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# SYMMETRY AND ASYMMETRY IN ATHEROSCLEROSIS

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**Abstract**
Atherosclerosis remains the main cause of death worldwide. Most important issues concerning atherosclerosis are hemodynamics and how it affects plaque prevalence and distribution, as well as the symmetry and asymmetry of vasculature and plaques. To present the symmetry in the vascular system an analysis of PubMed and MEDLINE databases was performed. As of February 21, 2023, the results were as follows: for "symmetry" AND "atherosclerosis" there were 47 results; for "symmetry" AND "atherosclerotic lesions" – 20 results; for "symmetry" AND "artery stenosis" – 82 results; for "asymmetry" AND "atherosclerosis" – 87 results. Not without meaning are preventive measures. In the light of the Fourth Industrial Revolution artificial intelligence (AI) solutions help to develop new tools outperforming already existing cardiovascular risk scales. The aim of this paper is to present a current view on symmetry within vasculature and atherosclerosis as well as present a new approach to assess individuals' cardiovascular risk in accordance with precision medicine assumptions. Symmetry and asymmetry within the human vascular system play a crucial role in understanding of arterial diseases, including atherosclerosis. Moreover, it is unavoidable to use AI in cardiovascular risk stratification.
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**Key words:**
**symmetry, atherosclerosis, cardiovascular risk, asymmetry, vascular system, artificial intelligence**

## INTRODUCTION

Dependencies between numerous biological structures and their inside, either physiological or pathological, have been described using *i.a.* Fibonacci number and numerous fractal models [1,2]. Attention to symmetry and asymmetry has been drawn, referring in particular to parity, odd parity, and asymmetry of organs, nerves, and primarily, blood vessels. Interestingly, especially central large vessels present asymmetry. Symmetry owes its current definition to the seventeenth century scientists and until now it has been defined as similarity or exact correspondence of objects. It is gaining in popularity in modern physics and mathematics, presenting mathematical proportions and harmony as a whole.

Geometry is one of the oldest branches of mathematics with origins dating back to antiquity. Friedman et al. [3] were probably the first to suggest an existence of "geometric risk factors" for atherosclerotic lesions. Later, other studies suggested geometry to affect the blood flow pattern, modulate the wall shear stress and therefore create local factors predisposing to the prevalence of atherosclerotic lesions, aneurysms and other pathologies [4]. This phenomenon had been proposed to affect both – symmetry and asymmetry in atherosclerosis distribution [5,6]. It proves that fluid biomechanics and atherosclerotic plaque formation are strictly connected and computational fluid dynamics simulations are a powerful tool to present and study vascular hemodynamics.

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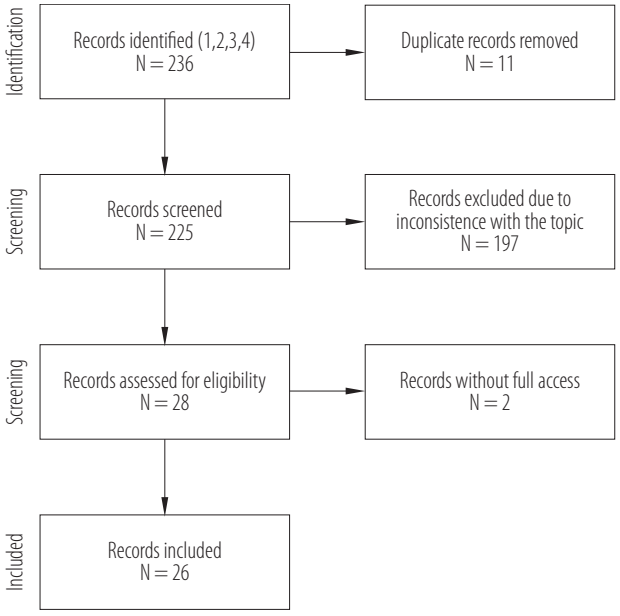


**Figure 1.** PRISMA flow diagram presenting search strategy of particular commands: 1) "symmetry" AND "atherosclerosis"; 2) "symmetry" AND "atherosclerotic lesions"; 3) "symmetry" AND "artery stenosis"; 4) "asymmetry" AND "atherosclerosis"

Hemodynamics and biomechanics have also been connected to create computations defining features of a vulnerable plaque that can strictly lead to plaque rupture and ischemia [7].

As the major cause of death worldwide despite the lowering in mortality rates in the majority of countries [8], atherosclerosis is a chronic and progressive disease manifested as a coronary heart disease (CHD), ischemic stroke and peripheral artery disease (PAD). One of the most important issues concerning atherosclerosis is hemodynamics and how it affects plaque prevalence and distribution. Because of the topicality of the issue, preventive measures are not less important. Well-known cardiovascular risk scales are currently being evaluated and refined with artificial intelligence (AI) tools. The aim of this paper is to present a current view on symmetry within vasculature and atherosclerosis as well as present a new approach to assess individuals' cardiovascular risk.

## METHODS

The study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

The main inclusion criteria was the consistency with the topic.

