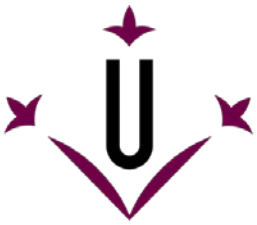


Non-invasive imaging techniques and assessment of carotid vasa vasorum neovascularization: promises and pitfalls

T. Pereira , A. Betriu , R. Alves

PII: S1050-1738(18)30106-3
DOI: 10.1016/j.tcm.2018.06.007
Reference: TCM 6535

To appear in: *Trends in Cardiovascular Medicine*

Received date: 24 April 2018
Revised date: 12 June 2018
Accepted date: 14 June 2018

Please cite this article as: T. Pereira , A. Betriu , R. Alves , Non-invasive imaging techniques and assessment of carotid vasa vasorum neovascularization: promises and pitfalls, *Trends in Cardiovascular Medicine* (2018), doi: 10.1016/j.tcm.2018.06.007

Non-invasive imaging techniques and assessment of carotid vasa vasorum neovascularization: promises and pitfalls

T. Pereira[1,2], A. Betriu[3,4] and R. Alves[1,2]

1 Institute for Biomedical Research in Lleida Dr. Pifarré Foundation, Catalonia, Spain

2 Departament de Ciències Mèdiques Bàsiques, University of Lleida, Catalonia, Spain

3 Unit for the Detection and Treatment of Atherothrombotic Diseases, Hospital Universitari Arnau de Vilanova de Lleida, Catalonia, Spain

4 Vascular and Renal Translational Research Group – IRBLleida, Catalonia, Spain

Disclosures: The authors have no conflicts of interest.

Please address correspondence to:

Tania Pereira, PhD

Current address: Level 6, 2 Koret Way, UCSF, San Francisco, CA 94143-0602, USA

Email: taniapereira10@gmail.com

Abstract: Carotid adventitia vasa vasorum neovascularization (VVn) is associated with the initial stages of arteriosclerosis and with the formation of unstable plaque. However, techniques to accurately quantify that neovascularization in a standard, fast, non-invasive, and efficient way are still lacking. The development of such techniques holds the promise of enabling wide, inexpensive, and safe screening programs that could stratify patients and help in personalized preventive cardiovascular medicine. In this paper, we review the recent scientific literature pertaining to imaging techniques that could set the stage for the development of standard methods for quantitative assessment of atherosclerotic plaque and carotid VVn. We present and discuss the alternative imaging techniques being used in clinical practice and we review the computational developments that are contributing to speed up image analysis and interpretation. We conclude that one of the greatest upcoming challenges will be the use of machine learning techniques to develop automated methods that assist in the interpretation of images to stratify patients according to their risk.

Key words: Carotid Imaging Techniques; Vasa Vasorum Neovascularization; Atherosclerotic Process, Automatic Methods.

1. Introduction

Atherosclerosis is a chronic progressive inflammatory disease of the arterial wall characterized by the localized thickening of that wall. This happens through the accumulation of inflammatory cells and lipid substances, combined with the proliferation of vascular smooth muscle cells, ultimately leading to the formation of atherosclerotic plaques (1,2).

In the normal carotid artery there is an extensive network of vasa vasorum (VV) in the adventitia that arise from branch points of parent arteries. Under physiological conditions, this specialized microvasculature delivers nutrients and oxygen to the outer layers of the arterial wall (2–6). In healthy states, microvessels arising from the vasa vasorum are spatially limited to the adventitia and outer media, and will only move towards and invade the intima during inflammatory processes that accompany atherosclerosis initiation and progression (5,7,8). According to this "outside-in" hypothesis, vascular inflammation and vasa vasorum neogenesis is initiated in the adventitia and progresses inward toward the intima (3,9). Initiation and expansion of VV neovascularization (VVn) remain incompletely understood (2). Nevertheless, it is clear that changes in physiological vascular conditions, endothelial injuries, or other events that cause dysfunction and alter homeostasis can induce the expansion of VV. Neovascularization resulting from that expansion precedes increases in the thickness of the carotid intima-media and in the development of atherosclerotic plaque (6,10), further playing a significant role in progression and destabilization of that plaque (2,4). In fact, histological studies of human atherosclerotic plaques revealed that symptomatic patients had a denser network of VV than patients with asymptomatic disease (2,11–13).

It is clear that a large scale use of histological methods to evaluate atherosclerotic progression in live patients is unfeasible. The development of alternative, non-invasive, methods to evaluate VVn as a proxy for atherosclerosis progression is thus an important goal. Imaging methods are obvious candidates for this role, and magnetic resonance imaging (MRI), contrast enhanced ultrasound (CEUS), and computed tomography (CT) are currently used in clinical practice for the visualization of anatomical structures in the adventitia VV (14). Still, initial validation of these techniques required that their results be compared to histological studies. In fact, it was shown that the intensity of histological markers for neovascularization significantly correlates with the quantification of neovascularization through imaging methods (11,15,16). The great objective of these

clinical tools, based on non-invasive image techniques, is the stratification of the risk level of patients (even in stages without plaque), and the assessment the vulnerability of the plaque (17).

This review starts by a brief description of invasive imaging techniques (Section 2), followed by a concise appraisal of features and limitations of the various non-invasive imaging methods being used for quantification of VVn (Section 3). It then summarizes the most relevant clinical findings brought about by the use of imaging techniques in the context of VVn and atherosclerosis (Section 4). This is trailed by a presentation of the processing methods used to extract information from the images (Section 5). The discussion (Section 6) then assesses how current methodological limitations and challenges present opportunities for future technological development. The paper concludes that better automated analysis methods could have a significant impact on the use of imaging methods to assess and stratify cardiovascular risk, remarking that machine learning and artificial intelligence methods are expected to have an important role in this.

2. Invasive Imaging Techniques for VV Quantification

Intravascular medical imaging methods collect images from the inside of blood vessels using specially designed catheters with a miniaturized probe attached to their distal end. These methods acquire images with higher resolution than non-invasive alternatives (18).Intravascular ultrasound (IVUS), Optical coherence tomography (OCT), and Near-infrared spectroscopy (NIRS) are imaging techniques that have recently been used for assessment of VVn (19–21). IVUS uses ultrasound technology to generate cross-sectional images of the lumen and walls of larger blood vessels, with a resolution of 150–300 μm (20,21). OCT uses near-infrared light to generate cross-sectional intravascular images, with a resolution of 10–20 μm (21). NIRS uses infrared spectroscopy to automatically assess the lipid content in atherosclerotic plaques, without providing visual images of plaque morphology or quantifying VVn (21).

Indocyanine green (ICG) fluorescence angiography is widely used to evaluate the blood flow in the operative field, for example during carotid endarterectomy. Indocyanine green (ICG) emits fluorescence in the far-red domain under light excitation and has been used to study the neovascularization of plaques in carotid (7,8). This was done using a surgical microscope, where the surgical field is illuminated using a laser-fluorescence imaging device. After ICG was administered intravenously, the perfusion of the affected area was

visualized by the fluorescence signal and diagnosed by visual inspection, either in real time or by looking at digitally recorded videos. This technique allows the evaluation of inwardly projecting neovessels. It also provides a method to evaluate the nutrient supply route for these neovessels, because endothelial neovessels are immediately visible, while vasa vasorum show delayed fluorescence (7,8).

The necessary invasiveness of these techniques is a limitation for their use in preventive care programs that aim at stratifying the population and assess cardiovascular risk level in individual patients. Intravascular imaging methods are outside the scope of this review. We focus only on non-invasive techniques.

