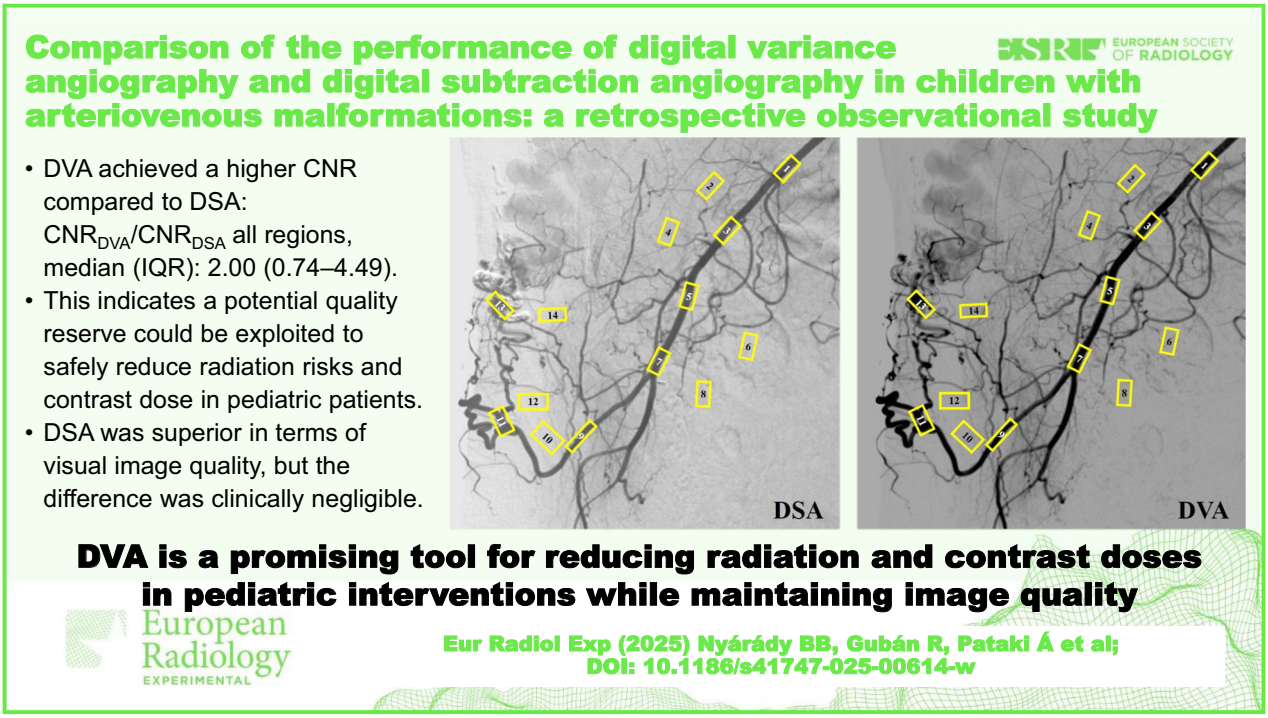
- While DVA exhibited a marked advantage in terms of the CNR, it was unable to surpass DSA in terms of visual assessment.
- The enhanced CNR seen with DVA indicates a potential quality reserve that could be exploited to safely reduce contrast agent dose and radiation risks in pediatric patients.

Keywords Angiography (digital subtraction), Arteriovenous malformations, Child, Contrast media, Radiation protection

Graphical Abstract



Background

Congenital vascular malformations are a subset of vascular anomalies typically diagnosed in the first two decades of life, affecting approximately 0.5% of the European population [1]. In 1996, the International Society for the Study of Vascular Anomalies established a comprehensive classification system for vascular anomalies, which was revised in 2018 [1, 2]. Arteriovenous malformations (AVMs) are a prevalent subtype of vascular malformations. The above classification defines AVMs as high-flow vascular anomalies [1, 2]. Catheter-directed angiography is essential for planning and performing invasive treatment of AVMs [3, 4]. Pediatric AVMs present a unique clinical challenge due to the complexity of the lesions and the long-term radiation risks, as reducing the size or preventing the growth of AVMs is usually achieved by multiple radiological interventions rather than a single one.

The conventional method of catheter-directed angiography involves administering an iodinated contrast agent, either intra-arterially or intravenously, to visualize blood vessels. Meticulous removal of the radiopaque structures from the images ensures an accurate assessment of blood vessels. The resultant images are digital subtraction angiography (DSA) images. Notably, iodinated contrast agents are potentially toxic, particularly in patients with impaired renal function. Moreover, ionizing radiation exposure has non-negligible adverse effects on the patient (especially in younger age groups) and the personnel conducting the procedure [5–7].

A substantial body of research is underway to determine the optimal approach for endovascular interventions, aiming to minimize the use of contrast agents and reduce radiation exposure, while preserving image quality. Digital variance angiography (DVA) is a relatively novel technology based on the principles of kinetic imaging. It

derives data from images obtained with penetrating radiation [8, 9]. Contrary to the DSA method, the DVA approach does not utilize a mask for subtraction. Instead, it calculates the standard deviation of the x-ray attenuation of each pixel. This processing algorithm extracts more information from the raw, unsubtracted acquisitions than the DSA method. Additionally, it improves image quality by amplifying the signal of the moving (flowing) contrast agent while suppressing background noise [10–16].

It has been shown that the superior quality of DVA can be used effectively to reduce the amount of contrast agent [17] or the radiation dose [18, 19]. This dose management capability would greatly benefit angiography in pediatric patients. However, the qualitative and quantitative indicators of DVA images have not yet been compared with those of DSA images in children, in whom catheter-directed diagnostic and/or therapeutic procedures are routinely performed with less contrast agent and reduced radiation doses. Therefore, this retrospective study aimed to investigate the performance of DVA in pediatric patients. AVMs were chosen as the model condition for this study because in these lesions, it is often possible to evaluate different types of vascular structures, tissue blush, and venous outflow simultaneously.

Methods

The study was carried out following the ethical standards outlined in the 1964 Helsinki Declaration [20] and the regulations set by the national research committee. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval number 182/2022). Prior to access, all data were fully anonymized, and the aforementioned ethics committee waived the requirement for informed consent for the study. This retrospective observational study analyzed 10 patients (mean age, 12 years (range, 7–17 years), four males and six females) with a solitary AVM who underwent 15 endovascular interventions between December 2022 and December 2024 at the Heart and Vascular Center of Semmelweis University.