To present the symmetry in the vascular system an analysis of PubMed and MEDLINE databases with the Boolean operators "AND" and "OR" was performed. As of February 21, 2023, the results were as follows: for "symmetry" AND "atherosclerosis" there were 47 results (1); for "symmetry" AND "atherosclerotic lesions" – 20 results (2); for "symmetry" AND "artery stenosis" – 82 results (3); for "asymmetry" AND "atherosclerosis" – 87 results (4). As of February 21, 2023, there were 236 articles identified. Two researchers conducted searches independently of each other.

There were 2 articles in which the authors could not verify the methods and decide whether they meet the inclusion criteria. These articles were excluded.

Finally, 26 articles met inclusion criteria. The results were divided into subsections presented in the review. The process is presented in Figure 1.

## Central vasculature

### Children

Arteries begin to form at the end of third embryonic week. Primary blood vessels create a primary vascular net and after connecting with the heart, a closed system arises. Further development of the vasculature progresses by budding. In the primary vascular system, the heart pumps the blood into the truncus arteriosus which bifurcation creates a geminate ascending aorta. Both penetrate pharyngeal arches as pharyngeal arch arteries (PAAs) and create 2 descending aortas that run along chorda dorsalis to create umbilical arteries traveling within the umbilical cord to the chorion. Finally, they connect in their middle part and create an odd descending aorta.

Pharyngeal arch arteries are bilateral structures located below the head of the embryo. The first and second PAAs regress quickly and their remnants build parts of the maxillary and stapedial arteries. The third PAAs form common carotid arteries. The fourth right PAA persists as a part of the right subclavian artery and the left PAA forms the central region of the aortic arch. Both sixth PAAs contribute to the proximal part of pulmonary arteries and the second part of the sixth left PAA creates ductus arteriosus, the ductus Botalli, that closes directly after birth [9]. It is interesting how during embryogenesis the symmetrical system becomes asymmetrical. There is only a little data available concerning pediatric patients. In children, the right aortic arch is a common pathology. Asymmetry in the blood volume flow between ascending and descending aorta was described in a study on 14 patients that may have an impact on the potential treatment plan [10]. Another study compared fetal renal arteries and found a 60% symmetry [11].

### Adults

Despite aorta being an asymmetrical vessel, its main branches remain an adequate source to define symmetry and asymmetry on the right and left side. Arterial regions mostly affected by atherosclerotic lesions are bifurcations, branch points and major curvatures [12]. It was shown that the asymmetry of an aortoiliac bifurcation has no influence on building of an atherosclerotic plaque [13]. Within the carotid tree atherosclerotic plaques mostly form in the common carotid and internal carotid artery. Also, not without meaning remains anatomy of an individual and sex [14,15]. First studies suggested that if an individual presents carotid atherosclerosis on one side, it is more likely to present similar lesions on the other side [16,17] which brought up thoughts that atherosclerosis is a symmetrical phenomenon. Adams et al. [16] presented correlations in total wall volumes and calcification scores between sides. The study of carotid plaque symmetry on 177 participants with MRI explored strong correspondence between left and right carotid artery – total vessel volumes, wall volumes, mean wall thickness and normalized wall index as well as a moderate correspondence (correlation) for the presence of calcification or lipid-rich necrotic core on both sides. As a result, a plaque morphology, presence of calcifications and necrotic core may develop symmetrically but the lipid content within plaques varied between sides [18]. In another study, the carotid atherosclerosis score for plaque risk stratification showed right-left discrepancies (only 16 of 47 patients with CAS – 4 presented the same value on the second side, the differences between plaque components have also been stated) which may suggest stronger influence of local rather than systemic factors on high-risk lesions [18]. A symmetry in the distribution of intima-media thickness (IMT) was observed in previous [19]. Another study reported that only 129 of 400 (32.25%) participants presented the same scores on both sides [5]. Benetos et al. [20] found a correlation in inflammatory processes affecting right and left carotid arteries as well as assessed that its severity depends on the presence and intensity of coronary artery disease (CAD), diabetes mellitus and hypertension. Interestingly, asymmetry of the intracranial carotid artery may have an influence on the presence of high-grade cervical stenosis [21].

## Peripheral vasculature

### Brain and intracranial arteries

The Willis circle is built with intracranial arteries (basilar artery, posterior cerebral arteries, posterior communicating artery, anterior cerebral arteries, and anterior communicating artery) and in the majority of cases is a symmetrical structure with a complete contour (50% of healthy brains). However, it can be observed in other anatomical variants (50% of healthy and 80% of dysfunctional brains) and geometrical variations. In these cases hemodynamics and, as a result, also perfusion of the brain may affect the tissue leading to various pathologies [22,23]. Brain base arteries have been analyzed in another study and the most

symmetrical one was the proximal segment of the middle cerebral artery [11]. It was proven that an asymmetry of the internal carotid artery can be connected with various anatomical changes in the circle of Willis [24]. Geometrical changes of the arteries may lead to varied shear stress values, increased risk of an aneurysm rupture, and the prevalence of atherosclerosis [25]. Moreover, the completeness of the Willis circle could affect atherosclerotic plaque distribution within the middle cerebral artery [26,27]. A plaque distribution and progression within intracranial arteries may have a mirror pattern [28].