3. Non-Invasive Imaging Techniques for VV quantification

The list of current non-invasive imaging methods being used for carotid analysis includes: CT, MRI and CEUS (14). Molecular imaging is a type of medical imaging that provides detailed information of what is happening inside the body. For CT and CEUS is necessary to use an imaging agent that allows to visualize physiologic activities such as chemical processes from the metabolism, oxygen consumption or blood flow. Magnetic resonance spectroscopy is able to measure chemical levels in the body, without the use of an imaging agent.

For the main techniques used for carotid VV assessment, non-invasive techniques were presented, and molecular imaging modalities were also referred since they have some advantages over traditional screening methods.

Computerized Tomography

CT uses ionizing radiation to reconstruct an image of the carotid and its walls, based on the differential x-ray attenuation of body tissue (22). During contrast-enhanced CT of arteries, a small fraction of the contrast media from the artery lumen enters the VV in the wall. The CT number of the wall is proportional to the spatial density of the VV (23). Example CT for carotid visualization in Figure 1 (24).

The main advantage of CT is that it generates reproducible images of high resolution that are operator-independent (24). The spatial resolution of CT can be further increased using image deconvolution, an approach that reduces blooming effects and enhances detection of increased VV (23,25).

CT imaging has some disadvantages. First, there is a risk for the patient associated with the use of iodinated contrast material to obtain tissue images. Second, there are extensive motion artifacts inherently associated

with arterial pulsations or other physiological movements(24,26,27). These disadvantages lead us to think that carotid CT imaging is unlikely to play a major role as a screening tool for large scale analysis of arterial VVn in the context of cardiovascular disease (28).

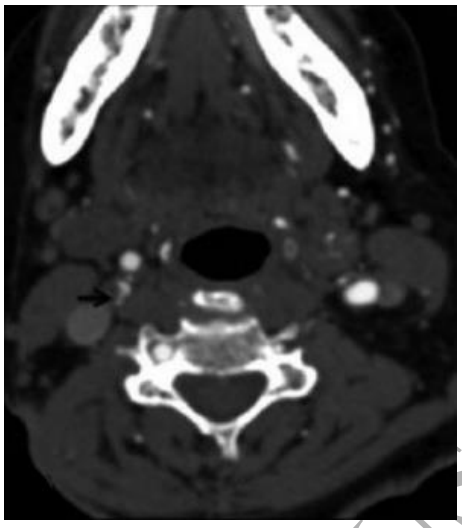
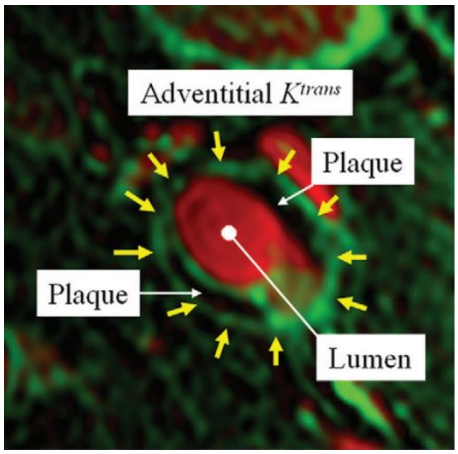


Figure 1: CT image showing ulcerations in right carotid bifurcation plaque (white arrow).

Reproduced from (24), Doi: 10.4103/0971-3026.113616

Magnetic resonance imaging

One of the techniques that relies on transport for contrast is perfusion imaging, which quantifies the entry and extravasation of intravenously injected contrast agents into the plaque. The combined use of contrast agents with MRI forms the basis of Dynamic contrast enhanced MRI (DCE-MRI) and permits the assessment of both, neovascular architecture and functional characteristics of blood vessels (29). DCE-MRI measures the tissue contrast enhancement–time curve after intravenous injection of a bolus of contrast material, estimating kinetic parameters that describe the blood plasma fraction (v_p), extracellular extravascular volume fraction (v_e), and a kinetic parameter K^{trans}. K^{trans} characterizes the transfer of the contrast agent from plasma to the extravascular space (for example, the adventitia), reflecting microvascular flow, permeability, and surface area (Figure2 (7)) (30). The intensity level of images during MRI can be adjusted by changing the sequence parameters of the magnetic pulses used for image acquisition. Using appropriate adjusted pulses one is able to evaluate the magnetic resonance signal intensity of the carotid plaque components (31).

a) 

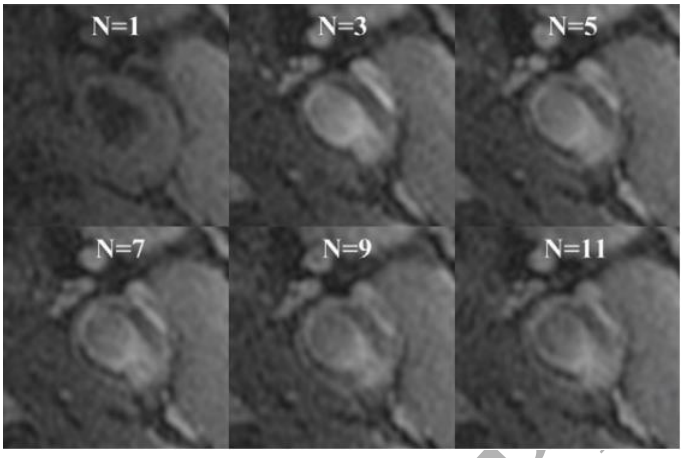
b) 

Figure 2: MRI of carotid vasa vasorum. a) Display of the kinetic modelling: Regions with flowing blood, such as the carotid artery lumen appear in red; v_p, regions with rapid transfer, such as the vessel adventitia (arrows) appear in green: K^{trans}. b) Representative sequence of DCE-MRI frames obtained before (image frame N = 1) and other frames after bolus injection of the contrast agent.

Reproduced, with permission, from (7), https://doi.org/10.1148/radiol.11101264

DCE-MRI enables a high-resolution characterization of both vessel structure, with the advantage of avoiding the ionizing radiation that is needed for CT imaging (28), (32). An important limitation of DCE-MRI is associated with the estimation of K^{trans}. That estimation is only accurate if the blood vessel has a minimum wall thickness of 2 mm, precluding the use of the technique to study arteries with thinner walls (29). Other important limitations of the technique are its cost and its longer scanning times (28), both of which do not bode well for a widespread use of the technique in large scale screening programs.

Contrast-enhanced ultrasonography

CEUS is a modality for vascular imaging that combines ultra-sonograms with contrast microbubbles (33). CEUS is sensitive to changes in the blood flow and permits acquiring tissue perfusion information that enables the visualization of the adventitial network of VV in human carotid arteries. CEUS imaging enhances the vessel lumen and, consequently, provides complete visualization of the carotid artery vasculature, luminal surfaces, near and far wall, and adventitial and intraplaque VVn (Figure 3 (34)).