DSA and DVA image generation

Before the diagnostic or therapeutic DSA examination, the interventional radiologist explained the procedure and its possible complications in detail to the patient (if the patient was at least of school age) and the parents, and obtained the parents' verbal and written consent. The endovascular procedures were executed by two interventional radiologists (Á.P. and E.D.), each with over 20 years of experience. The volume and rate of contrast agent administration were tailored to the patient and the lesion, ranging from 15 to 147 mL per intervention. The intra-arterial contrast agents utilized included Ultravist (370 mg I/mL; Bayer AG), Iomeron (300 mg I/mL; Bracco Imaging SpA), and Omnipaque (300 mg I/mL; GE HealthCare Technologies Inc.). The acquisition of raw angiography images was performed at a rate of two or four frames per second using a Siemens Artis zee angiography machine (Siemens Healthineers AG) with a 30 × 40 cm detector. DSA and DVA images were derived from the same raw angiography image series for the study. DSA images were created on the Syngo workstation (Siemens Healthineers AG), while the DVA images were produced using the Kinepict Medical Imaging Tool v5.3 (Kinepict Health Ltd, Budapest, Hungary). Generating DSA and DVA images involved postprocessing steps, such as motion correction (pixel shift) and brightness/contrast adjustment, performed by a dedicated interventional radiologist (E.D.) using Syngo (for DSA images) and Kinepict software (for DVA images). Therefore, there was no discernible difference between the two image types in this respect. The calculated images were then employed to determine the contrast-to-noise ratio (CNR) and web-based visual evaluation.

Image analysis: CNR

To obtain the CNR, regions of interest (ROIs) were manually selected on the AVM and the background. Then, pairs of ROIs were formed, consisting of a vascular ROI (placed on a contrast-filled vessel or blush) and an adjacent background ROI (placed on soft tissue or an unenhanced area). On average, 25 ROI pairs were defined for each AVM (Fig. 1). When a geometric discrepancy arose between the DSA and DVA images due to pixel shift, the ROIs of the DVA image were aligned with the ROIs of the corresponding DSA image. The calculation of the CNR for each ROI pair was completed using the following formula:

$$CNR = \frac{(Mean_v - Mean_b)}{SD_b}$$

where $Mean_v$ and $Mean_b$ refer to the mean pixel intensity value of the vascular ($Mean_v$) and background ($Mean_b$) ROIs, while SD_b refers to the standard deviation value of the pixel intensity of the background ROIs. The CNR was subsequently computed for both DSA and DVA ROI pairs. The ratio of the CNR of DVA to the CNR of DSA (CNR_{DVA}/CNR_{DSA}) was also determined. ROIs were identified using Fiji software (version 2.0.0-rc-68/1.52e; National Institutes of Health).

Image analysis: quality assessment

A web-based survey was conducted in a randomized and blinded manner, with DSA and DVA images evaluated by four interventional radiologists (Á.P., A.B., D.K., and D.H.)

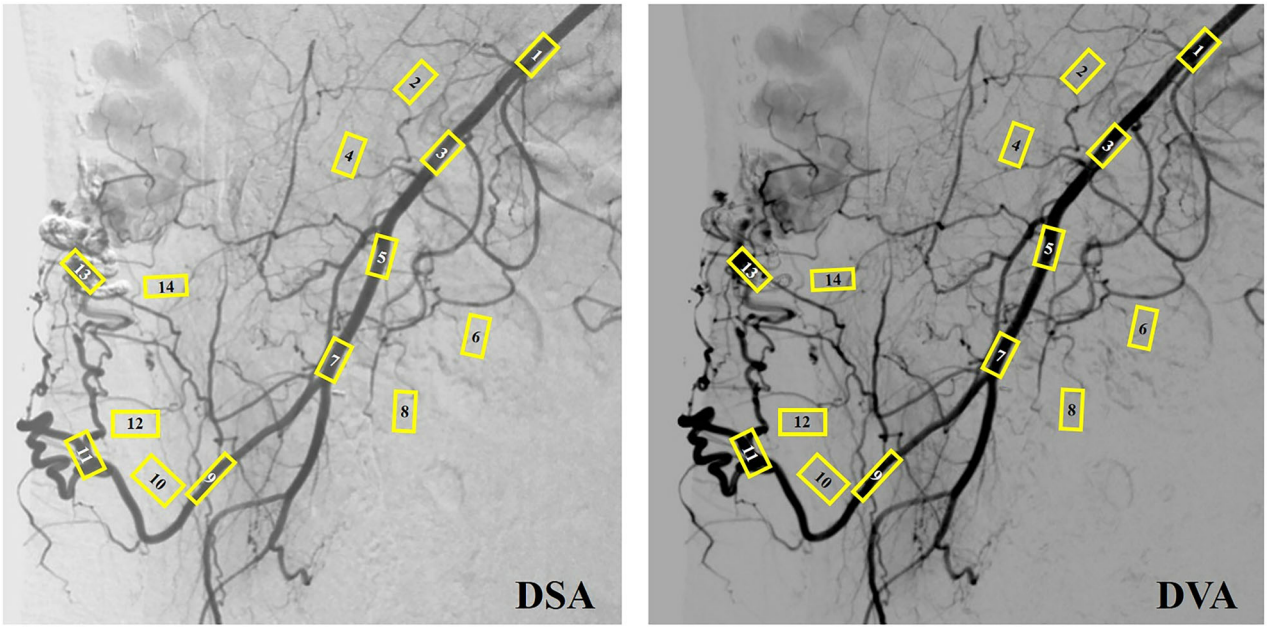


Fig. 1 Contrast-to-noise ratio comparison of digital subtraction angiography and digital variance angiography images in a chest wall arteriovenous malformation. DSA, Digital subtraction angiography; DVA, Digital variance angiography

and a vascular surgeon (Z.M.) with a minimum of five years of experience. The images were compared using a four-point Likert scale, with the visibility and diagnostic value of large vessels, small vessels, tissue blush (if applicable), and the venous phase (if present) considered. The images encompassed four anatomical regions: upper extremities (14 image pairs), lower extremities (56 image pairs), head and neck (23 image pairs), and chest (39 image pairs). The image pairs were graded as follows: 0 = same, 1 = slightly better, 2 = clearly better, and 3 = better in all respects. The image pairs were presented randomly, without revealing the image type. Each image pair was rated on a single occasion by each reader, and all five experts compared all image pairs.

Statistical analysis

The Stata 15.0 (StataCorp LLC) and GraphPad Prism 8.4.2 (GraphPad Software Inc.) programs were used for statistical analysis. The CNR values were expressed as median and interquartile range, and a comparison was made using the Wilcoxon signed-rank test. For the visual assessment scores, the mean and standard error of the mean were determined. The standard error of the mean was used instead of the standard deviation, as the primary goal was not to describe the variability of individual scores, but to report the reliability of the mean estimate. The deviation from 0, representing an equal quality level, was analyzed by the one-sample *t*-test. The normality of the distribution was investigated using the Kolmogorov–Smirnov test. Kendall's *W* was calculated to test for agreement among observers, with possible values of 0 (no agreement), 0.1 (weak agreement), 0.3 (moderate agreement), 0.6 (strong agreement), and 1 (perfect agreement). The sample size ($n = 132$ image pairs) was determined based on available data; a post hoc power analysis confirmed > 95% power to detect medium effect sizes ($r = 0.3$) at a two-sided alpha of 0.05. Statistical significance was defined as $p < 0.05$.

