Venous wall function in the pathogenesis of varicose veins

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Three theories have been proposed to explain the cause of varicose veins, citing three different factors as the primary cause: valvular incompetence, a weakness of the vein wall, and increased arterial inflow associated with multiple arteriovenous communications. This study was designed to determine the cause of varicose veins with respect to these three factors. Duplex scanning techniques were used to assess the venous valves, and simultaneous measurements of calf volume (strain-gauge plethysmography) and venous pressure made during venous occlusion plethysmography were used to determine the elasticity of the venous wall and the rate of arterial inflow. Fifty-one control legs and 36 legs with superficial venous insufficiency were examined. Risk factors were used to divide the control legs into two groups: low risk or normal (23 legs) and high risk (28 legs). The results obtained in the high-risk limbs demonstrated a significantly reduced vein wall elasticity (p < 0.001) and increased arterial inflow (p < 0.005) compared with the normal limbs, with no corresponding increase in the incidence of valvular incompetence. These results clearly suggest that the role of the venous valves in the development of varicose veins is secondary to changes in the elastic properties of the vein wall and the rate of arterial inflow.

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Varicose veins are associated, by definition, with incompetent malfunctioning valves and dilatation and weakening of the vein walls. It is not clear, however, whether the valvular incompetence occurs first and produces the vein wall dilatation or vice versa.

Three theories have evolved to explain the cause of varicose veins, each attributing their development to an inherent primary factor. The three factors proposed are a weakness of the venous valves, a weakness of the vein wall, and multiple arteriovenous communications. The association between varicose veins and malfunctioning venous valves or dilated vein walls is self-evident. This is not so with multiple arteriovenous anastomoses. The latter was proposed initially on the basis of serial arteriography demonstrating an abnormally rapid movement of blood from the arterial to the venous system in limbs with varicose veins and perioperative visualization of direct arteriovenous communications with an operating microscope. Subsequent noninvasive investigations that used plethysmographic techniques indicated that the maximum arterial inflow to the limb was significantly higher in limbs with varicose veins. The exact nature of the communications has not been established, however, and there is no evidence to refute the suggestion that they might be damaged and dilated capillary vessels.

The relative etiologic roles of the three factors proposed have not been resolved by previous investigation. This omission may largely be attributed to the absence of any established method of assessing venous wall function and the problems of identifying patients in the early stages of development of varicose veins suitable for such etiologic studies. The development of a method for determining the elasticity of the venous wall in vivo has helped to overcome these difficulties.

The aim of this study was to investigate normal limbs, high-risk limbs, and limbs with established varicose veins by evaluating the venous valve function, the vein...
 Venous wall function and varicose veins

Fig. 1. Schematic drawing of a typical ambulatory venous pressure recording shows the resting pressure (RP), the measured ambulatory venous pressure (AVP), and 90% refilling time (RT90).

wall function, and the rate of arterial inflow, in an attempt to determine the cause of varicose veins.

MATERIAL AND METHODS

Subjects. Twenty-three volunteers (32 limbs) and 36 patients (55 limbs) referred from the vein clinic were investigated. (Care was taken to exclude subjects who were taking vasoactive medication or wearing elastic support stockings.) The 87 limbs studied were comprised of 51 control limbs and 36 limbs with superficial venous incompetence and normal deep veins. The control limbs included both volunteer limbs (n = 32) and the apparently normal contralateral limbs of patients with unilateral venous disease (n = 19). These control limbs were classified into two groups of normal and high-risk limbs according to the following criteria: (1) family history of varicose veins, (2) occupation involving standing, (3) history of symptoms or signs associated with varicose veins, (4) presence of reflux detected with Doppler ultrasonography, and (5) abnormal ambulatory venous pressure recordings: ambulatory venous pressure greater than 40 mm Hg and 90% refilling time (RT90) less than 18 seconds.

If two or more of these criteria were present, the limb was classified as being at high risk of developing varicose veins (28 limbs). Otherwise they were classified as normal (23 limbs).

The material used in this investigation therefore is comprised of subjects in whom only one limb was studied and subjects in whom both limbs were studied and classified either in the same group or in different groups. The distribution of patients was allowed for in the statistical analysis of the measurements obtained by calculating an adjusted standard error.