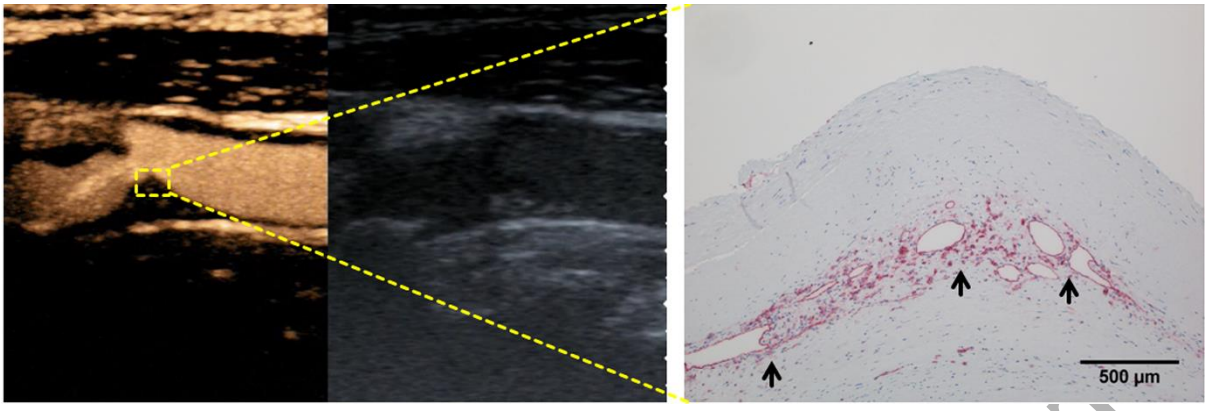


Figure 3: Contrast–enhanced ultrasound (CEUS) for assessing neo-vascularization of carotid plaque. Stenotic carotid plaque marked yellow-orange color of the contrast agent filling the lumen of the carotid artery. CEUS contrast effects are visible within the carotid plaque (yellow square), indicating plaque neovascularization. Immunohistological evaluation of the plaque area.

Reproduced, with permission, from (34), Doi: https://doi.org/10.1371/journal.pone.0175331.g001

Advantages of CEUS include that it is cost-effective, it can be performed at the bedside, it uses no ionizing radiation, and it has no nephrotoxicity. Furthermore, the technique combines a submillimetre resolution with the capability to detect individual microbubbles and provides diagnostic information with an accuracy that is comparable to that of CT and MRI (22,35,36).

Important limitations of CEUS are its dose-dependency and the nonlinear propagation artifact known as pseudo-enhancement, which occurs in the far wall adventitia of the carotid artery (37,38). This artifact strongly advices against the use of that wall for the VV assessment in CEUS imaging. An additional limitation of this method is its dependency on the operator. The variety of alternative procedures used for the analysis of the contrast enhancement limit the comparability of results from different centres. The creation of a common, reproducible, and well-established protocol for CEUS is essential to overcome that problem and enable multicentre studies that potentiate large-scale use of CEUS imaging for cardiovascular risk stratification. Also, the accuracy of CEUS in plaque analysis decreases for heavily calcified plaques that create acoustic shadows (5,29,39). This is important because acoustic shadowing limits the assessment of stenosis severity and other plaque characteristics (40,41). The use of specialized software, implementing blooming-reducing algorithms, to analyse images with acoustic shadows can mitigate the errors in image evaluation and enhance image quality and detection of VV (23).

4. Clinical Studies

The process of VVn is mainly associated to inflammatory mechanisms that are triggered in a wide range of pathologies: HIV, diabetes, chronic kidney disease, psoriasis, obesity, cardiovascular disease and events, etc. (42–46). In fact, (42–46) are only a few of the examples that emphasize the importance of VV assessment in multiple clinical contexts and studies, and accentuate the relevance of using imaging technology to investigate VVn.

We will now briefly discuss reported clinical studies using non-invasive imaging methods to evaluate VVn of the human carotid in the context of different pathologies. These studies emphasize the congruence of results between non-invasive imaging methods and histological tissue analysis and/or reveal important clinical results. A summary of the studies is presented in Table 1.

Computerized Tomography

The correlation between CT and histological images in the context of carotid VV and plaque evaluation is high (r=0.91 for fatty plaques, r=0.85 for mixed plaques and r=0.95 for calcified plaques) (47,48). Encouraged by these results, CT was used to screen carotid stenosis (26,49,50). Plaque volume, degree of stenosis and composition can be assessed using the method, emphasizing the usefulness of this and other imaging techniques as tools for risk stratification (51).

Magnetic resonance imaging

Several comparative analyses revealed a good agreement between the results obtained by using DCE-MRI to evaluate plaque and adventitia VVn and those obtained through histological analysis of surgical specimens (52,53,55,56,67,68). Furthermore, Kerwin *et al.* showed that K^{trans} in the carotid adventitia in the presence of plaques provides a quantitative proxy for the extent of VVn (55,56).

DCE-MRI can be used to estimate arterial and plaque calcification, loosening of the matrix, or haemorrhages, by measuring the response to a variety of magnetic pulses (53,54,69,70). The ability of DCE-MRI to measure these characteristics of the atherosclerotic plaque allows the identification of high-risk plaques (71–73) and opened new uses for the technique. For example, L. Dong proposed its use for assessing the therapeutic response of VV in patients with atherosclerotic plaque (29).

TABLE 1. Clinical studies of human carotid VV evaluated by image techniques.

Feature population	Number of patients	Age years ± SD	Histological studies	Main conclusions	Image technique	Year	Author
Severe carotid stenosis	13		Y	Plaque density on CT angiograms correlated with histologic findings	CT	1999	T. Oliver (47)
Neurological events	30		Y	High correlation between CT findings and histopathology	CT	2009	M. Das (48)
Carotid artery stenotic disease	268 carotids		N	The resultant sensitivity of CT stenosis screening for moderate stenosis is 75.0% with a specificity of 93.8%.	CT	2006	E. Bartlett (49)
Ischemic cerebrovascular disease	404	62 ± 14	N	CT angiography allows the assessment of atherosclerotic carotid plaque surface	CT	2009	T. Weert (50)
Patients with symptoms in the anterior circulation	346		N	CT allows the assessment of features of plaque in low degree of stenosis	CT	2011	P. Homburg (51)
Patients with internal carotid artery stenosis	428 (185 female /243 male)	73.3 ± 10.4	N	Association between VV and symptomatic individuals was significant (P = 0.011)	CT	2013	J. Romero et al. (26)
Patients with atherosclerotic carotid artery disease	20		Y	Histological evaluation showed kinetic modelling of dynamic contrast-enhanced MRI (CE-MRI) reflects the neovascularity (P < 0.001)	MRI	2003	W. Kerwin et al. (52)
Patients with symptomatic carotid disease and stenosis of more than 70%	11 (4 female /7 males)	68 ± 4	Y	Detection rate for each plaque component was above 80%	MRI	2005	V. Cappendijk et al. (53)
Patients with carotid stenosis	31	68 ± 9	Y	Good agreement between in vivo MRI and histology for quantitative measurements of the main plaque components	MRI	2005	T. Saam et al (54)
Patients with lesions of carotid; Subjects with moderate disease	25 males 20 males	66.3 ± 10.9 71.3 ± 9.5	Y	Histological evaluation showed that adventitial VV was significantly correlated with the amount of neovasculature (P<0.01)	MRI	2008	W. Kerwin et al. (55)
Patients with carotid stenosis of 15% or greater in an intensive lipid therapy	28 (18% female/ 82% male)	55 ± 6	N	Intensive lipid therapy is associated with a significant reduction in K^{trans}	MRI	2011	L. Dong et al. (29)
Patients with carotid plaque	64 (13 females/ 51 male)	66 ± 12	Y	Patients with cardiovascular events showed significantly higher adventitial (P< 0.001); Carotid adventitial was negatively correlated with time since clinical event (Spearman's rho = -0.40, p = 0.003)	MRI	2017	J. Wang et al. (56)
Male patient with diabetes	1	53	N	Showed the possibility to identify progression and regression of atherosclerosis in patients	CEUS	2006	S. Feinstein (57)
Patients with atherosclerotic carotid artery disease	17 (7 female /10 male)		Y	Histological evaluation was correlated with the CEUS results (Spearman's=0.68)	CEUS	2007	F. Shah et al. (15)