Results

The patients had no known comorbidities and were not taking any regular medications. Two AVMs were identified in the upper limb, four in the lower limb, two in the head and neck region, and two in the chest. Three of the 15 endovascular procedures performed were diagnostic, while 12 were therapeutic.

Image analysis: CNR

The DSA images from which the DVA images were generated contained an average of 15 frames (range, 5–53 frames) per image. A total of 132 DSA-DVA image pairs were evaluated (upper limb, $n = 14$; lower limb, $n = 56$; head and neck region, $n = 23$; and chest, $n = 39$). A total of 3,318 ROIs were selected for the 132 DSA-DVA image pairs (upper limb, $n = 501$; lower limb, $n = 1,659$; head and neck region, $n = 472$; and chest, $n = 686$). The CNR values of the DVA images were found to be significantly higher than those of the DSA images (all $p < 0.001$; see Fig. 2 for

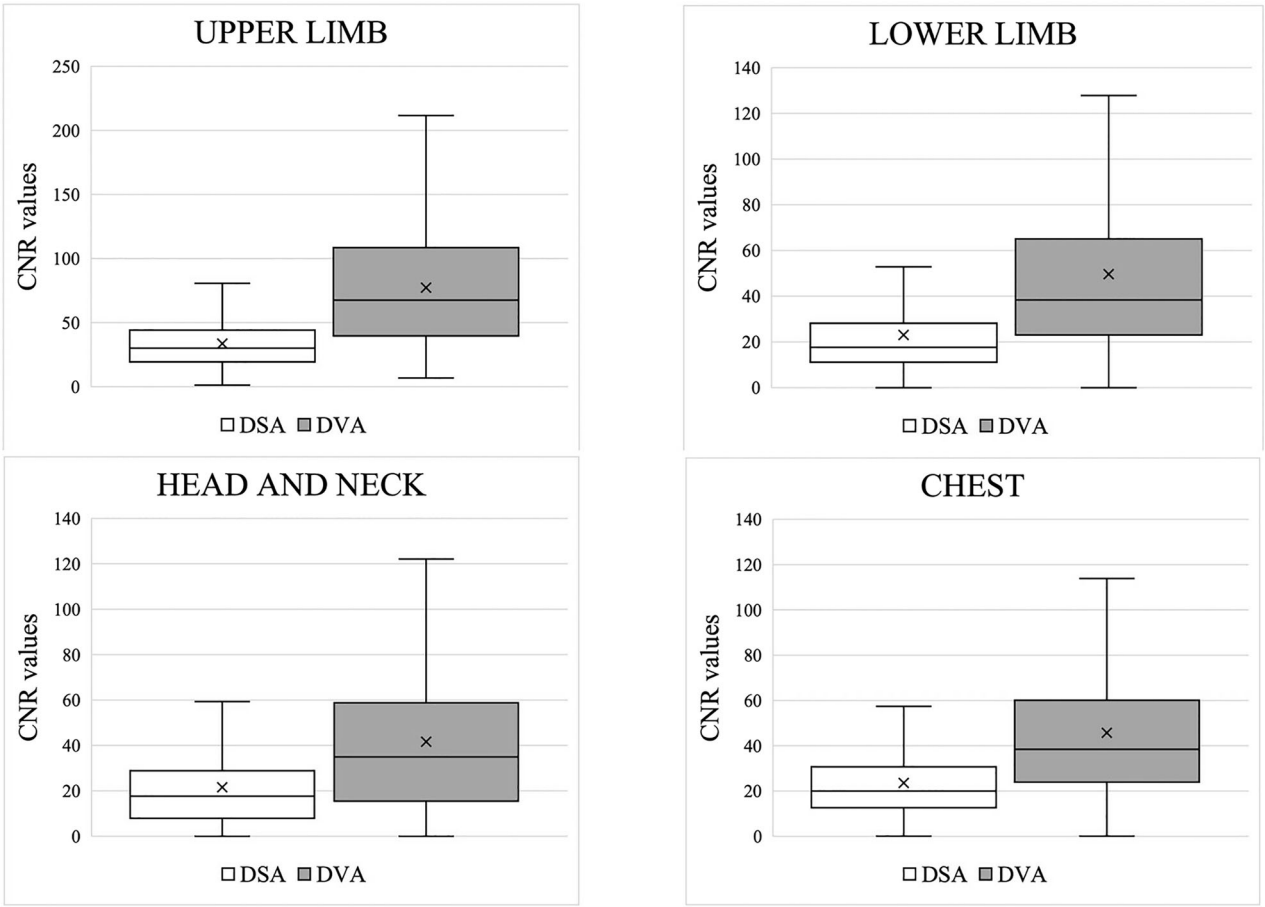


Fig. 2 Results of the contrast-to-noise ratio measurements. CNR, Contrast-to-noise ratio; DSA, Digital subtraction angiography; DVA, Digital variance angiography. The mean value, median value, interquartile range, and minimum and maximum values are shown (in symbol form) for each graph. All $p < 0.001$

Table 1 Results of the contrast-to-noise ratio measurements

AVM	DSA CNR, median (IQR)	DVA CNR, median (IQR)	Number of measurements	*p*-value	CNR_{DVA}/CNR_{DSA}, median (IQR)
All	19.71 (2.52–61.27)	41.29 (1.90–137.02)	3,318	< 0.001	2.00 (0.74–4.49)
Upper limb	29.98 (9.51–72.51)	67.41 (19.90–162.19)	501	< 0.001	2.23 (1.18–4.19)
Lower limb	17.64 (3.54–60.93)	38.32 (4.63–129.24)	1,659	< 0.001	2.06 (0.78–4.63)
Head and neck	17.65 (0.72–57.40)	34.99 (0.30–109.68)	472	< 0.001	1.72 (0.33–4.33)
Chest	20.01 (5.31–53.30)	38.41 (5.11–107.78)	686	< 0.001	1.84 (0.78–4.41)

AVM Arteriovenous malformation, *CNR* Contrast-to-noise ratio, *DSA* Digital subtraction angiography, *DVA* Digital variance angiography, *IQR* Interquartile range

box plots of CNR and Table 1). The highest ratio of the CNR of DVA to that of DSA was observed in upper limb AVMs (2.23 (interquartile range 1.18–4.19); Table 1).

Image analysis: quality assessment

As illustrated in Fig. 3 and Table 2, the Likert scale results depended on the localization of AVMs. For upper limb AVMs, the visibility of large vessels, small vessels, tissue blush, and the venous phase did not differ significantly between DSA and DVA images. Conversely, DSA images significantly outperformed DVA images in displaying large and small vessels and tissue blush for lower limb and head and neck AVMs, as well as large and small vessels for chest AVMs (see Fig. 3 for box plots of Likert scores and Table 2).

