PLETHYSMOGRAPHIC MEASUREMENT OF VENOUS FLOW RESISTANCE

AND VENOUS CAPACITY IN THE HUMAN LEG

Methodical and clinical aspects

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Methodical and clinical aspects

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van de geneeskunde en tandheelkunde

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In the past 25 years, research in the Vascular Laboratory of the Dermatological Department of the University Hospital in Nijmegen has been focussed on peripheral circulation in human beings. Various basic non-invasive function tests have been developed in this respect such as quantification of the muscle-pump function by means of strain-gauge plethysmography (Kuiper 1966), and the measurement of skin blood flow (Van de Staak 1966). Recently, a new basic function test has been added with the introduction of a method for the measurement of venous flow resistance (Rv) by means of strain-gauge plethysmography (Brakkee and Kuiper 1982). In addition, this method may provide values for the venous capacity.

In the literature, many plethysmographic studies on venous outflow from the leg following release of venous congestion have been published, especially concerning the diagnosis of deep venous thrombosis. All these flow data, however, depended on the actual congestion pressures. Unfortunately, the rather great variation in congestion pressures applied by the various investigators makes mutual comparison of these data difficult. Moreover, many of these studies provided only yes-or-no decisions about thrombosis, rather than showing any insight into local venous haemodynamics.

The present study is not intended primarily as the introduction of a new diagnostic criterion for deep venous thrombosis. Since Rv is essentially independent of the applied congestion pressures, this
quantitative and almost "universal" parameter is most suitable for basic phlebological research. Therefore, this study will have a broader scope, although the evaluation of the diagnostic accuracy of Rv for deep venous thrombosis may still be considered as a "fil rouge" in this study.

The aims of the present study have been threefold. The first was to evaluate which methodic factors may be important to an adequate measurement of venous flow resistance and venous capacity at different sites of measurement (CHAPTER 3). Secondly, for each site of measurement, reference (i.e. normal) values for comparative studies were to be provided, if necessary related to age and sex (CHAPTER 4). Thirdly, Rv and venous capacity (C10) were to be studied in several patient groups with different types of phlebological disorders:

- CHAPTER 5 presents the results of a study on Rv and C10 in legs with deep venous thrombosis, in both the acute phase and in the post-thrombotic period. In addition, the sensitivity and specificity of Rv - when used as a diagnostic criterion for thrombosis - is evaluated.

- In CHAPTER 6, a study is presented on Rv and C10 in legs with primary truncal varicosity of the great saphenous vein (PTV), in which a relatively low Rv might be expected in view of the relatively great caliber of PTV. In addition, the contribution of PTV to total venous outflow will be evaluated, as well the influence of PTV on the sensitivity of Rv when used as a thrombosis criterion.

- In CHAPTER 7, legs with primary lymphedema (PrLy) have been subject of investigation. In the literature, there are sparse indications that in non-thrombotic legs, venous flow may be impaired by edema. In this
study, the influence of PrLy on Rv and C10 will be studied in rela-
tionship to the clinical severity of the edema. In addition, it will
be evaluated to what extent PrLy influences the specificity of Rv when
used as a criterion for deep venous thrombosis.

The actual study is preceded by two introductory chapters. CHAPTER
1 presents morphological and physiological aspects of the venous
system in the lower extremities as far as relevant to the present
study. In CHAPTER 2, the units venous flow resistance and venous
capacity are explained in detail as well as the principles of their
measurement. In addition, several potentially influencing factors will
be discussed.

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VAN DE STAAK WJBM. Metingen van de huiddoorbloeding; Methodische en
klinische ervaringen met het "heated thermocouple" principe. Nijmegen,
1.1 INTRODUCTION

In this chapter, brief surveys are presented on morphology and physiology of the venous system in the lower extremities as far as they are relevant to the present study. In this respect, a global description of the anatomic arrangement of the major venous pathways in the lower extremities is followed by a brief disclosure on the composition and structure of the venous wall. In addition, since the contractional state of the smooth muscle fibres within the venous wall may influence both venous flow resistance and venous capacity, some important control mechanisms of this so-called venous tone will be explained.

1.2 ANATOMY

The major venous pathways of the lower extremities are represented by a deep and by a superficial system, conducting respectively about 90% and 10% of the venous blood (Bauer 1950, Santler 1962). The veins contain valves which, when they are intact, allow a flow only towards the heart. The superficial and the deep veins are connected by about 150 short vessels (Van Limborgh et al 1962), called communicating veins and or perforating veins since they perforate the fascia.
## Table 1.1: Anatomic variations of the venous system in the lower leg.

*(after May and Nissl, 1973)*

<table>
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<tr>
<th>Vein</th>
<th>Description</th>
<th>% (approx.)</th>
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<tr>
<td>Popliteal vein</td>
<td>single</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>double, joining into single femoral vein</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>double, draining into double femoral vein</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>triple</td>
<td>2</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>single</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>double, joining distal to the inguinal ligament</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>multiple</td>
<td>14</td>
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The major leading veins of the deep system in the lower leg are the three paired veins running parallel to their corresponding arteries all located within fascial compartments. Along their course, these veins receive communicating veins and tributaries from the deep muscle veins, the so-called venous sinuses. At about the level of the knee, these veins joint into the popliteal vein which runs through the adductor canal (Hunter) to become the superficial femoral vein. This vessel confluences with the deep femoral vein originating from the deep muscles of the upper leg and is subsequently called the common femoral vein. After crossing the Poupart ligament, its name changes to external iliac vein which joins with the internal iliac vein to form the common iliac vein. It has to be emphasized however, that this classical description often does not comply with reality, as is shown in table 1.1.

The main veins of the superficial system, which is located in the subcutaneous tissues, are the great and the small saphenous veins, both originating from the dorsal arch, which is the largest of the three venous arches in the foot. Three branches of the great saphenous vein run medially from the lower leg, joining into the truncus just below the knee, then ascending posterior to the medial femoral condyle and finally terminating in the uppermost part of the common femoral vein. The small saphenous vein runs on the dorsal side of the lower leg and terminates in the popliteal vein.
The venous wall is composed of a number of different materials with a complex structural arrangement. The components are embedded in a gelatinous substance called ground substance which consists predominantly of mucopolysaccharides in which a considerable amount of water is bound. For example, 76% of the great saphenous vein consists of water, while the remaining 24% consists mainly of elastin fibres, collagen fibres and smooth muscle proteins (Laszt 1972). In the great saphenous vein, for example, elastin fibres amount to about 10 per cent of the fat-free dry weight, collagen fibres are about 52 per cent and protein about 37 per cent (Svejcar et al. 1963, Laszt 1972). The smooth muscle content of the leg veins increases from proximal to distal, while superficial veins contain more smooth muscle than deep veins (Von Kügelgen 1955).

Based upon both histological and mechanical investigations on wall components in canine veins, a working model on the architecture of the venous wall has been developed (Azuma and Hasegawa 1973, Hasegawa 1983). In this model, smooth muscle fibres are arranged in a spiral form with a very short pitch along the circumference of the vein. The elastin fibres, which appeared to be continuous in the longitudinal, but discontinuous in the circumferential direction, form a network structure with several longitudinal cracks. The collagen fibres form another network, but are in a crimped, meandering state so that they develop relatively little tension unless their crimps have been straightened.
The venous system does not merely consist of passive conduits for the return of blood towards the heart. It also plays an active role in the maintenance of an optimum right atrium filling pressure, while in addition to this major physiological function it is involved also in the regulation of the body temperature. For these purposes, some parts of the venous system contain smooth muscle by which the veins may contract in response to various stimuli.

