What is the value of APG in the diagnosis of iliac vein obstruction?

Welches ist der Stellenwert der Luft-Plethysmographie zur Diagnostik der Iliakal-Venen-Obstruktion?

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ABSTRACT

It looks like treatment of central venous obstruction has become easy since the introduction of iliac stenting procedures. However, this treatment includes a minimum period of anticoagulation and the stent is for life. Furthermore, there are no accepted criteria for evaluation of the results. It is difficult also to establish robust indications of stenting especially since 25 % of the normal population have a diameter reduction > 50 % in the left iliac vein.

Another confounding fact is that chronic venous insufficiency (CVI) can be the consequence of multiple simultaneous pathologies, like varicose veins, obstruction and deep venous reflux. Thus, the treatment of one of these may not have a significant clinical effect if the cause is multifactorial.

Air Plethysmography (APG) is an objective, non-invasive and patient independent investigation of venous drainage. This includes gravitational filling (venous filling index) and elevation emptying (venous drainage index) all in the same test. This investigation should be performed as a screening test, prior to deep venous stenting and also as a follow-up instrument.

ZUSAMMENFASSUNG

Durch die Möglichkeit der Stenteinlage in iliakale Venen scheint die Behandlung der zentralen Obstruktion ein leichtes Unterfangen geworden zu sein. Allerdings bedingt diese Behandlung eine zumindest vorübergehende Antikoagulation – und der Stent wird lebenslang im Bein verbleiben. Und die Evaluation der Ergebnisse ist noch nicht gut etabliert. Auch die Indikationsstellung ist nicht immer objektivierbar gegeben, wenn man bedenkt, dass 25 % der Bevölkerung eine Stenose der linken V. iliaca von über 50 % aufweisen, auch wenn sie meist keine Symptome haben. Erschwerend kommt hinzu, dass die venöse chronische Insuffizienz als klinisches Syndrom (CVI) mehrere Ursachen haben kann, wie Varikose, Obstruktion oder Refluxe der tiefen Achse und die Behandlung eines einzelnen, anatomischen Befundes nicht unbedingt die Klinik nachhaltig verbessern muss. Die Luft-Plethysmographie (Air Plethysmography, APG) bietet in diesem Zusammenhang eine objektive, vom Untersucher und vom Patienten unabhängige Auswertungsmöglichkeit für die venöse Drainage und für die venöse Wiederauffüllzeit, die in jedem Fall vor einem Eingriff der zentralen Venen und zur Evaluation des Ergebnisses gefordert werden sollte

Introduction

Stenting of iliac veins after thrombosis or to treat congenital obstruction like May-Turner Syndrome has become widely accepted by Phlebologists, Angiologists, Vascular Surgeons and Interventionalists. It looks like an easy to perform and uncomplicated procedure to help patients with obstructive symptoms of the legs. It was proposed also for patients with large varicose veins supposing that deep vein obstruction is the reason to enlarge superficial reservoir of the leg [1] and recommended in advertisements from medical offices even though the opposite has been demonstrated [2]. Considering the high impact of these procedures around the world (top discussion frequency in international Whats-App and Mail Groups of Phlebologists), it is surprising that there is a lack of studies with objective preoperative evaluation and postoperative outcome criteria, apart from the technical description of visible enlargement of the lumen. And considering, also, that there is a foreign body introduced in the vein which is a no return situation, followed by 3–12 months or anticoagulation and sometimes longer, this development in Phlebology should be seriously re-considered...

General considerations about deep vein obstruction

Deep vein obstruction, specially proximal (Iliac or proximal femoral vein) due to thrombosis, stenosis, malformation or external compression impairs the venous drainage of the leg and thus accounts for severe chronic insufficiency and deterioration of quality of life. The difficulty in these patients is to find, whether a diameter reduction in the lumen of the vein is the reason for the symptoms, as liac vein compression of > 50 % occurs in 25 % of the normal population [3]. This allows to doubt whether the finding could not be in most of the cases a physiologic situation. Duplex ultrasound as diagnostic tool for iliac vein lesion has limited value, as it needs high skills and anatomic difficulties (overweight, external additional compression from the probe itself) can interfere with a good result. Intravasal Ultrasound (IVUS) is invasive, expensive and thus not able as screening method. Imaging in any way is limited to explore the haemodynamic impact of an iliac vein lesion, as either it does not evaluate collaterals (IVUS), or this is technically difficult (ultrasound) or impossible with tomography systems, as the tortuosities of collaterals exceed the limits of each icon. Phlebography or contrast MRI Phlebography is limited, also, because excepting for very skilled hands and depending on the breathing cycle, some collaterals are not filled or the contrast media will be diluted when arriving [4].