Methods of investigation. Four investigative procedures were performed in this study: ambulatory venous pressure measurements,\(^\text{10,11}\) duplex Doppler scanning,\(^\text{10,12,13}\) assessment of venous elasticity,\(^\text{9,10}\) and measurements of maximum arterial inflow.\(^\text{5-7,10}\) The ambulatory venous pressure measurements were performed to assist in selecting the high-risk limbs. The etiologic studies were based on the other three methods of investigation. Duplex Doppler scanning was used to assess the valve function, the measurement of venous elasticity to assess venous wall function, and the measurements of maximum arterial inflow to assess arterial inflow.

Ambulatory venous pressure measurements. Ambulatory venous pressure was measured directly by cannulating a vein on the dorsum of the foot. The patient was asked to stand, holding a frame for support and allowing the baseline resting pressure to be established. The patient was then asked to perform 10 tiptoe movements at a rate of one per second to empty the veins and then to remain still while the veins refilled. The two measurements taken from these recordings were the ambulatory venous pressure, defined as the pressure immediately after exercise, and the RT90, which is the time taken for the pressure to effect a 90% recovery of the preexercise level (Fig. 1).

Duplex Doppler scanning.\(^\text{10,12}\) Duplex scanning was used to assess valvular efficiency in the lower-limb veins of the subjects studied, with a 7.5 MHz imaging probe coupled with a 5 MHz Doppler crystal (DRF 300; Diasonics Incorporated, Milpitas, Calif.). The probe was placed over the vessel of interest, and the Doppler sample volume was positioned within the vein so that the angle of insonation was approximately 60
degrees. Manual compression of the limb was applied distally, producing an outflow of blood. The presence of retrograde flow on release of compression indicated valvular incompetence.

This method was used to determine the function of the valves in the deep (femoral, popliteal, gastrocnemius, posterior tibial, anterior tibial, and peroneal) and superficial (long saphenous, short saphenous, and Giacomini) veins of the lower limbs. (The Giacomini vein ascends from the proximal part of the short saphenous vein deep in the posterior aspect of the thigh, parallel to the skin, and terminates as the posteromedial tributary of the long saphenous vein.) Variations from the standard anatomy of the lower-limb venous system are frequent, and the investigations of the valve function were modified to the requirements of the individual limb, examining each vein at multilevels to ensure that there was no localized incompetence.

Measurement of venous elasticity.9,10 The elasticity of the lower-limb venous system was assessed by standard strain-gauge plethysmography and direct measurements of venous pressure (Fig. 2). The patient was placed supine with one leg elevated 27 cm at the heel to allow the veins to empty. The knee was flexed and rotated externally, and the thigh was supported to ensure that the leg was relaxed. Strain-gauge plethysmography was performed with an electrically calibrated mercury-in-silicone rubber strain gauge placed around the calf at the maximum circumference, allowing percentage volume change to be determined. Measurements of venous pressure were obtained by inserting a 21-gauge butterfly needle in a vein on the dorsum of the foot. The strain-gauge plethysmograph and pressure monitor were connected to a two-channel chart recorder, allowing simultaneous measurements of pressure and volume to be made.

The pressure-volume relationship of the lower-limb venous system was then obtained by placing a 17 cm wide cuff around the thigh and inflating it to 80 mm Hg to occlude venous outflow. The subsequent changes in pressure and volume were recorded simultaneously and corresponding readings of pressure and volume were taken from these recordings at 15-second intervals and plotted on a graph (Fig. 3).

The change in pressure (ΔP) and the corresponding change in volume (ΔV) were measured in the linear, high-pressure part of the pressure-volume curve (Fig. 3). This linear region of the curve and the initial slope were extrapolated, as shown in Fig. 3, to obtain V₀, the theoretic value of the initial volume pertaining to the changes in volume at high pressures. The elastic modulus (K) was calculated by substituting ΔP, ΔV, and V₀, as shown in equation 1. This was converted to SI units of N/m² with a standard conversion factor from millimeters of mercury (132.9): K = ΔP/ΔV/V₀ (1).

This method of calculating K is inherently variable because of the difficulty in determining the extent of the linear region of the curve and selecting the gradient. To standardize this maximum and minimum gradients were obtained from each graph, and the mean value was used to calculate K.