In the past decades, many anatomical, physiological and clinical studies have been performed in order to gain insight into the control mechanisms of venous smooth muscle contraction. Especially the splanchnic venous system, which may act as a major blood mobilizing system under sympathetic control, and the limb veins have been subjects of investigation. The results have been extensively reviewed by Vanhoutte and Janssens (1978), Vanhoutte (1981), Van Welsum (1982) and Shepherd (1983). Based on this literature, the main aspects which may be of relevance to the present study will be briefly summarized below.

The main controller of venomotor function is the sympathetic nervous system by which many peripheral receptor systems can initiate reflex venomotor responses. The degree of participation of a venous bed in these reflex responses depends on a) the amount of smooth muscle fibres present in the venous wall, b) the density of the innervation and c) the part of the nervous system by which it is governed. In the extremities, the response to nerve stimulation is large only in the
densely innervated superficial veins and small in the sparsely innervated deep veins. However, in contrast to this selectivity of the neurogenic sympathetic control, generalised venoconstriction can be evoked by high levels of circulating catacholamines.

In warm and relaxed subjects, venous tone in the extremities is negligible. Cold and stress may increase venous tone. Cooling a subject may cause a contraction of the superficial venous system in order to decrease the surface for heat exchange. In contrast, the deep veins do not show such constrictive response to cooling. Mental and physical stress may increase venous tone, probably by neurogenic control as well as by circulating catacholamines.

In our measurements of venous flow resistance and venous capacity, congestion of venous blood within a leg plays an important role. Therefore, the potential changes in venous tone by both local venous distension and (central) depletion of blood volume have to be discussed also. In this respect it may be noted that local venous distension may cause venoconstriction only in the portalmesenteric bed and not in the extremities. Depletion of (central) blood volume however may set in motion a series of reflex adaptations in order to maintain arterial blood pressure. These reflex adaptations are governed by the baroreceptor areas and may cause constriction of the splanchnic venous bed as well as in large veins such as the venae cavae and femoral veins. Deep muscle veins and cutaneous veins have little or no involvement in arterial baroreceptor reflexes. With large blood losses however, in addition to the reflex adaptations, widespread venoconstriction may be due to circulating vasoactive substan-
Experimentally it was found that pooling of venous blood in the legs may result in constriction of the cutaneous veins in human arms (Wood and Eckstein 1958).

Some cardiovascular conditions are likely to influence venous tone. For example, venous tone in arm veins appeared to be increased in patients with congestive heart failure; reports on an increased venous tone in hypertensive subjects have been controversial.

Furthermore in the literature, a number of other mechanisms which may initiate alterations in venous tone have been described, such as by chemoreceptor stimulation, muscular excercise, respiratory reflexes, naturally occurring vaso-active substances and drugs. For further information on these items which are beyond the scope of this text, the reader is referred to the previously mentioned authors.

1.5 REFERENCES


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CHAPTER 2: VENOUS FLOW RESISTANCE AND VENOUS CAPACITY

2.1 VENOUS FLOW RESISTANCE

2.1.1 Introduction

This section presents some important notions about venous flow resistance. In this respect, some elementary conceptions of fluid dynamics are presented at first, followed by various anatomical and pathological factors that may influence venous flow resistance in the human leg. Subsequently, some consequences will be discussed regarding the venous flow resistance as it is used in this thesis.

2.1.2 Some elementary notions on fluid dynamics

The flow resistance $R$ of a vessel is defined as the ratio of the pressure difference $\Delta P$ across the vessel and the (volume) flow rate $I$ through the vessel: $R = \Delta P/I$. For laminar flow in a rigid cylindrical tube this resistance is, according to the Hagen-Poiseuille law, proportional to the length of $l$ of the tube and the viscosity $\eta$ and inversely proportional to the fourth power of the radius $r$:

$$R \propto \eta \cdot l \cdot r^{-4}.$$ Changes in the shape of the cross-section of a tube may have profound effects on flow resistance. The more it becomes elliptically shaped, the higher the resistance to flow.
When tubes are connected in series, the total flow resistance is given by summation, while for tubes connected in parallel the total flow resistance may be deduced from the total conductance ($= 1/R$), which is given by summation of the conductances of the corresponding individual tubes.

For further information on the subject of fluid dynamics, the reader is referred to e.g. the textbook of Caro et al (1978) in which the mechanics of the circulation is explained in detail.

2.1.3 **Influencing factors**

From the foregoing it follows that the venous flow resistance may be influenced by changes in blood viscosity, vascular length, diameter and also by changes in the shape of the cross-section of the vessel. Relatively little is known about changes in blood viscosity. A low-grade whole blood hyperviscosity has been demonstrated in patients who had developed deep venous thrombosis (Volker and Trübstein 1983). In human extremities changes in the length of the venous system are unimportant as an influencing factor. Changes in the venous diameter are closely connected to the venous tone as has been discussed in chapter 1.4. Moreover, an abnormally low venous flow resistance might be expected in cases of primary truncal varicosis in which an abnormally great diameter can be demonstrated (Zsoter et al 1967, Laszt 1972, Bocking and Roach 1974, Mellmann 1981). The shape of the cross-section of the venous lumen however may be influenced by a number of
factors such as external compression and intraluminal obstructions, which in part are related to specific anatomic sites.

The popliteal vein is especially prone to external compression. For example, excessive stretching and in some cases seemingly normal extension of the knee joint may be associated with compression of the popliteal vein (Britton 1964, Arkoff et al 1968, Thomas and Carthy 1975, Roberson et al 1979). In the popliteal entrapment syndrome, most commonly only the artery is involved but popliteal vein entrapment has also been reported (Rich and Hughes 1967, Edmondsson and Crowe 1972, Connel 1978), even without arterial entrapment (Connel 1978). Various types of tumors may cause a compression of the popliteal vein, e.g. the well-known Backer's cysts (Britton 1964, Hach 1980). The same holds for cystic adventitia degeneration (Gomez-Ferrer 1966, Matsubara et al 1978, Hach 1980), which is considered as a true ganglion occurring in the vessel wall (Sperling et al 1972, Leu 1977, Matsubara et al 1978). This degeneration has an obscure etiology, is nearly always found near joints and is most frequently localised in the popliteal artery (Matsubara et al 1978) but has also been reported in veins (Mentha 1963, Gomez-Ferrer 1966, Leu 1977, Matsubara et al 1978).

The iliac veins may be compressed by arteries. This is particularly the case where the right common iliac artery crosses the left common iliac vein (May 1973, Thomas and Carthy 1975, Hach 1980) and to a lesser extent where the right external iliac artery crosses the right external iliac vein (Hach 1980). Moreover, (partial) intraluminal obstruction of the iliac vein may be caused by band i.e. spur forma-
tion. Band formation can be demonstrated in about 21% of the adult population at the site of the crossing of the left common iliac vein and the right common iliac artery (May and Thurner 1957, Negus et al 1968). Most likely it is of an acquired origin, resulting from an intimal reaction caused by the enduring irritating effect of the pulsating artery against the vein which is pressed against the vertebral column (May and Thurner 1957, Negus et al 1968). Arterial compression and band formation, when extensive, may even be associated with an increased peripheral venous pressure (Menne and Jaszczak 1979).