Mujagić et al. [29] evaluated symmetry, asymmetry, and hypoplasia of intracranial carotid arteries and found that in 94.6% of men and 93.4% of women this artery was symmetrical. Interestingly, the functional asymmetry of the brain may predispose to coronary atherosclerosis [30]. Also, the asymmetry of the stenotic artery region is correlated with characteristic sound emission and its variations [31]. Sfyroeras et al. [32] investigated 29 patients undergoing carotid angioplasty and stenting to assess brain perfusion. The relevance of carotid stenosis did not correlate with brain perfusion. On the other side, asymptomatic patients presented reduced brain perfusion on the ipsilateral side when compared to symptomatic patients.

### Extremities

The distribution of atherosclerosis within lower limbs indicates that in 40% of cases the terminal aorta, its main branches, the distal femoral artery, and popliteal artery are affected [6,33]. Also due to hemodynamic conditions and the local wall shear stress aortic bifurcation and superficial femoral artery are involved in this pathological process more often than others [34]. One of the first studies concerning symmetry in the distribution of lower limb atherosclerosis described 53–76% inter-leg symmetry in arteriographic pictures [35]. Peripheral artery disease (PAD) within lower extremities was proven to be distributed symmetrically but not uniformly. The symmetry of lesions was described as general and concerning all patients with an advanced stage of atherosclerosis, quantified in 13% for external iliac artery and 38% for internal iliac artery if defined as the same stenosis score in both legs, and quantified in 20% if defined as bilaterally diseased artery segments regardless the stenosis score [6]. The study of Vink et al. [36] on femoral arteries of 42 individuals revealed a concordance in the average plaque size, expansive remodelling, and a presence of a lipid-rich core within plaques. Inflammation as a process leading to plaque vulnerability is an important factor investigated in this study. Interestingly, there was no correlation in the distribution of inflammation between sides. Last but not the least is the report of Wikström et al. [37] who found no correlation in the distribution of atherosclerosis between 2 lower extremities in the group of 306 randomly selected individuals. Similarly, another study reported discrepancies in IMT and prevalence of atherosclerotic plaques within the right and left femoral arteries [19]. Another anatomical study among patients with the aortoiliac occlusive disease, assessing the bilateral symmetry and anatomical variants of arteries was performed [38,39]. Barden et al. [40] investigated gate pattern, regularity, and the relationship between PAD severity (assessed with an ankle-brachial index) among PAD patients.

Unfortunately, there is very limited data according to the upper limb vasculature. Only 1 study assessing the symmetry of obstructions itself has been found [41].

### Other arteries

The left subclavian artery, common carotid artery, and intracranial vertebral artery have presented a higher diffusion of atherosclerotic plaques than contralateral arteries in a study performed on 284 stroke patients [42].

Recently, a paper presented by Artysuk et al. [43] have stated that renal size asymmetry >12 mm can be connected with renal artery stenosis.

**Artificial intelligence**

A history of AI begins in 1950 when Alan Turing published a paper "Computing machinery and intelligence" [44]. In 1956, the term "artificial intelligence" was used for the very first time by John McCarthy and David Minsky. Nowadays, a subset of AI, machine learning (ML), is a powerful technology applied to classify already existing data (supervised learning), find unique patterns among these data (unsupervised learning) as well as automatically find new patterns in a specified environment in order to maximize a reward (reinforcement learning). Among these, a special subset of ML – deep learning (DL) – building artificial neural networks and consisting of interconnected nodes should be mentioned. Moreover, various algorithms such as: linear and logistic regression, artificial neural networks, support vector machines, and tree-based methods are used to create new solutions [45]. In the context of environmental health, one of the most actual applications has been the COVID-19 pandemic [45,46]. Artificial intelligence can be also used to improve the safety and health of workers [47]. As atherosclerosis affects the whole population, and even children show initial atherosclerotic changes within arteries, the problem of personalized medicine in the context of every working person is of utmost importance. A cardiovascular risk of an individual can be also assessed by ML solutions.

**Cardiovascular risk prediction and AI**

Techniques based on machine learning can significantly improve the performance of risk predictions, identify potential new ones or find new patterns connecting complex features. Integration of data gathered by large institutions, such as the UK Biobank or the National Institutes of Health (NIH) All of Us Research Program, needs a special approach and algorithms to integrate and interpret them properly. Similarly, more prediction models assessing potential cardiovascular risk have been applied and validated. One of them is the study based on the UK Biobank population including 423 604 individuals without earlier CVD and analyzing 473 available variables [48]. Authors created the machine learning-based model using an algorithmic tool AutoPrognosis. Results outperformed already existing risk scores as well as uncovered new predictors for CVD such as the self-reported health rating and usual walking pace. However, instead of a large population, there were some limitations such as the lack of blood lipid profile, markers of inflammation, and natriuretic peptides which are important in the pathogenesis and treatment of CVD. New predictors have not been further evaluated. Interestingly, Weng et al. [49] presented a comparison of ML methods (random forest, regression model, neural networks, and gradient boosting machines) with an already established American College of Cardiology (ACC)/American Heart Association (AHA) risk prediction algorithm. All AI models performed better in identifying patients at risk for CVD in the future pointing to artificial neural networks to have the biggest improvement in risk stratification. In another study, the ML-based calculator using the support vector machine method (SVM) was evaluated with a 13-year follow-up data set from the Multi-Ethnic Study of Atherosclerosis (MESA) and demonstrated a significant improvement when compared to the ACC/AHA Risk Calculator [50]. A similar study of Unnikrishnan et al. [51] showed better performance of ML methods.

