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Annals of Vascular Medicine & Research

Review Article

Pedal Artery Angioplasty in Patients with Diabetes and the Alchemy of Turning Stone into Flow: A Review

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Submitted: 14 March 2023
Accepted: 27 April 2023
Published: 27 April 2023
ISSN: 2378-9344

Keywords
- Chronic limb-threatening ischemia
- Angioplasty
- Critical limb ischemia
- Wound healing
- Limb salvage
- Pedal arteries
- Arterial calcification
- Diabetic foot

Abstract

Objective: Chronic limb-threatening ischemia (CLTI) resulting from multilevel arterial occlusive disease carries a high risk of limb loss and mortality. Because scarcely analyzed in contemporary literature, our study proposes a specific review of available pedal artery angioplasty (PAA) indications and clinical results in CLTI, particularly in patients with diabetes.

Methods: We examined PAA application and outcomes in CLTI, specifically in patients with diabetes, by analyzing data from the PubMed, Medline, and available online databases.

Results: After the initial identification of 881 publications that matched the present research criteria, 16 articles were selected for PAA analysis, from which only 4 exclusively focused on patients with diabetes. While 2 articles analyzed isolated PAA applications in CLTI, 12 others studied the clinical utility of PAA in association or non-association with above-the-ankle (ATA) angioplasty. Because of the huge heterogeneity in the profile of these studies, absence of standardized reference groups, insufficient clinical data, low level of prospective information, and absence of randomized controlled analysis, optimal level of data evidence was not attainable.

Technical success rates for PAA varied between 76% and 93% of treated cases. Statistically superior wound healing and limb salvage rates were observed after applying PAA either alone or in tandem with ATA angioplasty in CLTI treatment. However, amputation-free survival (AFS) was not influenced by PAA in 4/14 (29%) of the selected studies.

Conclusions: Standardized indications, uniform clinical evaluation, and acceptable levels of evidence are missing in current investigations concerning PAA. Despite the scarce documentation of clinical outcomes, PAA alone or in combination with ATA angioplasty seems to afford better wound healing and limb preservation rates but does not improve AFS. While some authors describe lower feasibility and clinical success rates in patients with diabetes, others do not. Further standardized and prospective studies are required to validate the clinical usefulness of PAA.

ABBREVIATIONS

AFS: Amputation-Free Survival; ATA: Above-The-Ankle; BTA: Below- The-Ankle; BTK: Below-The-Knee; CLTI: Chronic Limb-Threatening Ischemia; CTO: Chronic Total Occlusion; DEB: Drug Eluting Balloons; DR: Direct Revascularization; ESRD: End-Stage Renal Disease; EVT: Endovascular Therapy; GLASS: Global Limb Anatomic Staging System; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GVG: Global Vascular Guidelines; IR: Indirect Revascularization; LBP: Limb Based Patency; LFA: Linked Foot Arches; MAC: Medial Artery Calcification; P0-P2: run-off score GVG foot grading system; PAA: Pedal Artery Angioplasty; PAD: Peripheral Artery Disease; PAS: Pedal Artery Stenting; PFFR: Peripheral Fractional Flow Reserve; SAD: Small Artery Disease; TAP: Target Artery Path; WTR: Wound Targeted Revascularization; WTRc: Wound Targeted Revascularization via collaterals.

INTRODUCTION

Chronic limb-threatening ischemia (CLTI) is defined as the most severe manifestation of peripheral arterial disease and is caused by end-stage atherosclerotic occlusive disease of the lower limb [1,2]. Nearly 2–6% of patients with diabetes mellitus develop a form of foot ulcers annually [1,3]. Approximately 37% of diabetic neuro-ischemic foot ulcers exhibit additional latent or manifest ischemic features [1,3]. Diabetic macro- and micro-angiopathies represent common features of tibial and pedal arterial atherosclerotic lesions.

Because of the extreme heterogeneity of anatomical and hemodynamic flow alteration in CLTI and limited published clinical experience, current pedal artery angioplasty (PAA) standardized indications and expected results remain unclear [1,2].