A number of influencing factors are unrelated to specific sites. Venous compression may be caused e.g. by malignant tumors, in the legs mostly sarcomas, while more proximally, primary and secondary lymph-node cancers are the major cause (Hach 1980). Furthermore, arterial aneurysmata (Britton 1964, Leitz et al 1976, Hach 1980, Mansfield 1982), may cause venous compression. Probably the most commonly known cause of intraluminal obstruction is by partial or even complete intraluminal obstruction due to thrombosis of the deep veins (DVT). A variety of risk factors for DVT have been reported (Coon 1977, Briet et al 1985), of which immobilization seems to be a major one. High incidences of 34 and 60 per cent were found in postmortem studies on unselected medical and surgical patients respectively (Le Quesne 1975). Vein valve pockets are considered as an important source of venous thrombi (Ljunger and Bergqvist 1983), most commonly originating in the deep veins of the lower leg (Stamatakis et al 1978) although other, sometimes multiple sites of origin are no exception (Sevitt
Patients undergoing hip surgery differ from other patients developing deep venous thrombosis in that they have a relatively high incidence of isolated femoral vein thrombi (Stamatakis et al 1977).

Apart from all above-mentioned factors, the venous flow resistance may also be influenced in post-thrombotic legs by the process of collateralization (Hofliger and Wirth 1976) and or recanalization.

2.1.4 The venous flow resistance $R_v$ and its specific influencing factors

As is pointed out in detail in chapter 3, the measurement of venous flow resistance $R_v$ as used in this thesis is based on an advanced analysis of limb volume changes as measured by strain-gauge plethysmography. These volume changes are induced by a series of venous congestions with different preset pressures. Following the release of each congestion, the corresponding flow rates are deduced from the emptying curves. By analogy to Ohm's law, $R_v$ is deduced from the relationship between these congestion pressures and the corresponding flow rates. Since the flow rate is a volume per unit of time and - in our method - the volume is expressed as a percentage of the limb volume, $R_v$ depends on this volume. This implies that identical venous configurations in different limb volumes have different $R_v$-values. If e.g. the limb volume increases because of edema formation, $R_v$ increases in the same proportion.
Theoretically, the measurement of $R_v$ may be influenced by the distensibility of the venous system and hence by the effective stiffness of all tissues that surround the venous blood. With increasing venous congestion pressures, the increase in venous emptying rates following release of venous congestion depends not only on this pressure-increase but also on the associated increase of the caliber of the venous system. So, $R_v$ is deduced from a pressure-flow relationship that will be steeper (i.e. $R_v$ will be lower), the more the venous system shows distension with increasing congestion pressures. Consequently, the lower the effective stiffness of the tissues that surround the venous blood, the lower is $R_v$ and vice versa. More detailed information about the stiffness of these tissues is given in part B of section 2.2.5.

2.2 VENOUS CAPACITY

2.2.1 Introduction

As is pointed out below, the venous capacity of a limb segment as used in this study, greatly depends on volume changes of the venous system as induced by venous congestions. Since these volume changes depend in part on the elastic properties of all tissues that surround the venous blood, an elementary disclosure of elasticity will be presented at first. This is followed by some elementary notions on
the terms compliance and distensibility, which are important to the understanding of the term venous capacity as it is used in this study. Finally, some important influencing factors will be discussed, regarding this venous capacity.

2.2.2 Notions on elasticity

Experimentally, the elastic properties of a given material in a given direction may be deduced from a so-called stress-strain relationship in which stress is defined as the force per unit area and strain as the amount of deformation relative to the unstressed state. At a given stress level, coefficients of elasticity can be calculated directly from the slope of the stress-strain relationship, representing the ratio of a small increment in stress and the corresponding increment in strain. It follows that the stiffer the material, the higher the coefficient of elasticity. Since most biological structures show essentially non-linear stress-strain relationships, "the" coefficient of elasticity is usually calculated from the "best" linear part of the stress-strain relationship.

A material is called purely elastic if the ultimate strain resulting from a suddenly applied stress and the return to its original configuration when the stress is suddenly removed, is reached instantaneously i.e. without any time dependency. Generally, biological structures show a more complex i.e. visco-elastic response. In such materials, a suddenly applied stress is followed by a gradual (i.e. time-dependent) change in strain until an equilibrium state has been reached. Then
the stress-strain relationship represents ultimate and stable equilibrium states due to so-called static stretch.

2.2.3 **Notions on distensibility and compliance**

The wall of a tube may be strained in the circumferential direction by increasing the transmural pressure i.e. the intraluminal pressure minus the extraluminal pressure. According to Laplace's law, the wall stress in the circumferential direction is then proportional to the transmural pressure and to the tube radius. The distensibility $D$ of a tube at a given transmural pressure level may be deduced from the fractional volume increment ($\frac{\Delta V}{V}$) resulting from an increment in transmural pressure ($\Delta P_t$) according to the following equation:

$$D = \frac{\Delta V}{\Delta V/\Delta P_t}$$

whereas compliance $C$ may be defined as the ratio between the absolute volume increment ($\Delta V$) and the increment in transmural pressure ($C = \Delta V/\Delta P_t$) (Caro et al 1978).

When the transmural pressure approaches zero, thin walled structures like veins lose their circular cross-sections and when elliptically shaped, small changes in transmural pressure result in relatively large volume changes due to a combination of predominantly bending and only finite wall stretch (Moreno et al 1970). However, when vessels are circular, the distensibility $D$ is proportional to the ratio of the radius $r$ to wall thickness $h$ and inversely proportional to the coefficient of elasticity $E$:

$$D \propto \frac{r}{E \cdot h}$$

(Caro et al 1978)
Since by definition compliance C equals the product of distensibility and volume, it follows that C = r³ / E.h.

2.2.4 The venous capacity C₁₀

In this study, a so-called venous capacity is deduced from the slope of the volume distensibility curve of a given limb segment as obtained experimentally by a series of venous congestions. This slope is calculated always at a fixed intravenous pressure level of 10 mmHg. Therefore, the symbol C₁₀ has been selected for this venous capacity. From the foregoing it follows that the terms "compliance" or "distensibility" rather than "capacity" would have been an inappropriate choice in this respect. It must be noted, however, that the term venous capacity as used in this study is different from the term "venous capacity" as used by many authors, then often indicating the maximum volume change of a limb (segment) resulting from only one single period of venous congestion. The adjective "venous" has been connected to the parameter C₁₀ since, when venous congestion is applied to a leg, the resulting volume changes depend almost exclusively on volume changes of the venous system. The volume changes of the precapillary vessels play an insignificant role in this respect (Oberg 1967) while, as data from experiments on bat wings suggest, the same holds true for volume changes in the capillary system (Wiedemann 1963). Moreover, volume changes due to capillary filtration are virtually negligible in this respect (Kuiper 1966, Wijn 1980), especially for low venous pressure levels.
2.2.5 Influencing factors

From the foregoing it follows that the venous capacity $C_{10}$ is approximately equivalent to the ratio of the compliance of the venous system in a given limb segment to the volume of that limb segment. This implies that the venous capacity may be influenced by the following factors:

A) The ratio of venous volume and limb volume

The venous capacity depends on the venous volume as a fraction of the limb volume. This means that identical vascular configurations in different limb volumes have different $C_{10}$ values. If e.g. the limb volume increases because of edema formation, $C_{10}$ decreases in the same proportion.