In addition, it is very seldom to find a person with obstruction of iliac veins and no other reason for chronic venous insufficiency (CVI). It is rare to find only obstruction, but mostly reflux (deep or superficial) in addition and less tone in the reservoir veins (deep veins, specially of the calf) after thrombosis, reducing the venous recoil, as well as impairment of muscle pumping.

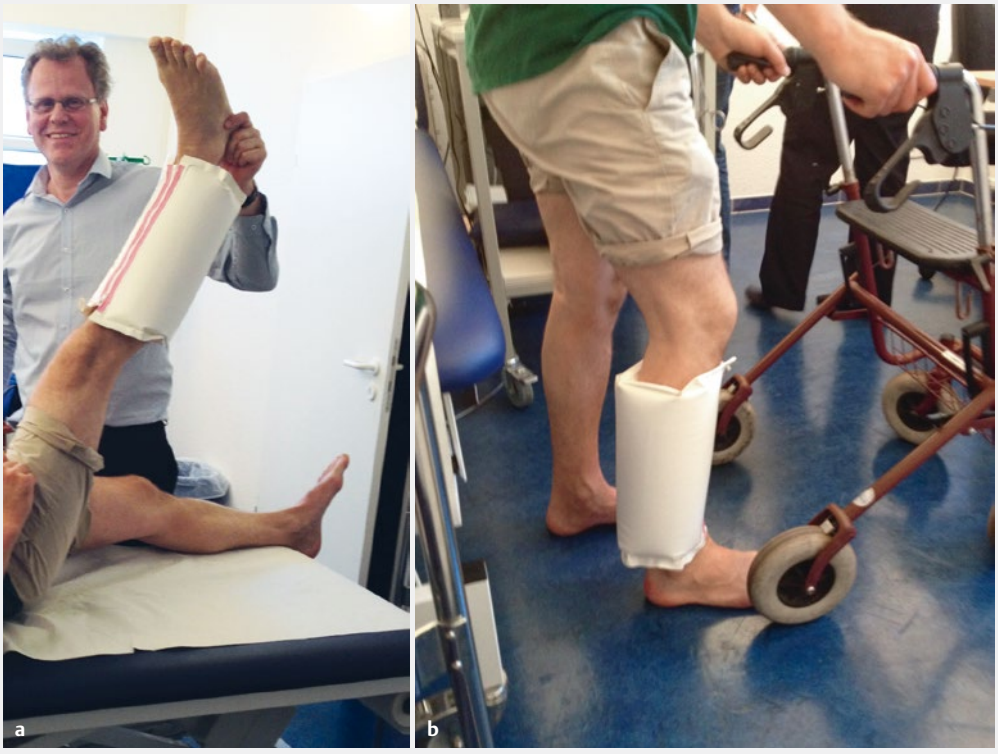
Corrections of the non-obstructive components are mostly less invasive than stenting the deep vein [4]. This includes compression stocking to improve the recoil [5], correction of superficial reflux after sorting out, that the vein is not a bypass for deep vein obstruction analysing the net flow in the lumen [6] or performing air plethysmography (APG) under great saphenous vein compression (see below), training programs and physiotherapy to improve muscle pumping.

General information to Air plethysmography (APG)

Air-plethysmography is a test easy to use by technicians. It is non-invasive and non-harming. It is performed to quantify volume changes in the calf. This is thanks to an air sensor-cuff wrapped around the calf that records volume changes through a transducer, reporting the absolute changes in mL and the rate of volume change in mL/s. To test the venous drainage, the dependent leg is elevated suddenly and so the venous blood flows toward the heart and the calf reduces its volume. To test the competence of valves, the leg is then lowered returned to dependency and the time needed to achieve the complete filling is recorded. The velocity of draining is related to the degree of obstruction and the velocity of filling related to reflux, respectively. Rapid emptying in non-obstructed legs prompt a curve with the shape of a waterfall [2]. Already Trendelenburg observed this and described his elevation drainage manoeuvre. The first paper describing the use of leg position changes to test drainage with APG on a tilt-table but without evaluation of numbers was published in 1964 by JC Allan [7]. In addition, APG gives information about the working venous volume, which is the total amount the leg volume changes between standing and elevation of legs.