Patients with carotid stenosis; Patients without artery plaque	25 (80% male) 15 (66.7% male)	64.5 + 11.7 70.6 + 7.7	N	Adventitial VV higher in patient with carotid artherosclerosis (P<0.001)	CEUS	2009	M. Magnoni et al. (58)
Asymptomatic cerebrovascular disease; Patients with symptomatic carotid artery stenosis	64 9	67 ± 6	Y	Histology assessment confirmed the presence of vascularization in all symptomatic plaque identified by the CEUS	CEUS	2009	M. Giannoni et al. (59)
Subjects with pre-existing cardiovascular disease and events	147 (61% male)	64 ± 11	N	Adventitial VVwas associated with cardiovascular disease and events (P < 0.05)	CEUS	2010	D. Staub et al. (60)
Patients carotid atherosclerotic disease	27 (8 female /19 male)	68.4 ± 9.72	Y	CEUS measurements were well correlated with the histopathologic ratio (R^2 = 0.7905)	CEUS	2011	A. Hoogi et al. (11)
Patients with internal carotid artery stenosis	31 (7 female /24 male)	71 ± 11	N	Far wall of the common carotid artery was significantly more echogenic than the near wall at contrast agent doses (P < 0.001)	CEUS	2012	A. Thapar et al. (37)
Patients with a carotid artery stenosis	14 (4 female /10 male)	67.6 ± 10.2	Y	CEUS results showed a significant correlation with histology, however, they refer brightness enhancement during CEUS in carotid atherosclerotic plaques may not always reflect the presence of VV (P = 0.018)	CEUS	2013	M. Vavuranakis et al. (61)
Control Group; Patients with diabetes without retinopathy; Patients with diabetes with retinopathy	65 (34 female /31 male) 56 (27 female /29 male) 51 (29 female /22 male)	50 [41; 57] 58 [49; 67] 60 [54; 67]	N	Type 2 diabetic patients with retinopathy showed increased angiogenesis of the VV carotid artery (P<0.0039)	CEUS	2013	M. Arcidiacono et al. (62)
Patients with carotid atherosclerotic disease and cardiovascular events	45		N	New quantitative methods for analysing CEUS were significantly correlated with visual scoring image (P < 0.01)	CEUS	2013	Z. Akkus et al. (63)
Patients without intraplaque neovascularization (IPN); Patients with IPN	30 59	62.9 ± 10.1 68.4 ± 9.65	N	IPN showed a trend for a history of cardiovascular disease (P<0.19)	CEUS	2014	H. Kim et al. (64)
Patients with no symptoms of carotid atherosclerotic diseases	159	56.9 ± 8.7	N	Females had significant more intraplaque neovascularization compared to males (P < 0.05)	CEUS	2014	S. van den Oord et al. (65)
Healthy subjects	65 (48% men)	[30; 70]	N	Increase of carotid adventitial VV with age in individuals with zero risk for atheromatosis (P = 0.015)	CEUS	2015	M. Arcidiacono et al. (66)
Control; Diabetes without retinopathy; Diabetes with retinopathy	78 53 60	48 [40; 57] 46 [39; 51] 48 [42; 54]	N	Type 1 diabetic patients showed an increased angiogenesis of the VV of carotid compared with non-diabetic subjects	CEUS	2015	E. Rubinat et al. (42)
Chronic kidney disease patients without previous cardiovascular events Patients in stages 3-4; Patients in stage 5D; Healthy	 44 37 65	 59.5 60.0 49.0	N	Patients with cardiovascular events showed significantly higher adventitial was negatively correlated with time since clinical event after adjusting for age	CEUS	2017	M. Arcidiacono et al. (44)
Patients with high-grade carotid stenosis	17 (61.2% females/ 58.8% males)	66 (58–76)	Y	Scores on the CEUS-based on the level classifications were correlated with the density of intraplaque vessels (P<0.05)	CEUS	2017	C. Schmidt et al. (34)

CT - Computed Tomography; MRI - Magnetic Resonance Imaging; CEUS - Contrast-enhanced ultrasonography; P – P-value; IPN: Intraplaque Neovascularization

Contrast-enhanced ultrasonography

The initial use of ultrasound imaging for carotid plaque assessment did not include the use of contrast agents (74), which were a posterior addition to this imaging modality (75). CEUS uses an intravenous microbubble contrast agent. The contrast agent is an intraluminal tracer and can be used to obtain angiography-like images of the carotid arteries (16). Currently, CEUS is on the frontline of methodological development for carotid VVn assessment and plaque characterization.

As is the case with CT and DCE-MRI, CEUS imaging measurements correlate well with features derived from histological analysis of carotid plaques (11,12,15,59,60). One of these studies specifically showed that adventitial VVn is significantly associated to cardiovascular diseases and past cardiovascular events (60). CEUS analysis revealed an increase in adventitial VVn with age, even in individuals with no apparent risk factors for atherosclerosis (66). In addition, CEUS examination revealed that females had significantly more presence of intra-plaque neovessels than males (65), and that higher VVn was associated to a history of cardiovascular disease (64). Other CEUS studies also highlighted increased VVn in Type 1 and 2 diabetic patients (42,76).

5. Automatic methods for VV quantification

Automatic computational solutions that are quantitative, accurate, and reproducible represent an important development for assessing intraplaque neovascularization and for assessing VVn in the carotid adventitia. The later marks the asymptomatic, pre-plaque, stages of atherosclerosis. Such computational solutions assist in removing human subjectivity from image analysis.

Early automatic methods for plaque detection and analysis in CT images often required extensive manual adjustment, especially if image noise, calcification, or other artifacts were present in the images (77). Semi-automated methods for segmenting vessel walls and identifying the carotid artery lumen were also developed for the analysis of CT images (77–80). Results obtained using those semi-automated methods strongly correlated with the results generated by manual analysis of the same images (78–80). They also strongly correlated with results from histological analysis of carotid endarterectomies (81), and could be used for automated, high accuracy, classification of plaque samples into asymptomatic and symptomatic (81).

Methods that (semi)automatically detect the lumen, the outer boundary, and the contours of the plaque in carotid are also important in the field of DCE-MRI. An early semi-automated method required the operator to select two points in the image that define the vessel segment of interest. The computer then automatically connected the two points, using the centre line of the vessel to delineate the boundaries of the lumen, and assess the severity of carotid atherosclerosis (67,82). More recent methods automatically trace the contours of the lumen, as well as the outer boundary of the vessel wall and the plaque components (68,83–85). Overall, automated analysis of DCE-MRI images performs on par with manual quantification of images by the operator (82–85).

Automated quantification methods to analyse CEUS images of adventitia VVn and plaque VVn are under development to further improve the accuracy of image interpretation and to decrease inter-operator variability (16,86). During the manual process for CEUS image quantification, the operator defines the regions to consider. In general, and for currently available contrast quantification tools, the regions of interest (ROI) cannot be the same between different frames of a CEUS movie. For each frame, a user has to draw a new ROI, making for a cumbersome process that is disproportionately time consuming and hard to reproduce exactly. Automating this analysis would significantly reduce the analysis and processing time.

Image processing techniques that detect ROI in the ultrasound image can identify wall structure (46,87), presence or absence of plaque (88), or levels of VVn (46,89). These solutions improve accuracy of carotid plaque measurements and quantification of VVn, either in plaque or in asymptomatic artery walls. Artificial intelligence and machine learning algorithms for pattern recognition are also being used to analyse CEUS images (90). Recently, machine learning techniques have trained to identify symptomatic and asymptomatic carotid plaque, with accuracy and sensitivity above 90% (91), which is a promising result.