B) The effective stiffness of the extraluminal tissues

The venous capacity depends on the effective stiffness of all tissues that surround the venous blood. Hence, provided that the cross-sections of the veins are circular, $C_{10}$ depends on the effective stiffness of both the venous walls and the tissues that surround the venous system. The greater this effective stiffness, the lower is $C_{10}$ and vice versa.

When venous walls are stressed in the circumferential direction, the first part of the stress-strain relationship expresses stress development by vascular smooth muscle, while a relatively sudden change in slope represents the successive recruitment of the relatively stiff
collagen fibres which almost solely govern the latter part of the relationship (Azuma and Hasegawa 1973, Hasegawa 1983). The coefficient of elasticity of smooth muscle fibres as calculated from the "best" linear part of the stress-strain relationship ranges from about \(10^5\) \(\text{Nm}^{-2}\) in the relaxed state to about \(2 \times 10^6\) \(\text{Nm}^{-2}\) when contracted, while the coefficient of elasticity of collagen fibres is about \(10^8\) \(\text{Nm}^{-2}\) (Caro et al 1978). The role of elastin fibres seems very limited in circumferential stress-development, since in highly stretched preparations, the elastic fibres appear still fragmentary and show no straightening (Azuma and Hasegawa 1973, Hasegawa 1983).

The effective stiffness of the tissues that surround the venous system may also be an important influencing factor. When the venous volume increases by rising (intra-) venous pressures, the counter-pressure on the venous system depends on the effective stiffness of these surrounding tissues. The greater this stiffness, the smaller is the transmural pressure increase that corresponds to a given increase in venous pressure and hence, the lower is the venous capacity. In the literature, no data were found on the effective stiffness of the tissues that surround the venous system. It may be assumed however, that if the very stiff fascia becomes strained, e.g. by development of intrafascial edema, the effective stiffness of the surrounding tissues increases and hence venous capacity decreases. For the skin it has been established that its functional significance in counteracting venous distension in human legs is negligible (Wijn 1980, Jagtman 1983).
C) **Extraluminal pressure**

The venous capacity \( C_10 \) is deduced at a given (intra-) venous pressure level. The corresponding transmural pressure level however, is unknown. This implies that the venous capacity also depends on the extraluminal pressure i.e. the pressure that is exerted on the venous system by the surrounding tissues. The higher this pressure, the lower the transmural pressure level that corresponds to the known (intra-) venous pressure level at which the venous capacity is determined. Since generally, volume distensibility curves of limb segments are concave to the pressure-axis, it follows that the higher the extraluminal pressure, the higher is the venous capacity. Note however, that if such increased extraluminal pressure is associated with an increased effective stiffness of the tissues that surround the venous system - e.g. by straining of the fascia due to the development of edema -, this potentially capacity-increasing effect might be overruled by the capacity-decreasing effect resulting from the greater stiffness of the surrounding tissues.

In the literature, there are no exact data about the extraluminal pressures corresponding to the sites at which \( C_10 \) is determined (i.e. the middle of the calf and the foot). For the calf, the pressure within the posterior fascial compartment might be a good approximation for this extraluminal pressure. For resting conditions in subjects who were sitting with their legs kept horizontally, the mean pressure within the superficial posterior compartment was found to be 4 mmHg (range 0-16 mmHg) (Quarfordt et al 1982).
2.3 REFERENCES


3.1 INTRODUCTION

In 1982, a method for the assessment of venous flow resistance ($R_v$) was introduced (Brakkee and Ruiper 1982). Essentially this method is an advanced analysis of volume changes in a limb segment as measured by strain-gauge plethysmography. The volume changes are induced by a series of venous congestions with different pressures. Following the instantaneous release of each venous congestion, values for the venous emptying rate (VER) and the corresponding venous pressures ($P_v$) are calculated. For reasons to be discussed, these values are determined at .5 seconds after pressure release. By analogy to Ohm's law, the venous flow resistance ($R_v$) proximal to the site of the strain-gauges is deduced from the slope of the linearly approximated relationship between pressure ($P_v$) and flow (VER). In addition, the venous capacity of the limb segment underneath the strain-gauges is deduced from the slope of the relationship between the applied congestion pressure and the corresponding maximum volume of the limb.

Based on a study of the methodological aspects of the method, the current standard measurement procedure is presented here as well as an account of this procedure.
Fig 3.1: Schematic drawing of the mercury filled strain-gauges connected to their mounting.
3.2 THE METHOD

3.2.1 Instrumentation

The measurement of limb volume changes is done by strain-gauge plethysmography. Fig 3.1 shows a strain-gauge connected to the adjustable mounting as we use it. For practical reasons, it consists of two mercury-filled tubes mounted mechanically in parallel and electrically in series. A practical design for routine investigations was developed by Brakkee and Vendrik (1966). In this study a newly designed system was used consisting of a four-lead mounting connected to an autobalancing bridge-amplifier circuit with electrical calibration and suitable for both manual and computer-controlled operation. The output of the plethysmograph is fed into a computer to be stored on file for further off-line data processing. Software is available that allows interactive calculations of various quantities and parameters. For a number of operations, the operator is asked for confirmation or corrective decisions.

3.2.2 Measurement procedure

All tests are performed in a quiet temperature-controlled room with an ambient temperature of 28-30 degrees Celsius, after an acclimatization period of at least 20 minutes. The subjects are positioned in a
Fig 3.2: Positioning of leg, cuff and strain-gauge.

Fig 3.3: Schematic drawing of the plethysmographic record in two successive periods of venous congestion. From each record $\Delta V/V$ is determined as well as $\Delta V/V (.5)$ and $\text{VER} (.5)$ at 0.5 seconds after release of venous congestion (o).
comfortable supine position with both lower legs evenly elevated in a horizontal plane, about 30 cm above the top of the couch (fig 3.2). Furthermore, the legs are slightly abducted and externally rotated, while the slightly flexed knees are supported laterally by foam pads. Maximum calf muscle relaxation is achieved with the help of an adjustable foot support, which allows maximum plantar flexion of the ankle joint in every patient.

Measurements are carried out at two different sites (fig 3.2). In a so-called 'calf measurement', strain-gauges are placed around each calf at its maximum circumference, while conically shaped 14x40 cm pneumatic cuffs are placed around the middle of each thigh. In a so-called 'foot measurement' the strain-gauges are placed around the middle of each foot, while the cuffs are placed around the proximal part of the lower leg.