Contemporary advances in endovascular therapy (EVT) in the last two decades have shown that effective treatment with below-the-ankle (BTA) angioplasty can be associated with above-the-ankle (ATA) revascularization [2,3].

This study aimed to present the most relevant available data regarding the current role of PAA for CLTI limb salvage, particularly in patients with diabetes.

Grounding experience for PAA

Distal foot reperfusion in CLTI remains technically challenging for interventionists. Despite persistent efforts in recent decades for improved vascular treatment, severe concomitant anatomical and functional flow alterations owing to CLTI syndrome may lead to unavoidable amputations despite "acceptable" PAA angiographic end-procedural results [4-6]. Although most contemporary series analyze specific morphological (anatomical) pre- and post-procedural PAA features of pedal arteries and foot arch levels [2-7], very few include a deeper evaluation of the ischemic foot by equally assessing large-to-small arterial collaterals [8-10]. The aggregate anatomical aspects of the CLTI foot before and after PAA remain undefined or poorly defined in literature from the last two decades [6,11,12]. The availability of appropriate inflow throughout the upstream tibial arteries, which often requires tandem BTA or ATA lesion treatment, is of crucial importance for PAA [3,7-9]. Many PAA studies emphasize the need to overcome extended CTO in pedal arteries with dense wall calcifications (with highest prevalence and grimmer prognosis in patients with diabetes and renal diseases) [1-3,5-9]. BTA arterial calcifications (alike the tibial trunks) pose a severe technical obstacle in crossing, dilating, and revascularizing these rigid millimeter-sized foot vessels and collaterals [5-8].

Although venous bypass is regularly considered the anatomical and physiological gold standard for below-the-knee (BTK) and BTA revascularization [3,6,13,14]. PAA may appear as an acceptable alternative to surgery [1,3,5], with comparable clinical results, higher reproducibility, and reduced invasiveness, particularly in patients with high risk of CLTI [1,3,5,8,15-20].

MATERIAL AND METHODS

Publications research

Tandem Medline database collection and unrestricted online records research were performed for publications related to generic PAA and its specific application in diabetic CLTI feet, over the last three decades. Sixteen keywords were used, including anatomical, endovascular, and diabetic clinical topics, without restrictions on paper design or language.

Data collection

Because of the huge heterogeneity in the profile of selected studies, scarce data for technical and clinical success, low level of prospective information (Table 1), and the absence of randomized controlled analysis for achieving an optimal level of evidence, the "grading of recommendations assessment, development, and evaluation" (GRADE) [21-30] was not applied to data interpretation.

Conformity criteria

All studies focusing on BTA angioplasty, with or without ATA endovascular performance, and those with isolated BTA/PAA application (case reports excluded) were chosen for interpretation (Figure 1).

The extracted data were evaluated in accordance with the Global Vascular Guidelines (GVG) for revascularization [3] such as a target artery path (TAP) policy and limb-based patency (LBP) indicator, if available.

The main endpoints in this study were wound healing and limb salvage allowed by PAA application in CLTI patients with diabetes. Parallel efficacy indicators such as technical feasibility, patency rates, amputation-free survival (AFS), and quality of life were equally noted (when available).

RESULTS

Although 881 publications were initially screened online, the final selection for PAA analysis focused on 16 articles with eligible criteria, from which only 4 articles focused solely on PAA application in diabetic neuro-ischemic feet (Table 2) [8,22,29,31]. Disregarding limitations inflicted by the small number papers answering the goals of this review, the following information was collected.

Eleven retrospective and five prospective studies (all featuring non-controlled and non-randomized profiles) were