6. Discussion

Technical limitations and opportunities

Improving the large scale applicability of CT imaging requires hardware developments that reduce the dose of contrast agent and radiation exposure, thus facilitating a more widespread use of the technology (92). Similarly, improving the large scale applicability of MRI imaging requires that the costs of the technology be reduced. In addition, technical developments are require to enable accurate MRI measurements of either

adventitial VV in thinner-walled blood vessel or small wall injuries (29,56). CEUS could also benefit from hardware and technological improvements. First, new contrast agents, with fewer and weaker side effects, need to be developed (17). Second, methods that correct the artifacts generated in this type of imaging and leading to an over estimation of VV are also needed. Third, hardware that decreases the influence of the operator on image acquisition is still lacking.

Molecular image techniques allow studying perfusion routes in vessels, by timing the appearance of contrast and fluorescence in the vessels and neovessel (93). This feature could be helpful in designing experiments to understand the "direction" of vascular neogenesis in pathological states and validate the theory whereby vascular inflammation begins in the adventitia and advances to the media and intima (3,9).

Overall, and due to the limitations and features of each technique, a strategy that combine more than one technique will prove most valuable, as different techniques offer complementary information (93).

Improving image analysis

In general, computer-assisted analysis for better quantification of image parameters have been longstanding issues in the medical imaging field (94,95). Artificial intelligence based methods are increasingly being applied to cardiology to interpret complex data ranging from advanced imaging technologies. Advances in high-performance computing and the increasing accessibility of machine learning algorithms capable of performing complex tasks have heightened clinical interest in applying these techniques in research and clinical care (96). Recent advances in machine learning methods (ML) led to promising results in the automated interpretation of medical images and these ML could hold the key for the development of efficient and accurate applications for automated analysis of medical images (95,97–99).

Routine care of cardiovascular patients accumulates large amounts of data in electronic health records. The use of significant amount of diverse data is crucial to develop ML for medical applications. ML techniques can be useful for different types of the problems using different approaches. Supervised learning approaches use data to develop a model that can then predict or classify new events, while unsupervised learning approaches identify relationships between variables. Both approaches have been used for carotid imaging in the last years. However, ultrasound imaging has been most used to develop ML that assess plaque and VV neovascularization.

Supervised and unsupervised MLM have been used to assess segmentation and characterize carotid plaques from ultrasound images (99,100). It must be stressed that unsupervised MLM need to be validated in several independent cohorts, in order to confirm general cluster patterns and avoid potential classification biases (101). In supervised learning, small training datasets can lead to inaccurate decisions in testing datasets if the training datasets are biased. This means that training datasets for supervised learning should large and very well annotated. Developing the annotated datasets requires an enormous annotation effort by the experts.

Due the time-consuming for feature engineering, used by unsupervised and supervised machine learning, deep learning (DL) has emerged as the leading technique for image task (102), DL algorithms automatically learn features through the implementation of multi-layer hierarchies for the purpose of classification (102). DL methods have successfully been used for example in early-stage atherosclerosis detection and automatic measurement of intima-media thickness (103), or to characterize carotid plaque composition (104). DL algorithms require substantial computational memory resources and this presents a potential limitation for the application of these methods.

The accuracy of ML approaches is making them the best choice for assisted image analysis and interpretation, independently of the type of imaging method being used (94,105,106). These methods are expected to improve their performance, generating novel insights about pathological processes, enabling more precisely tailored treatment plans, and ultimately improving patient outcomes (94).

Clinical and Health system outlook

Atherosclerosis is a chronic inflammatory disease that leads to several acute cardiovascular complications with poor prognosis. Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide. Considering its poor prognosis, understanding the pathophysiology of atherosclerosis and exploring potential means to discover populations at risk as well as preventing its progression remain of significant importance.

Carotid imaging has focused mostly on the detection of atherosclerotic plaque and on the evaluation of its composition and structure. As the community becomes better at assessing these two aspects of a patient using imaging methods, we will become better at stratifying cardiovascular risk assessment and at personalizing treatment. Nevertheless, detection of biomarkers for early onset of atherosclerosis can have a big impact on the prevention and treatment of this disease group. One such biomarker is VVn before plaque formation. It seems

likely that better methods for quantifying this biomarker could have a strong impact on the evaluation of cardiovascular risk and personalization of preventive measures to reduce that risk.

Additionally, a more widespread use of accurate non-invasive image techniques will help to better characterize the physiopathological dynamics of adventitial VVn, which is still a poorly understood process (2). This improved characterization will increase our understanding of the origin and evolution of atherosclerotic processes and cardiovascular diseases. For these reasons alone, the application of progressively better, more efficient and more economic non-invasive image techniques in cardiovascular screening programs is likely to have a big societal impact.

7. Conclusions

Important efforts are underway to understand the impact of VVn in vascular health and disease. A large fraction of these efforts focus on developing non-invasive imaging methods to assess carotid plaque. Quantification of VVn remains a major issue, as our ability to perform this assessment *in vivo* is still limited. To improve that ability, efforts should focus on further developing new imaging methodologies and automated image analysis algorithms. Improvements in these areas could potentially impact the clinician's ability to stratify patients according to their risk levels and to better identify and treat individuals with premature cardiovascular disease (107).

Acknowledgments

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no [609396]. We thank the anonymous reviewers for clearly improving the clarity and quality of this paper.

References

1. Ritman EL, Lerman A. The Dynamic Vasa Vasorum. Cardiovasc Res. 2007;75(4):649–58.
2. Xu J, Lu X, Shi GP. Vasa vasorum in atherosclerosis and clinical significance. Int J Mol Sci. 2015;16(5):11574–608.
3. Mulligan-Kehoe MJ, Simons M. Vasa vasorum in normal and diseased arteries. Circulation. 2014;129(24):2557–66.
4. Williams JK, Heistad DD. Structure and function of vasa vasorum. Trends Cardiovasc Med. 1996;6(2):53–7.