Venous congestion is induced by rapid inflation of the cuffs to a preset pressure level (Pc). When the volume increase has reached its maximum, the cuffs are deflated instantaneously (i.e. the cuff pressure falls below 5% of the congestion pressure within .5 seconds) and the volume record shows the subsequent limb volume decrease due to the emptying of the congested veins. This procedure is repeated several times, each time with a 5 mmHg higher cuff pressure. Usually the minimum applied cuff pressure is not below 15 mmHg, while the maximum applied cuff pressure does not exceed 35 mmHg. Generally, the time needed for calf- or foot measurements does not exceed 15 minutes.

For each venous congestion, the maximum volume change (\(\Delta V/V\)) is determined from the difference between the stable volume levels just
Fig 3.4: Example of a Pv-V relation, fitted through the points (o) that relate limb volume increase $\Delta V/V$ and venous pressure $P_v$. C10 is calculated from the slope of the Pv-V relation at $P_v = 10$ mmHg (●).
before and after completion of the emptying process (fig 3.3). The corresponding venous pressure \((P_v)\) at the strain-gauge level is then lower than the applied cuff pressure \((P_c)\) and is given by the following formula: \(P_v = f.P_c - h\). In this formula, \(h\) is the hydrostatic pressure difference between the cuff and the strain-gauges, and \(f.P_c\) is the effective congestion pressure, being generally a fraction \(f\) of the cuff pressure \(P_c\). The fraction \(f\), which depends on the width of the cuff and the diameter of the thigh can be determined individually if necessary (Kuiper 1966). For the 14 cm wide cuffs as used in this study, the mean \(f\)-values in calf and foot measurements were found to be \(0.8\) (0.03; SD=0.09; \(n=17\)) and \(0.9\) (0.93; SD=0.04; \(n=11\)) respectively, which result in a venous pressure estimation that is generally accurate within 10 per cent.

### 3.2.3 Calculation of the venous capacity \(C_{10}\)

For the assessment of the venous capacity the following procedure is followed. Generally, when plotting the volume changes \((\Delta V/V\text{-values})\) against the corresponding congestion pressure values \((P_v)\), a non-linear relationship is obtained. For parameterization of this so-called "\(P_v\)-\(V\) relation", a curve fitting procedure is employed, based upon a logarithmic function: \(\Delta V/V = 1/k\ln [1+k.C_{10}(P_v-10)]\). The curve-fitting procedure makes use of the computer program BMD07R (Dixon 1974). The parameter \(C_{10}\) (expressed in %/mmHg) is the venous capacity of limb segment underneath the strain-gauges (i.e. \(C_{10}\)-calf or \(C_{10}\)-
Fig 3.5: Example of the use of the $P_V$-$V$ relation for the conversion of $\frac{\Delta V}{V}$ (.5) into the corresponding pressure $P_V$ (.5).
Fig 3.6: $R_v$ is calculated from the slope of the linearly approximated initial part of the relationship between pressure $P_v$ (mmHg) and flow $VER$ ($\%/min$).
foot) at a venous pressure level of 10 mmHg. So, C10 is calculated from the slope of the tangent to the P_v-V relation at p_v=10 mmHg (fig 3.4). The dimensionless parameter k is the coefficient of alinearity. The more the pressure-volume relation is concave to the pressure axis, the higher is k, while for a (rather exceptional) linear P_v-V relation, k is zero.

3.2.4 Calculation of venous flow resistance (R_v)

The determination of the venous flow resistance is as follows. Following the release of each venous congestion, venous emptying rates (VER, expressed in %/min) are derived from the tangents, drawn at the emptying curves at 0.5s after pressure release: VER(.5) (fig 3.3). Subsequently, with the use of the P_v-V relation, the volume levels at 0.5s after each pressure release ΔV/V(.5) (fig 3.3) are converted into the corresponding pressure levels P_v(.5) (fig 3.5). More details are given in the original paper by Brakkee and Kuiper (1982). The venous flow resistance (R_v) proximal to the site of the strain-gauges is calculated from the slope of the linearly approximated initial part of the relationship between pressure (P_v.5) and flow (VER.5) (fig 3.6). R_v is expressed in mmHg.min/%, which - for practical reasons - will be abbreviated to ru (resistance unit). In calf- and foot measurements, R_v is referred to as R_v-prox and R_v-dist respectively.

Apart from the acclimatization of the subjects, the over-all determination of both R_v and C10 at one site of measurement takes about 20
minutes (i.e. 15 minutes for the measurement procedure and about 5 minutes for the (computerized) calculation procedure.

3.2.5 Reproducibility

The reproducibility of the parameters was studied by repeated measurements (3-6 times) in six normal subjects (3 males, 3 females) with intervals of at least one week, over a time period up to three months. It appeared that both $R_v$ and $C10$ are reproducible within 10% in calf measurements as well as in foot measurements.

3.3 Comments on the Measurement Procedure

3.3.1 Volume measurement

Since $R_v$ and $C10$ are deduced from volume changes in limbs, it is essential that these volume changes are due exclusively to changes in venous blood volume. However, as has been reported previously by Wheeler (1974), inflation and deflation of the congestion cuff may be responsible for changes in limb volume due to tissue displacement. The occurrence of this phenomenon must be highly suspected in cases when rapid (1) inflation of the pneumatic cuff is followed by a rapid
initial rise of the volume record, followed by a definitely slower rise after a few seconds. In these cases, instantaneous deflation of the congestion cuff may be followed by an inprobably steep initial part of the volume decay curve, due to the rapid return of the tissues to their original position. In our experience, this phenomenon may occur predominantly in foot measurements. Generally, it can be avoided simply by a slight change in the position of the pneumatic cuff(s). This is important since, when not recognized, it may easily become confused with biphasic emptying curves as discussed in section 3.3.5. Moreover, the occurrence of this phenomenon may influence the slope of the $P_V-V$ relation and hence $C_{10}$.

3.3.2 Actual congestion pressures

Generally, the pressure exerted by the congestion cuff on the blood vessels in the limb is only a fraction $f$ of the cuff pressure $P_c$ because of the counterforces that arise from the deformation of the tissues underneath the cuff (Hesse 1970). The value of this fraction $f$ increases only slightly with increasing cuff pressures (within 10%) and can be determined with sufficient accuracy in supine subjects - within 3% when using a 14 cm wide cuff - by taking the ratio of the arterial systolic pressure in the upper arm to the systolic pressure in a given leg segment (Kuiper 1966, Kuiper and Van de Staak 1970). Generally, the highest $f$-values were found in small-sized legs. It must be noted however, that e.g. atherosclerosis may interfere with
the reliability of this method since in such cases the congestion pressure needed to achieve arterial occlusion may be (much) higher than the actual arterial pressure and hence, the obtained f-value will be too low. Although generally, mean f-values of 0.8 and 0.9 can be used in calf- and foot measurements respectively (see 3.2.2), individual determination of f is advisable in subjects with clearly abnormal limb circumferences.