Probably the most commonly used example of supervised learning in medicine is the Framingham risk score (FRS), dedicated to determining chances of the individual's to develop cardiovascular disease and identify those who are most likely to benefit from preventive measures. A nonlinear approach proposed by Orfanoudaki et al. [52] achieved even higher sensitivity and specificity rates than the established score model. Another AI-based model created on >86 thousand patients and then evaluated on >4 thousand individuals who have undergone coronary artery calcium score, as compared with the FRS [53].

Since the carotid ultrasound is concerned an economic, ergonomic, and non-invasive method of indirect cardio-

vascular risk assessment (especially carotid intima-media thickness [cIMT] and carotid plaque burden), combining it with AI methods constantly gains in popularity in stroke and cardiovascular risk prediction [54]. It is known that this factor is predictive for cardiovascular endpoints as well as there is a clear relationship between intima-media thickness and the severity of coronary artery disease and its risk. Yet it is not useful in individuals' risk stratification and the intima-media thickness is a less predictive factor than carotid plaque burden alone [55].

In 2019 guidelines ESC does not recommend cIMT measurement in standard risk estimation among asymptomatic patients, however acknowledged the presence of carotid atherosclerotic plaque as a factor potentially modifying the risk [56]. Interestingly, papers concerning the correlation between IMT and SYNTAX scores have been designed as well, assessing the usefulness of automated measurements and comparing it with manual measurements in the Japanese population [57]. Another study created assumptions and training sets based on conventional risk factors (AtheroRisk-conventional) and carotid ultrasound image-based phenotypes (AtheroRisk-integrated) and then compared them. This is another method proposed to evaluate cardiovascular and stroke risk with the use of AI as a low-cost and effective solution that can be applied into clinics [58]. Studies of Araki et al. [59] and Banchhor et al. [60] combined images of coronary arteries made with intravascular ultrasound and the measurement of cIMT to classify patients into high and low risk.

It is not less important to classify and characterize coronary atherosclerotic plaques, also by assessing their and the vessel's symmetry, in order to perform automated measurements of prognostic biomarkers directly from image data. Optical coherence tomography (OCT) created a possibility to perform AI-based analyses concerning plaque characteristics [61], differentiate coronary artery layers [62], analyze formations within coronary arteries [63], recognize plaque erosion [64], assess the fibrous cap [65], or even perform reconstructions of coronary artery calcifications [66]. Together with visual and manual methods, knowledge and experience of the physician, AI methods achieve the best results in plaque characteristics and quantification [67]. In the era of precision medicine, these AI-based parameters can be integrated with clinical data and used for an individual risk prediction.

## RESULTS

The definition of symmetry and asymmetry of vessels is complicated. Most researchers do not precisely define symmetry, asymmetry, and hypoplasia in their articles [20,40]. In the majority of cases, the symmetry is derived from subjective parameters such as length and mean diameter of the vessel rather than its objective (quantitative or qualitative) evaluation. Zurada and Gielecki [11] presented a mathematical method to assess all these parameters that can be used in adults, children, and even fetuses [20]. Pascalau et al. [22] additionally point out the fact that asymmetric vessels cannot be classified as hypoplastic which have the highest resistance to flow. This is the reason why hemodynamics is not highly affected but still, the diameter and length of the vessel influence the blood flow.

The most important and of clinical meaning in vascular symmetry and asymmetry is shear stress. This phenomenon emerges from friction between 2 layers – 2 virtual fluid layers or between blood and endothelium [50]. Arterial bed in regions with uniform geometry presents a constant blood flow in one direction which generates physiological shear stress. On the other hand, regions with tortuosity, arches, and bifurcations present an oscillatory and nonhomogeneous flow that generates low shear stress. It has been proven that regions predisposed to atherosclerosis are these with low shear stress and those where asymmetry appears [21,68]. Moreover, hemodynamic and epigenetic factors can modulate endothelial cell function

and have an important impact on vascular pathologies, including atherosclerosis [69]. Physical forces may also influence changes in membrane and membrane-cytoskeletal proteins that lead to cell activation [68]. In this assessment a subjective element can be found. Nevertheless, these phenomena may at least partially explain the localization of atherosclerotic plaques within the vasculature and its measurement can be used to identify high-risk and vulnerable plaques, evaluate executed pharmacological interventions, search for rupture-prone aneurysms, predict potential restenosis after angioplasty [50].

In this paper, the authors analyze vascular symmetry by dividing body vasculature into central and peripheral. In normal conditions, central arteries are classified as the aorta and its main branches. In this study the carotid tree with the common carotid artery and the extracranial internal carotid artery have been additionally included. The reason was the majority of research concerns this anatomic region as a whole. Also all definitions of symmetry and asymmetry have been analyzed because of the topic specificity and a limited number of available sources.

