Most incompetent calf perforating veins are found in association with superficial venous reflux

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Purpose: **The indications for surgical perforator interruption remain undefined. Previous work has demonstrated an association between clinical status and the number of incompetent perforating veins (IPVs). Other studies have demonstrated that correction of IPV physiology results from abolition of saphenous system reflux. The purpose of this study was to identify which, if any, patterns of venous reflux and obstruction are particularly associated with IPV.**

Patients and Methods: **Two hundred thirty patients and subjects (103 men, 127 women, 308 limbs) with varying grades of venous disease were examined both clinically and with duplex ultrasound scan. The odds ratios (ORs) for the presence of IPVs were calculated for different anatomical distributions of main-stem venous reflux and obstruction. The base group are those with no main-stem venous disease.**

Results: **There were no significant associations between the proportions of limbs demonstrating IPVs and patient age or sex. The ORs for the presence of IPVs in association with other venous disease are as follows (age/sex adjusted): long saphenous vein reflux, OR = 1.86, range = 1.32-2.63; short saphenous vein reflux, OR = 1.36, range = 1.02-1.82; deep system venous reflux, OR = 1.61, range = 1.2-2.15; superficial system reflux, OR = 3.17, range = 1.87-5.4; and deep system obstruction, OR = 1.09, range = 0.51-2.33. The ORs for combinations of venous disorders were calculated. Combinations of disease produced higher odds for the presence of IPVs than those above, the highest being long saphenous vein, short saphenous vein, and deep reflux combined, OR = 6.85 (95% CI, 2.97-15.83; *P* = .0001).**

Conclusions: **Although the presence of IPVs is associated with venous ulceration, the highest ORs for the presence of IPVs were found in patients with superficial disease alone or in combination with deep reflux. Many of these may be corrected by saphenous surgery alone. (J Vasc Surg 2001;34:774-8.)**

Subfascial endoscopic perforator surgery (SEPS) now has the status of being an established surgical technique with well-tested supporting technology.[1-6] The procedure has been shown to be safe and superior to open perforator ligation (Linton's[7] or Cockett's[8] procedure) in terms of complications and postoperative stay in hospital.[6] However, the benefits of SEPS over and above those of saphenous surgery alone are yet to be demonstrated and so the clear indications for surgical interruption of incompetent medial calf perforating veins (IPVs) are as yet undefined.[9-11]

Saphenous surgery alone has been demonstrated to correct perforator physiology in the absence of deliberate intervention aimed at these vessels in patients without deep system reflux.[12,13] The median diameters of the medial calf perforating veins were also seen to decrease after saphenous surgery. However, the total eradication of IPVs was dependent on the abolition of all main-stem venous reflux from both the superficial (saphenous) and deep venous systems.

Previously published data from this group have established a strong association between increasing number and diameter of IPVs and advanced clinical, anatomical, etiological, and pathological (CEAP) clinical grade.[14,15] The present analysis addresses three further issues—the effect of patient age and sex on perforator competence, the relationship between the distribution of main-stem venous disease (superficial system reflux and deep system reflux and obstruction) and perforator anatomy and physiology, and the identification of sites of reflux in the deep and superficial veins particularly associated with IPV.

PATIENTS AND METHODS

The clinical groups were comprised of 50 limbs with no clinical or duplex scan evidence of venous disease in the deep or superficial venous systems (CEAP clinical group 0), 95 limbs exhibiting varicose veins but no skin changes (CEAP 2/3), 55 limbs that were affected by lipodermatosclerosis but with no history of venous ulceration (CEAP 4), and 108 limbs that had a history of venous ulceration, active or healed (CEAP 5/6).[15] The subjects were recruited as volunteers who had no history or signs of venous disease (normal controls) and from patients attending the ward or outpatient department for treatment of venous disease.

All subjects were examined clinically and by means of color-flow duplex scanning (Ultramark 9 4-MHz linear array transducer, Advanced Technology Laboratories,

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Competition of interest: nil.

