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Sonographic grading of recurrent stenosis after carotid stenting and stented peripheral arteries

"The stent as an incomprehensible entity" or "The art of measuring"

Electronic supplementary material

This article (https://doi.org/10.1007/s00772-018-0496-3) includes videos on the sonographic grading of recurrent stenosis. The article and supplementary material are available in the electronic full-text archive at http://www.springermedizin.de/gefaesschirurgie. The supplementary material can be found at the end of the article under Supplementary Material.

Ultrasound follow-up after PTA and internal carotid artery stenting

Background

Percutaneous transluminal angioplasty (PTA) of the internal carotid artery (ICA) with carotid artery stenting (CAS) has evolved to become an effective alternative to carotid thromboendarterectomy (TEA) for the revascularization of high-grade carotid stenosis, particularly in patients at high surgical risk (comorbidities, previous surgery in the neck area, radiotherapy). As in carotid TEA, follow-up is also necessary after CAS, and duplex ultrasound is the method of choice. In-stent recurrent stenosis rates (>70%) are reported to be on average 6% within the first year, and 3–12% within the first 2 years. Reports in the literature, however, put in-stent recurrent stenosis at between 1% and 50% [1–5]. This variation is due to a number of different factors:

- Definition of recurrent stenosis (degree of stenosis)
- Patient collective composition
- Duration of follow-up and stent design
- Prevalence of predictors for recurrent stenosis in the patient collective
- Measurement methods (peak systolic velocity, PSV, in duplex ultrasound) to grade stenosis. For example, higher recurrent stenosis rates (up to 32%) for 50% carotid in-stent stenosis have been reported when working with the duplex ultrasound criteria for native, unstented carotid stenosis (>130 cm/s) [2, 4–6].

The main duplex ultrasound criterion in the diagnosis of recurrent stenosis is increased systolic PSV; however, it is essential here to clarify whether elevated PSV really is caused by neointima-related recurrent stenosis or by stent-related hemodynamic changes.

The larger multicenter studies comparing recurrent stenosis rates between carotid TEA and CAS also worked with different PSV as threshold velocities as a criterion for relevant recurrent stenosis (>70%): CAVATAS [7], SPACE [8] with >2.1 m/s and CREST [9] with >3 m/s. Differing recurrent stenosis rates were also attributed to this. Therefore, the EVA 3S study [3] took a PSV of >2.1 m/s for >70% recurrent stenosis following carotid TEA and a PSV of >3 m/s following CAS.

Predictors of recurrence

Knowledge of the predictors of recurrent stenosis is an important criterion for determining postoperative follow-up intervals. Several studies revealed primarily diabetes, with its high potential for neointimal proliferation, as well as hyperlipidemia, female sex, nicotine abuse, and a plaque length of over 2 cm [4, 5, 10–13] as predictors for in-stent recurrent stenosis, but not plaque morphology as determined preoperatively by ultrasound (gray scale median analysis), plaque echogenicity [14, 15], or plaque calcification [16]. The causes of hemodynamically relevant recurrent stenosis primarily include the onset of in-stent neointimal proliferation usually within the first year, as well as atherosclerosis that progresses in the further course with in-stent stenosis due to plaque. Rare, but very early onset stent narrowing can occur due to restoring forces of plaque pressed against the vessel wall.

These cause the stent to be pushed back into the lumen without resulting in deposits occurring primarily in the stent. They generally cause non-treatment relevant lumen reduction that cannot be adequately visualized in radiological follow-up, e.g. digital subtraction angiography (DSA), computed tomography angiography (CTA) and magnetic resonance imaging (MRI), particularly if the stent segment protruding into the

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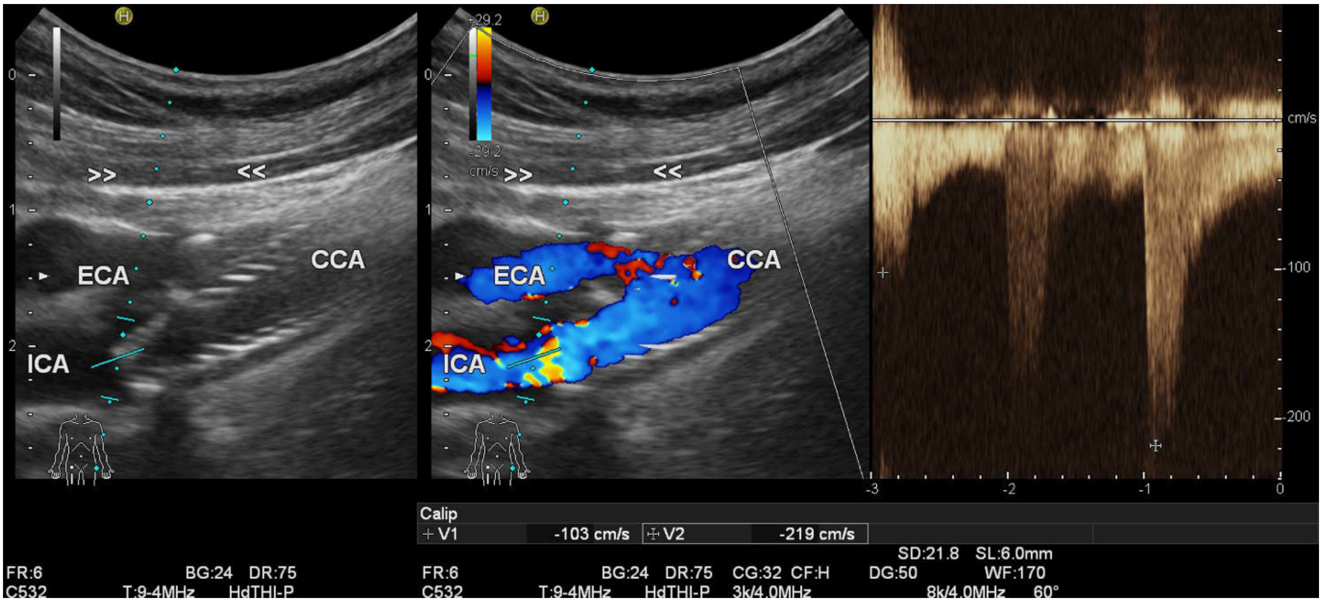

Fig. 1 ▲ The restoring forces of the plaque at the internal carotid artery (*ICA*) bifurcation on the wall stent result in a tapered lumen reduction at the end of the stent despite a primarily good stent position. A lumen reduction of approximately 50% corresponds to a duplex ultrasound doubling of an in-stent peak systolic velocity (PSV) from 100 to 210 cm/s at the end of the stent in the narrowed area (according to the continuity law). The *arrows* indicate the area over which the region of elevated PSV can be determined by shifting the transducer at the same Doppler angle. *ECA* external carotid artery, *CCA* common carotid artery

vessel lumen is surrounded by contrast medium (**Fig. 1**; video clip 2).