Overestimation of f results in a proportional overestimation of venous pressure and hence of Rv, while underestimation of f results in a proportional underestimation of Rv. For C10, the effect of e.g. overestimation of f is far less predictable. In 16 calf measurements on 8 normal subjects it was found e.g. that a given 25% overestimation of f resulted in a mean underestimation of C10 by about 3%, varying from a 10% underestimation to a 7% overestimation. This variable effect might be explained by the fact that overestimation of f and the corresponding overestimation of venous pressure may have two opposing consequences. Firstly, overestimation of venous pressure - i.e. the denominator of C10 -, results in a proportional underestimation of this parameter. Secondly, the actual venous pressure at which C10 is determined is also overestimated. Since generally, Pv-V relations in calf measurements are concave to the pressure axis, this tends to overestimate C10 to an unknown extent. In cases of linear Pv-V relations however, only the first argument comes into play and hence a proportional underestimation of C10 results.
3.3.3 Influence of venous tone

To minimize the influence of variations in venous tone on the parameter values, all measurements were carried out in warm and relaxed subjects, in which venous tone is known to be minimal. In order to evaluate the influence of temperature, experiments were done in 5 normal subjects before and after the standard acclimatization procedure. It appeared that without acclimatization, the parameter values in foot measurements may show wide variations. Rv-dist before acclimatization was found to be up to a factor 4 higher than afterwards, while C10-foot may be reduced by more than 50 per cent. For calf measurements, the changes were far less pronounced, amounting up to about 20 per cent for Rv-prox and to about 10 per cent for C10-calf. It follows that - in contrast to foot measurements - the usefulness of acclimatization is relatively low in calf measurements. The discrepancy between the effect of temperature in calf- and foot measurements may be explained by the fact that low temperature induces an increased venous tone only in the superficial venous system which represents a relatively large proportion of the venous system in the foot region. In the calf region, the major part of the venous system consists of the deep veins which do not show an increase in venous tone in response to cold (see 1.4).

The selectivity of the venomotor response with respect to changes in temperature is in contrast to the non-selectivity of the venomotor response due to the administration of vaso-active substances as e.g. dihydro-ergotamin (DHE). This was illustrated in one subject in which
measurements were done before and after intravenous administration of 0.5 mg of DHE. For both Rv-prox and Rv-dist an increase of about 100 per cent was found, while C10-calf and C10-foot decreased by about 40 per cent.

3.3.4 Influence of posture

Presently, the measurements are carried out in subjects with slightly flexed knee joints. It was found that Rv-prox may be increased up to a factor 4 when measurements are carried out with stretched knees. In the literature it has been reported that in these cases, venous flow impediment can be demonstrated in approximately one half of the cases (Barentsen and Van den Berg 1976, Baker 1978). This impediment is then due to a concomitant compression of the popliteal vein, as has been demonstrated in various phlebographic studies (Britton 1964, Arkoff et al 1968, Thomas and Carthy 1975, Robertson et al 1979). It must be noted however, that pronounced flexion of the knee joint may also result in a higher Rv-value; knee-flexion of about 60 degrees was found to result in an Rv-increase up to 50 per cent. This can be explained by a concomitant bending or even kinking of the popliteal vein as was demonstrated phlebographically by Rudofski (1980).

Care must be taken that the measurements are carried out with minimum calf muscle tension. In calf measurements it is a consistent finding that if the calf muscle tension is increased by e.g. (passive)
dorsiflexion of the foot, both the Pv-VER and the $P_v-V$ relationships show steeper initial slopes. As a consequence, $R_v$-prox is decreased while $C_{10}$-calf is increased. Similar results were obtained in calf measurements over elastic stockings.

The analogy of the findings in measurements with passively increased calf muscle tension and over elastic stockings suggests that in both cases, an increased extraluminal pressure is likely to be responsible for the above-mentioned results. As has been pointed out in part C of section 2.2.5, such increased extraluminal pressure may explain the increased $C_{10}$-calf in these cases.

The decreased $R_v$-prox is a somewhat surprising finding since in fact, an increased $R_v$-prox due to compression on the deep veins had been expected. Two factors however might possibly over-rule the effect of this compression and hence cause a decrease in $R_v$:

- Firstly, by analogy to what has been pointed out for $P_v-V$ relations in part C of section 2.2.5, the transmural pressures corresponding to the initial part of the $P_v$-VER relationship will be relatively low because of the increased extraluminal pressure. For the venous system it generally holds true that the lower the transmural pressure, the more it shows distension with increasing congestion pressures. This is especially the case in the so-called opening up phase of the veins (see 2.2.3), which is likely to come into play in the above-mentioned cases. Consequently, as has been explained in section 2.1.4, the associated relatively great venous distension with increasing congestion pressures may explain some decrease in $R_v$.

- Secondly, in the above-mentioned experiments with increased extraluminal pressure...
luminal pressures, it was a consistent finding that relatively high congestion pressures were needed during the experiments, apparently in order to counteract the increased extraluminal pressure. Hence, the uncompressed veins between the strain-gauges and the congestion cuff will show a relatively great caliber which may also help to explain the decrease in Rv-prox. Moreover, following the release of venous congestion, the resulting relatively high pressure in the venous system proximal to the congestion cuff is likely to induce a relatively great venous distension, thereby still providing an additional explanation for the decrease in Rv-prox.

3.3.5 Calculation of venous emptying rates at 0.5s after cuff deflation

In this study, venous emptying rates are calculated at 0.5s after deflation of the congestion cuff: VER(.5). As a consequence, somewhat cumbersome calculations are needed in order to find the corresponding venous pressure levels Pv(.5). The reason for this procedure is that venous emptying curves may be biphasic with an initial rapid phase changing distinctly into a slower phase. Biphasic emptying curves have been found in patients with isolated venous obstructions, proximal to the congestion cuff (Zetterquist et al 1975, Partsch 1976, Bergqvist and Hallböök 1977, Boccalon 1982, Wupperman 1984) as well as in normal subjects (Brakkee and Kuiper 1982). Generally in cases with an isola-
ted obstruction of the iliac vein, the duration of the rapid initial part of the venous emptying is less than .5s if the obstruction is near the inguinal ligament but may be greater than .5s when the obstruction is near the inferior caval vein (Bergqvist and Hallböök 1977). In supine normal subjects with straight limbs, the rapid initial part of the venous emptying can be explained by the initially unimpeded venous flow from the limb into the previously compressed veins underneath the congestion cuff (Brakkee and Kuiper 1982). Since, when a 14 cm wide pneumatic cuff is used, the duration of this process almost never exceeds 0.5s it was decided to omit the initial 0.5s of the emptying curves.

In the currently used measurement position no indications were found that biphasic venous emptying occurs in normal subjects. This is the conclusion of a study in 25 healthy volunteers. For each of them various Pv-VER relationships were constructed by choosing delay times other than .5 seconds (from 0 up to .9s); the calculated Rv-values did not differ significantly. Apparently, in contrast to the situation in straight-limbed supine subjects, the venous flow resistance proximal to the congestion cuff is negligible in normal subjects when in the current measurement position.
3.3.6 Closing remarks

The major difference in measurement performance since the introduction of the method (Brakkee and Kuiper 1982) is the positioning of the subjects. Measurement in subjects with straight (i.e. stretched) knees has been abandoned because of its association with relatively high $R_v$ values (see 3.3.4). Moreover, the measurement of venous capacity has been standardized at $P_v = 10 \, \text{mmHg}$, instead of its determination at the intersection of the $P_v-V$ relation and the pressure axis. The venous pressure level at this intersection appeared to be quite variable and was often higher than $10 \, \text{mmHg}$.