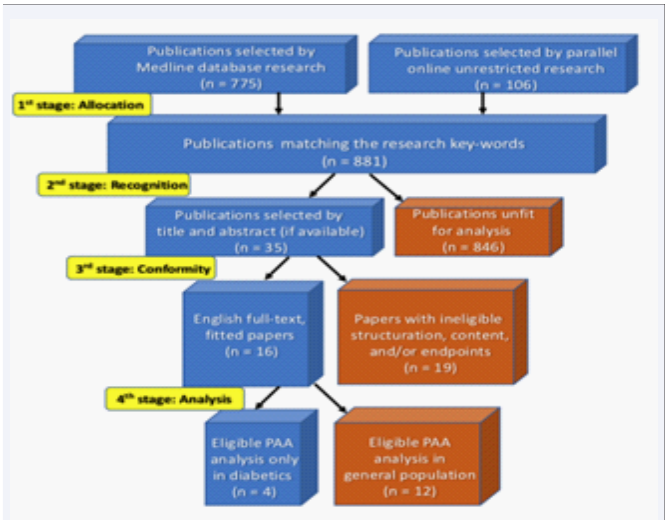

Figure 1 A succinct flow-chart representation of main stages for specific articles selection: stage 1, allocation of all publications matching the research specific keywords; stage 2, recognition of publications selected by title and abstract; stage 3, conformity assessment of English full-text structuration; stage 4, specific qualitative analysis of eligible PAA articles in diabetic patients, in parallel to the general population, and following characteristic endpoints of this review. More specifically, during stage 2 all inadequately structured papers, narrations, duplicate texts, dissertations, book chapters, interviews, editorials, conference proceedings, etc. were excluded, and well as during stage 3 concerning sole technical angioplasty notes, abstracts only available, case reports, and papers lacking specific endpoints. The stage 4 analysis was further detailed in discussion, and Tables I and II.

Table 1: Finishing selection of articles included for PAA analysis.

Articles included for PAA analysis								
Author	Year	Design	*n*	Wound healing		Limb salvage		Follow-up (months)
				PAA sole, or associated to ATA angioplasty	Sole ATA angioplasty without PAA	PAA sole, or associated to ATA angioplasty	Sole ATA angioplasty without PAA	
Manzi et al. [18]	2009	Prospective	135	$TcPO_2$=59mm	$TcPO_2$=42mm	97%	-	12
Abdelhamid et al. [19]	2010	Retrospective	42	-	-	81.9%	-	24
Kawarada et al. [24]	2011	Retrospective	31	-	-	82.1%	-	19.3 ± 11.4
Palena et al. [20]	2013	Prospective	38	$TcPO_2$=65mm	$TcPO_2$=18mm	Major=0% Minor=17%	-	6.7 ± 2.3
Katsanos et al. [23]	2013	Retrospective	37	-	-	94.6%	-	36
Wei et al. [21]	2014	Prospective	96	-	-	93.8%	-	24
Nakama et al. [25]	2017	Retrospective	257	57.5%	37.3%	-	-	1, 3, 12
Dua et al. [33]	2019	Prospective	57	-	-	96%	-	6
Jung et al. [26]	2019	Retrospective	239	76%	67%	96.3%	84.2%	12
Settembre et al. [30]	2020	Retrospective	407	-	-	76.1%	-	24
Alexandrescu et al. [8]	2022	Retrospective	336	-	-	Type of lesions Grade A = 85% Grade B = 78% Grade C = 67% Grade D = 42%	-	12
Sato et al. [6]	2022	Retrospective	159	79%	62%	88%	84%	12

Table 2: Concluding analysis of PAA articles punctually addressing diabetic patients.

Selected articles for PAA analysis in patients with diabetes mellitus								
Author	Year	Design	*n*	Wound healing		Limb salvage		Follow-up (months)
				PAA sole, or associated to ATA angioplasty	Sole ATA angioplasty without PAA	PAA sole, or associated to ATA angioplasty	Sole ATA angioplasty without PAA	
Teymen et al. [22]	2018	Retrospective, (only diabetic pts.)	48	-	-	Major=0% Minor=15%	Major=8% Minor=24%	12
Cheun et al. [29]	2018	Retrospective (only diabetic pts.)	109	76%	-	. 41±9%	-	3 60
Alexandrescu et al. [8]	2020	Prospective (only diabetic pts.)	167	67%	59%	86%	79%	6
Meloni et al. [31]	2021	Retrospective (only diabetic pts.)	80	56.2%	-	84%	-	12

investigated (Figure 1, Table 1). While all these studies focused exclusively on patients with CLTI (with one exception) [21], they differed or did not specify the proportion of subjects with high risk for extended calcifications, specifically those with diabetes, renal insufficiency, and end-stage renal disease (ESRD). While the anatomical severity classification of BTA lesions mainly refers to individual foot arch status [6,18,24,25,21, 26,30] (with three exceptions), [8,30,32] specific collateral assessment and systematic calcification classification (qualitative or quantitative) in the selected studies were scarce or missing.