Color duplex ultrasound follow-up intervals following carotid artery stenting

Intravascular stents can be readily evaluated by means of color duplex sonography; the carotid pathway exhibits the same ultrasound conditions as before stent placement and the stent itself can be well-differentiated due to its mesh-like structure. Ultrasound follow-up should be performed at 3 months and then every 6 months in the first 2 years, particularly in patients with the abovementioned predictors for recurrent stenosis. Thereafter, annual follow-up is sufficient in hitherto non-stenosed stent areas. An examination 1 week following stent placement, including determination of post-interventional PSV, makes it easier to grade recurrent stenosis, whereby an increase compared to this baseline (more than double) signals relevant recurrent stenosis [17].

Influence of the stent on hemodynamics

Several publications postulated altered arterial hemodynamics in the stent area following stent placement [18, 19]. Increased vascular stiffness in the stented area should cause increased pulsatility (**Fig. 2**), with a drop in the diastolic portion in the spectrum and increased PSV. This increase in PSV may be further accentuated by stent-related lumen reduction.

In vitro stent placement in an ovine carotid artery without simulated stenosis produced a PSV increase of 22% and, in artificially induced stenosis, a stenosis-dependent increase of 20–30% in stented compared to unstented arteries [18]. In cases where the cause for this is unknown, pseudo-acceleration of PSV due to interference between the ultrasound signal and stent material is assumed; however, the question is then whether this in vitro assumption in the case of stent incorporation with neointimal proliferation is still relevant in vivo. Furthermore, this investigation described a three-fold drop in compliance in the stented area in its in vitro test series. A mismatch between stented and native segments of the artery is also hypothetically postulated [20]. Another study described significantly reduced compliance (ratio of systolic/diastolic diameter changes and systolic/diastolic blood pressure changes) in stented arteries [21]; however, other in vitro experiments failed to detect any relevant, or at most only a slight, increase in flow velocity in stented areas in flow models between unstented and stented vessel areas [22, 23]. Thus, in this experiment, the mean PSV increased by only 6.4% in a stented compared to a non-stented model [22], and in a comparison of different stents, a stent-dependent difference in PSV, partly an increase and partly also a drop in PSV, was observed [23]; however, closed-cell stents in particular exhibit a higher PSV compared to open-cell stents [24]. Thus, in vitro experiments show divergent results and cast doubt on stenosis grading on the basis of absolute PSV values.

Discrepancies in the grading of recurrent stenosis and evidence after CAS

In several studies, follow-up of CAS showed threshold velocities of 150–240 cm/s in >50% stenosis and 300–450 cm/s as the threshold velocity in over 70% (up to 80%) stenosis (Table 1). These predominantly Anglo-American studies carried out exclusively according to the degree of distal stenosis (the North American Symptomatic Carotid Endarterectomy Trial, NASCET, criterion) from 2002 to 2008, led to additional misunderstandings in German-speaking countries in the comparison of threshold velocities in native carotid stenosis, since the threshold velocities of these study results for recurrent stenosis were compared with the degree of local stenosis (European Carotid Surgery Trial, ECST, criterion) used at that time in the German-speaking regions for de novo stenosis [25]. When converted, this grade of local stenosis shows approximately 30% higher PSV values for 50–70% stenosis compared to the degree of distal stenosis (NASCET criterion). According to the NASCET criterion, the main criterion for stenosis is a PSV of 325 cm/s in 70% de novo carotid stenosis [26]. The PSV according to the ECST criterion (local degree of stenosis) was converted at a consensus conference to the NASCET criterion and adjusted from 200 cm/s (ECST criterion) to 300 cm/s [27]. On the other hand, parallel to this discussion process and following further Anglo-American studies, the PSV for native ICA stenosis, according to the NASCET criterion (distal degree of stenosis), was adjusted downwards on the basis of receiver operating characteristic (ROC) curves: PSV > 140 cm/s for >50% stenosis and PSV > 230 cm/s for >70% stenosis.

The same working group, using an ROC curve analysis in an extensive study with a good study design [19], defined the ideal threshold velocity for >30% in-stent recurrent stenosis (NASCET criterion) as a PSV of >150 cm/s, a PSV of 225 cm/s for >50% stenosis, and a PSV of 325 cm/s for >80% stenosis. What is striking, however, is the wide spectrum of PSV values, ranging from 142 cm/s to 256 cm/s (mean PSV of 180 cm/s) for 30–50% stenosis, 201–408 cm/s (mean PSV of 278 cm/s) for 50–80% stenosis, and 58–613 cm/s (mean PSV 403 cm/s) for 80–99% stenosis. The most comprehensive study [36] found a PSV of 175 cm/s as the cut-off for >50% in-stent recurrent stenosis and a PSV of 300 cm/s for >70% stenosis. The increased PSVs in in-stent recurrent stenosis were also confirmed by intravascular ultrasound in a study with a small number of cases [38].

The studies (Table 1) showed similar PSV threshold velocities for in-stent recurrent stenosis >50% and >70% to the original NASCET criterion [26] and as defined in the Interdisciplinary Guidelines Conference [27] for native ICA stenosis (according to the distal degree of stenosis/NASCET criterion); however, compared to the PSV for native ICA stenosis corrected downwards, the

Abstract · Zusammenfassung

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Sonographic grading of recurrent stenosis after carotid stenting and stented peripheral arteries. "The stent as an incomprehensible entity" or "The art of measuring"

Abstract

The increasing endovascular treatment of arterial stenoses requires reliable sonographic criteria for the detection of recurrent stenosis. Placement of a stent reduces the vessel lumen and is assumed to lead to greater rigidity, thereby causing more pulsatile blood flow and a higher peak systolic velocity (PSV). In vitro experiments and clinical trials with duplex ultrasound follow-up after percutaneous transluminal angioplasty (PTA) of the internal carotid artery with carotid artery stenting (CAS) provide inconsistent data on the magnitude of the increase in PSV of in-stent restenosis. They range from unchanged PSV up to 30% higher increases in PSV measurement values compared with those established for stenosis grading in native carotid stenoses. In stented leg arteries, studies even show somewhat lower PSV values compared with stenosis in unstented vessels. The option of applying the continuity law, so far not mentioned in the international literature, allows more accurate grading of in-stent restenosis. This method relates the PSV measured at the site of in-stent restenosis to the prestenotic PSV measured within the stent, thereby eliminating the need to take altered hemodynamics in stented arteries versus unstented arteries into account.