The arising enormous amount of data (big data) requires special solutions. Artificial intelligence is a field of computer science that mimics human intelligence in order to perform tasks normally performed by human beings. In medicine, these data are generated by "omic" subfields-genomics, proteomics, metabolomics, etc. A special subfield of AI mostly used to process multi-omic data is ML. Not only to analyze them but also to propose specific solutions for particular individuals in compliance with assumptions of precision medicine. Artificial intelligence and internet of things solutions have brought us quickly to a Fourth Industrial Revolution. In the light of the current pandemic situation, the demand for these solutions has substantially increased. According to the World Economic Forum, <9% of companies have applied such solutions and the number is constantly growing.

## CONCLUSIONS

Large skeletal and middle muscular arteries are favored to occur in symmetrical or mirror patterns. Physical forces affect the arterial wall which may result in vascular pathologies and yet, the whole mechanism is not fully understood. As a result, symmetry and asymmetry within the human vascular system play a crucial role in understanding arterial diseases, including atherosclerosis. Future directions should take into consideration CT-based assessment of an atherosclerotic plaque and its potential application in the risk stratification models, as it has been only applied in the coronary atherosclerotic disease. Moreover, it is unavoidable to use AI in cardiovascular risk stratification as the amount of data is constantly growing.

**Author contributions**

**Research concept:** Oliwia Kolaszyńska, Jacek Lorkowski

**Research methodology:** Oliwia Kolaszyńska, Jacek Lorkowski

**Collecting material:** Oliwia Kolaszyńska, Jacek Lorkowski

**Statistical analysis:** Oliwia Kolaszyńska, Jacek Lorkowski

**Interpretation of results:** Oliwia Kolaszyńska, Jacek Lorkowski

**References:** Oliwia Kolaszyńska, Jacek Lorkowski

## REFERENCES

1. Korolj A, Wu H-T, Radisic M. A healthy dose of chaos: Using fractal frameworks for engineering higher-fidelity biomedical systems. Biomaterials. 2019;219(119363):119363. https://doi.org/10.1016/j.biomaterials.2019.119363.
2. Meyer HV, Dawes TJW, Serrani M, Bai W, Tokarczuk P, Cai J, et al. Genetic and functional insights into the fractal structure of the heart. Nature. 2020;584(7822):589–94. https://doi.org/10.1038/s41586-020-2635-8.
3. Friedman MH, Ding Z. Relation between the structural asymmetry of coronary branch vessels and the angle at their origin. J Biomech. 1998;31(3):273–8. https://doi.org/10.1016/s0021-9290(98)00013-x.

4. Mahrous SA, Sidik NAC, Saqr KM. Numerical study on the energy cascade of pulsatile Newtonian and power-law flow models in an ICA bifurcation. PLoS One. 2021;16(1):e0245775. https://doi.org/10.1371/journal.pone.0245775.
5. Gnasso A, Irace C, Carallo C, De Franceschi MS, Motti C, Mattioli PL, et al. In vivo association between low wall shear stress and plaque in subjects with asymmetrical carotid atherosclerosis. Stroke. 1997;28(5):993–8. https://doi.org/10.1161/01.str.28.5.993.
6. Secchi F, Di Leo G, Delnevo A, Alì M, D'Angelo ID, Nardella VG, et al. Peripheral artery disease: how much inter-leg symmetry? A contrast-enhanced magnetic resonance angiography study. Medicine (Baltimore). 2020;99(16):e19637. https://doi.org/10.1097/MD.0000000000019637.
7. Cicha I, Wörner A, Urschel K, Beronov K, Goppelt-Struebe M, Verhoeven E, et al. Carotid plaque vulnerability: a positive feedback between hemodynamic and biochemical mechanisms: A positive feedback between hemodynamic and biochemical mechanisms. Stroke. 2011;42(12):3502–10. https://doi.org/10.1161/STROKEAHA.111.627265.
8. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res. 2016;118(4):535–46. https://doi.org/10.1161/CIRCRESAHA.115.307611.
9. Anderson RH, Webb S, Brown NA, Lamers W, Moorman A. Development of the heart: (2) Septation of the atriums and ventricles. Heart. 2003;89(8):949–58. https://doi.org/10.1136/heart.89.8.949.
10. Fogel MA, Weinberg PM, Haselgrove J. Flow volume asymmetry in the right aortic arch in children with magnetic resonance phase encoded velocity mapping. Am Heart J. 2003;145(1):154–61. https://doi.org/10.1067/mhj.2003.28.
11. Zurada A, Gielecki JS. A novel formula for the classification of blood vessels according to symmetry, asymmetry and hypoplasia. Folia Morphol (Warsz). 2007;66(4):339–45.
12. Gimbrone MA Jr, García-Cardeña G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. Cardiovasc Pathol. 2013;22(1):9–15. https://doi.org/10.1016/j.carpath.2012.06.006.
13. Shakeri AB, Tubbs RS, Shoja MM, Nosratinia H, Oakes WJ. Aortic bifurcation angle as an independent risk factor for aortoiliac occlusive disease. Folia Morphol (Warsz). 2007;66(3):181–4.
14. Schulz UG, Rothwell PM. Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque. Stroke. 2001;32(7):1525–31. https://doi.org/10.1161/01.str.32.7.1525.
15. Schulz UGR, Rothwell PM. Major variation in carotid bifurcation anatomy: A possible risk factor for plaque development? Stroke. 2001;32(11):2522–9. https://doi.org/10.1161/hs1101.097391.
16. Adams GJ, Simoni DM, Bordelon CB Jr, Vick GW 3rd, Kimball KT, Insull W Jr, et al. Bilateral symmetry of human carotid artery atherosclerosis. Stroke. 2002;33(11):2575–80. https://doi.org/10.1161/01.str.0000035736.30488.7a.
17. Sollberg LA, McGarry PA, Moossy J, Strong JP, Tejada C, Löken AC. Severity of atherosclerosis in cerebral arteries, coronary arteries, and aortas. Ann N Y Acad Sci. 1968;149(2):956–73. https://doi.org/10.1111/j.1749-6632.1968.tb53849.x.
18. Li F, Wang X. Bilateral symmetry of human carotid artery atherosclerosis: a multi-contrast weighted MR study. Int J Cardiovasc Imaging. 2016;32(8):1219–26. https://doi.org/10.1007/s10554-016-0890-4.
19. Bossuyt J, Van Bortel LM, De Backer TLM, Van De Velde S, Azermai M, Segers P, et al. Asymmetry in prevalence of femoral but not carotid atherosclerosis. J Hypertens. 2014;32(7):1429–34. https://doi.org/10.1097/HJH.0000000000000205.
20. Benetos G, Toutouzas K, Drakopoulou M, Tolis E, Masoura C, Nikolaou C, et al. Bilateral symmetry of local inflammatory activation in human carotid atherosclerotic plaques. Hellenic J Cardiol. 2015;56(2):118–24.
21. Naggara O, Touzé E, Seiller N, Gobin-Metteil M-P, Mas J-L, Meder J-F, et al. Asymmetry of intracranial internal carotid