PAA CHARACTERISTICS

Endovascular technique

PAA was mainly performed by endoluminal approach, except in two publications [18,19] where either endoluminal or extraluminal techniques were employed. TAP was successfully treated in an antegrade manner in 72% of the studies (Table 1). Only one study (7%) used drug-eluting balloons for ATA and BTA angioplasty. [22] Additional bailout stenting was used in two studies (16%) [23,24].

Patency rates

Restenosis and thrombosis rates were documented in 54% [21] –66% [23] of PAA interventions with 19–24 months of follow-up. Freedom from reintervention varied between 79%, [26] 94%, [23] 95%, [19] and 59% [29] after 1 year of follow-up. Despite these variable patency rates [1,3,7], achieving clinical success (temporarily but repeatedly by PAA) offered these CLTI limbs the chance to be among the +/-64% patients alive documented at 2 years of follow-up [3,5-7].

Pedal run-off

The importance of appropriate pedal run-off in BTK and BTA angioplasty outcomes appears undeniable. The recent Global Limb Anatomical Staging System (GLASS) document proposes an infra-malleolar three-variable (P0, P1, and P2) run-off grading system to define the anatomical TAP down to the pedal arteries [3]. Using a prospective database, Abdelhamid et al., found that poor collateral foot run-off directly and significantly hampers PAA outcomes [19]. In a parallel 159- patient retrospective study, Sato et al. [6], equally noted that the absence of target vessel outflow in the foot ($p<0.001$) and the occluded pedal arches ($p=0.030$) represent significantly poor run-off indicators of PAA failure (79% observed in patients with diabetes) and worse clinical outcome at 12 months [6]. These data confirm analogous information by Baer–Bositis et al. [14], concerning foot run-off

for exhaustive BTK interventions. In their article, [14] an original pedal patency score (1–10) corresponding to good (<7) vs. compromised (>7) run-off in pedal vessels strongly influenced clinical outcomes (p=0.0001) [14].

Technical feasibility

Technical success for PAA varied between 76% and 93% [18-25] (85% by Manzi et al., [18] 88% by Abdelhamid et al., [19] and 93% by Kawarada et al.) [24]. Failure to perform PAA by retrograde pedal access or using the "pedal-plantar loop" was noted in 14%–15% of patients in two studies [18,20]. Sato et al. [6], documented that the degree of pedal artery calcification and pedal arch occlusion represents significant indicators for PAA technical feasibility and clinical success; however, the authors do not observe a powerful correlation for these parameters between diabetics and non-diabetics [6]. In a 96-patient prospective study, Wei et al. [21], studied the feasibility of using antegrade PAA vs. retrograde access in the ischemic foot. The study also included patients with diabetic limbs (mean duration of diabetes, 14 years) and patients without CLTI. The authors observed a 75.9% technical success rate in the antegrade, against 74% technical success in the retrograde PAA group [21].

A parallel 8-year retrospective study by our institutional group [8] described a 4-grade anatomical stratification of the pedal trunks, foot arches, and foot collaterals for CLTI atherosclerotic lesions [8]. PAA feasibility varied from 95% for grade A (less severe lesions) to only 12% for grade D (worse occlusive disease) and was directly correlated to the presence of diabetes, the complexity of CTO and the extent of calcification [8].