Keywords

In-stent restenosis · Duplex ultrasound · Stenosis criteria · Carotid stenting · Stented peripheral arteries

Sonographische Graduierung von Rezidivstenosen nach PTA und Stentimplantation. „Der Stent, das unverstandene Wesen" oder „Die Kunst des Messens"

Zusammenfassung

Die zunehmende endovaskuläre Therapie arterieller Stenosen erfordert zuverlässige sonographische Kriterien zur Detektion von Rezidivstenosen. Die angenommene erhöhte Rigidität sowie die Lumenreduktion führen nach Stentimplation im Gefäß zu einer erhöhten Pulsatilität und einer erhöhten systolischen Spitzengeschwindigkeit (PSV). Sowohl In-vitro-Versuche als auch Studien mit duplexsonographischer Verlaufskontrolle nach perkutaner transluminaler Angioplastie (PTA) der A. carotis interna mit Stentimplantation (CAS) zeigen jedoch sehr unterschiedlich Angaben über die PSV-Erhöhung bei Rezidivstenosen. Sie reichen von unveränderter PSV bis zu einer Erhöhung um 30 % gegenüber den PSV-Messwerten, die in der Stenosegraduierung nativer Karotisstenosen etabliert sind. Bei gestenteten Beinarterien zeigen Studien sogar etwas geringere PSV-Werte gegenüber Stenosen nativer Arterien. Die bisher in der internationalen Literatur nicht erwähnte Möglichkeit der Stenosegraduierung über das Kontinuitätsgesetz, mit dem Vergleich der prästenotischen, aber im Stent gemessenen PSV mit der PSV in der Rezidivstenose, führt zu einer exakteren Stenosegraduierung, ohne dass dabei die Veränderung der Hämodynamik zwischen nativem und gestentetem Gefäß berücksichtigt werden muss.

Schlüsselwörter

In-Stent-Rezidivstenose · Duplexsonographie · Stenosekriterien · Karotis-Stenting · PTA peripherer Arterien

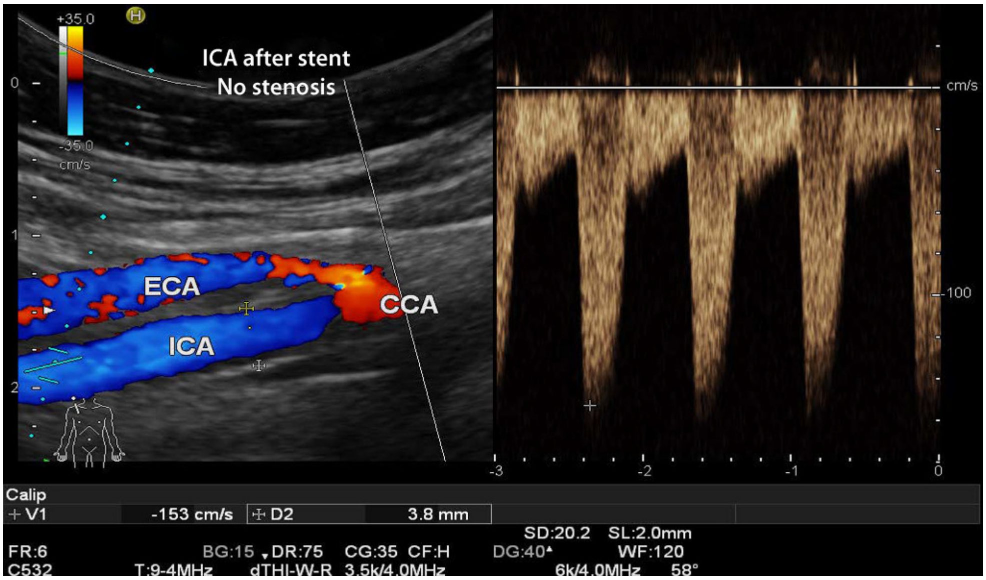

Fig. 2 ▲ Change in peak systolic velocity (PSV) and pulsatility following stent placement: a stent with morphologically normal flow in the internal carotid artery (*ICA*) with a PSV of 153 cm/s, which can be inferred for the entire length of the stent. According to studies, this PSV would in actual fact correspond to approximately 30–40% stenosis (the North American Symptomatic Carotid Endarterectomy Trial, NASCET, criterion). Stent rigidity is the cause of the increased pulsatility and elevated PSV. *ECA* external carotid artery, *CCA* common carotid artery

threshold velocity for in-stent recurrent stenosis increased by 20–30% [28, 29]. The consequences of the different approaches to stenosis grading is impressively illustrated in two studies, which together put the ideal threshold velocity for de novo ICA stenosis of >50% at 180 or 200 cm/s (NASCET criterion) and for recurrent stenosis after stenting for >50% stenosis at 220 or 240 cm/s [30, 32], i. e., increased by only approximately 10% (–20%).

The weaknesses of number games of this kind with respect to threshold velocities is highlighted in a publication on a small number (6) of cases of recurrent stenosis (in 141 CAS) [37]. On the basis of 5 cases of recurrent stenosis >80% and recurrent stenosis between 50% and 80%, an ideal cut-off of 195 cm/s for >50% stenosis and only 205 cm/s for >80% stenosis was determined. Compared to other literature reports, they recommended by inference that each laboratory develops its own criteria.

Some studies also examined the end-diastolic velocity (EDV) and the ratios of in-stent internal carotid artery to common carotid artery (ratio ICA:CCA) as a possible stenosis criterion for recurrent stenosis (◘ **Table 1**); however, PSV shows the highest accuracy and the highest correlation compared to CTA or angiography (e. g., DSA) performed as a reference method. In addition, however, these criteria (◘ **Table 1**) should also be taken into account for equivocal or unclear findings. Furthermore, the secondary criteria known from the diagnosis of native ICA stenosis should also be taken into consideration [25, 27].

The validity of previous retrospective studies is diminished by their small case numbers, although some studies showed follow-up in over 100 patients after CAS. These are usually compared to CTA as a reference method and, depending on the study, only 10–30 patients were compared using the gold standard of angiography for stenosis grading, i. e., only patients with higher-grade recurrent stenosis, often as part of re-intervention (◘ **Table 1**). Furthermore, stent design, which was not taken into account in many studies, seems to have an impact on the rigidity and thus the rise in PSV following stent placement. For example, closed-cell stents show a significantly higher PSV compared with open-cell stents (mean PSV 115 cm/s versus 93 cm/s, $p = 0.003$) [22]. This was confirmed in another study [39] (mean PSV 122 cm/s versus 93 cm/s, $p = 0.007$).

One way to minimize the varying impact of different stent types on PSV is by means of a baseline PSV, which is determined 1 week after stent implantation and forms the basis for further follow-up. For example, a doubling of this PSV over time was interpreted as a sign of relevant stenosis and evaluated with high accuracy [17].