artery on 3D TOF MR angiography: a sign of unilateral extracranial stenosis. Eur Radiol. 2008;18(5):1038–42. https://doi.org/10.1007/s00330-007-0835-3.

22. Pascalau R, Padurean VA, Bartos D, Bartos A, Szabo BA. The geometry of the circle of Willis anatomical variants as a potential cerebrovascular risk factor. Turk Neurosurg. 2019;29(2):151–8. https://doi.org/10.5137/1019-5149.JTN.21835-17.3.
23. Feng L, Zhai F-F, Li M-L, Zhou L-X, Ni J, Yao M, et al. Association between anatomical variations of the circle of Willis and covert vascular brain injury in the general population. Cerebrovasc Dis. 2022;1–7. https://doi.org/10.1159/000527432.
24. Johansson E, Aviv RI, Fox AJ. Atherosclerotic ICA stenosis coinciding with ICA asymmetry associated with Circle of Willis variations can mimic near-occlusion. Neuroradiology. 2020;62(1):101–4. https://doi.org/10.1007/s00234-019-02309-7.
25. Vrselja Z, Brkic H, Curic G. Arterial tree asymmetry reduces cerebral pulsatility. Med Hypotheses. 2015;85(5):622–7. https://doi.org/10.1016/j.mehy.2015.07.030.
26. Nixon AM, Gunel M, Sumpio BE. The critical role of hemodynamics in the development of cerebral vascular disease: A review. J Neurosurg. 2010;112(6):1240–53. https://doi.org/10.3171/2009.10.jns09759.
27. Li J, Zheng L, Yang W-J, Sze-To C-Y, Leung TW-H, Chen X-Y. Plaque wall distribution pattern of the atherosclerotic middle cerebral artery associates with the circle of Willis completeness. Front Neurol. 2020;11:599459. https://doi.org/10.3389/fneur.2020.599459.
28. Kim YD, Choi HY, Jung YH, Nam CM, Yang JH, Cho HJ, et al. Mirror pattern of cerebral artery atherosclerosis in patients with ischaemic stroke. Eur J Neurol. 2009;16(10):1159–64. https://doi.org/10.1111/j.1468-1331.2009.02690.x.
29. Mujagić S, Kozić D, Huseinagić H, Smajlović D. Symmetry, asymmetry and hypoplasia of the intracranial internal carotid artery on magnetic resonance angiography. Acta Med Acad. 2016;45(1):1–9. https://doi.org/10.5644/ama2006-124.150.
30. Nikolaeva EI, Oteva EA, Nikolaeva AA, Shterental IS. Prognosis of myocardial infarction and brain functional asymmetry. Int J Cardiol. 1993;42(3):245–8. https://doi.org/10.1016/0167-5273(93)90055-l.
31. Ozden K, Sert C, Yazicioglu Y. Effect of stenosis shape on the sound emitted from a constricted blood vessel. Med Biol Eng Comput. 2020;58(3):643–58. https://doi.org/10.1007/s11517-020-02119-7.
32. Sfyroeras GS, Arsos G, Karkos CD, Liasidis C, Spyridis C, Boundas D, et al. Interhemispheric asymmetry in brain perfusion before and after carotid stenting:A99mTc-HMPAO SPECT study. J Endovasc Ther. 2006;13(6):729–37. https://doi.org/10.1583/06-1857.1.
33. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. J Clin Epidemiol. 1992;45(5):529–42. https://doi.org/10.1016/0895-4356(92)90102-s.
34. Cecchi E, Giglioli C, Valente S, Lazzeri C, Gensini GF, Abbate R, et al. Role of hemodynamic shear stress in cardiovascular disease. Atherosclerosis. 2011;214(2):249–56. https://doi.org/10.1016/j.atherosclerosis.2010.09.008.
35. Walden R, Adar R, Rubinstein ZJ, Bass A. Distribution and symmetry of arteriosclerotic lesions of the lower extremities: an arteriographic study of 200 limbs. Cardiovasc Radiol. 1985;8(4):180–2. https://doi.org/10.1007/bf02552893.
36. Vink A, Schoneveld AH, Richard W, de Kleijn DP, Falk E, Borst C, et al. Plaque burden, arterial remodeling and plaque vulnerability: determined by systemic factors? J Am Coll Cardiol. 2001;38(3):718–23. https://doi.org/10.1016/s0735-1097(01)01444-9.
37. Wikström J, Hansen T, Johansson L, Ahlström H, Lind L. Lower extremity artery stenosis distribution in an unselected elderly population and its relation to a reduced ankle-brachial index. J Vasc Surg. 2009;50(2):330–4. https://doi.org/10.1016/j.jvs.2009.03.008.
38. Szpinda M. An angiographic study of the anterior tibial artery in patients with aortoiliac occlusive disease. Folia Morphol (Warsz). 2006;65(2):126–31.