5. Mulligan-Kehoe MJ. The vasa vasorum in diseased and nondiseased arteries. Am J Physiol Hear Circ Physiol. 2010;298(298):295–305.
6. Kawabe JI, Hasebe N. Role of the vasa vasorum and vascular resident stem cells in atherosclerosis. Biomed Res Int. 2014;2014.
7. Horie N, Morofuji Y, Morikawa M, Tateishi Y, Izumo T, Hayashi K, et al. Communication of inwardly projecting neovessels with the lumen contributes to symptomatic intraplaque hemorrhage in carotid artery stenosis. J Neurosurg [Internet]. 2015;123(5):1125–32. Available from: http://thejns.org/doi/10.3171/2014.12.JNS142371
8. Katano H, Yamada K, Sakurai K, Takahashi S. Depiction of the vasa vasorum during carotid endarterectomy by intraoperative videoangiography. J Stroke Cerebrovasc Dis. 2014;23(10):2920–7.
9. Maiellaro K, Taylor WR. The role of the adventitia in vascular inflammation. Cardiovasc Res. 2007;75(4):640–8.
10. Kwon TG, Lerman LO, Lerman A. The vasa vasorum in atherosclerosis: The vessel within the vascular wall. J Am Coll Cardiol. 2015;65(23):2478–80.
11. Hoogi A, Adam D, Hoffman A, Kerner H, Reisner S, Gaitini D. Carotid plaque vulnerability: Quantification of neovascularization on contrast-enhanced ultrasound with histopathologic correlation. Am J Roentgenol. 2011;196(2):431–6.
12. Vavuranakis M, Sigala F, Vrachatis D a, Papaioannou TG, Filis K, Kavantzas N, et al. Quantitative analysis of carotid plaque vasa vasorum by CEUS and correlation with histology after endarterectomy. Vasa. 2013;42(3):184–95.
13. Fleiner M, Kummer M, Mirlacher M, Sauter G, Cathomas G, Krapf R, et al. Arterial neovascularization and inflammation in vulnerable patients: Early and late signs of symptomatic atherosclerosis. Circulation. 2004;110(18):2843–50.
14. Naim C, Douziech M, Therasse É, Robillard P, Giroux MF, Arsenault F, et al. Vulnerable atherosclerotic carotid plaque evaluation by ultrasound, computed tomography angiography, and magnetic resonance imaging: An overview. Can Assoc Radiol J. 2014;65(3):275–86.
15. Shah F, Balan P, Weinberg M, Reddy V, Neems R, Feinstein M, et al. Contrast-enhanced ultrasound imaging of atherosclerotic carotid plaque neovascularization: a new surrogate marker of atherosclerosis? Vasc Med. 2007;12(4):291–7.
16. Ten Kate GL, Van Den Oord SCH, Sijbrands EJG, Van Der Lugt A, De Jong N, Bosch JG, et al. Current status and future developments of contrast-enhanced ultrasound of carotid atherosclerosis. J Vasc Surg. 2013;57(2):539–46.
17. Brinjikji W, Iii JH, Rabinstein AA, Kim G, Lerman A, Lanzino G. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. J Neurosurg. 2016;124:27–42.
18. Goel S, Miller A, Agarwal C, Zakin E, Acholonu M, Gidwani U, et al. Imaging Modalities to Identity Inflammation in an Atherosclerotic Plaque. Radiol Res Pract. 2015;2015:1–13.
19. Cheng KHY, Sun C, Cruz JP, Marotta TR, Spears J, Montanera WJ, et al. Feasibility of endovascular optical coherence tomography for high-resolution carotid vessel wall imaging. In: Proceedings Volume 8207, Photonic Therapeutics and Diagnostics VIII; 2012.
20. Goertz DE, Frijlink ME, Tempel D, Van Damme LCA, Krams R, Schaar JA, et al. Contrast harmonic intravascular ultrasound: A feasibility study for vasa vasorum imaging. Invest Radiol. 2006;41(8):631–8.
21. Yonetsu T, Jang I. Advances in Intravascular Imaging : New Insights into the Vulnerable Plaque from Imaging Studies. Korean Circ J. 2018;48(1):1–15.
22. Joshi FR, Lindsay AC, Obaid DR, Falk E, Rudd JHF. Non-invasive imaging of atherosclerosis. Eur Heart J Cardiovasc Imaging. 2012;13(3):205–18.
23. Rajendran K, Leng S, Jorgensen SM, Abdurakhimova D, Erik L, Mccollough CH, et al. Detection of increased vasa vasorum in artery walls: Improving CT number accuracy using image deconvolution. In: Proc SPIE Int Soc Opt Eng. 2017. p. 1–10.
24. Hingwala D, Kesavadas C, Sylaja PN, Thomas B, Kapilamoorthy TR. Multimodality imaging of carotid atherosclerotic plaque: Going beyond stenosis. Indian J Radiol Imaging. 2013;23(1):26–34.
25. Jorgensen SM, Anderson JL, Halaweish AF, Ritman EL, Mccollough CH, Rajendran K, et al. Measuring arterial wall perfusion using photon-counting computed tomography (CT): improving CT number accuracy of artery wall using image deconvolution. 2018;4(4).
26. Romero JM, Pizzolato R, Atkinson W, Meader A, Jaimes C, Lamuraglia G, et al. Vasa vasorum

enhancement on computerized tomographic angiography correlates with symptomatic patients with 50% to 70% carotid artery stenosis. Stroke. 2013;44(12):3344–9.
27. Ammirati E, Moroni F, Pedrotti P, Scotti I, Magnoni M, Bozzolo EP, et al. Non-invasive imaging of vascular inflammation. Front Immunol. 2014;5(AUG):1–15.
28. Zhang Y, Guallar E, Qiao Y, Wasserman BA. Is carotid intima-media thickness as predictive as other noninvasive techniques for the detection of coronary artery disease? Arterioscler Thromb Vasc Biol. 2014;34(7):1341–5.
29. Li Dong, Kerwin WS, Chen H, Chu B, Underhill HR, Neradilek MB, et al. Carotid Artery Atherosclerosis: Effect of Intensive Lipid Therapy on the Vasa Vasorum—Evaluation by Using Dynamic Contrast-enhanced MR Imaging. Neuroradiology. 2011;260(1).
30. Gaens ME, Backes WH, Rozel S, Sanders SN, Sluimer JC, Heeneman S. Dynamic Contrast-enhanced MR Imaging of Carotid Atherosclerotic Plaque: Model Selection, Reproducibility, and Validation. 2013;266(1).
31. Kerwin WS, Canton G. Advanced Techniques for MRI of Atherosclerotic Plaque. Top Magn Reson Imaging. 2009;20(4):1713–23.
32. Magnoni M, Ammirati E, Camici PG. Non-invasive molecular imaging of vulnerable atherosclerotic plaques. J Cardiol. 2015;65(4):261–9.
33. Granada JF, Feinstein SB. Imaging of the vasa vasorum. Nat Clin Pract Cardiovasc Med. 2008;5(SUPPL. 2):18–25.
34. Schmidt C, Fischer T, Rückert RI, Oberwahrenbrock T, Harms L, Kronenberg G, et al. Identification of neovascularization by contrast-enhanced ultrasound to detect unstable carotid stenosis. PLoS One. 2017;12(4):1–11.
35. Ten Kate GL, Sijbrands EJG, Valkema R, Ten Cate FJ, Feinstein SB, Van Der Steen AFW, et al. Molecular imaging of inflammation and intraplaque vasa vasorum: A step forward to identification of vulnerable plaques? J Nucl Cardiol. 2010;17(5):897–912.
36. Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: What is the evidence and what are the obstacles? Am J Roentgenol. 2009;193(1):55–60.
37. Thapar A, Shalhoub J, Averkiou MA, Mannaris C, Davies AH, Leen ELS. Dose-dependent artifact in the far wall of the carotid artery at dynamic contrast-enhanced US. Radiology. 2012;262(2):672–9.
38. ten Kate GL, Renaud GGJ, Akkus Z, van den Oord SCH, ten Cate FJ, Shamdasani V, et al. Far-Wall Pseudoenhancement During Contrast-Enhanced Ultrasound of the Carotid Arteries: Clinical Description and In Vitro Reproduction. Ultrasound Med Biol. 2012;38(4):593–600.
39. Varetto G, Gibello L, Castagno C, Quaglino S, Ripepi M. Use of Contrast-Enhanced Ultrasound in Carotid Atherosclerotic Disease: Limits and Perspectives. Biomed Res Int. 2015;2015.
40. Rafailidis V, Pitoulias G, Kouskouras K, Rafailidis D. Contrast-enhanced ultrasonography of the carotids. Ultrason (Seoul, Korea). 2015;34(4):312–23.
41. Katano H, Yamada K. Analysis of calcium in carotid plaques with agatston scores for appropriate selection of surgical intervention. Stroke. 2007;38(11):3040–4.
42. Rubinat E, Ortega E, Traveset A, Arcidiacono MV, Alonso N, Betriu A, et al. Microangiopathy of common carotid vasa vasorum in type 1 diabetes mellitus. Atherosclerosis. 2015;241(2).
43. Pillay B, Ramdial P, Naidoo D. HIV-associated large-vessel vasculopathy: a review of the current and emerging clinicopathological spectrum in vascular surgical practice: review article. Cardiovasc J Afr. 2015;26(2):70–81.
44. Arcidiacono MV, Vilar A, Martín M, Craver L, Betriu À, Mauricio D, et al. High Levels of Hemoglobin Promote Carotid Adventitial Vasa Vasorum Neoangiogenesis in Chronic Kidney Disease. 2017;2017.
45. Armstrong AW, Voyles S V., Armstrong EJ, Fuller EN, Rutledge JC. Angiogenesis and oxidative stress: Common mechanisms linking psoriasis with atherosclerosis. J Dermatol Sci. 2011;63(1):1–9.
46. Pereira T, Vilaprinyo E, Mária V, Muguruza J, Solsona F, Fernadez E, et al. Automatic method for the analysis of carotid adventitial vasa vasorum. In: IEEE International Symposium on Biomedical Imaging. Melbourne, Australia; 2017.
47. Oliver TB, Lammie GA, Wright AR, Wardlaw J, Patel SG, Peek R, et al. Atherosclerotic plaque at the carotid bifurcation: CT angiographic appearance with histopathologic correlation. Am J Neuroradiol. 1999;20(5):897–901.
48. Das M, Braunschweig T, Mühlenbruch G, Mahnken AH, Krings T, Langer S, et al. Carotid Plaque