Stenosis grading according to the continuity law

Since the majority of restenotic lesions develop within the stent, some in the mid-third but most at the distal end [40], the stenosis criterion used in peripheral artery diagnosis of a sudden increase in the intrastenotic PSV compared to prestenotic velocity (◘ **Figs. 1, 3, 4 and 5**) can be used (video clips 1–3). According to the continuity law a ratio (intrastenotic PSV/prestenotic PSV) of >2 in concentric stenosis is an indication of >50% stenosis and a ratio of >4 an indication of >75% stenosis. Using ratios determined in this way, the prestenotic PSV in the stent is measured slightly proximal to the stenotic area (◘ **Figs. 4 and 5**) and not, as in some studies (◘ **Table 1**), as the ratio of the in-stent velocity in the ICA to the velocity in the CCA (similar to the diagnosis of na-

Table 1 Duplex ultrasound criteria for in-stent recurrent stenosis after carotid PTA and CAS (patients examined after CAS: duplex ultrasound vs. computed tomography (CT) angiography ///(rarely) angiography (*N*))

Author/year	*N*	PSV (cm/s)			Ratio ICA/CCA		
	Ultrasound versus CTA or MRA /// angiography	>50% Stenosis	>70% Stenosis	>80% Stenosis	>50% Stenosis	>70% Stenosis	>80% Stenosis
AbuRhama 2008 [19]	144 /// 19	224	–	325	3.4	–	4.5
Lal 2008 [30]	189 /// 29	220	–	340	2.7	–	4.1
Stanziale 2005 [31]	118 /// 19	225	350	–	2.5	4.75	–
Peterson 2005 [17]	458	–	170	–	–	Sudden increase, doubling of PSV	–
Chi 2007 [32]	13	240	450	–	2.45	4.3	–
Zhou 2008 [33]	237 /// 22	–	300	–	–	4	–
Kwon 2007 [34]	–	200	–	–	2.5	–	–
Chahwan 2007 [35]	71	125	300	–	–	–	–
Setacci 2008 [36]	814 /// 95	175	300	–	3.8	–	–
Cumbie 2008 [37]	141	195	–	205	–	–	–

PSV peak systolic velocity, *ICA* internal carotid artery, *CCA* common carotid artery, *CTA* computed tomography angiography, *MRA* magnetic resonance angiography, *PTA* percutaneous transluminal angioplasty

tive ICA bifurcation stenosis); however, this determination of such a PSV ratio (ICA/CCA) is subject to similar errors as the same stenosis grading used as a secondary criterion for native ICA stenosis: the hemodynamics of the external carotid artery (ECA), which is also supplied by the CCA, are not taken into account and, depending on flow and collateral efficacy of the external circulation as well as on CCA diameter, PSV values vary.

The prestenotic (but measured in the stent) PSV of the ICA is a reliable base value for the ratios (**Figs. 4 and 5**). Since one can assume the same rigidity along the length of the stent, this is of no relevance for this PSV ratio. In addition, systemic factors effecting PSV are circumnavigated, as is a compensatory flow increase in the case of contralateral ICA stenosis. In an initial summary on an as yet small collective of patients, stenosis grading performed according to this method (PSV ratio) in all 9 patients with high-grade stenosis in whom 75% stenosis was determined according to the continuity law with the ratios (>4) described above, was confirmed on subsequent angiography. The PSV in this group was 230–455 cm/s. A total of 18 patients with a ratio of 2–4 had a PSV of 125–280 cm/s [25] in 50–75% stenosis. Here, however, the ratio and not the absolute PSV forms the basis for stenosis grading. There are no further data in the literature on this specially developed measuring method.

The relevance of and need for studies on grading according to the continuity law (prestenotic cross-sectional vessel area/intrastenotic area = intrastenotic PSV/prestenotic PSV) can be called into question, since physical laws that were confirmed in in vitro experiments form the basis of stenosis grading. This ratio (intrastenotic PSV/prestenotic PSV) corresponds closely, from low-grade up to 90% stenosis, in terms of stenosis grade with the values determined by the continuity law, where the degree of stenosis = (1–1/PSV ratio) × 100 [25].

It is important in terms of the measuring method, particularly in bent stents, that the Doppler angle along the vessel is adequately corrected. The investigator-dependence of the method is evident in the collection of measurement data.

Plaque configuration

It is important to note, however, that in any stenosis grading method concentric plaques are of greater hemodynamic relevance than eccentric plaques. A 50% reduction in diameter (angiography) in the case of eccentric plaques corresponds to a 50% reduction in area with a PSV ratio of 2, but a 75% reduction in area with a PSV ratio of 4 [25] in the case of concentric plaques, as well as a significantly higher absolute PSV value (**Fig. 6**); however, this is not taken into account in the stenosis grading studies cited here. Although eccentric plaques are of less hemodynamic relevance, they pose a greater risk for embolism due to their higher plaque density (at the same degree of stenosis), to which shearing forces are applied. This needs to be taken into account when considering re-intervention for recurrent stenosis.

A morphological assessment of in-stent recurrent stenosis, similar to angiography but at a higher spatial resolution due to B-flow [25] or contrast-enhanced ultrasound (CEUS) [41], can be performed with great accuracy; however, it should be used as an adjunct to duplex ultrasound.

Other stent complications

Other complications following stent implantation include stent dislocation and kinking stenosis distal to the stent in the case of an elongated ICA. In contrast to aortic stent dislocations, for which ultrasound can provide no valid information, the high spatial resolution with high-frequency transducers in carotid stent dislocations visualized in color duplex ultrasound, with flow signals in the stent and between the wall and stent, shows good