When evaluating the large and small vessels across all regions, Kendall's *W* coefficient ranged from 0.3 to 0.6,

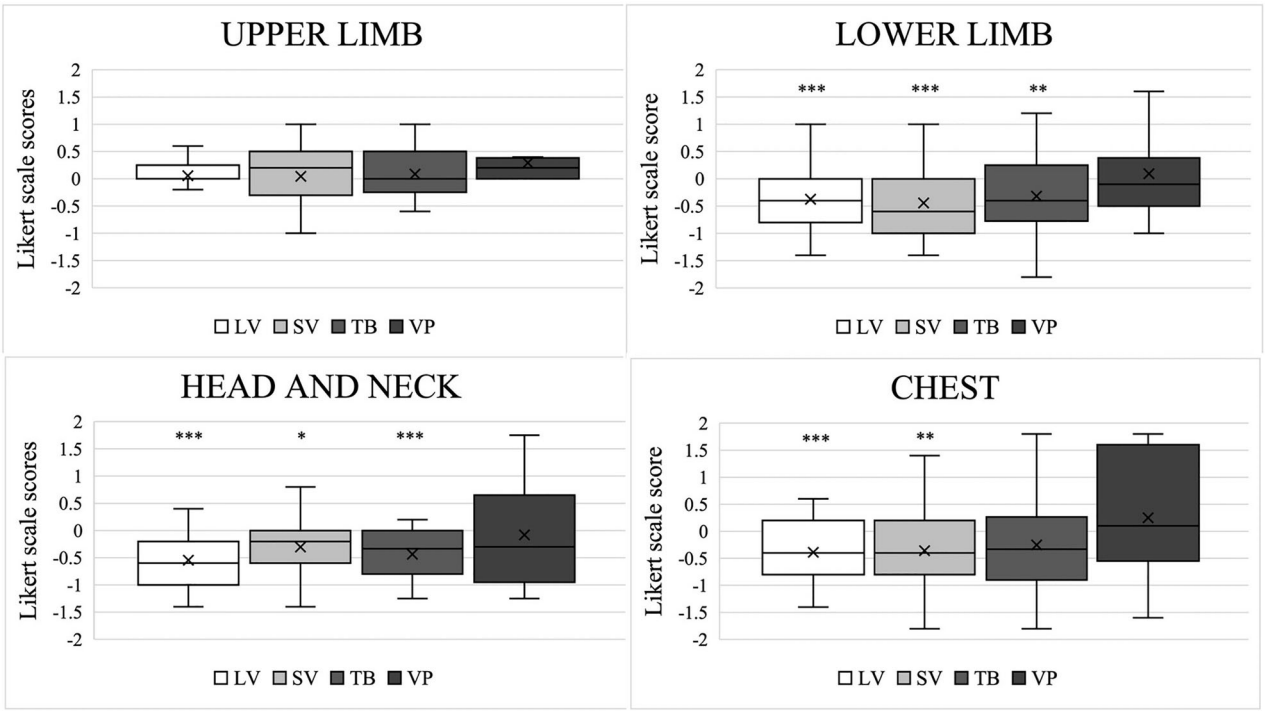


Fig. 3 Likert scale comparison of digital subtraction angiography and digital variance angiography images. The mean value, median value, interquartile range, and minimum and maximum values are shown (in symbol form) for each graph. Negative values indicate an advantage of digital subtraction angiography. AVM, Arteriovenous malformation; LV, Large vessel; SV, Small vessel; TB, Tissue blush; VP, Venous phase. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2 Likert scale comparison scores for digital subtraction angiography and digital variance angiography images

AVM location	Large vessels	Small vessels	Tissue blush	Venous phase
	Likert score, mean ± SEM (number of comparisons, *n*)			
Upper limb	0.06 ± 0.09	0.04 ± 0.19	0.09 ± 0.18	-0.29 ± 0.14
	(14)	(14)	(8)	(8)
Lower limb	-0.38 ± 0.07***	-0.44 ± 0.09***	-0.32 ± 0.12**	0.09 ± 0.21
	(56)	(56)	(49)	(16)
Head and neck	-0.55 ± 0.11***	-0.30 ± 0.12*	-0.44 ± 0.11***	-0.08 ± 0.36
	(23)	(23)	(19)	(8)
Chest	-0.39 ± 0.09***	-0.36 ± 0.12**	-0.25 ± 0.19	0.25 ± 0.36
	(39)	(39)	(21)	(10)

Negative values represent an advantage of digital subtraction angiography
AVM Arteriovenous malformation, *SEM* Standard error of the mean
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

suggesting moderate interrater agreement. A weaker agreement was observed among the raters for the tissue blush and venous phase, with Kendall's *W* values ranging from 0.1 to 0.3 (Table 3).

Discussion

This study aimed to compare the performance of DVA technology with that of DSA in pediatric patients with AVM undergoing endovascular procedures. The study found that, while DVA exhibited a marked advantage in terms of CNR (CNR_{DVA}/CNR_{DSA} ratio of 2.00), it was unable to surpass DSA in terms of visual assessment per the prevailing protocol because the visual image quality of DVA was either equivalent to or marginally inferior to that of DSA. We believe that this small discrepancy in visual quality is of negligible clinical relevance and is unlikely to impact the overall diagnostic efficacy of DVA.

Table 3 Interrater agreement

Arteriovenous malformation	Kendall's concordance coefficient *W*	*p*-value
All		
Large vessels	0.368	< 0.001
Small vessels	0.317	< 0.001
Tissue blush	0.288	< 0.001
Venous phase	0.200	< 0.001
Upper limb		
Large vessels	0.463	< 0.001
Small vessels	0.387	< 0.001
Tissue blush	0.402	< 0.010
Venous phase	0.561	< 0.001
Lower limb		
Large vessels	0.364	< 0.001
Small vessels	0.339	< 0.001
Tissue blush	0.312	< 0.001
Venous phase	0.216	< 0.001
Head and neck		
Large vessels	0.423	< 0.001
Small vessels	0.421	< 0.001
Tissue blush	0.359	< 0.001
Venous phase	0.182	< 0.050
Chest		
Large vessels	0.363	< 0.001
Small vessels	0.303	< 0.001
Tissue blush	0.204	< 0.001
Venous phase	0.145	0.108