Analysis: Comparison of Dual-Source Computed Tomography (CT) Findings and Histopathological Correlation. Eur J Vasc Endovasc Surg. 2009;38(1):14–9.
49. Bartlett ES, Walters TD, Symons SP, Fox AJ. Quantification of carotid stenosis on CT angiography. AJNR Am J Neuroradiol. 2006;27(8):13–19.
50. De Weert TT, Cretier S, Groen HC, Homburg P, Cakir H, Wentzel JJ, et al. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. Stroke. 2009;40(4):1334–40.
51. Homburg PJ, Rozie S, Van Gils MJ, Van Den Bouwhuijsen QJA, Niessen WJ, Dippel DWJ, et al. Association between carotid artery plaque ulceration and plaque composition evaluated with multidetector CT angiography. Stroke. 2011;42(2):367–72.
52. Kerwin W, Hooker A, Spilker M, Vicini P, Ferguson M, Hatsukami T, et al. Quantitative magnetic resonance imaging analysis of neovasculature volume in carotid atherosclerotic plaque. Circulation. 2003;107(6):851–6.
53. Cappendijk VC, Cleutjens KBJM, Kessels AGH, Heeneman S, Schurink GWH, Welten RJTJ, et al. Assessment of Human Atherosclerotic Carotid Plaque Components with Multisequence MR Imaging: Initial Experience. Radiology. 2005;234(2):487–92.
54. Saam T, Ferguson MS, Yarnykh VL, Takaya N, Xu D, Polissar NL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol. 2005;25(1):234–9.
55. Kerwin WS, Oikawa M, Yuan C, Jarvik GP, Hatsukami TS. MR imaging of adventitial vasa vasorum in carotid atherosclerosis. Magn Reson Med. 2008;59(3):507–14.
56. Wang J, Chen H, Sun J, Hippe DS, Zhang H, Yu S, et al. Dynamic contrast-enhanced MR imaging of carotid vasa vasorum in relation to coronary and cerebrovascular events. Atherosclerosis. 2017;263:420–6.
57. Feinstein SB. Contrast Ultrasound Imaging of the Carotid Artery Vasa Vasorum and Atherosclerotic Plaque Neovascularization. J Am Coll Cardiol. 2006;48(2):236–43.
58. Magnoni M, Coli S, Marrocco-Trischitta MM, Melisurgo G, De Dominicis D, Cianflone D, et al. Contrast-enhanced ultrasound imaging of periadventitial vasa vasorum in human carotid arteries. Eur J Echocardiogr. 2009;10(2):260–4.
59. Giannoni MF, Vicenzini E, Citone M, Ricciardi MC, Irace L, Laurito A, et al. Contrast Carotid Ultrasound for the Detection of Unstable Plaques with Neoangiogenesis: A Pilot Study. Eur J Vasc Endovasc Surg. 2009;37(6):722–7.
60. Staub D, Patel MB, Tibrewala A, Ludden D, Johnson M, Espinosa P, et al. Vasa vasorum and plaque neovascularization on contrast-enhanced carotid ultrasound imaging correlates with cardiovascular disease and past cardiovascular events. Stroke. 2010;41(1):41–7.
61. Vavuranakis M, Sigala F, Vrachatis D a, Papaioannou TG, Filis K, Kavantzas N, et al. Quantitative analysis of carotid plaque vasa vasorum by CEUS and correlation with histology after endarterectomy. J Vasc Dis. 2013;42(3):184–95.
62. Arcidiacono MV, Traveset A, Rubinat E, Ortega E, Betriu A, Hernández M, et al. Microangiopathy of large artery wall: A neglected complication of diabetes mellitus. Atherosclerosis. 2013;228(1):142–7.
63. Akkus Z, Renaud G, De Jong N, Van Der Steen AFW, Bosch JG, Van Den Oord SCH, et al. New quantification methods for carotid intraplaque neovascularization in contrast enhanced ultrasound. IEEE Int Ultrason Symp IUS. 2013;40(1):1236–9.
64. Kim HS, Woo JS, Kim BY, Jang HH, Hwang SJ, Kwon SJ, et al. Biochemical and clinical correlation of intraplaque neovascularization using contrast-enhanced ultrasound of the carotid artery. Atherosclerosis. 2014;233(2):579–83.
65. van den Oord SCH, van der Burg J, Akkus Z, Bosch JG, van Domburg RT, Sijbrands EJG, et al. Impact of gender on the density of intraplaque neovascularization: Aquantitative contrast-enhanced ultrasound study. Atherosclerosis. 2014;233(2):461–6.
66. Arcidiacono MV, Rubinat E, Borras M, Betriu A, Trujillano J, Vidal T, et al. Left carotid adventitial vasa vasorum signal correlates directly with age and with left carotid intima-media thickness in individuals without atheromatous risk factors. Cardiovasc Ultrasound. 2015;13(20):1–6.
67. Skagen K, Evensen K, Scott H, Krohg-Sørensen K, Vatnehol SA, Hol PK, et al. Semiautomated Magnetic Resonance Imaging Assessment of Carotid Plaque Lipid Content. J Stroke Cerebrovasc Dis. 2016;25(8):2004–10.
68. Liu F, Xu D, Ferguson MS, Chu B, Saam T, Takaya N, et al. Automated in vivo segmentation of