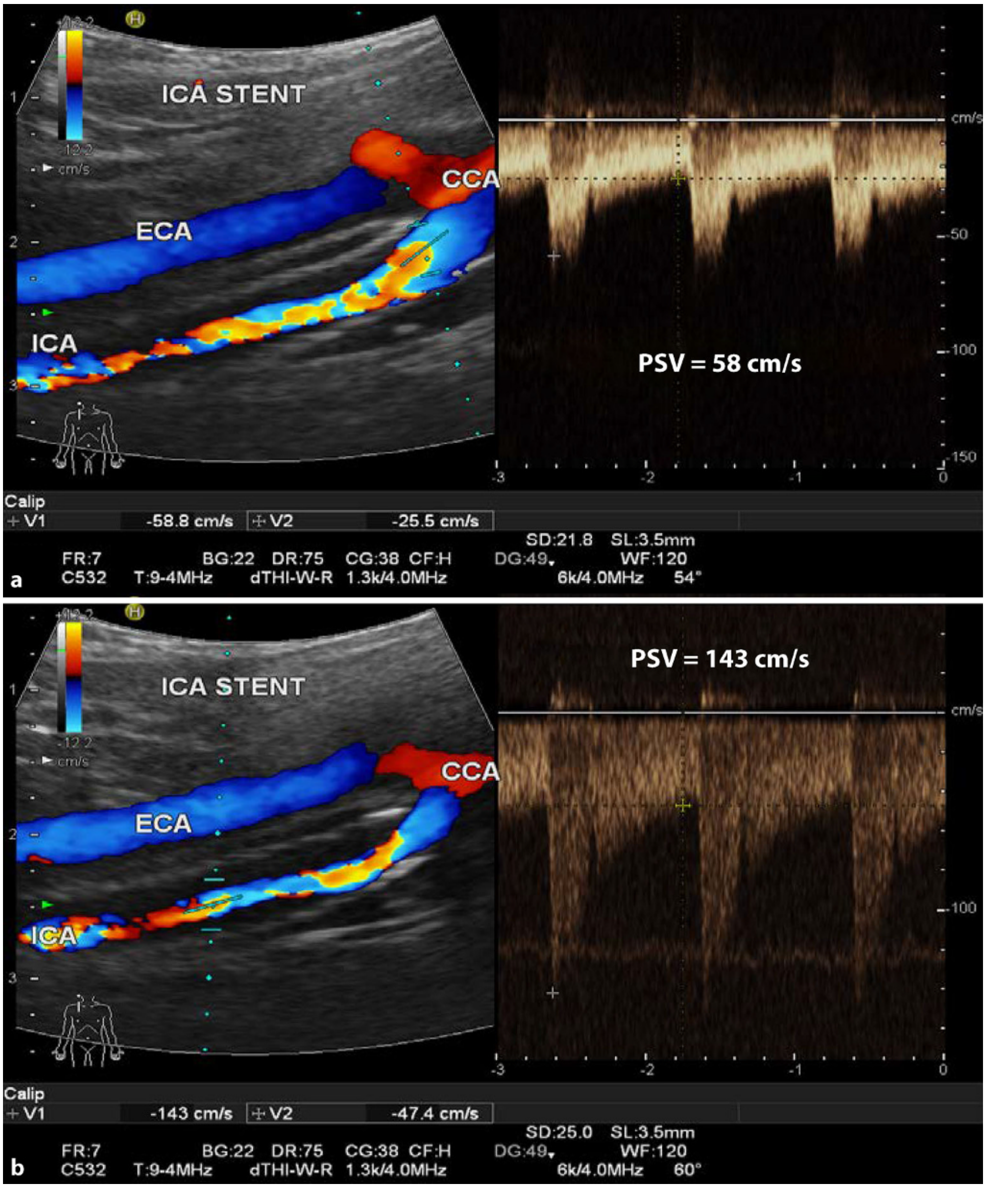

Fig. 3 ▲ Recurrent stenosis of the internal carotid artery (*ICA*) due to neointima formation at 1 year following stent placement: color duplex ultrasound shows, morphologically, approximately 50%, long segment narrowing due to neointima in the stent area (**a**); however, the peak systolic velocity (*PSV*) is only 143 cm/s in the stenosed area. The PSV measured in-stent but at the ICA bifurcation is 58 cm/s, from which the author obtains a ratio of >2 (**b**) according to the continuity law, i. e., 50–60% recurrent stenosis; however, the intrastenotic PSV of 143 cm/s is lower than that in ◘ **Fig. 2** with a non-stenosed, normal ICA (PSV: 153 cm/s) after stenting as an indication of the high variability of PSV measured in-stent. *ECA* external carotid artery, *CCA* common carotid artery

validity (◘ **Fig. 7**). Contrast-enhanced ultrasound can reinforce this validity. Using B-mode/time-motion mode makes it possible to visualize additional pressure-dependent, paradoxical wall movements of the stent against the vascular lumen. Ultrasound is more reliable than angiography in the case of uncoated stents, since angiographic imaging of stent areas that protrude into the lumen, and which contrast medium flows through and around, is virtually impossible.

Ultrasound follow-up after PTA and peripheral artery stenting

Background

Endovascular treatment has to some extent replaced bypass surgery for critical ischemia and has become the first-line treatment approach. As in bypass surgery, the patency of revascularization can be impaired by neointimal hyperplasia-related recurrent stenosis, in addition to early stenosis caused by a technical error. Local vascular wall trauma due to angioplasty and stent irritation trigger intimal thickening, which in turn leads to high-grade recurrent stenosis of varying degree or vascular occlusion in the revascularized vessel segment.

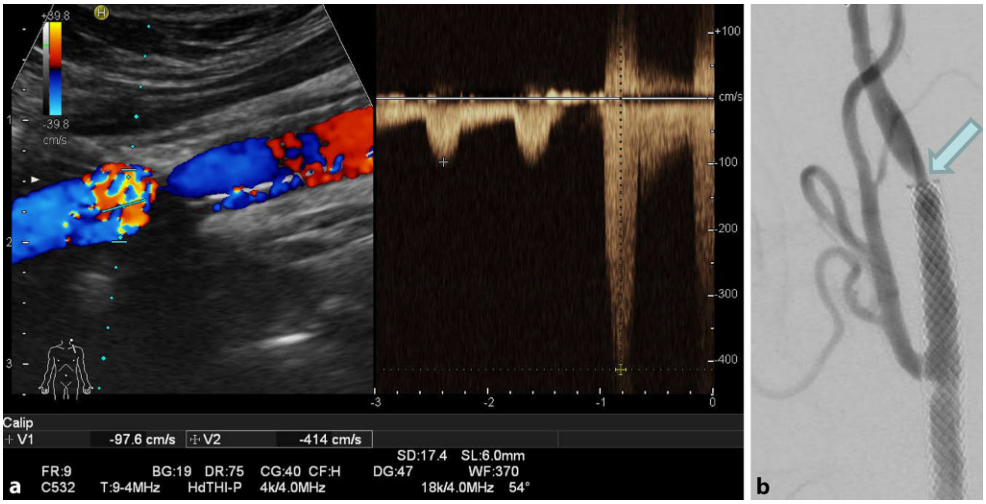

Fig. 4 ▲ **a** High-grade in-stent recurrent stenosis at the distal end of the stent with a ratio (in-stent intrastenotic/in-stent prestenotic and in the internal carotid artery (ICA) shortly after external carotid artery bifurcation) of >4: intrastenotic peak systolic velocity (PSV) 414 cm/s and prestenotic PSV 97 cm/s. The sudden increase in PSV in the Doppler frequency spectrum was visualized by moving the transducer over the skin in a cranial direction at the same Doppler angle (curved-array transducer; tilted to achieve a Doppler angle of 54°) during continuous recording. **b** Control angiography with a higher degree of recurrent stenosis at the end of the stent