39. Szpinda M. Angiographic study of the tibioperoneal trunks in patients with aorto-iliac occlusive disease. Ann Anat. 2005;187(4):405–10. https://doi.org/10.1016/j.aanat.2005.02.012.
40. Barden JM, Hoffert L, Ruf S, McCarville D, Kopriva D. The effect of peripheral arterial disease and intermittent claudication on gait regularity and symmetry. J Biomech. 2022;141(111205):111205. https://doi.org/10.1016/j.jbiomech.2022.111205
41. Erlandson EE, Forrest ME, Shields JJ, Cho KJ, Zelenock GB, Cronenwett JL, et al. Discriminant arteriographic criteria in the management of forearm and hand ischemia. Surgery. 1981;90(6):1025–36.
42. Cai Y, Liu X, Zhang L, Guo H, Gong Q, Lv F. Prevalence and characteristics of atherosclerotic plaque: Left compared with right arteries and anterior compared with posterior circulation stroke. Eur J Radiol. 2021;142(109862):109862. https://doi.org/10.1016/j.ejrad.2021.109862.
43. Artyszuk Ł, Symonides B, Gaciong Z, Cienszkowska K, Ludwiczak M, Wrzaszczyk M, et al. A new threshold for kidney asymmetry improves association with abnormal renal-aortic ratio for diagnosis of renal artery stenosis. Vasc Med. 2022;27(6):551–6. https://doi.org/10.1177/1358863x221118604.
44. Turing AM. Computing machinery and intelligence. Mind. 1950; 59: 433–460. https://doi.org/10.1093/mind/LIX.236.433.
45. Lorkowski J, Grzegorowska O, Pokorski M. Artificial Intelligence in the Healthcare System: An Overview. Adv Exp Med Biol. 2021;1335:1-10. https://doi.org/10.1007/5584_2021_620.
46. Lorkowski J, Kolaszyńska O, Pokorski M. Artificial Intelligence and Precision Medicine: A Perspective. Adv Exp Med Biol. 2022;1375:1-11. https://doi.org/10.1007/5584_2021_652.
47. Pishgar M, Issa SF, Sietsema M, Pratap P, Darabi H. REDECA: A Novel Framework to Review Artificial Intelligence and Its Applications in Occupational Safety and Health. Int J Environ Res Public Health. 2021;18(13):6705. https://doi.org/10.3390/ijerph18136705.
48. Alaa AM, Bolton T, Di Angelantonio E, Rudd JHF, van der Schaar M. Cardiovascular disease risk prediction using automated machine learning: A prospective study of 423,604 UK Biobank participants. PLoS One. 2019;14(5):e0213653. https://doi.org/10.1371/journal.pone.0213653.
49. Weng SF, Reps J, Kai J, Garibaldi JM, Qureshi N. Can machine-learning improve cardiovascular risk prediction using routine clinical data? PLoS One. 2017;12(4):e0174944. https://doi.org/10.1371/journal.pone.0174944.
50. Kakadiaris IA, Vrigkas M, Yen AA, Kuznetsova T, Budoff M, Naghavi M. Machine Learning outperforms ACC/AHA CVD Risk Calculator in MESA. J Am Heart Assoc. 2018;7(22):e009476. https://doi.org/10.1161/JAHA.118.009476.
51. Unnikrishnan P, Kumar DK, Poosapadi Arjunan S, Kumar H, Mitchell P, Kawasaki R. Development of health parameter model for risk prediction of CVD using SVM. Comput Math Methods Med. 2016;2016:3016245. https://doi.org/10.1155/2016/3016245.
52. Orfanoudaki A, Chesley E, Cadisch C, Stein B, Nouh A, Alberts MJ, et al. Machine learning provides evidence that stroke risk is not linear: The non-linear Framingham stroke risk score. PLoS One. 2020;15(5):e0232414. https://doi.org/10.1371/journal.pone.0232414.
53. Han D, Kolli KK, Gransar H, Lee JH, Choi S-Y, Chun EJ, et al. Machine learning based risk prediction model for asymptomatic individuals who underwent coronary artery calcium score: Comparison with traditional risk prediction approaches. J Cardiovasc Comput Tomogr. 2020;14(2):168–76. https://doi.org/10.1016/j.jcct.2019.09.005.
54. Banchhor SK, Londhe ND, Araki T, Saba L, Radeva P, Khanna NN, et al. Calcium detection, its quantification, and grayscale morphology-based risk stratification using machine learning in multimodality big data coronary and carotid scans: A review. Comput Biol Med. 2018;101:184–98. https://doi.org/10.1016/j.compbiomed.2018.08.017.
55. Paraskevas KI, Sillesen HH, Rundek T, Mathiesen EB, Spence JD. Carotid intima-media thickness versus carotid plaque