Regarding CNR, the present results agree with previous studies on vascular interventions. In these studies, DVA consistently demonstrated a higher CNR than DSA. Most previous studies focused on lower limb endovascular procedures, with a median overall CNR_{DVA}/CNR_{DSA} ratio between 1.84 and 2.8 [12, 13, 18, 19, 21]. These results align closely with our findings (median overall CNR_{DVA}/CNR_{DSA} ratio of 2.00), particularly when considering the results in the lower (CNR_{DVA}/CNR_{DSA} ratio of 2.06) and upper limb regions (CNR_{DVA}/CNR_{DSA} ratio of 2.23), where radiation must penetrate less tissue, and motion-related artifacts affecting image quality are minimal. Studies in the carotid region have reported CNR ratios ranging from 2.06 to 2.25, with DVA prevailing [17]. The rapid and irregular breathing patterns observed in children, in conjunction with involuntary swallowing or crying, have been shown to induce significant motion in the head and neck region, thereby contributing to motion artifacts during imaging procedures. This may explain why lower CNR values were noted in cases of pediatric AVMs located in the head and neck region, with a median CNR_{DVA}/CNR_{DSA} ratio of 1.72. In the context of transarterial chemoembolization of the liver, an intervention susceptible to motion artifacts due to respiration and cardiac pulsations, the median overall CNR_{DVA}/CNR_{DSA} ratio was 1.24 [15]. Notably, our study revealed higher CNR values in the chest region (CNR_{DVA}/CNR_{DSA} ratio of 1.84), where comparable motion artifacts, although present, were less pronounced than in the upper abdominal region. The interference of bowel movements and intestinal gas, which can impede the interpretation of images during transarterial chemoembolization of the liver, may explain the difference between the thoracic and abdominal regions. It is also noteworthy that the AVMs observed in this study were in the chest wall, rather than in the lungs. The findings of a recent intervention, prostatic artery embolization, are very promising, evidencing a more than fourfold advantage of DVA (CNR_{DVA}/CNR_{DSA} ratio of 4.11) [14].

In contrast to prior studies, which indicated the superiority of DVA in visual quality assessments, this study showed that DVA was not superior to DSA in visual quality. The following factors may be responsible for this discrepancy. First, pediatric patients have smaller vessels and anatomical structures that are sensitive to even the slightest movements, and motion-related artifacts may be amplified in certain instances by the variance-based DVA algorithm. Second, (super)selective angiography typically produces high-quality DSA images, thereby setting a high standard that is challenging to exceed. Third, children's smaller body size and lower tissue mass facilitate higher image quality with conventional DSA techniques. Given the optimization of DSA for high-quality imaging, a "ceiling effect" may emerge, where further enhancements in visual quality become difficult to achieve.

The improved CNR observed with DVA suggests a possible quality reserve that could be employed for dose management in pediatric patients, who are more vulnerable to the long-term consequences of radiation. In a prospective study conducted in 2021, Gyánó et al. found that DVA allows for an approximately 70% reduction in DSA-related radiation exposure in lower extremity interventions [18]. The results of a recently published randomized clinical trial demonstrated that the quality reserve of DVA established in previous retrospective studies can be used in selective lower limb procedures to reduce radiation exposure in clinical practice without compromising image quality or the diagnostic value of angiograms [19].

Our study has several limitations. First, the sample size is small (10 patients; 132 image pairs). Second, the study design is retrospective and observational, which introduces potential selection bias, as only patients who underwent clinically indicated procedures for AVM treatment at a single center were included. Third, image interpretation was influenced by subjective expert judgment, although interrater agreement was moderate to strong for most parameters. These factors may limit the generalizability of the findings.

Prospective studies are needed to validate the purported benefits of DVA in pediatric radiological interventions, especially regarding radiation dose reduction. These studies can intentionally reduce the volume of contrast agent and radiation exposure during DVA acquisitions to test whether image quality remains diagnostically acceptable, and then use stepwise dose reduction tiers to set safety thresholds for each vascular region. It is essential to adapt imaging protocols to the distinctive physiological characteristics of children, including implementing age-appropriate sedation strategies to minimize motion during acquisitions, adjusting frame rates, and utilizing shorter acquisition windows. Additionally, the optimization of motion correction algorithms is crucial. Establishing standardized pediatric DVA protocols that incorporate these adaptations would support safer imaging practices.

In conclusion, the results of this study propose that DVA possesses a considerable capacity for enhancing CNR. In light of the encouraging outcomes revealed in earlier prospective studies conducted on lower extremity endovascular procedures, our findings offer a promising avenue for addressing the critical issue of radiation dose management, particularly in the context of pediatric populations. Consequently, further exploration is warranted to investigate the potential of DVA to reduce radiation exposure while maintaining diagnostic image quality in pediatric patients.

Abbreviations

AVM	Arteriovenous malformation
CNR	Contrast-to-noise ratio
DSA	Digital subtraction angiography
DVA	Digital variance angiography
ROI	Region of interest

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We did not use Large Language Models in the manuscript.

Author contributions

Balázs Bence Nyárády: conceptualization, methodology, data curation, writing—original draft preparation, visualization. Renáta Gubán: formal analysis. Ákos Pataki: project administration, data analysis. András Bibok: data curation, data analysis. Zsuzsanna Mihály: data curation, data analysis. Dávid Korda: data curation, data analysis. Dénes Horváthy: data curation, data analysis. Anikó Ilona Nagy: writing—review and editing, funding acquisition. János Pál Kiss: conceptualization, methodology, validation, writing—original draft preparation. Edit Dósa: resources, writing—review and editing, supervision, funding acquisition. All authors have read and agreed to the submitted version of the manuscript.

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Data availability

The data presented in this study are available upon request from the corresponding author. Due to concerns regarding patient privacy, the data are not publicly available.

Declarations

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Semmelweis University (approval number 182/2022).

Consent for publication

Written informed consent was waived by the Institutional Review Board.

Competing interests

During the data collection period, János Pál Kiss was employed by Kinepict Health Ltd, whose proprietary software was utilized for image generation in this study. The remaining authors declare no conflicts of interest.

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Short-Term Blood Pressure Variability among Young Adults at High or Low Risk for Depression

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Abstract: Background: Depression has been shown to have adverse effects on blood pressure (BP) and is associated with high blood pressure variability (BPV). In turn, high short-term BPV has been related to eventual cardiovascular risk. But it is not clear how early in adulthood the detrimental effects of depression on BPV may be discerned, if being at high risk for depression also compromises BPV, and whether the clinical features of depression moderate its adverse effects. We investigated these three issues among young adults using an office-like setting. **Methods:** In total, 218 subjects with a history of childhood-onset major depressive episodes (probands), 206 never-depressed full biological siblings of the probands (high-risk siblings), and 166 emotionally healthy unrelated controls received a psychiatric evaluation and three standardized-sitting BP measurements 5 min apart. Short-term BPV was defined as the maximum difference between measures (range) for each case. The statistical methods included analyses of variance/covariance, chi-square tests, and multiple regression. **Results:** Systolic and diastolic BP decreased over consecutive measurements ($p < 0.001$). After controlling for age, the probands, siblings, and controls did not differ significantly in terms of BPV. However, the number of lifetime depressive episodes did predict the diastolic BP range ($p = 0.005$): probands with the highest number of depressive episodes had the largest short-term diastolic BPV. **Conclusions:** On a group level, the adverse effects on BPV of having experienced or being at high risk for depression are not yet evident during young adulthood. However, the number of major depressive episodes, which is an index of lifetime depression burden, predicts higher BPV. Thus, BPV monitoring for young adults with clinical depression histories could be part of an early intervention program to reduce the risk of eventual cardiovascular disease.