The positions to adopt during the investigation are recumbent with elevated leg and standing, which can be achieved in a classic investigation room (▶ **Fig. 1**) or by the use of a hand operated tilt table (▶ **Fig. 2**). Motor operated tilt tables take more than 15 seconds to move from standing to horizontal and are therefore not helpful to detect a normal emptying of leg veins, which occurs within seconds. A curve with the volume change is provided on a screen (▶ **Fig. 3**). There are 4 cardinal points to be chosen: The plateau-level at filled and empty leg and the start of the postural change from recumband to standing and back. The volume between the complete filling and complete drainage is the venous working volume (vWV). As the curves end with a long period of steady state, it is difficult to define at which point 100 % is reached. Thus, the level of the plateau is chosen as 100 %, and then 90 % of filling is calculated. The time from start of elevation or dependency until the 90 % volume is achieved is the 90 % time. Dividing 90 % of volume through 90 % of time the Venous Drainage Index (VDI) or Venous Filling Index (VFI) is calculated and expressed in mL/s. For the drainage index the cut-off point was found to be 10.8 mL/s, lower values showing clearly an obstruction (▶ **Table 1** and ▶ **Fig. 4**) [8]. For the refilling time the cut-off point discriminating reflux was 2.9 ml/s, higher values demonstrating venous incompetence.

The measurement is independent of skin changes, room temperature, muscle pump impairment, cooperation of the patient, which can change the value of photoplethysmography (PPG) [9]. The only limitation could be patients with dizziness or – if in absence or a tilt table – non-mobile patients.