burden for predicting cardiovascular risk. Angiology. 2020; 71(2):108–11. https://doi.org/10.1177/0003319719878582.

56. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77. https://doi.org/10.1093/eurheartj/ehz425.
57. Ikeda N, Saba L, Molinari F, Piga M, Meiburger K, Sugi K, et al. Automated carotid intima-media thickness and its link for prediction of SYNTAX score in Japanese coronary artery disease patients. Int Angiol. 2013;32(3):339–48.
58. Jamthikar A, Gupta D, Khanna NN, Saba L, Araki T, Viskovic K, et al. A low-cost machine learning-based cardiovascular/stroke risk assessment system: integration of conventional factors with image phenotypes. Cardiovasc Diagn Ther. 2019;9(5):420–30. https://doi.org/10.21037/cdt.2019.09.03.
59. Araki T, Ikeda N, Shukla D, Jain PK, Londhe ND, Shrivastava VK, et al. PCA-based polling strategy in machine learning framework for coronary artery disease risk assessment in intravascular ultrasound: A link between carotid and coronary grayscale plaque morphology. Comput Methods Programs Biomed. 2016;128:137–58. https://doi.org/10.1016/j.cmpb.2016.02.004.
60. Banchhor SK, Londhe ND, Araki T, Saba L, Radeva P, Laird JR, et al. Wall-based measurement features provides an improved IVUS coronary artery risk assessment when fused with plaque texture-based features during machine learning paradigm. Comput Biol Med. 2017;91:198–212. https://doi.org/10.1016/j.compbiomed.2017.10.019.
61. He C, Li Z, Wang J, Huang Y, Yin Y, Li Z. Atherosclerotic plaque tissue characterization: An OCT-based machine learning algorithm with ex vivo validation. Front Bioeng Biotechnol. 2020;8:749. https://doi.org/10.3389/fbioe.2020.00749.
62. Abdolmanafi A, Duong L, Dahdah N, Cheriet F. Deep feature learning for automatic tissue classification of coronary artery using optical coherence tomography. Biomed Opt Express. 2017;8(2):1203–20. https://doi.org/10.1364/BOE.8.001203.
63. Abdolmanafi A, Duong L, Dahdah N, Adib IR, Cheriet F. Characterization of coronary artery pathological formations from OCT imaging using deep learning. Biomed Opt Express. 2018;9(10):4936–60. https://doi.org/10.1364/BOE.9.004936.
64. Wang Z, Jia H, Tian J, Soeda T, Vergallo R, Minami Y, et al. Computer-aided image analysis algorithm to enhance in vivo diagnosis of plaque erosion by intravascular optical coherence tomography. Circ Cardiovasc Imaging. 2014;7(5):805–10. https://doi.org/10.1161/CIRCIMAGING.114.002084.
65. Zahnd G, Karanasos A, van Soest G, Regar E, Niessen W, Gijsen F, et al. Quantification of fibrous cap thickness in intracoronary optical coherence tomography with a contour segmentation method based on dynamic programming. Int J Comput Assist Radiol Surg. 2015;10(9):1383–94. https://doi.org/10.1007/s11548-015-1164-7.
66. Mehanna E, Bezerra HG, Prabhu D, Brandt E, Chamié D, Yamamoto H, et al. Volumetric characterization of human coronary calcification by frequency-domain optical coherence tomography. Circ J. 2013;77(9):2334–40. https://doi.org/10.1253/circj.cj-12-1458.
67. Boi A, Jamthikar AD, Saba L, Gupta D, Sharma A, Loi B, et al. A survey on coronary atherosclerotic plaque tissue characterization in intravascular optical coherence tomography. Curr Atheroscler Rep. 2018;20(7):33. https://doi.org/10.1007/s11883-018-0736-8.
68. Dewey CF Jr. Haemodynamic flow: symmetry and synthesis. Biorheology. 2002;39(3–4):541–9.
69. Lee D-Y, Chiu J-J. Atherosclerosis and flow: roles of epigenetic modulation in vascular endothelium. J Biomed Sci. 2019;26(1):56. https://doi.org/10.1186/s12929-019-0551-8.