Measurement of maximum arterial inflow.5-7,10 The maximum arterial inflow was measured from the plethysmographic recording obtained in measuring the venous elasticity. The maximum arterial inflow was determined from the initial slope of the recording, as illustrated in Fig. 4, and expressed in units of percentage volume change per minute.

The gradient of the initial slope of the volume curve was not always clear, because in some recordings there was a very sharp change in volume initially, and the subsequent changes in volume were more typical. This
initial artifactual change in volume may be attributed to one of two causes: patient movement or rapid distal movement of the blood in the veins beneath the occluding cuff. The maximum arterial inflow in these limbs was measured by determining the initial gradient of the curve relating to the subsequent changes in volume.

RESULTS

Duplex Doppler findings. The presence of valvular incompetence in the superficial veins only was established in all the limbs with primary varicose veins and in four of the high-risk limbs; in the remaining 24 high-risk limbs and all of the normal limbs no sites of reflux were detected (Table I). It should also be noted that the reflux found in the four high-risk limbs was consistently evident in only one limb; in the other three limbs it was detected on one visit but not on a subsequent visit. This phenomenon has been described as intermittent reflux. These findings were statistically compared with a $\chi^2$ test (Table II).

Measurements of $K$. The measurements of $K$ obtained in the three groups of normal, high-risk, and primary varicose veins are shown in Fig. 5 on a logarithmic scale. It is clearly evident that $K$ is higher in the normal group than in either the high-risk group or the group of limbs with primary varicose veins, and
Table I. Summary of results of etiologic investigations, valve function (reflux), K, and arterial inflow

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>HRG</th>
<th>SVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of limbs</td>
<td>0</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>K (10⁴ Nm⁻²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range ± 2 SD</td>
<td>2.0-90.6</td>
<td>0.4-2.8</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>MAI (ml/dl/min)</td>
<td>2.1</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Median</td>
<td>0.4-5.0</td>
<td>0.6-5.9</td>
<td>1.0-5.9</td>
</tr>
<tr>
<td>No. of limbs</td>
<td>23</td>
<td>28</td>
<td>36</td>
</tr>
</tbody>
</table>

N, Normal limbs; HRG, high-risk limbs; SVI, limbs with superficial vein incompetence; MAI, maximum arterial inflow.

there is no discernible difference in elasticity between the latter.

The measurements of K were transformed to a normal distribution by taking logarithms. The mean and range given in Table I were obtained by calculating the mean and the mean ± 2 SD for the transformed data and taking antilogarithms. The levels of significance given in Table II were obtained by application of the Student t test to the transformed data (p < 0.001).

Measurements of maximum arterial inflow. The measurements of arterial inflow obtained in the three groups of limbs investigated are shown in Fig. 6, and the mean and range are given in Table I. These measurements are not normally distributed, so the Mann-Whitney U test was used for statistical comparison between the three groups. This showed that the maximum arterial inflow is significantly higher in the high-risk limbs (p < 0.01) and in the limbs with primary varicose veins (p < 0.005) than in the normal limbs, but no significant difference was found between the former (Table II).

Etiologic findings. The results obtained are summarized in Table I, giving the incidence of valvular incompetence, the mean and range of K, and the median and range of the maximum arterial inflow in the three groups of normal, high-risk, and primary varicose veins. The statistical significances of these findings are summarized in Table II.

These results indicate that there is a significant difference in the overall findings of all three investigations between the normal limbs and the limbs with primary varicose veins. The results from the high-risk limbs demonstrate that although K and the maximum arterial inflow measured in these limbs are comparable with

Table II. Comparison between the three groups of limbs studied of the statistical significance (p value) obtained with the three methods of assessment used: valve function (reflux), K, and arterial inflow

<table>
<thead>
<tr>
<th></th>
<th>N vs HRG</th>
<th>N vs SVI</th>
<th>HRG vs SVI</th>
</tr>
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<tbody>
<tr>
<td>Reflex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>K</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arterial inflow</td>
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<td></td>
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</tbody>
</table>

N, Normal; HRG, high-risk; SVI, superficial vein incompetence.

these same measurements in the patients with established varicose veins, there is no corresponding similarity in the incidence of valvular incompetence.