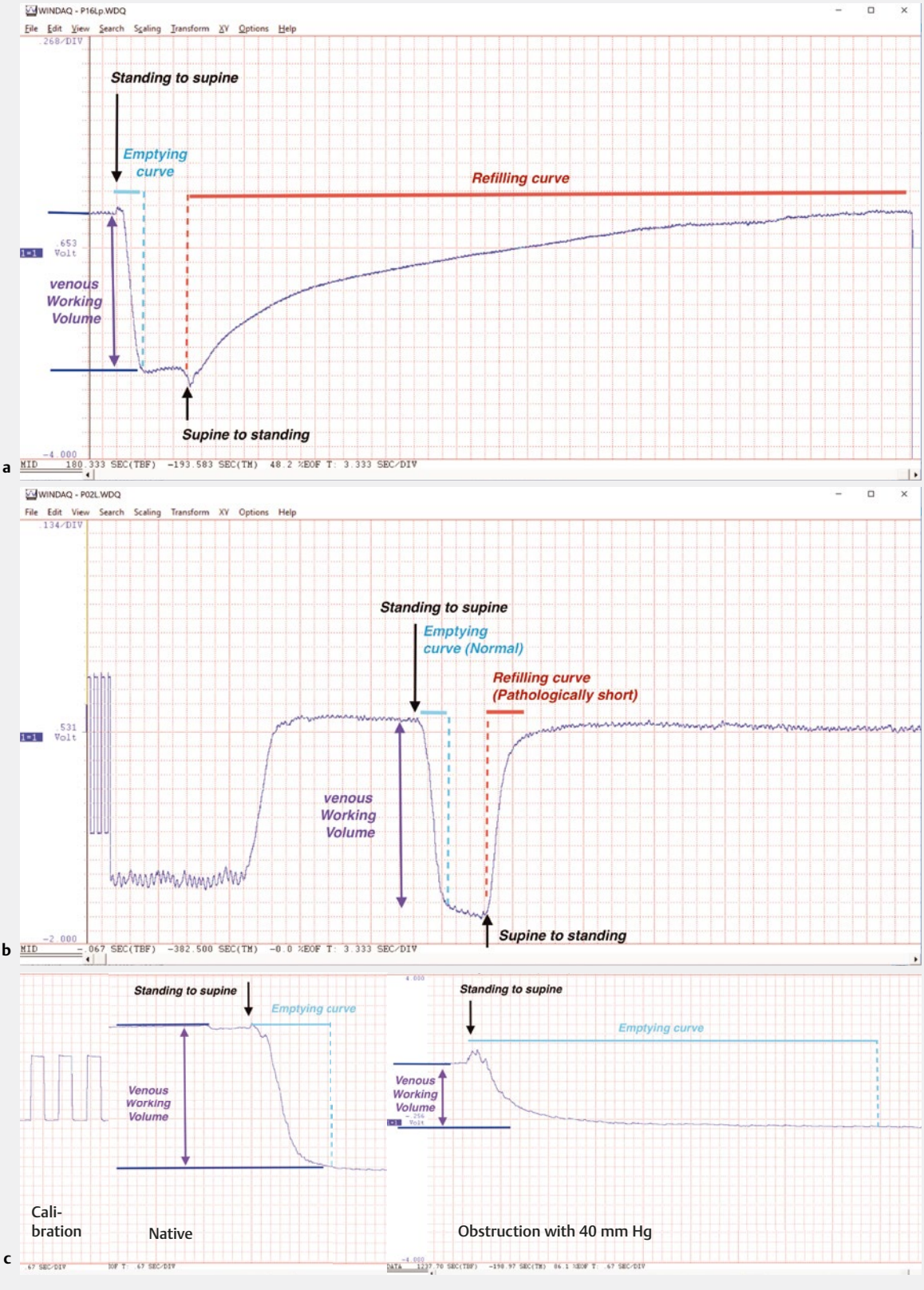


▶ **Fig. 1** Performing Air Plethysmography in exploration room. **a** Recumbent patient with the cuff around the calf with elevated leg sustained by investigator (CL). **b** Patient in standing position with hands on solid grips to avoid movements.

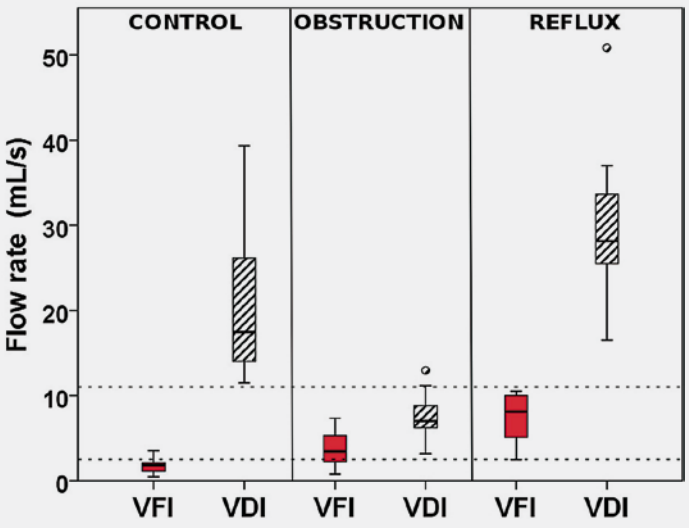
▶ **Fig. 2** performing Air Plethysmography on a hand operated tilt table. **a** Trendelenburg at – 45°. **b** Standing position.

Studies confirming the validity of APG

APG has been validated in 3 different studies. In the first, the APG cuff was applied to the calf, as usual and a proximal thigh-cuff as known from venous obstruction plethysmography was used to produced standardized obstruction pressures in healthy volunteers [10]. In this study, the leg drainage as measured with VDI on APG decreased significantly as pressures on the thigh cuff were higher. This confirmed the responsiveness of VDI to proximal obstruction.



▶ **Fig. 3** APG curves with emptying of the leg after moving the patient from standing to Trendelenburg and refilling curve after moving the patient from Trendelenburg to standing. **a** Normal curve with quick emptying (no obstruction) and slow refilling (no valve incompetence). **b** Pathological curve with quick emptying (no obstruction) and quick refilling (great valvular incompetence). **c** Pathological curve with slow emptying (obstruction) changing from standing to supine with legs elevated 70°. *with legs elevated 70°



▶ **Fig. 4** Box plots comparing the results of APG on tilt table: venous filling index (VFI) and venous drainage index (VDI) among three groups of subjects: Healthy controls, patients with obstruction of iliacal vein and patients with large refluxin saphenous veins. The horizontal dashed lines represent 10.8 mL/seconds (lower limit) and 2.9 mL/seconds (upper limit), which are suggested cut- off values for obstruction and reflux, respectively. (Data from [8]).