carotid plaque MRI with morphology-enhanced probability maps. Magn Reson Med. 2006;55(3):659–68.
69. Singh N, Moody AR, Roifman I, Bluemke DA, Zavodni AEH. Advanced MRI for carotid plaque imaging. Int J Cardiovasc Imaging. 2016;32(1):83–9.
70. McNally JS, Kim S-E, Mendes J, Hadley JR, Sakata A, De Havenon AH, et al. Magnetic Resonance Imaging Detection of Intraplaque Hemorrhage. Magn Reson Insights. 2017;10:1178623X1769415.
71. Yuan C, Oikawa M, Miller Z, Hatsukami T. MRI of Carotid Atherosclerosis. J Nucl Cardiol. 2008;15(2):266–75.
72. Speelman L, Teng Z, Nederveen AJ, Lugt A Van Der, Gillard JH. MRI-based biomechanical parameters for carotid artery plaque vulnerability assessment. Thromb Haemost. 2016;115:493–500.
73. Yuan C, Mitsumori LM, Beach KW, Maravilla KR. Carotid Atherosclerotic Plaque: Noninvasive MR Characterization and Identification of Vulnerable Lesions. Radiology. 2001;221(6):285–99.
74. Sztajzel R. Ultrasonographic assessment of the morphological characteristics of the carotid plaque. Swiss Med Wkly. 2005;135(43–44):635–43.
75. Feinstein SB. The powerful microbubble: from bench to bedside, from intravascular indicator to therapeutic delivery system, and beyond. AJP Hear Circ Physiol. 2004;287(2):H450–7.
76. Arcidiacono MV, Rubinat E, Ortega E, Betriu A, Fernández E, Mauricio D. Pseudo-enhancement does not explain the increased carotid adventitial vasa vasorum signal in diabetic patients. Atherosclerosis. 2013;229(2):459–61.
77. Maurovich-Horvat P, Ferencik M, Bamberg F, Hoffmann U. Methods of plaque quantification and characterization by cardiac computed tomography. J Cardiovasc Comput Tomogr. 2009;3(SUPPL.2):S91–8.
78. Hemmati HR, Alizadeh M, Kamali-Asl A, Shirani S. Semi-automated carotid lumen segmentation in computed tomography angiography images. J Biomed Res. 2017;31(6):1–11.
79. Santos FLC, Joutsen A, Terada M, Salenius J, Eskola H. A Semi-Automatic Segmentation Method for the Structural Analysis of Carotid Atherosclerotic Plaques by Computed Tomography Angiography. J Atheroscler Thromb. 2014;21(9):930–40.
80. Vukadinovic D, Rozie S, Van Gils M, Van Walsum T, Manniesing R, Van Der Lugt A, et al. Automated versus manual segmentation of atherosclerotic carotid plaque volume and components in CTA: Associations with cardiovascular risk factors. Int J Cardiovasc Imaging. 2012;28(4):877–87.
81. Diab HMH, Rasmussen LM, Duvnjak S, Diederichsen A, Jensen PS, Lindholt JS. Computed tomography scan based prediction of the vulnerable carotid plaque. BMC Med Imaging. 2017;17(1):1–8.
82. Adame IM, De Koning PJH, Lelieveldt BPF, Wasserman BA, Reiber JHC, Van Der Geest RJ. An integrated automated analysis method for quantifying vessel stenosis and plaque burden from carotid MRI images: Combined postprocessing of MRA and vessel wall MR. Stroke. 2006;37(8):2162–4.
83. Adame IM, Van Der Geest RJ, Wasserman BA, Mohamed MA, Reiber JHC, Lelieveldt BPF. Automatic segmentation and plaque characterization in atherosclerotic carotid artery MR images. Magn Reson Mater Physics, Biol Med. 2004;16(5):227–34.
84. Smits LP, Van Wijk DF, Duivenvoorden R, Xu D, Yuan C, Stroes ES, et al. Manual versus automated carotid artery plaque component segmentation in high and lower quality 3.0 tesla MRI scans. PLoS One. 2016;11(12):1–12.
85. Van 't Klooster R, Naggara O, Marsico R, Reiber JHC, Meder JF, Van Der Geest RJ, et al. Automated versus manual in vivo segmentation of carotid plaque MRI. Am J Neuroradiol. 2012;33(8):1621–7.
86. Cattaneo M, Staub D, Porretta AP, Gallino JM, Santini P, Limoni C, et al. Contrast-enhanced ultrasound imaging of intraplaque neovascularization and its correlation to plaque echogenicity in human carotid arteries atherosclerosis. Int J Cardiol. 2016;223:917–22.
87. Cheng DC, Schmidt-Trucksass A, Liu CH, Liu SH. Automated detection of the arterial inner walls of the common carotid artery based on dynamic B-mode signals. Sensors. 2010;10(12):10601–19.
88. Akkus Z, Van Burken G, Van Den Oord SCH, Schinkel AFL, De Jong N, Van Der Steen AFW, et al. Carotid intraplaque neovascularization quantification software (CINQS). IEEE J Biomed Heal Informatics. 2015;19(1):332–8.
89. Pereira T, Jose Muguruza, Maria V, Vilaprinyo E, Sorribas A, Fernandez E, et al. Automatic methods for contrast-enhanced carotid ultrasound imaging quantification of adventitial Vasa Vasorum. Under Rev. 2018;

90. Jodas DS, Pereira AS, Tavares JMRS. A review of computational methods applied for identification and quantification of atherosclerotic plaques in images. Expert Syst Appl. 2016;46:1–14.
91. Molinari F, Raghavendra U, Gudigar A, Meiburger KM, Rajendra Acharya U. An efficient data mining framework for the characterization of symptomatic and asymptomatic carotid plaque using bidimensional empirical mode decomposition technique. Med Biol Eng Comput. 2018;
92. Fujimoto S, Kondo T, Narula J. Evaluation of Plaque Morphology by Coronary CT Angiography. Cardiol Clin. 2012;30:69–75.
93. Hingwala DR, Chandrasekhakan K, Thomas B, Sylaja PN, Unnikrishnan M, Kapilamoorthy TR. Atherosclerotic Carotid Plaques: Multimodality Imaging with Contrast- enhanced Ultrasound, Computed Tomography, and Magnetic Resonance Imaging. Ann Indian Acad Neurol. 2017;20(4):378–86.
94. Razzak MI, Naz S, Zaib A. Deep Learning for Medical Image Processing: Overview, Challenges and Future. arXiv.org. 2017;1704.06825:1–30.
95. Shen D, Wu G, Suk H, Engineering C. Deep Learning in Medical Image Analysis. Annu Rev Biomed Eng. 2017;19(1):221–48.
96. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? Heart [Internet]. 2018;heartjnl-2017-311198. Available from: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2017-311198
97. Poplin R, Varadarajan A V., Blumer K, Liu Y, McConnell M V., Corrado GS, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng. 2018;2(March).
98. Park C, Took CC, Seong J-K. Machine learning in biomedical engineering. Biomed Eng Lett. 2018;8(1):1–3.
99. Menchón-Lara RM, Sancho-Gómez JL. Fully automatic segmentation of ultrasound common carotid artery images based on machine learning. Neurocomputing. 2015;151(P1):161–7.
100. Mench R, Plaza C. Ultrasound Image Processing based on Machine Learning for the Fully Automatic Evaluation of the Carotid Intima-Media Thickness. 2014;1–4.
101. Krittanawong C, Zhang HJ, Wang Z, Aydar M, Kitai T. Artificial Intelligence in Precision Cardiovascular Medicine. J Am Coll Cardiol. 2017;69(21):2657–64.
102. Loh BCS, Then PHH. Deep learning for cardiac computer-aided diagnosis: benefits, issues and solutions. mHealth [Internet]. 2017;3:45–45. Available from: http://mhealth.amegroups.com/article/view/17021/17339
103. Menchón-Lara RM, Sancho-Gómez JL, Bueno-Crespo A. Early-stage atherosclerosis detection using deep learning over carotid ultrasound images. Appl Soft Comput J [Internet]. 2016;49:616–28. Available from: http://dx.doi.org/10.1016/j.asoc.2016.08.055
104. Lekadir K, Galimzianova A, Betriu A, Del Mar Vila M, Igual L, Rubin DL, et al. A Convolutional Neural Network for Automatic Characterization of Plaque Composition in Carotid Ultrasound. IEEE J Biomed Heal Informatics. 2017;21(1):48–55.
105. Mohsen H, El-Dahshan E-S a., Salem a M. A machine learning technique for MRI brain images. Informatics Syst (INFOS), 2012 8th Int Conf. 2012;BIO-161-BIO-165.
106. Arbabshirani MR, Fornwalt BK, Mongelluzzo GJ, Suever JD, Geise BD, Patel AA, et al. Advanced machine learning in action: identification of intracranial hemorrhage on computed tomography scans of the head with clinical workflow integration. npj Digit Med [Internet]. 2018;1(1):9. Available from: http://www.nature.com/articles/s41746-017-0015-z
107. Staub D, Schinkel AFL, Coll B, Coli S, Van Der Steen AFW, Reed JD, et al. Contrast-enhanced ultrasound imaging of the vasa vasorum: From early atherosclerosis to the identification of unstable plaques. JACC Cardiovasc Imaging. 2010;3(7):761–71.