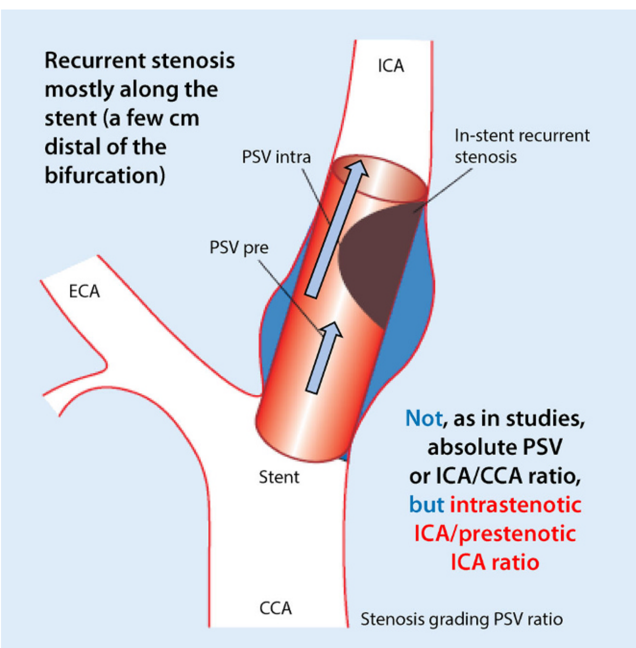

Fig. 5 ▲ The author's own approach to in-stent stenosis grading according to the continuity law: since most in-stent recurrent stenosis occurs along the course of the stent or often at the distal end of the stent, the ratio of peak systolic velocity (*PSV*; intrastenotic PSV/prestenotic PSV) but in the stent area of the internal carotid artery (*ICA*) can be graded most accurately according to the continuity law. There is no discussion of stenosis grading according to local or distal stenosis, since the stent levels out fluctuations in the bulge, and the in-stent diameter in the bulge region is comparable to the diameter of the distal ICA. *ECA* external carotid artery, *CCA* common carotid artery

The value of ultrasound in follow-up

Despite the risk to revascularization outcome posed by technical errors with intimal flaps or dissections, as well as through recurrent stenosis due to intimal hyperplasia and progressive atherosclerosis, there are only scant studies on the relevance of duplex ultrasound for survival following endovascular revascularization.

Stented peripheral arteries show significantly lower stenotic progression (only 7%) at ultrasound follow-up compared to initial findings following PTA alone (39%) or arterectomy (18%). It is possible that the stent reduces restenosis by elastic plaque-restoring forces or flaps; however, a subsequently higher occlusion rate [42] in the stented group (22%) compared to PTA (6.8%) or arterectomy (8.7%) suggests that the stent triggers a delayed thrombogenic, inflammatory or proliferative response followed by thrombosis. According to Bui et al. 2012 [42], ultrasound follow-up is unnecessary, since in contrast to re-occlusion following bypass surgery, the majority of patients would react with ischemic symptoms in the case of high-grade recurrent stenosis. Furthermore, occlusion of the stented area was foreseeable

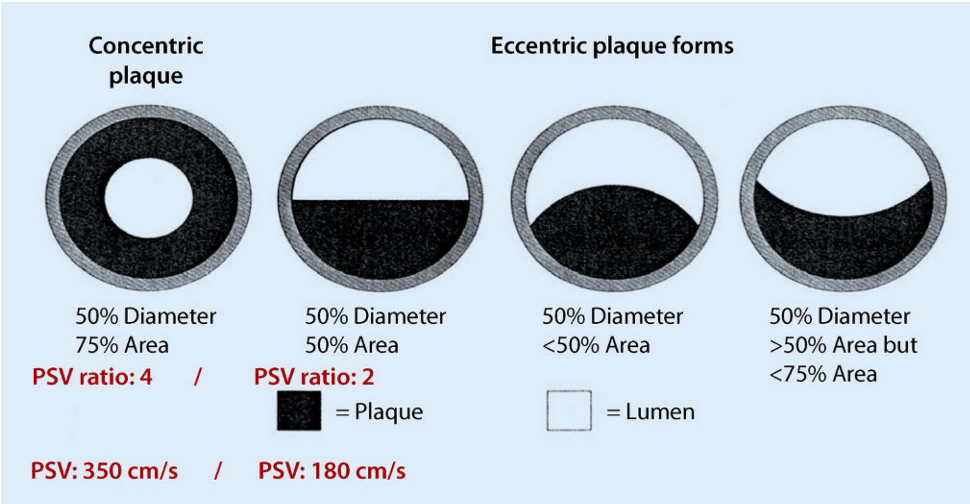

Fig. 6 ▲ The higher area reduction (hemodynamically higher grade stenosis) in concentric stenosis (75%) compared to eccentric stenosis (50%) at the same diameter reduction (50%). Thus, in the case of a 50% angiographic reduction in diameter, concentric stenosis is clinically (patient symptoms) and hemodynamically (PSV ratio 4) far more relevant than eccentric stenosis (PSV ratio 2). *PSV* peak systolic velocity