Keywords: blood pressure; short-term blood pressure variability; cardiovascular risk; childhood-onset depression; depressive episodes; hypertension prevention

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1. Introduction

Clinical depression has been recognized as an independent risk factor for cardiovascular disease [1]: it affects cardiovascular regulation [2], impairs autonomic functioning [3], and predicts hypertension [4], coronary heart disease, and all-cause mortality [5]. While the exact mechanism whereby depression affects cardiovascular health and targets organ damage is only partly understood [6], atypical blood pressure (BP) is believed to be one physiological link [4]. In turn, high blood pressure variability (BPV), one of the defining

features of atypical BP, has also been shown to prognosticate cardiovascular problems, eventual multi-systemic damage, and even all-cause mortality [4,6–9]. Blood pressure variability can be determined within various time frames (ultra short-term, such as beat-to-beat; short-term, such as <24 h; long-term, such as visit-to-visit) and quantified via several metrics (e.g., standard deviation [SD], range, coefficient of variation, independent variation, mean true variability) [8,10,11].

As recent reviews reveal [8,10,11], a substantial amount of research has been conducted on BPV and its prognostic utility is widely accepted. There is also an emerging body of literature, that points to an association between BPV and depression. For example, Shahimi et al.'s [12] recent review addressed the relationship between BPV and mental disorders, including depression: they identified 12 studies that met their selection criteria, including six that examined patients with depression or depressive disorders. The review concluded that, in general, individuals with mental illness are significantly likely to have increased BPV regardless of age. Specifically, depressed individuals were found to have higher short-term BPV [12].

However, while the studies of depression and BPV have covered a wide age range, the typical sample generally comprises middle-aged or older individuals. Given that depression (as well as most other major mental disorders) initially emerges in adolescence or earlier [13], it is important to know whether its detrimental effects on BPV are evident already during young adulthood. Relatedly, little is known about whether the clinical features of a person's depression (e.g., number of episodes) contribute to its detrimental effects. And while individuals with a family history of depression are at high risk of developing depression themselves [14], there is no information as to whether being at high risk (versus having already had depression) also predicts elevated BPV.

Finally, given that increased BPV predicts multiple adverse cardiovascular outcomes separately and independently of the average BP, and thus has considerable value [10,11], one question is why this index has not been embraced in everyday clinical practice [11]. One contributing factor may be that there is no standardized protocol for the measurement of BPV [10,12]; alternatively, the various approaches used in research settings may be too cumbersome or burdensome. Indeed, Schutte et al. [11] have noted that despite the dynamic nature of BP and advances in measurement techniques, the most important clinical decisions are usually based on three, static, office-based BP measures using the upper-arm-cuff method.

To study the effect of depression on BPV among young adults, we therefore designed a protocol that should be easy to reproduce in typical clinical settings. We focused on short-term (<24 h) BPV and measured BP in a standardized manner via the upper-arm-cuff method. We studied a sample of young adults who had psychiatrically diagnosed childhood-onset major depressive disorder (referred to as probands from here on), their full biological siblings who never had depression (a group at high risk for depression), and emotionally normative controls free of lifetime depression. Further information on the relationship between clinical depression and BPV may help to identify and address both mental health and cardiovascular issues as early as possible across the age span and thereby improve overall health outcomes later in life.

2. Patients and Methods

2.1. Subjects

Subjects for the present study were ascertained by contacting individuals who have participated in a prior study of juvenile-onset depression and made their contact information available to future research. The prior study recruited probands and their siblings in Hungary from 23 child mental health facilities, serving both urban and rural areas [15], from the year 2000 to 2006 for a genetic and clinical study. Probands had to meet the following criteria: have had a current or recent DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) [16] major depressive or dysthymic episode; be 7–14 years of age; be free of intellectual disability and major medical disorders; and have

at least one biological parent and a 7–17.9-year-old full biological sibling available for the study [17,18]. Controls were recruited from schools in the areas in which most of the probands resided. For more details on the recruitment of school-based controls, please see a previous publication [17].

To gather the overall sample for the present investigation, we re-contacted all available probands, siblings (age 18 or older), and controls. After explaining the study and receiving informed consent, we assessed all those who wanted to participate. We then enrolled all probands; that is, all the young adult subjects with a history of childhood-onset major depressive episodes (n = 218), the full biological siblings of the probands (high-risk siblings) who had no history of depressive disorders (n = 206), and the controls who have continued to remain free of major psychiatric disorders (n = 166).

Table 1 includes characteristics of the samples in the current study. As shown, probands were older than the siblings and controls; and siblings were older than the controls. There were more females among the probands and siblings than the controls (Table 1). The current research study was approved by the Hungarian National Ethical Committee as well as the institutional review boards of the University of Pittsburgh and the Hungarian clinical research sites. All subjects provided written informed consent.

Table 1. Demographic, clinical, and blood pressure characteristics of the samples.

Parameters	Probands (n = 218)	Siblings (n = 206)	Controls (n = 166)	F or χ^2
Female, n (%)	103 (47.2) [a]	108 (52.4) [a]	62 (37.3) [b]	8.54 *
Age at assessment (years), mean (SD)	25.1 (2.5) [a]	24.3 (3.7) [b]	21.7 (1.5) [c]	73.61 ***
BMI (kg/m^2), mean (SD)	24.65 (5.36) [a]	24.83 (5.61) [a]	23.16 (3.49) [b]	6.02 **
Current smokers, n (%)	116 (53.5) [a]	87 (42.4) [b]	41 (24.7) [c]	31.15 ***
Current BP medication, n (%)	2 (0.9)	3 (1.5)	2 (1.2)	0.26
Systolic BP (mm Hg)				
Average (SD)	112.2 (12.1)	111.8 (10.7)	111.4 (11.5)	0.24
Range (SD)	8.6 (6.0)	9.0 (5.6)	9.2 (6.1)	0.41
Diastolic BP (mm Hg)				
Average (SD)	73.0 (8.2) [a]	73.4 (8.1) [a]	70.4 (7.8) [b]	7.29 **
Range (SD)	7.0 (7.0)	6.9 (4.4)	7.2 (5.4)	0.14
BDI-II score, mean (SD)	7.08 (8.15) [a]	4.66 (5.61) [b]	3.56 (4.22) [b]	15.75 ***
Age at onset of first depressive episode (years), mean (SD)	10.4 (2.4)	n.a.	n.a.	n.a.
Number of depressive episodes, n (%)				
1	94 (43.1)	n.a.	n.a.	n.a.
2	80 (36.7)	n.a.	n.a.	n.a.
3 or more	44 (20.2)	n.a.	n.a.	n.a.
Percent of lifetime spent in depressive episodes, mean (SD)	12.24 (11.99)	n.a.	n.a.	n.a.