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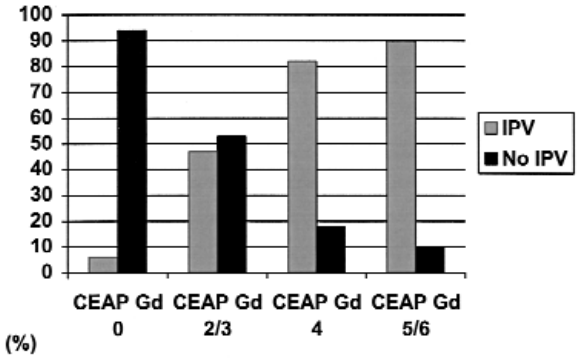

Fig 1. The relationship between CEAP grade and the presence of IPV. $P \leq .001$, χ^2 test. *Gd*, Grade.

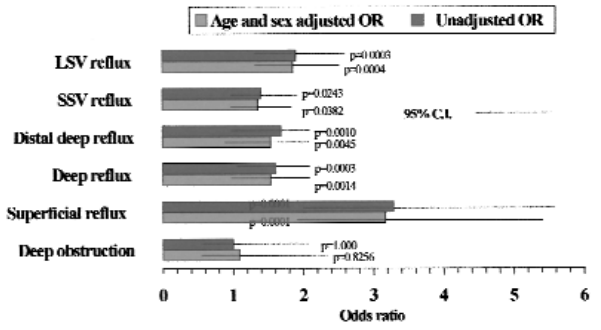

Fig 2. Odds ratios for the presence of IPV within various patterns of venous disease. Base group is no venous reflux or obstruction. *OR*, Odds ratio.

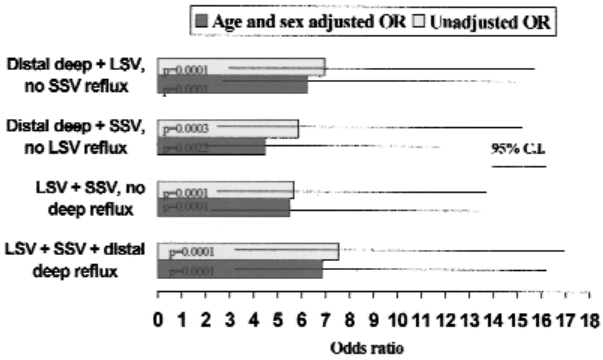

Fig 3. Odds ratios (95% CI) for the presence of IPV within various combinations of venous disease. Base group is no venous reflux or obstruction. *OR*, Odds ratio.

Bothell, Wash). The method of duplex ultrasound scanning has previously been described.[13,14]

The deep and superficial (saphenous) venous systems were examined with the patient almost upright, supported on a tilting examination table. Blood flow was induced by means of a calf squeeze-and-release maneuver. This is the standard technique in our institution. Pathologic reflux was defined as that exceeding 0.5 seconds in duration.[16]

Medial calf perforating veins were defined as vessels situated between the medial subcutaneous border of the tibia and the posterior midline of the calf and which were seen to cross the deep fascia and connect the deep (usually posterior tibial) with the superficial venous systems. Medial calf perforators were sought with the subject seated on a couch with the legs dependent, hanging freely.

Each perforator was examined using the color-flow Doppler scan and, where possible, the spectral Doppler analysis functions of the machine. A vessel was determined to be competent if it exhibited only inward flow and to be incompetent if it allowed deep to superficial (venous) flow, whether or not flow was unidirectional outward or bidirectional. The maximum diameter of the vessel was also recorded on the grayscale function rather than during color-flow analysis. The lower limit of resolution of the duplex scanner allowed detection of perforators down to 1 mm in diameter.

Data were entered into a computer for analysis using SPSS for Windows release 10.0 (SPSS, Inc, Chicago, Ill) and SAS (SAS Institute, Inc, Cary, NC). The χ^2 test was used to examine differences in nominal variables across both CEAP grade and presence or absence of IPV. Student *t* test was used to examine differences in mean age between IPV categories. PROC GENMOD of SAS was used to calculate the odds ratios (95% CIs) of the risk of IPVs for various patterns of disease. The odds ratios were then adjusted for age and sex.

RESULTS

The population studied included 308 limbs from 230 subjects. The demographic features and CEAP grades of the subjects are given in Table I. There were 168 (55%) limbs from female subjects and 140 (45%) from male subjects. The age of the subjects ranged from 19 to 87 years with a median of 58 years. The distribution of main-stem venous disease across the population is given in Table II.