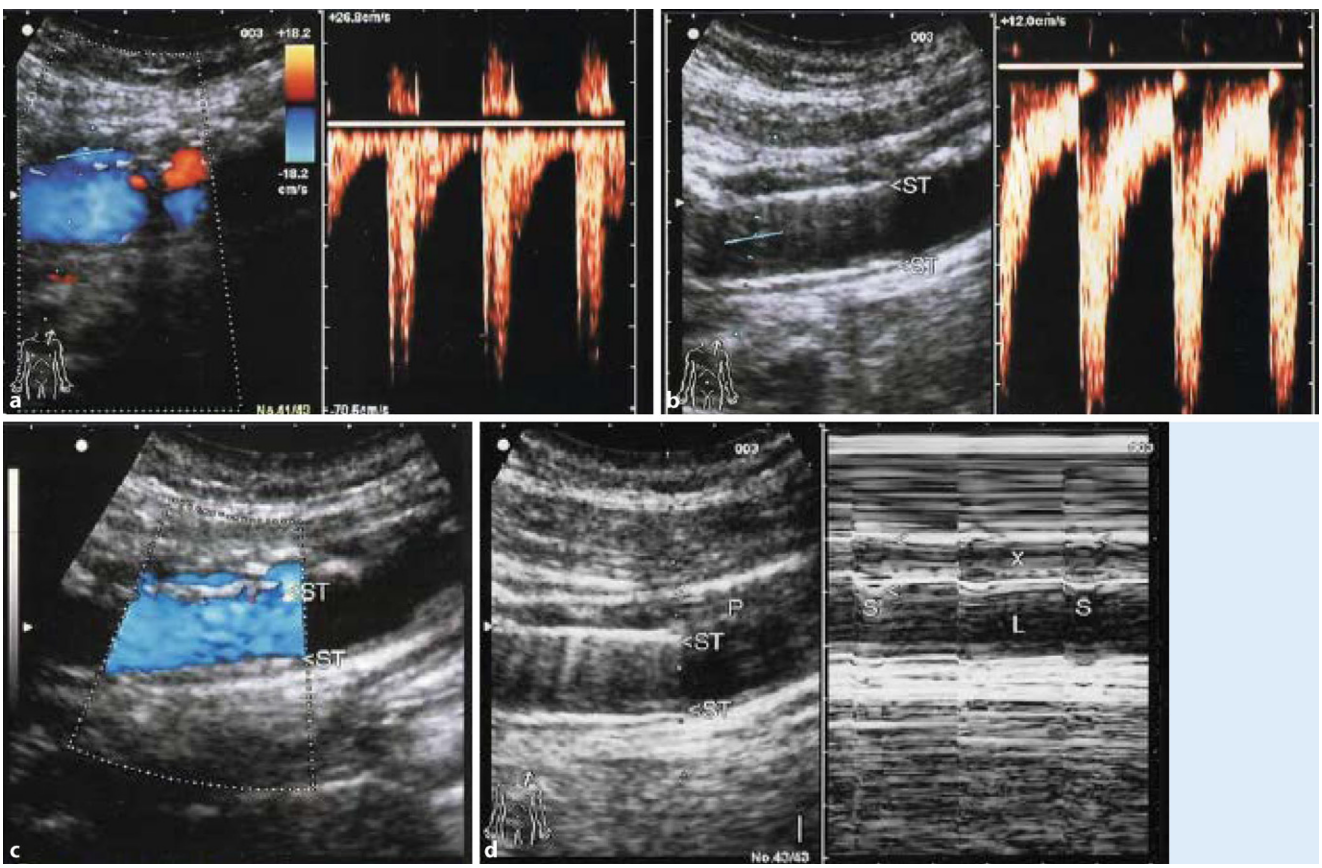

Fig. 7 ▲ The Doppler frequency spectrum in the lumen (**b**) and in the area between the detached stent and vessel wall (**a**) in stent dislocation: evidence for this is the pulsation in the false lumen in time-motion mode (**c**, **d**). In systole (*S*), the stent (*ST*) moves from the vessel wall pathway towards the vessel lumen (*L*) due to the build-up of systolic pressure in the false lumen (*x*). *P* plaque

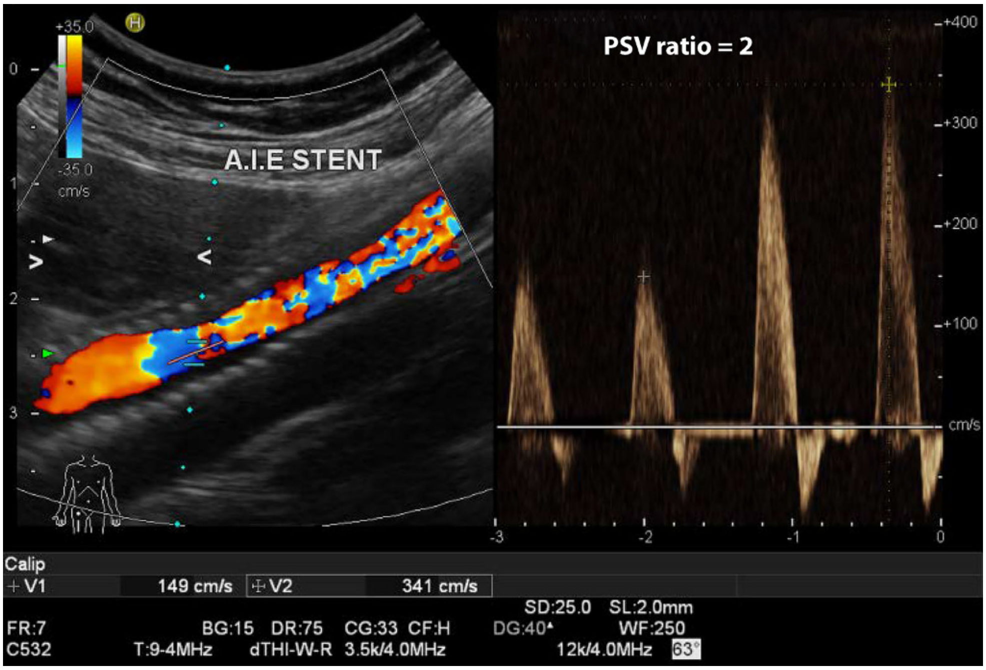

Fig. 8 ▲ External iliac artery (A.I.E) with 50–60% recurrent stenosis in the mid-third of the stent, graded using a peak systolic velocity ratio (PSV ratio) of >2 at a prestenotic PSV of 148 cm/s and an intrastenotic PSV of 341 cm/s. The stent area examined with the transducer to show the spectrum at the same Doppler angle at skin level is marked with *arrows* (>…<). *PSV* peak systolic velocity

in only 10% on the basis of high-grade stenosis.

Controversially, two earlier studies [43, 44] already demonstrated the relevance of duplex ultrasound in PTA follow-up and the increased accuracy in predicting recurrent stenosis, particularly in the case of flap-like residual stenosis protruding into the lumen and flow obstruction. Duplex ultrasound was more sensitive here compared to angiography: duplex ultrasound classified 20% of residual stenosis as >50%, whereas angiography classified these as <30%. Stenosis classified as >50% on ultrasound showed significantly reduced patency and a success rate (without high-grade recurrent stenosis or occlusion) of only 11% at 1 year compared to a success rate of 80% if <50% residual stenosis was measured on ultrasound.

Other studies confirmed the importance of duplex ultrasound follow-up. A series of 267 duplex ultrasound examinations in 134 patients following endovascular treatment showed severe stenosis or occlusion in 32.4%. Clinical follow-up and Doppler occlusion pressure alone would have missed 30% of these [45]. Further endovascular correction was necessary in 25% within the 11-month follow-up of this study. Other investigations [46, 47] reported a re-intervention rate of up to 35% in the first year. Another study [48] demonstrated the benefits of ultrasound follow-up after PTA in critical ischemia based on a reduction in the amputation rate: 20% in a group with abnormal ultrasound findings compared to 5% in the group with normal post-interventional ultrasound findings. Early post-interventional ultrasound demonstrated relevant residual stenosis in 56% of cases that were not visualized angiographically.

A limitation that should be mentioned includes the fact that these investigations were retrospective, single-center studies with relatively heterogeneous patient collectives and mixed endovascular treatment forms: PTA, PTA and stent, and arterectomy. The aim of these studies was to evaluate the relevance of follow-up after endovascular treatment and not duplex ultrasound stenosis criteria following PTA and stenting. As such, they worked with the criteria established in duplex ultrasound for native peripheral arteries (PSV > 180 cm/s and PSV ratio >2) as the cut-off for 50% residual or recurrent stenosis (**Fig. 8**).