BDI-II—Beck Depression Inventory II; BMI—body mass index; BP—blood pressure; SD—standard deviation. Average and range of BP were calculated as the mean and the biggest difference among the three assessments in the sitting condition, respectively. All statistics are unadjusted. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Superscript letters denote significant pairwise contrast at $p < 0.05$.

2.2. Assessments

Subjects took part in a larger project that involved a psychiatric assessment and cardiovascular evaluation, including measurements of BP. Psychiatric diagnoses were derived according to DSM criteria [16,19]. The information needed was obtained in direct interviews with subjects by trained clinicians via the semi-structured Interview Schedule for Young Adults: Follow-Up Diagnostic version (ISYA-D), which is an age-appropriate modification

of the tools used with this sample when they were pre-adults [18]. Operational criteria were used to date on- and offsets of psychiatric disorder episodes, which was necessary in order to determine episode numbers for any given disorder [20]. Final diagnoses, including confirmation of number of episodes, were based on consensus among senior diagnosticians. Subjects also completed the self-rated Beck Depression Inventory II (BDI-II) [21], which is a widely used, reliable, and valid index of the severity of current (past 2 weeks) depressive symptoms. In the current article, we report only on outcomes of psychiatric assessment and BP measurements.

2.3. Procedures

Subjects were asked to abstain from caffeine, alcohol, and tobacco for 1 h prior to BP measurements. The lab assistants followed a written protocol in assessing BP. After a brief rest period, three sitting brachial BP measurements were taken on each subject at 5 min intervals. Subjects were asked to sit on a chair with their arms resting at the level of the heart and both feet on the floor. All BP measurements were taken on the right arm by a trained assistant with an Omron M6 digital BP machine (Omron Corp., Kyoto, Japan). Short-term BPV was defined as the maximum difference between measures (range).

2.4. Statistical Analysis

Statistical analyses were conducted using SAS 9.4 software. One-way analyses of variance (ANOVA) and χ^2 tests were used to compare continuous and categorical variables across groups. Data were screened for outliers, and ANOVA was used to examine group differences in average BP and short-term BPV. Then, we used analysis of covariance (ANCOVA) to examine group effects while sequentially controlling for variables known to influence BP, namely sex, age, body mass index (BMI), and smoking (yes/no). To account for dependent observations (probands and siblings were not independent), ANOVA and ANCOVA were estimated using linear mixed-effects models with random intercepts for each family. Least-squares mean estimates were used to perform pairwise comparisons of groups. A power analysis of a one-way ANOVA using the current sample sizes showed that, at 80% power, we could detect an overall significant F-test with the largest pairwise mean difference as little as 0.29 SD (i.e., a medium effect size). This effect size represents a difference of 1.7 mm Hg in systolic BPV and 1.6 mm Hg in diastolic BPV.

In the second set of analyses, confined to probands, BP range as the dependent variable was regressed on three separate variables that mirror clinical features of depression history: number of depressive episodes, age at onset of the first depressive episode, and percent of lifetime spent in depression, controlling for sex, age, BMI, and smoking. Effect sizes of predictors were estimated by partial R^2 in the mixed-effects models and by partial η^2 in the regression models.

3. Results

3.1. Characteristics of the Groups

As shown in Table 1, the three groups did not differ in BP medication use. However, probands and siblings had larger BMIs and were more likely to be smokers than the controls. Not surprisingly, the BDI scores were higher in probands than in siblings and controls. Additionally, probands and siblings had similarly higher diastolic BP (mean of three readings) than the controls (Table 1).

Based on the psychiatric evaluations, 9.2% (n = 20) of the probands were in a depressive episode at assessment and the rest were in remission; none of the siblings and controls were currently depressed (χ^2 = 35.33, $p < 0.001$). Furthermore, while no controls were taking any psychotropic medication, 1.5% (n = 3) of the siblings and 4.1% (n = 9) of the probands were on psychotropic medication at the time of BP assessment (χ^2 = 8.59, p = 0.014).

3.2. Blood Pressure Characteristics and Variability

As shown in Table 1, unadjusted group differences in systolic BP means or ranges were not statistically significant (F [2, 586] < 0.5, $p > 0.60$). Adjusting for age, sex, BMI, and family clusters did not change the means (F [2, 413] = 0.27, $p = 0.77$) or ranges (F [2, 440] = 0.70, $p = 0.50$). While there was a significant group difference in mean diastolic BP (F [2, 586] = 7.29, $p < 0.001$), this effect was no longer significant after covarying for age. Overall, the three groups did not differ significantly in diastolic BP ranges either in an unadjusted model (F [2, 586] = 0.14, $p > 0.80$) or after adjusting for age, sex, BMI, smoking, and family clusters (F [2, 587] = 0.62, $p = 0.54$).

The second set of analyses confined to probands revealed that the number of depressive episodes predicted the diastolic BP range, even after adjustment for covariates ($\beta = 1.76$, t [210] = 2.87, $p = 0.005$, $\eta p^2 = 0.039$) (Figure 1). Namely, probands with the highest number of depressive episodes had the largest diastolic BPV. For example, for probands with one depressive episode, the diastolic BP range was 5.86 (SD = 4.8), while for probands with three or more depressive episodes, the diastolic BP range almost doubled at 9.53 (SD = 12.0). The importance of the number of depressive episodes received partial support when we modeled systolic BPV: while the overall model was not significant (F [5, 210] = 1.13, $p = 0.34$), there was a trend for the number of depressive episodes to be related to larger systolic BP ranges ($\beta = 0.98$, t [210] = 1.82, $p = 0.071$).

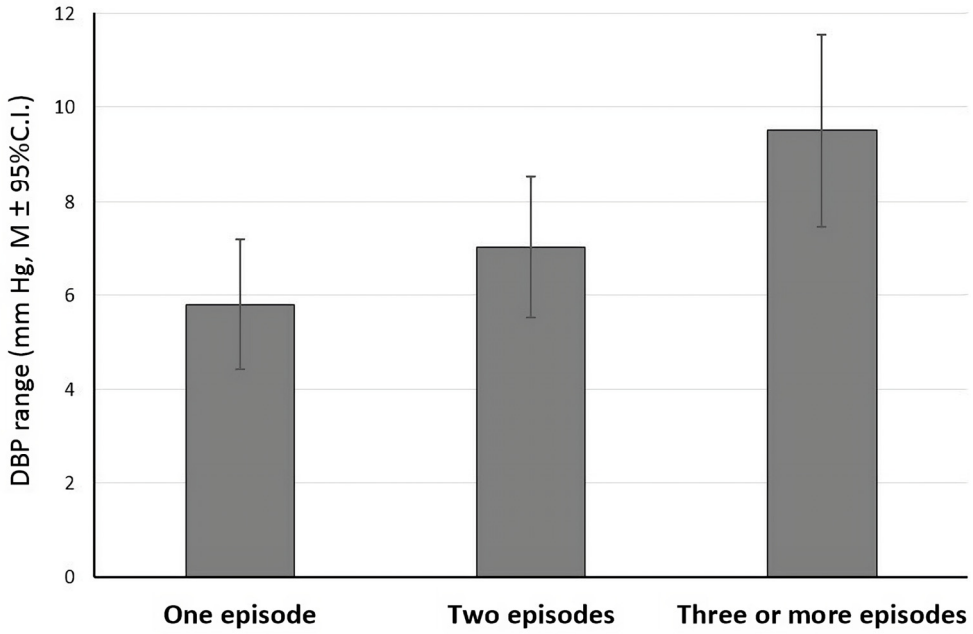

Figure 1. Number of lifetime depressive episodes and diastolic blood pressure range among probands (adjusted for sex, age, body mass index, and smoking). C.I.—confidence interval; DBP—diastolic blood pressure; M—mean.