There was no association between the proportion of limbs demonstrating IPVs and gender (Table III). The limbs demonstrating IPVs belonged to patients who were significantly older than those not demonstrating IPVs ($P \leq .001$). However, this reflects the age differences across CEAP clinical grades, as shown on Table I, rather than a true association between increasing age and increasing frequency of IPVs. Worsening CEAP clinical grade was significantly associated with an increasing proportion of IPVs (Fig 1). Nonetheless, the data for further analyses are presented showing the calculations with and without the age/sex adjustments.

In the absence of main-stem venous reflux, incompetent perforators were rarely observed (3 limbs, 2%). However, a significantly higher proportion of subjects with superficial system reflux alone, deep system reflux alone, and mixed superficial and deep reflux demonstrated IPVs (Table IV). A similar pattern was observed when analysis was repeated for

Table I. Demographic features and CEAP clinical grades of patients and subjects

CEAP grade	*0*	*2 or 3*	*4*	*5 or 6*	P *value*
Subjects (n)	28	71	44	87	
Male:female ratio	14:14	24:47	24:20	41:46	NS
Limbs (n)	50	95	55	108	
Median age (y) (range)	49.5 (23-81)	54 (19-87)	58 (39-76)	64.5 (29-87)	≤.01

Analysis was χ^2 test or Kruskal-Wallis test. *NS*, Not significant.

Table II. Distribution of venous disease (reflux and obstruction) among the 308 limbs

Site of reflux	*n*	*%*
No reflux	50	16.2
LSV reflux	205	66.6
SSV reflux	89	28.9
Any superficial reflux	242	78.6
Any deep reflux	106	34.4
Superficial reflux alone	152	49.4
Deep reflux alone	16	5.2
Both superficial and deep reflux	90	29.2
Deep system obstruction	11	3.6

Table III. Association between sex and age and the presence of IPV*

Patient characteristic	*No IPV (n = 112)*	*IPV (n = 196)*	P *value*
Male	46.4 (52)	44.9 (88)	
Female	53.6 (60)	55.1 (108)	.795
Age (y)	52.7 (1.62)	60.5 (0.94)	.0001

*Values are percentage (n) or mean (standard error). Analysis used the χ^2 test or the *t* test.

the presence of any deep disease or any superficial disease on a limb regardless of disease in another site.

Odds ratios for the risk of IPVs within various patterns of venous disease were calculated with and without adjustment for age and sex (Fig 2). Superficial reflux appears to have the greatest association with IPVs (adjusted odds ratio, 3.17; 95% CI, 1.87-5.40). Deep system obstruction was not associated with an increased risk of IPVs (adjusted odds ratio, 1.09; 95% CI, 0.51-2.33).

Further odds ratios were calculated for the risk of IPVs within various combinations of venous disease. There were 31 (27 of these with IPVs) limbs with deep distal reflux and long saphenous vein (LSV) disease but no short saphenous vein (SSV) disease, 15 limbs (11 with IPVs) with deep distal reflux and SSV disease but no LSV disease, 24 limbs (17 with IPVs) with LSV and SSV disease but no deep distal disease, and 35 limbs (33 with IPV) with deep distal reflux disease and LSV and SSV disease. There were 56 limbs with no deep distal disease, no LSV reflux, and no SSV reflux, and the risk of IPVs in each of the four combinations was compared with this group (Fig 3). After adjustment for age and sex, the risk of IPVs was highest among the group with SSV, LSV, and deep distal disease (odds ratio, 6.85; 95% CI, 2.97-15.83). The risk of IPVs was lowest among those with deep distal disease and SSV disease but no LSV disease (odds ratio, 4.47; 95% CI, 1.71-11.67). However, all of the odds ratios were highly statistically significant ($P \leq .001$).

DISCUSSION

Definite proof of a contributory role for IPVs in the processes of lipodermatosclerosis and chronic venous ulceration has yet to be produced. Similarly, clear evidence of clinical benefits derived from SEPS is not yet forthcoming, although it would appear that SEPS continues to be performed.[3] Fortunately, there is little to suggest that the procedure is detrimental to patients or that it delays ulcer healing.