Wound healing and limb salvage

Although the initial experience with PAA represented only a handful of case reports, its real usefulness in CLTI treatment has been thoroughly considered during the last decade [18-21]. In a single-center, 42-patient case cohort study selected from a prospective database, Abdelhamid et al. [19], reported 61% AFS, 82% limb salvage and clinical success, and 74% survival after PAA at 1 year. The authors also stated that diabetes, impoverished run-off, and the extent of CTOs represent major determinants of limb loss in PAA outcomes [19]. In a similar 40-limb study (74% patients with diabetes), Kawarada et al. [24], combined PAA with specific pedal artery stenting, and reported 69% AFS and 91% limb salvage at 12 months. All examined stents appeared deformed, while 13% expressed external compression, and 13% others were fractured at a mean 12 months follow-up [24].

Succeeding multicentric and retrospective "Rendezvous" registry [25] included 257 patients (73% patients with diabetes), of which 140 had associated tibial angioplasty and PAA, and 117 with only ATA angioplasty. Wound healing was particularly higher (57% vs. 37%, p=0.003), and the mean time for healing was shorter (211 vs. 365 days, p=0.008) in the PAA group (including patients with diabetes). However, after risk stratification of patients, the "high risk" subgroup did not show significant benefits of PAA in wound healing, overall limb salvage (p=0.47), and AFS (p=0.92) [25]. In another notable 239-patient retrospective analysis, Jung et al. [26], proposed an original foot arch stratification (Type 1–3) and observed that wound healing, time for healing, and AFS were significantly higher (p<0.001) in the PAA group. The study included equivalent 85% and 88% patients with diabetes in its two arms. Diabetes did not show statistical significance in affecting clinical outcome [26]. Successful PAA, high levels of C-reactive protein, and absence of visible foot arches represented major risk factors for impaired wound healing [26]. The authors conclude, "efforts should be made to revascularize pedal arteries, especially when the pedal arch appears completely absent [26]." These data are also supported by a recent analysis by Sato et al. [6], based on an extensive BTA endovascular approach that proved better wound healing and limb preservation rates following successful PAA in both, patients with and without diabetes [6].

In recent years, PAA indications and clinical results have become subjects of controversies and require more frequent interrogations in literature [6,8,22,26-29]. While some authors observe no significant relation between PAA clinical results and the extent of pedal arch disease [27,29], others show a significant association [6,25,28]. Other important negative predictors include "wound infection," "the presence of ESRD," and "the status of foot collaterals" (as evoked by Kawarada et al.) [28]. The influence of diabetes on PAA outcomes remains controversial. This latest point is confirmed by a recent study by Settembre et al. [30] who, using multivariable analysis, showed that at 2 years, the presence of elevated C-reactive protein level, diabetes and rheumatoid arthritis incidence, increased number of affected angiosomes, and incomplete or total absence of pedal arches (vs. patent foot arches) appear as powerful predictors for wound healing and leg salvage following angiosome-guided PAA [30]. Better and faster tissue regeneration after PAA was observed by Meloni et al. [31], in a recent homogeneous 80-diabetic patient cohort. In comparing successful vs. unsuccessful foot perfusion, they found major differences (89% vs. 9%) in wound healing, minor amputations (44% vs. 78%), and major amputations (2% vs. 36%) in the studied group. These observations also fit our group's experience [8,32] studying BTA angioplasty in patients with diabetes [8,32]. At 1 year, wound healing was noted to be 70% in wound targeted revascularization (WTR), 54% in wound targeted revascularization via collaterals (WTRc), and 20% in the indirect revascularization (IR) groups [32]. AFS was not influenced by the revascularization strategy (p=0.093) [32]. This same point of view is thoroughly supported by another parallel analysis published by Cheun et al. [29] This original study is also one of the few available [22,29,32] that associates homogeneous PAA application exclusively in diabetic neuro-ischemic limbs. All patients uniformly received PAA revascularization without associated ATA interventions. The authors found 76% wound healing at three months, with 33% AFS at five years. Favorable predictors for tissue recovery in this diabetic population were once again the improved foot run-off, direct angiosome-targeted revascularization, and absence of end-stage renal disease (with additional calcifications added to the diabetic context) [29]. Using a 0.014-inch endovascular platform, the authors described particularly challenging situations to cross and dilate

calcified pedal artery lesions [29]. This also corresponds to our interventional team observation [32]. Recent data by Sato et al. [6], strengthen the fact that better tissue cicatrization (p=0.030) is observed because PAA can be successfully applied. However, despite these convergent opinions, it appears though not straightforward, if the true arches integrity stands as an argument for PAA utility [8,26,30] or rather as the expected reinsuring result following PAA intervention [1,29].