Additional analyses showed that age at onset of the first depressive episode did not predict the systolic BP range ($\beta = -0.01$, t [210] = −0.02, $p = 0.99$) or the diastolic BP range ($\beta = 0.11$, t [210] = 0.44, $p = 0.66$). Similarly, percentage of lifetime spent in depression had no significant effects on the systolic BP range ($\beta = 0.04$, t [210] = 1.21, $p = 0.23$) or the diastolic BP range ($\beta = -0.02$, t [210] = −0.37, $p = 0.71$). Finally, psychiatric variables appear to have had minimal effects on the BP parameters that were examined. Specifically, subjects who were taking psychotropic medication and those who were not on medication did not differ significantly in either systolic or diastolic BP ranges ($F < 1.77$, $p > 0.19$).

4. Discussion

In the present study, we investigated whether the harmful impact of depression on short-term BPV, which has been reported in mostly middle-aged and older cohorts [12], can also be detected among young adults in their twenties. To extend the study of depression and BPV, we also examined young adults at familial risk for depression and whether the clinical features of depression played a role in BPV. The characteristics of our probands are similar to those previously reported for depressed patients, including higher rates of smoking, lower levels of physical activity, and higher BMI than controls [22,23]. Our finding of declining BP with consecutive measurements (the "white-coat effect") in all groups is also in line with the literature [24,25].

A motivator for the present study was the review by Shahimi et al. [12], which concluded that depression is associated with increased BPV (regardless of age). However, we failed to support that conclusion. We found that young adults with diagnosed depression histories, never-depressed individuals at high familial risk for depression (the siblings), and controls did not differ in either systolic or diastolic BPV. Thus, pathological BPV as a function of depression is not yet detectable when individuals are in their twenties, possibly because that outcome requires a certain level (or amount) of lifetime depression burden that can be reached only with more advanced age. However, because most of the probands were in remission from their last episode of depression, an alternative explanation for our finding is that current rather than past depression (depression history) is the decisive factor in pathological short-term BPV. Post hoc analyses provide some support for the latter explanation: differing in the expected direction, although not significantly so, probands who were experiencing depression (n = 20) compared to those in remission (n = 197) had both higher diastolic BPV (M = 9.0, SD = 15.3 and M = 6.8, SD = 5.5, respectively) and higher systolic BPV (M = 12.2, SD = 11.5 and M = 8.3, SD = 5.1, respectively). However, the n = 20 subset did not provide sufficient power to detect across-group differences in BPV.

The duration and recurrence of depressive episodes may also contribute to the cardiovascular effects of depression [26,27]. Relatedly, we found that short-term BPV was predicted by how many times a person had a diagnosable depression (number of depressive episodes) but not by how much that person's life had been taken up by depression (percent of one's lifetime spent in depression). Thus, BPV appears to be particularly vulnerable to disruptions or discontinuities in functioning, which are mirrored by the starts and ends of discrete episodes of depression, whereas the extent of exposure to depression had only a scant discernable effect. However, as noted above, being a young adult constrained the extent of potential exposure to depression. On the other hand, the relationship between number of depressive episodes and BPV may also derive from the behavioral concomitants of depression, including higher rates of smoking and lower levels of physical activity, both of which are known to affect BP parameters [22,23].

Another feature of depression, age at first onset, had no discernible effect on BP parameters. This result may reflect that our probands had their depression onset in childhood, which yielded a restricted age range. By studying a broader age group and following samples to older ages, at which time the effect of depression on cardiovascular risk becomes more evident, future research will be in a better position to address how the various clinical features of depression contribute to atypical BPV. Early identification of and intervention with depression-prone cohorts may forestall atypical BPV and thus perhaps reduce eventual cardiovascular problems.

Finally, we note that the association of BPV and depressive episodes in our study was evident only for diastolic BPV. Sible et al. [28] likewise found that depression symptoms and diastolic (but not systolic) BPV were related and noted that diastolic BPV is believed to reflect factors such as endothelial dysfunction and sympathetic autonomic nervous system (ANS) over-reactivity. Indeed, depression is known to be associated with atypical ANS functioning, as reflected by an overall reduction in parasympathetically mediated cardiac vagal control [29]. Relatedly, there is evidence that short-term BPV increases are primarily under sympathetic control [30]. Alternatively, given the evidence that probands

have adverse levels of metabolic syndrome components (e.g., lower high-density lipoprotein, higher triglycerides) [31], metabolic syndrome could have mediated the relationship between BPV and depressive episodes.

Our study has several strong features, including a large clinical sample, a sample of high-risk siblings, and standardized psychiatric evaluations by trained clinicians. Additionally, we selected BP range as our measure of BPV because it is clinically meaningful and understandable to healthcare professionals; this measure of variability has also been used in other recent studies (e.g., Sible et al. [28]). Although researchers often prefer more complex metrics of short-term BPV than the range, the alternative indices tend to be highly inter-correlated, as reported by Schutte et al. [11]. In our own dataset, for example, the SD of the mean (one index of variability) correlated with both systolic and diastolic BP range at $r = 0.99$ ($p < 0.01$). Our monitoring method of three consecutive measurements at 5 min intervals can be performed quickly and effectively in an ambulatory office setting and serve as an adjunct to home-based assessment. However, in spite of our study's strengths, the results should be considered in light of the limitation that BP was only sampled on a single day. Assessments spread over several days may provide a more accurate picture of BPV and eventual cardiovascular risks. Another limitation is that the lab assistants may have differed in how precisely they followed the BP measurement protocol. This source of potential variability may be remedied in future studies by monitoring lab assistants' behavior. It is worth noting that our study, like all cross-sectional studies, can uncover associations among the variables of interest, but cannot speak to causal relationships among them. Furthermore, whereas our study included one of the largest samples of young adults with childhood-onset depression, much larger samples are needed to detect very small effect sizes.

In conclusion, the disruptive effect of depression on BP is not yet discernible in young adults in their twenties. However, a greater lifetime burden (indexed by episode number) predicts higher BPV. Thus, BP monitoring for young adults with depression histories may help to identify those at elevated risk for eventual cardiovascular problems and allow the implementation of preventive services.

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