The strongest link between IPVs and the skin changes of chronic venous insufficiency is associative. The median number of IPVs imaged per limb has been demonstrated to increase with deteriorating clinical status.[14,17] The median diameter of medial calf perforating veins also rises with deteriorating clinical status. Evidence of a hemodynamic role for IPVs is less clear. The evidence is contradictory and inconsistent.[9,18] Furthermore, there is strong evidence that the most important prognostic factor in terms of venous disease is the presence of popliteal vein reflux.[19-21]

Previous data published by our group have demonstrated that if main-stem venous reflux is eradicated, the majority of IPVs return to a caliber and functional state similar to "normal" values.[13] The principal finding of the present work is a demonstration that IPVs are most likely to be found associated with correctable superficial venous reflux disease. The odds ratios for the presence of IPVs in a limb were greater for superficial reflux, in both LSVs and SSVs (either together or separately), than for deep venous reflux. This suggests that more IPVs are found in association with correctable, superficial main-stem venous disease.

The odds ratio analysis was calculated for those limbs in which the deep system showed reflux in the popliteal venous segment and distally. The values were similar to those for either long saphenous or short saphenous reflux in isolation. More surprisingly, the odds ratios for limbs with deep system obstruction were approximately unity. In other words, the presence of IPVs was similar to the base

Table IV. Association between patterns of venous disease and the presence of IPV

Site of reflux	*No IPV (n = 112)*	*IPV (n = 196)*	P *value*
No reflux	42 (47)	1.5 (3)	≤.001
Superficial reflux only	45.5 (51)	51.5 (101)	≤.001
Deep reflux only	3.6 (4)	6.1 (12)	≤.001
Superficial and deep reflux	8.9 (10)	40.8 (80)	≤.001
Any deep disease	12.5 (14)	46.9 (92)	≤.001
Any superficial disease	54.5 (61)	92.4 (181)	≤.001
Deep obstruction	3.6 (4)	3.6 (7)	1.0
LSV disease	44.6 (50)	79.1 (155)	≤.001
SSV disease	16.1 (18)	36.2 (71)	≤.001
Deep distal reflux*	12.5 (14)	42.9 (84)	≤.001

*Distal reflux is defined as that observed in the popliteal vein or below. Values are percentage (n) and analysis using the χ^2 test.

group that was comprised of limbs with no clinical or duplex ultrasound scan evidence of venous disease. These findings would suggest the possibility that calf perforator function is determined by the presence of reflux disease in the main-stem vessels and, in particular, the superficial main-stem vessels.

Calculations were performed for the combinations of venous reflux disease across the long saphenous, short saphenous, and deep distal venous systems. Because of the small numbers in each subgroup, the 95% CIs were found to be wide, and, although all odds ratios were statistically significant, no particular combination seemed more likely to be associated with IPVs than any other.

Similar odds ratio calculations were not attempted for differential CEAP grades because the numbers in each group were so small that the analysis would be meaningless, and even if trends were present, the senior statistical author considered it inappropriate to present potentially misleading data.

In summary, IPVs would appear to be most strongly associated with superficial (saphenous) system main-stem venous reflux. This finding may significantly influence the outcome of a randomized controlled trial of perforator surgery. If IPVs are most commonly found in limbs with correctable venous disease, the trial may return a negative result. It is possible that the group of patients most likely to benefit from SEPS are those with deep venous incompetence and IPVs regardless of the state of the superficial system. A randomized controlled trial would require stratification to take this into account to avoid a potential false-negative result. However, this may be problematic because studies have demonstrated that the long-term prognosis for recurrent ulceration is poorest in this population.[19,20] The present work is an observational study, and it is therefore not appropriate to draw firm conclusions regarding the potential effects of surgical intervention for IPVs from these data.

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DISCUSSION

Dr Peter Gloviczki (Rochester, Minn). Thank you very much, Dr Stuart. This was an excellent presentation. Professor Ruckley and his team in Edinburgh have had a long-term interest and expertise in the management of chronic venous disease, and I am sure that this paper will be another important contribution to the literature on this topic.

Based on duplex scan analysis of 380 limbs with venous disease of different severity, the authors concluded that, number one, incompetent perforating veins are associated most strongly with superficial venous reflux and that therefore, number two, incompetent perforating veins may not require specific surgical interventions. While I have some reservations and questions on both of these conclusions, let me point out again what I think is the most important finding of this paper. That is the high prevalence of incompetent perforating veins in patients with chronic venous disease and the correlation of the incompetent perforating veins with the severity of disease. If you remember Dr Stuart's slides, 90% of the patients with C5-6 disease have an incompetent perforating vein, while less than a half of the patients with C2 disease have incompetent perforators. So incompetent perforator veins are clearly associated with venous ulcers, and the question, of course, what we all search for an answer for, is whether these incompetent perforating veins have any hemodynamic significance and whether they really contribute to the inflammatory changes in these limbs.