Limb salvage consistently appears to be positively enhanced by PAA application, either as an isolated BTA procedure [18,29] or in conjunction with ATA angioplasty [21-24,27-29].

These findings on limb preservation in CLTI fit with a majority of publications from the last decade (Table 1) [8,22-25,30-33]. In a conspicuous contemporary study Dua et al., also observes better limb preservation, lower minor amputation rates, and superior quality of life scores with successful PAA [33]. According to our team's clinical experience [8], limb salvage clearly shifted from 85% in grade A foot artery disease (gathering less complex lesions and lower calcifications) to only 24% in grade D disease (more challenging occlusions and extended calcifications) [8].

Amputation-free survival

While several publications state that AFS proves superior since PAA is associated with ATA [19,25,26], other researchers report only poor benefits for AFS [25,29] due to underlying severe vascular disease at the systemic level, particularly in patients with diabetes and renal diseases [29].

Follow-up

The few reported follow-ups in the chosen articles varied between 6 and 24 months (mean 17.9 months). Restenosis is not regularly specified in the present analysis [18,19,21-24,28,30-33]. The restenosis rates mentioned vary from 54.5% (Wei et al. [21]) to 64.1% (Katsanos et al. [23]) at variable intervals between 24 and 36 months.

DISCUSSION

Despite several encouraging yet heterogeneous data publications [1,8,18-25,29-32], standardized information with a good level of clinical evidence for PAA is still awaited [1,3,5]. Although tandem morphological and physiological assessment of BTA arterial flow in CLTI may help uniformization of PAA indications and results, [3,6,13,16] this dual approach is also lacking currently.

Regional particularities of BTA arterial perfusion

Pedal circulation has unique anatomical and functional features in the human body [4,6,11].

Pedal flow delineates a specific zone in the inferior limb where the main arteries and branches act as "terminal territory ramifications," or "end-artery disease branches [4,11,12]." Unlike other arterial territories subject to angioplasty treatment, PAA application addresses this specific foot arterial environment which exhibits native and acquired variations in the number and type of collaterals and related vascular resistances [4,11]. For example, arterial collateral supply in the heel and backfoot appears natively poor, exacerbated by the development of CLTI when compared with the forefoot collateral reserve [6,11,13]. An accurate BTA angiographic (anatomical) and functional (hemodynamic) assessment of foot flow, including the main arterial trunks, arches, and appended collaterals, appears to be of great utility when planning PAA revascularization [8,11,13-15].

Current anatomical hurdles for PAA

Abundant data in the vascular literature underline the importance of a thorough anatomical evaluation of BTA atherosclerosis in CLTI [3,6-10].

GLASS also highlights the need for appropriate run-off appraisal for TAP revascularization [3]. For this purpose, GLASS uses an infra-malleolar three-variable (P0, P1, and P2) run-off angiographic score to define appropriate TAP and appended LBP (as an associated hemodynamic parameter) [3]. While most authors propose anatomical "single level" stratification scales (guided by the foot arches lesions) [3,7,26], others expand this interpretation to the main foot collaterals (from large-to-small caliber), in a more detailed CLTI assessment [8-10,14,30]. A recent single-center study by Bekeny et al. [10], observed 80%, 92%, and 63% wound healing rates associated with direct, indirect collateral-based, and total IR, respectively, depending on the topography of remnant collaterals [10].

Ferraresi et al. [9], described an original pedal arterial disease classification to categorize medial arterial sclerosis and calcification (MAC) assimilated as small artery disease (SAD) at the foot level [9]. The authors showed that MAC and SAD could be labeled as anatomical manifestations of the same infra-malleolar disease, which hampers the prognosis of limb preservation in CLTI (with, and without PAA) [9]. A parallel publication by our institutional team [8] stresses the importance of detailed, multilevel angiographic evaluation of BTA arterial disease. It defines four severity "grades" (grades A-D) that characterize concomitant multilevel arterial disease that affects the pedal arteries, linked foot arches (LFA), and main groups of foot collaterals [8]. Similar correlations as for SAD [9] and MAC [9] concerning advanced "grades" of BTA occlusive disease (grade D) and limb loss, particularly in patients with diabetes [8] are noted.