▶ **Table 1** Tilt-table results with air-plethysmography in the 3 study groups (n = 11/group). Expressed as median (inter-quartile range) (8)

	Control	Obstruction	p value [a] (control vs. obstruction)	Reflux	p value [a] (control vs. reflux)
Working venous volume, wVV (mL)	138 (119–198)	117 (80–154)	<.0005	202 (180–240)	.008
Venous drainage time, VDT90[b] (s)	4.9 (4.3–5.9)	9.7 (8.5–12.9)	<.0005	5.2 (4.4–5.9)	.622
Venous filling time, VFT90[b] (s)	69.4 (33.5–135.3)	33.7 (14.4–39.5)	.014	21 (16.6–36.3)	.004
Venous drainage index, VDI (mL/s)	17.4 (13.9–27.2)	7 (6–9)	<.0005	28.1 (25.4–34.4)	<.0005
Venous filling index, VFI (mL/s)	1.8 (1–2.1)	3.4 (2.1–5.4)	.014	8.1 (4.2–10)	<.0005

[a] Mann Whitney U test; [b] Filling or drainage time to 90 % of the wVV

A second study used rapid Trendelenburg tilting on a tilt-table (▶ **Fig. 2**) [8]. Venous draining index of patients with known obstruction of iliac veins were measured and compared to healthy controls and to patients with large varicose veins but without known deep vein obstruction. The VDI was significantly lower in the post-thrombotic patients with iliac vein obstruction versus controls and varicose vein patients, with a cut-off point of 10.8 mL/s.

Finally, a study on a small group of patients with non-thrombotic iliac vein lesions (NIVL) the VDI before and after stenting resulted in a significant VDI improvement [11].

Clinical assessment of obstruction

Leg symptoms in chronic venous insufficiency are very unspecific, like discomfort, heaviness, pain, swelling, pruritus and cramps. They are common not only in patients with deep vein obstruction, but also in venous valvular incompetence and also in healthy population [12, 13]. Independently of the existence of venous disease most of the probands will develop some of the described symptoms as well as oedema after prolonged standing and will profit for the symptoms as well as for the oedema with compression stockings [13]. The origin of the symptoms, thus, may not be venous, even though varicose veins are visible or obstruction diagnosed.

Furthermore, there is no strong relationship between venous symptoms and clinicals signs of CVI. Approximately 20 % of patients with leg ulceration due to venous disease have no visible varicose veins [14] and further 20 % do not feel pain [15].

As a clinical tool, the Villalta scale in the diagnosis and assessment of PTS is not reliable [16], as it has been shown to be non-specific: 42 % of patients with non-thrombotic venous disease are found to have values above the threshold defining PTS, even though they have never had a thrombosis event nor reflux in deep veins [17]. The scale does not ask for some specific symptoms like

venous claudication, and also does not include diagnostic signs like abdominal collaterals [18].

Why to use APG in venous screening?

The primary function of veins is drainage, which is impaired by obstruction and reflux. APG measures both in a simple way, without confounders. It is reliable independently on the situation of the leg (pre- or postoperative), it is operator independent and reproducible. Therefore, APG provides an objective test quantifying the degree of haemodynamic impairment (valve insufficiency and obstruction). It should be recommended for screening in general population, thus avoiding unnecessary duplex investigations, diagnosis of the extent of haemodynamic dysfunction before treatment and during follow up.

Many countries have a medical system based on self-managed clinics and offices with the complete economic risk of every enterprise. In this setting treatment decisions are not only made for the well-being of the patient. This is the reason, why objective assessment for diseases prior to discuss treatment options are more and more important.

In Germany the outflow fraction (OF) in venous occlusion plethysmography (VOP) has been used for years as the way of assessing acute or chronic proximal venous obstruction. It measures the change in calf capillary filling with photo plethysmography under obstruction of the thigh with a pneumatic thigh cuff up to 80 mmHg and then the velocity of emptying of the capillaries after a sudden deflation of the cuff in 1 second. This is performed in the supine position. The result is given as a percentage. Unfortunately, it has been shown, that outflow obstruction is not properly assessed [19]. Recent data using APG and proximal pneumatic thigh cuff have demonstrated that the use of compression stockings at the thigh influences the outflow fraction increasing it from a median of 44 % to 63 % [5]. It has been shown, that the VDI is responsive to stenting [11] and to experimental proximal obstruction [10].