I have three questions for Dr Stuart. The first concerns the main conclusion of the study which means that incompetent perforating veins are most frequently associated with superficial reflux. We found, and I presented some of the data yesterday, that in patients who are candidates for perforator interruptions, the incidence of deep vein reflux can be as high as 90%. In other large studies on patients who have ulcers, the incompetence of the deep system is at least 50%, so I am wondering if your conclusion that incompetent perforating veins are most frequently associated with superficial reflux is true in patients with C5 and C6 disease?

My second question deals with the second main conclusion, which is in the title of your paper, that incompetent perforating veins may not require specific interventions. You obviously refer to your previous paper, which found in a limited number of patients at an average of 6 months after surgery a lower rate of incompetent perforating veins after saphenous vein stripping when the patients did not have deep venous incompetence. We observe that the number of recurrent incompetent perforating veins increases with time. In our material, even patients who underwent SEPS had an increasing number of recurrent perforating veins, and this number increases beyond 6 months. I am wondering if your original paper has a conclusion that has merit and whether you have investigated those patients with a longer follow-up and maybe by now you have a larger number of patients.

The final question concerns the importance of perforating veins in deep venous occlusion. We find that deep venous occlusion is a predictor of incompetent perforating veins, but indeed your studies have not confirmed that so I wonder if you can explain that.

It looks to me that Professor Ruckley really created the school in Edinburgh, and I think, Professor, you can enjoy your retirement right now because you have a great team of workers who will continue your work. I enjoyed very much the presentation, and I thank the society for the privilege of discussing this paper.

Dr Stuart. Dr Gloviczki, thank you very much for your kind comments and also for your helpful questions. Dr Lee performed the analysis of these data and I asked her if she would do the same analysis for C5 and C6 grades only. She performed this analysis and told me that in fact the numbers had become too small. I asked her for the figures anyway, and she said she was not going to give them to me because I am a surgeon and the figures were not of statistical significance but I would go ahead and present them anyway and call them a trend, so she was protecting me from standing up and presenting statistical lies. I cannot answer your question as to whether these analyses hold true when you move into the patients with grade 5 and grade 6 disease.

With regards to whether perforators recur, I think that is a very interesting question, and extended follow-up on patients that I originally examined would be very interesting, as would extended follow-up on the patients that Professor Burnand, who I see standing there, and Professor Bradbury have also presented. They demonstrated that people with popliteal venous reflux, in particular people with popliteal venous reflux secondary to DVT, had an appalling prognosis for recurrent ulceration. It would be interesting to get a hold of these patients, find out how many of these people had recurrent perforating veins, and whether this indicated that periodic revisitation of these patients for harvesting of further perforators would help the situation.

I accept his criticism regarding deep venous obstruction and I would also accept that this may in fact be a statistical error reflecting a small sample size. Thank you very much.

Dr Kevin Burnand (London, England). I have, like Dr O'Donnell, an extreme sense of I am sure deja vu because if you actually go back to the literature you will see that with rather less complex systems than duplex scanning we showed very similar results, that there are a lot of perforating veins that are associated with superficial reflux.

My real anxiety is your conclusion two, which is that because they are found in association with superficial reflux, it is unlikely that they need to be treated. If ever there is something calling out for a prospective study to be done, this is; you should randomize half to stripping alone in association with Peter Gloviczki, who it pains me to be in agreement with, and the other half with stripping plus perforator ligation. It is only in that way that we will really know, and you have to follow them up unfortunately for 5 years, but that is the study that you should be doing rather than drawing that conclusion in advance.

Dr Stuart. I accept that point. One of the differences between doctors and scientists is that scientists are quite prepared to discuss theoretical outcomes long before experiments are performed to demonstrate the outcome. I would argue that speculating theoretically as to what might happen is quite an interesting intellectual exercise and may in fact allow us to define which studies should be done more clearly, and I think this is a case in point. If we do not develop an appropriate stratification for a randomized controlled trial, we may end up throwing the baby out with the bath water. I strongly suspect that the patients who have long saphenous disease alone will have no benefit from SEPS, whereas patients with deep disease are the ones most likely to benefit, and, because of this, stratification will be critically important in a randomized controlled trial. I hope that answers your comment.