Based on miscellaneous infra-malleolar classification systems, all of which hold foot arches as "common denominators" of CLTI lesions), some interventionists recommend aggressive PAA indications in spite of BTA extent and severity of the lesions [26,27,29], while others do not [5,8-10]. This leads to certain number of discrepancies in the current interpretation of PAA indications and results, and may partially explain contemporary controversies.

Specific influence of foot arterial calcification on PAA

Severe infra-malleolar atherosclerotic disease enhances the parallel development of arterial wall calcifications as associated characteristics of the same multi-faceted pathogenetic phenomenon. This has only been partially understood [34-36]. Recent studies have revealed a significant correlation between

vascular calcification and increased cardiac and peripheral vascular morbidity and mortality [17-19]. While type I (dystrophic or inflammatory) calcifications are currently located at the arterial intima level, type II (metabolic or metastatic) calcifications are mostly described at the medial arterial level and are closely interrelated with calcium metabolism [35,36]. Medial arterial calcification (MAC) in CLTI is predominantly detected in patients with diabetes and/or renal disease [34,36].

A demonstrative paper and scoring system by Liu et al. [34], documented a significant association between MAC in the pedal arteries and a higher risk of impaired wound healing and inferior limb amputation in CLTI [34].

Unsurprisingly, the presence of extended infra-inguinal arterial calcification (particularly for tibial and pedal MAC) was considered a fierce barrier in BTK and BTA revascularization, especially for EVT applications [3,6-9,14,34].

In our previously published experience [8,32], BTK and BTA arterial calcifications were scored using a semiquantitative scale as "scarce" (category 1), "moderate" (category 2, or <50% of the lesion's length), and "severe" (category 3, or >50% of the vessel lesion's length, including circular and continuous calcifications and "ossifications") [8]. A detrimental effect of calcifications for PAA application was observed starting with grade C occlusive lesions (harboring category 2 calcifications), which were associated with a modest technical feasibility rate of 74% [8]. Technical success further decreased to only 12% for grade D pedal artery disease (mostly associated with category 3 calcifications) [8]. Although the presence of extended (category 3) calcification is considered a contraindication for PAA in our experience [8], there are no parallel recommendations in literature [1,3,27].

MAC located at the pedal arteries also seems to hamper large foot collaterals (diameter 1 mm) and arches of the foot [34]. Medial calcifications are currently associated with evolving stages of "fibrotic-to-sclerotic" medial arterial thickening in medium-to-small arterial collaterals (diameter <1 mm) [8,9,34-36].

This observation suggests that even "reassuring" PAA angiographic results obtained in the main pedal arteries may not be associated with equivalent hemodynamic success in the small arterial branches and tiny collateral perfusion (particularly in patients with diabetes and renal diseases), affected by medial sclerosis stiffness and calcifications of different degrees [9,27,29). By defining an original SAD entity at the foot level [9], Ferraresi et al. [9], recently showed that MAC and SAD represent dual anatomical manifestations of the same BTA disease, strongly associated with higher limb loss rates in CLTI [9].

Future clinical implementation of a highly sensitive BTK (and separately BTA) quantitative "Limb Calcium Index" may bring useful information, and eventually change some of current PAA evoked indications, feasibility rates, clinical results, and patency prognosis, particularly in patients with diabetic CLTI [8,35].

Current pathophysiological flow challenges for PAA

Recent GVG recommendations emphasize the importance of tandem anatomical and physiological evaluation of each ischemic presentation by associating the TAP profile with functional LBP [3].