In contrast to most parameters related to venous distension and venous flow as presented in the literature, $R_v$ and $C_10$ are essentially independent of congestion pressures and may therefore be considered as an important enrichment, notably for purposes of phlebological research. However, for a good understanding, the following considerations must be taken into account:

About $R_v$:

a) $R_v$ is the flow resistance of the venous system proximal to the strain-gauges up to at least the site of the congestion cuff. However, since the values for VER are measured at .5s after the release of congestion, $R_v$ generally will be influenced by some (unknown) part of the venous system that is proximal to the congestion cuff. This implies that e.g. isolated venous obstructions that are located
proximal to the congestion cuff may - in some cases - influence \( R_v \) (see 3.3.5).

b) \( R_v \) is a pressure to flow ratio whereas flow is a volume per unit of time. Since the volume in this ratio is expressed as a percentage of the limb volume, \( R_v \) depends on this volume. This implies that identical venous configurations in different limb volumes have different \( R_v \) values. If e.g. the limb volume increases because of edema formation, \( R_v \) increases in the same proportion. Another consequence is that, although \( R_v\)-prox and \( R_v\)-dist globally refer to the venous system of the upper and lower leg respectively, \( R_v \) of the whole leg cannot be estimated by simply adding both \( R_v \)-values.

c) Theoretically, as has been explained in section 2.1.4, \( R_v \) might be influenced by the elastic properties of the venous wall, in the sense that the lower the stiffness of the venous wall, the greater the venous diameter and the lower \( R_v \).

d) For the calculation of \( R_v \), the - linearly approximated - initial part of the \( P_v\)-VER relationship is used. With higher congestion pressures, this relation tends to become concave to the pressure axis and hence, inclusion of these sample points will artificially increase \( R_v \). The reason for this concavity is still a matter of speculation which is beyond the scope of this text.

About C10:

Several important implications with respect to the measurement of the venous capacity have been pointed out in detail in section 2.2.5 of
this thesis. From this discussion it follows that:

a) $C_{10}$ depends on the stiffness of the venous wall: the greater this stiffness in the circumferential direction, the lower is the venous capacity and vice versa.

b) $C_{10}$ depends on the volume fraction of the venous system relative to the limb volume; if e.g. the limb volume increases because of edema formation, $C_{10}$ decreases in the same proportion.

c) $C_{10}$ depends on the extraluminal pressure; Generally, although not obligatory (see 2.2.5), it may be stated that the higher the extraluminal pressure, the higher is $C_{10}$.

d) $C_{10}$ depends on the (unknown) effective stiffness of the tissues that surround the venous system; the greater this stiffness, the lower is $C_{10}$.

For maximum standardization of the method, the extraluminal pressure is kept as low as possible by means of maximum passive calf muscle relaxation. Generally, under these circumstances, the extraluminal pressure is likely to be below 10 mmHg (2.2.5). As a result, at $P_v = 10$ mmHg, the veins are likely to be cylindrical with only little wall stretch. Under these conditions, the elastic properties of the venous wall are determined predominantly by the stiffness of its smooth muscle fibres (Azuma and Hasegawa 1973, Hasegawa 1983).


4.1 INTRODUCTION

The first values for $R_v$ were presented by Brakkee and Kuiper (1982), while the same paper also provided values for the venous capacity as measured at low venous pressure levels. Since then however, based on the study as described in chapter 3 of this study, some essential adjustments in measurement performance have resulted. After finishing the first objective of this study, the second was to provide normal values for $R_v$ and $C_{10}$, corresponding to the ultimate measurement procedure.

This chapter presents a study on $R_v$ and $C_{10}$ in calf and foot measurements of normal subjects, in order to provide reference values for comparative studies. In addition, the influences of age and sex on the parameters will be evaluated and - if necessary - the reference values will be related to these variables. Finally, some correlations between selected parameters will be evaluated.

4.2 MATERIAL AND METHODS

The material consisted of the lower limbs of 85 normal subjects; 75 were responders to a request for volunteers in a local newspaper and
10 were medical students. All subjects were screened on the absence of varicose veins, signs of chronic venous insufficiency, edema and a history of deep venous thrombosis. Their ages were distributed about evenly in four age groups between 22 and 65 years (20-27; 28-40; 45-55; 55-65 years).

All measurements were carried out in both limbs simultaneously. Calf measurements were done in all 85 subjects (48 males, 37 females) and foot measurements in 58 subjects (29 males, 29 females).

All statistical procedures were carried out by the MSA (mathematisch statistische adviesafdeling) of our university. The statistical program package SAS (1985) was used to analyse the data. At first, all parameters were tested on normality (D'Agostino test). Since many parameters did not seem to be normally distributed, distribution-free methods were used in this study whenever possible. To compare age and sex groups, the tests of Kruskal-Wallis and Wilcoxon's rank sum test were used respectively. Wilcoxon's signed rank test was used to compare parameters in left and right limbs. Spearman's rank correlation coefficients (r) were computed for selected parameters. P-values of 0.05 or less were considered significant.

Reference values for the parameters were computed from the normal order statistics. Whenever possible, the 90% confidence intervals were constructed for the 5th- and the 95th-percentile. Parameter values between the inner limits may be considered normal, values outside the outer limits may be considered abnormal, while values between the inner and outer limits are in a warning zone i.e. they are possibly abnormal.
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<td>0.57</td>
<td>0.13</td>
<td>0.20</td>
<td>0.46</td>
<td>0.57</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>R</td>
<td>m+f</td>
<td>58</td>
<td>0.29</td>
<td>0.12</td>
<td>0.13</td>
<td>0.61</td>
<td>0.13</td>
<td>0.21</td>
<td>0.50</td>
<td>0.61</td>
</tr>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>m</td>
<td>48</td>
<td>0.15</td>
<td>0.04</td>
<td>0.07</td>
<td>0.25</td>
<td>0.07</td>
<td>0.10</td>
<td>0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>f</td>
<td>37</td>
<td>0.11</td>
<td>0.05</td>
<td>0.06</td>
<td>0.18</td>
<td>-</td>
<td>0.08</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
<td>C10-calf</td>
<td>R</td>
<td>m</td>
<td>48</td>
<td>0.13</td>
<td>0.05</td>
<td>0.08</td>
<td>0.23</td>
<td>0.08</td>
<td>0.11</td>
<td>0.21</td>
<td>0.23</td>
</tr>
<tr>
<td>C10-calf</td>
<td>R</td>
<td>f</td>
<td>37</td>
<td>0.11</td>
<td>0.05</td>
<td>0.06</td>
<td>0.18</td>
<td>-</td>
<td>0.08</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>C10-foot</td>
<td>L</td>
<td>m</td>
<td>29</td>
<td>0.11</td>
<td>0.04</td>
<td>0.06</td>
<td>0.18</td>
<td>-</td>
<td>0.09</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>C10-foot</td>
<td>L</td>
<td>f</td>
<td>29</td>
<td>0.10</td>
<td>0.03</td>
<td>0.05</td>
<td>0.19</td>
<td>-</td>
<td>0.06</td>
<td>0.12</td>
<td>-</td>
</tr>
<tr>
<td>C10-foot</td>
<td>R</td>
<td>m</td>
<td>29</td>
<td>0.11</td>
<td>0.03</td>
<td>0.06</td>
<td>0.22</td>
<td>-</td>
<td>0.08</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>C10-foot</td>
<td>R</td>
<td>f</td>
<td>29</td>
<td>0.09</td>
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<td>0.04</td>
<td>0.14</td>
<td>-</td>
<td>0.05</td>
<td>0.12</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.1: Venous flow resistance Rv (mmHg.min/%) and venous capacity C10 (%/mmHg) in normal human legs: Inter-quartile ranges (IQR), indicate the difference between the 75th- and 25th-percentile. Normal ranges are given by the inner and - if possible - outer limits of the 5th- and 95th-percentile.
4.3 RESULTS