The manoeuvres to be used for the APG measurement use only gravitation as provocation – the responsiveness of blood flow to postural changes. APG works independently of any investigator dependent features like the size of the hand in calf compression or the skills of the investigator. Unlike other investigations, like diameter measuring of GSV, which is not possible after ablation of the vein, APG is possible also after treatment. Dependency manoeuvres just test the ability of the veins to defend from postural changes and are independent of the patient's ability to move the muscles, which is the case in PPG.

Of course, once an obstruction or reflux has been determined by the APG screening method, imaging is mandatory to define the hemodynamic problem and to think of a treatment strategy, which then should influence the APG results after intervention.

APG against inappropriate stenting

Currently, if the patients show clinical symptoms and signs that fit to an obstruction (usually > 50 % diameter reduction, which is present even without symptoms in a 25 % of the population), this may induce the application of a venous stent as a modern treatment option [20]. Depending on the background of the centre or the specialist, this can result in indiscriminate stenting, as both – diameter reduction and venous symptoms – are frequent in the population. But remember: A stent is for life. A stent will be followed by oral anticoagulation or aggregation for a time or for life.

If the symptoms were not due to obstruction, the patients will not improve clinically. The purpose of APG prior to any intervention is to determine if there is a significant and hemodynamic active obstruction present. In the absence of drainage impairment on APG, there is no indication to place a stent.

In addition, after stenting the lesion, the APG values should improve (if they were impaired before treating). The interventionalist usually does not see the patient after his intervention. He is happy when technical results show opening of the lesion. Studies show, that the mere imaging success does not correlate with clinics [21]. Venous drainage index improvement after stenting may help.

In addition, lots of patients have combined obstructive and refluxive disease, in these cases, it has to be thought about which system to treat first. Stenting a hemodynamic significant obstruction might reduce symptoms, perhaps reducing the volume charge in reflux of the superficial system. On the other hand, there is the opposite option: First to treat the superficial venous reflux, as this intervention is less invasive. If the clinical improvement is enough after this step, the deep venous obstruction will not need to be treated and perhaps the obstruction might not have been as severe as originally thought.

Another possible situation is a post thrombotic syndrome (PTS) combined with great saphenous vein (GSV). Thanks to duplex investigations it can be ruled out, whether the saphenous vein is a drainage route bypassing the femoral obstruction, in which case it should not be treated. To discriminate the net flow can be useful in duplex (6). Or the intervention can be simulated by an APG test (draining and filling) with GSV occlusion under pressure with duplex probe. With this maneouver it is possible to predict the haemodynamic effect of GSV draining and refluxing path elimination.

The idea, that iliac vein obstruction may be the cause of large varicose veins [1] as a dilatation due to proximal obstruction – thought this model forgets that the reason for varicose veins is the volume overload due to reflux, not due to obstruction. APG could demonstrate the opposite. Gravitational drainage on leg elevation in patients with large varicose veins was even faster than in controls, finding a higher VDI as the draining volume was larger – draining occurred in the same, quick way as in controls [8].

The extra value of APG is, that you can easily discriminate between drainage impairment during the tilting from standing to Trendelenburg, expressed in the venous drainage index (VDI) and refluxive components of the leg with the filling rate of the leg turning the patient from Trendelenburg to standing, expressed in the venous filling index (VFI) – and both are performed in the same exploration setting.

Conclusion

Air-plethysmography is an objective assessment tool for drainage impairment and reflux quantification. Venous insufficiency is measured with the venous filling index (VFI) and venous obstruction is assessed with the venous drainage index (VDI). The test is not invasive and is not influenced by abilities or features of patients or

investigators, nor of the existence of veins or stents. It is easy to perform and can be introduced in the every-day assessment of the patient, specially to warrant an objective follow-up prior to decide an intervention and afterwards

APG should be mandatory prior to any invasive explorations and specially before any stenting of deep veins.

Conflict of interest

The authors declare that they have no conflict of interest.

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