From a parallel functional perspective, pedal flow appears to be totally dependent on the upstream inflow shaped by the tibial vessel diameter and rigidity (particularly in diabetic and renal calcified vessels) [11,17]. The pedal flow is also linked to cardiac output [11] and specific foot regional vascular resistance [13,17,37). An approximate 50% loss of foot collaterals (by CLTI aggression) may be associated with a 5–10-fold increase in the distal foot flow resistance, despite successful tibial and PAA recanalization [11,37,38]. In the CLTI foot, the skin, muscles, and nerves become "terminal" territories dependent on specific groups of surviving collaterals [4, 12]. PAA may initiate correct angiographic and physiological reperfusion in the main pedal trunks; however, clinical success still depends on the ability to transmit pulsatile blood flow [38] to tissues via the lasting collateral reserve [4,37].

Angiographically successful PAA stresses the hemodynamic role of the foot arches that store and circulate pulsatile blood flow and kinetic energy throughout the connected collaterals (similar to the circle of Willis in the brain). Targeted PAA in arch reperfusion may open an important functional collateral hub of the foot [37,38] with a major role in wound healing and limb salvage [30,32].

PAA applied in severe occlusive and highly calcific arterial diseases (similar to patients with diabetes) may enhance only a modest pulsatile flow that remains strongly dependent on local arterial stiffness and peripheral flow resistance [11,17,37]. These functional specificities of PAA resulting flow may explain the relatively modest patency and limb preservation rates described at 12-24 months in the reviewed literature [1,5,21,23,24,30].

A novel functional parameter, peripheral fractional flow reserve (PFFR) was recently described in clinical practice. It is based on trans-stenotic arterial pressure evaluation [39]. PFFR can be helpful before and after ATA and BTA angioplasty application by providing parallel hemodynamic information about local collateral resistances and eventual post-angioplasty patency rates [16,39]. Current BTK/PFFR evaluation provides limited accessibility in CLTI diagnostics [39], and is practically unavailable for BTA flow assessment. Some related questions still need an answer. Do all PAA-treated limbs require unvarying antiplatelet postoperative medications? Does the presence of high PFFR collateral resistance following PAA require more specific vasodilation or temporary anticoagulation therapy? Do the indications for PAA direct/IR provide better selection following specific flow pressure resistance threshold detection by the PFFR?

It appears that future PFFR research stressing collateral resistance and pulsatility index evaluation may provide complementary information, useful for answering these and other future persistent questions.

Two recent systematic review analyses by Huizing et al. [40], and Machin et al. [1], concluded that despite encouraging clinical results, the current evidence for PAA utility in modern

CLTI treatment is still awaited. Although lacking homogeneous contemporary standards for treatment [1], additional PAA may appear as a feasible and "safe" procedure [1,40], owing "a 92% pooled proportion of limb salvage at 12 months" [40] including in patients with diabetes. However, all current challenges and unanswered interrogations for PAA application in above-mentioned BTA environmental conditions [41] still allow increasing consideration in contemporary literature.

LIMITATIONS

The present review had some limitations. The homogeneity of the data available for the analysis was modest. Nearly all the selected papers had different profiles, inclusion criteria, and endpoints for reporting research and results. The low level of evidence and statistical quality of data (mainly single-center and retrospective studies) may add inherent inconsistencies in analyzing outcomes. The main data interpretation focused on only four articles that met the eligibility criteria for this research. The reduced number of acceptable publications for analysis featuring disparate clinical outcomes and findings prevented this review from containing more structured information and performing a parallel meta-analysis.

CONCLUSION

Standardized indications with uniform clinical evaluation and acceptable levels of evidence are missing in the current literature on PAA. Despite scarce documentation in literature, pedal angioplasty alone or in association with ATA angioplasty seems to provide better wound healing and limb preservation, but without superior AFS rates. While some authors prove diabetes to be a significant factor for lower PAA feasibility and clinical success rates, others do not. Further standardized and prospective studies are required to validate its clinical usefulness.

ACKNOWLEDGEMENTS

The corresponding author acknowledges all members of our institutional diabetic foot clinic, and surgery department for their effective support and consultancy in data collection and referral of this review. We appreciatively acknowledge our institutional computing staff for conspicuous analysis and Medline data selection during this research. We equally thank "Language services department" for professional English language editing of this text.

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