DISCUSSION

The findings of an etiologic investigation are strongly influenced by the patients investigated and the methods of investigation used. The former is important because the progression of a given physiologic change is dependent on how far the disease has progressed. The latter is also important because it affects the sensitivity of the investigation to detecting the physiologic changes, particularly in the earlier stages.

The identification of limbs in the early stages of developing varicose veins is therefore crucial. In this study these limbs were found from the control population, which was comprised of normal limbs from volunteers and patients with unilateral venous disease. Recent studies have shown the presence of venous disease in the apparently normal contralateral limbs of patients with unilateral venous ulceration.13 Extending this idea, it is not unreasonable to assume that any apparently normal limb might have some degree of venous disease. It is the identification of these control limbs with subclinical disease that is difficult. This has been achieved in this study by a combination of risk factors and measurements. The limbs assumed to be in the early stages of developing varicose veins have in fact been referred to as a high-risk group, because this is appropriate to the method of classification used, and until follow-up studies are performed, there is no evidence to show that they will develop varicose veins.

Four of the limbs classified in the high-risk group were found to have reflux in the long saphenous vein. Despite having incompetent valves in their long saphenous veins, these four limbs were nonetheless classified in the high-risk group, because on clinical examination they appeared normal, having no visible varicosities and no evident signs of venous disease.
The other aspect of this study that should be considered is the sensitivity of the methods of investigation used in detecting early physiologic changes. The techniques used fall into two categories: duplex scanning provides an anatomically specific and localized assessment of the presence of reflux in individual veins within the limb, and the other two techniques provide an overall and generalized assessment of the limb.

The localized nature of the duplex scanning technique indicates the importance of an extensive and thorough examination to minimize the possibility of missing any localized incompetence. The duplex examination performed in this study was both careful and extensive, checking the deep and superficial veins at multilevels for sites of reflux. This examination cannot exclude histologic changes in the venous valves, but in terms of the etiologic theories it is the function of the valve that is important, because in the presence of valvular competence there is no increased pressure distally to produce localized dilatation of the vein wall.

The generalized nature of the plethysmographic techniques indicates that the assessment of venous elasticity and arterial inflow may be less sensitive to small or localized changes, particularly if they are localized proximal to the calf.

The results obtained show increased arterial inflow and decreased elasticity in the high-risk limbs but no corresponding increase in the incidence of valvular incompetence. The thoroughness of the duplex examination precludes the explanation of this finding in terms of undetected localized incompetence. These results do not differentiate between the roles of the vein wall and the arterial inflow. This may indicate that the selected high-risk limbs have venous disease that has progressed beyond a stage in which only one physiologic parameter has changed. Alternatively this may indicate that the changes in these two physiologic parameters are interactive and effectively occur simultaneously.

The theory proposed to explain the development of varicose veins in terms of arteriovenous malformations is based on the premise that the anastomoses are multiple and localized and produce localized changes in the
vein wall and venous valves. It would therefore be logical to assume that these anastomoses are localized in that region of the limb where varicosities first appear and valvular incompetence is first noted (i.e., in the region of the knee). However, if the increase in arterial inflow is localized in this region, the observed increase in maximum arterial inflow at the level of the calf is surprising.

These considerations suggest that an alternative explanation for the observed increase in arterial inflow should be sought. This has been explained previously in terms of dilated and enlarged capillaries. Recent studies with laser Doppler have confirmed this increased blood flow through the skin in limbs with venous hypertension and have shown the abolition of the venoarteriolar vasodilatation on standing found in normal limbs. It has also been demonstrated that after 4 weeks of elastic compression the skin blood flow and venoarteriolar reflex tend to normalize. The latter finding is in favor of an increased capillary flow rather than the presence of arteriovenous anastomoses.

It is clear that no conclusions can be drawn from our investigation in terms of the relative etiologic roles of the venous wall and the arterial inflow, other than to postulate that they may be interactive and that the increased arterial inflow may be attributed to capillary dilatation rather than to multiple arteriovenous anastomoses. However, the results obtained with respect to the roles of the venous valves and the venous walls are more conclusive, providing preliminary evidence to suggest that valvular incompetence is a phenomenon caused by weakness of the venous wall.

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REFERENCES