Stenosis grading following peripheral artery stenting

Compared to the carotid arteries, there are only a handful of studies [49, 50] comparing duplex ultrasound with angiography as the so-called gold standard to find, using ROC curves, an ideal cut-off value of absolute PSV values and a PSV ratio for >50% and higher grade stenosis in peripheral arteries. For example, a threshold velocity of 190 cm/s, with a sensitivity of 88%, specificity of 95%, positive predictive value (PPV) of 98%, negative predictive value (NPV) of 72% and a PSV ratio of 1.5 (93%, 89%, 96%, 81%, respectively) were selected for the femoropopliteal artery in 59 legs examined following PTA for >50% in-stent recurrent stenosis. A PSV of >275 cm/s (sensitivity 97%, specificity 68%, PPV 67% and NPV 97%) and a PSV ratio of >3.5 (sensitivity 74%, specificity 94%, PPV 77% and NPV 88%) was deemed the ideal cut-off value for >80% in-stent stenosis [50]. In another study, the ideal cut-off for >70% stenosis using ROC

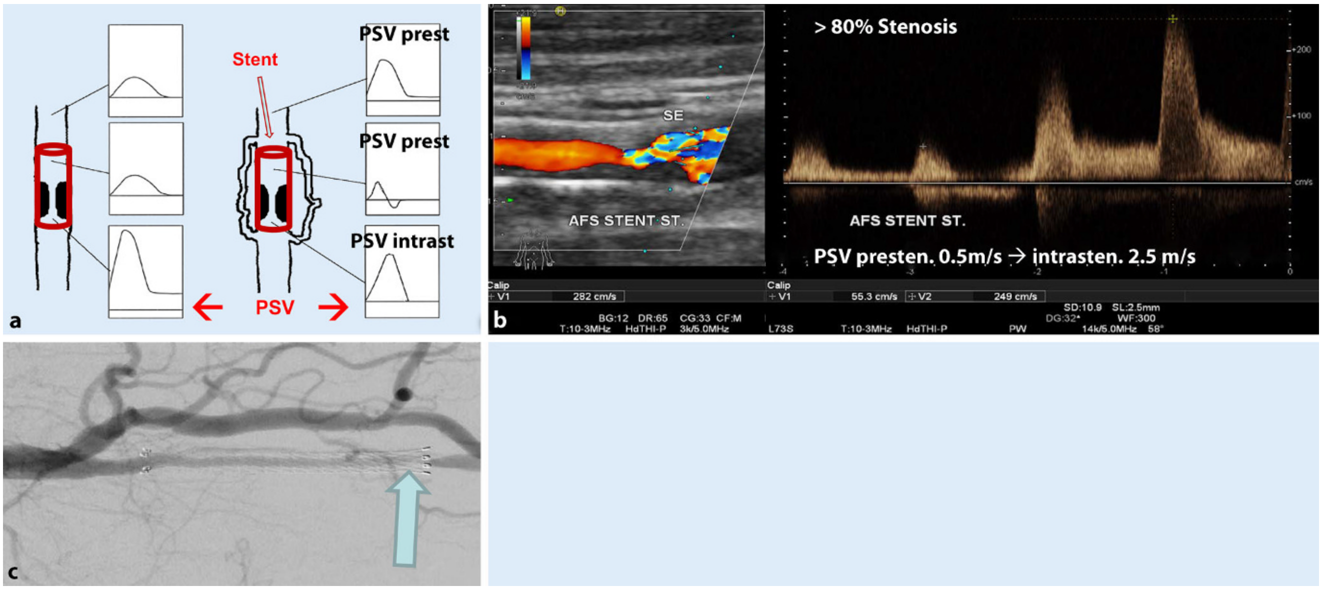

Fig. 9 ▲ **a** The collateral function on the prestenotic and intrastenotic peak systolic velocity (*PSV*) in in-stent stenosis: if collateralization is good (*right*), flow and thus also prestenotic in-stent PSV (*PSV prest*) and intrastenotic in-stent PSV (*PSV intrast*) are lower compared to lower or absent collateralization (*left*); this leads to lower absolute PSV values at the same degree of stenosis. **b** The intrastenotic (*intrastent.*) PSV in the well-collateralized high-grade in-stent stenosis is only 249 cm/s; however, in the case of a prestenotic (*presten.*) PSV of only 55 cm/s, due to good collateralization (**a**, **c**), the PSV ratio is approximately 5 and indicates >80% stenosis according to the continuity law. **c** Angiography of **b** with well collateralized in-stent stenosis (*arrow*). *SE* stent end, *AFS* superficial femoral artery, *ST* stenosis

curves was determined to be 223 cm/s in 143 patients with a sensitivity of 94% and a specificity of 95% [49]. What is striking is that, in contrast to some studies on the stented ICA, the cut-off was set at the level of native stenosis of the femoropopliteal artery and surprisingly somewhat lower in the case of high-grade recurrent stenosis; however, here again, these analyses are, without exception, retrospective with relatively low case numbers and using different endovascular procedures.

The somewhat lower PSV as cut-off in stenosed arteries versus native stenosis could be explained hemodynamically if in-stent stenosis occurred at a more eccentric site. Eccentric stenosis has a smaller area reduction at the same diameter reduction (angiography; also lower clinical relevance due to lower reduction in blood flow) compared to concentric stenosis and thus also a lower PSV (◘ **Fig. 5**). Furthermore, increasing collateralization in the course of restenosis can lead to reduced blood flow in the stenosed vascular area and thus to reduced PSV at the same degree of stenosis (◘ **Fig. 9a–c**).

Systemic factors influencing the absolute PSV value, as well as the stent-induced changes in hemodynamics discussed above, can be circumvented by grading stenosis localized along the course of the stent using the PSV ratio (determined in the stent, ◘ **Fig. 8**; video clips 4 and 5). With the exception of proximal in-stent stenosis in the aortic bifurcation or at the superficial femoral branch, recurrent in-stent stenosis, as in carotid stenosis is therefore most reliably graded using the ratio of intrastenotic PSV/prestenotic PSV according to the continuity law (◘ **Fig. 9a–c**).

In order to promptly detect technical errors with recurrent stenosis, the first examination in a follow-up program should take place within the first 4 weeks, then at 3–6 months and at 1 year. Patients treated for critical ischemia should be checked every 3 months in the first year and every 6 months thereafter (modified from [51]).

Conclusion

- **Both in vitro and ICA studies showed discrepant PSV measurement results in the grading of in-stent recurrent stenosis (but also of native ICA stenosis) with PSV.**
- **In summary, according to the evidence, a PSV of >220 cm/s for >50% and a PSV of >300 cm/s for >70% in-stent recurrent stenosis emerge as threshold velocities following CAS.**
- **Increased rigidity of the stented vessel and stent-related lumen reduction are cited as the causes of increased threshold velocity.**
- **Since most cases of in-stent recurrent stenosis both in the ICA and peripheral arteries are localized along and in the distal area of the stent, recurrent stenosis can be most accurately graded according to the continuity law using the PSV ratio (intrastenotic PSV/prestenotic PSV in the stent). An in-stent PSV ratio disregards stent-related hemodynamic changes.**

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Compliance with ethical guidelines

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