Normal values for Rv and C10 are presented in table 4.1. Since many parameters did not seem to be normally distributed, median values and inter-quartile ranges (IQR, i.e. difference between 75th- and 25th-percentile) are given rather than mean values and standard deviations. For sex-dependent parameters (see 4.3.1), the values are given for both sexes separately. Normal ranges are given by the 90% confidence limits of the 5th- and the 95th-percentile. In the female subgroup and sometimes in the male subgroup, the number of testees was too small to calculate outer limits for these percentiles.

4.3.1 Influence of age, sex and site of measurement

No age dependency was found for Rv and C10 in our material.

The sex-dependency of the parameters is presented in table 4.2. It follows that Rv-prox in males is significantly lower than in females, while C10 in males is significantly higher than in females. For Rv-dist, no significant sex-dependency was found.

The left-right dependency of the parameters is presented in table 4.3. It is demonstrated that for both sexes, Rv-prox in left legs is significantly lower than in right legs. For Rv-dist these differences are dubiously significant. C10 in left legs tends to be higher than in the right leg but significant differences are found only in two of the four subgroups.
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SIDE</th>
<th>m/f(%)</th>
<th>p (m&lt;f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rv-prox</td>
<td>L</td>
<td>80</td>
<td>0.01</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>R</td>
<td>87</td>
<td>0.07</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>L</td>
<td>94</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>R</td>
<td>91</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SIDE</th>
<th>m/f(%)</th>
<th>p (m&gt;f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>136</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C10-calf</td>
<td>R</td>
<td>118</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C10-foot</td>
<td>L</td>
<td>110</td>
<td>0.06</td>
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<tr>
<td>C10-foot</td>
<td>R</td>
<td>122</td>
<td>0.008</td>
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</tbody>
</table>

Table 4.2: Rv and C10 in males (m) as compared to females (f). The factor m/f(%) indicates median values in males, expressed as a percentage of median values in females; p indicates the significance of the differences. (n.s. = not significant)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SEX</th>
<th>L/R(%)</th>
<th>p (L&lt;R)</th>
</tr>
</thead>
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<tr>
<td>Rv-prox</td>
<td>m</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>f</td>
<td>87</td>
<td>0.002</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>m+f</td>
<td>94</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SEX</th>
<th>L/R(%)</th>
<th>p (L&gt;R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10-calf</td>
<td>m</td>
<td>115</td>
<td>0.004</td>
</tr>
<tr>
<td>C10-calf</td>
<td>f</td>
<td>100</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-foot</td>
<td>m</td>
<td>100</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-foot</td>
<td>f</td>
<td>111</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 4.3: Rv and C10 in left legs (L) as compared to the right (R). The factor L/R(%) indicates median values in left legs, expressed as a percentage of median values in right legs; p indicates the significance of the differences. (n.s. = not significant)
4.3.2 Correlations between selected parameters

A moderately high positive correlation was found between corresponding parameters in the right and the left leg (table 4.4), while a moderately high negative correlation was found between Rv and C10 at the same site of measurement (table 4.5). No significant correlations were found between: a) corresponding parameters in calf and foot measurements within the same limb, b) Rv-prox and C10-calf within the same leg and c) calf circumference and any of the parameters.

4.3.3 The coefficient of alinearity (k)

In calf measurements (Pv range 10-30 mmHg), mean values for the coefficient of alinearity (k) of the Pv-V relation were lower in males (0.51) than in females (0.66). These differences were highly significant for left legs (p < 0.0001) and dubiously significant for right legs (p = 0.02). For the alinearity in foot measurements (Pv range up to 25 mmHg), no significant differences were found between males and females (mean value 0.15). Moreover, no significant left-right differences for k were found in either calf or foot measurements.
### Table 4.4: Spearman rank-correlation coefficients (r) with statistical significance (p) between corresponding parameters in the right and the left leg.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SEX</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rv-prox</td>
<td>m</td>
<td>0.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>f</td>
<td>0.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>m+f</td>
<td>0.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C10-calf</td>
<td>m</td>
<td>0.60</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C10-calf</td>
<td>f</td>
<td>0.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C10-foot</td>
<td>m</td>
<td>0.42</td>
<td>0.02</td>
</tr>
<tr>
<td>C10-foot</td>
<td>f</td>
<td>0.62</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 4.5: Spearman rank-correlation coefficients (r) with statistical significance (p) between Rv and C10 at the same site of measurement.

<table>
<thead>
<tr>
<th>SITE</th>
<th>SIDE</th>
<th>SEX</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>calf</td>
<td>L</td>
<td>m</td>
<td>-0.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>calf</td>
<td>R</td>
<td>m</td>
<td>-0.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>calf</td>
<td>L</td>
<td>f</td>
<td>-0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>calf</td>
<td>R</td>
<td>f</td>
<td>-0.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>foot</td>
<td>L</td>
<td>m</td>
<td>-0.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>foot</td>
<td>R</td>
<td>m</td>
<td>-0.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>foot</td>
<td>L</td>
<td>f</td>
<td>-0.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>foot</td>
<td>R</td>
<td>f</td>
<td>-0.64</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
4.4 DISCUSSION

4.4.1 General remarks

The results as presented in this chapter may serve as reference values for future studies. The left-right and sex dependency as found for various parameters however, implies that generally, a statistically sound comparison with e.g. patient groups can be made only for corresponding subgroups and not for patient groups as a whole.

The first $R_v$-values that were presented (Brakkee and Kuiper 1982), were higher than in the present study, while the same paper also provided values for venous capacity that were lower than in the present study. Similarly low values for venous capacity have been presented also by co-workers of our department, who studied potential correlations between skin elasticity and venous capacity (Wijn 1980, Jagtman 1983). The difference with the present study may be explained notably by two alterations in measurement performance as have resulted from the study on the methodic aspects. Firstly, the body positioning with the subjects having streched knees has been abandoned because of its association with relatively high $R_v$-values (see 3.3.4). Secondly, measurement of venous capacity has been standardized at $P_v = 10$ mmHg, instead of its determination at the point of intersection between the $P_v$-$V$ relation and the pressure axis. The relatively low values for the venous capacity in the above-mentioned studies may be explained by the fact that in the supine position, $P_v$ at this point is often higher.
than 10 mmHg (3.3.6, Wijn 1980). Consequently, since most \( P_V - V \) relations are concave to the pressure axis, this tends to decrease values for venous capacity.

4.4.2 Influence of age

In this study, no age dependency was found for \( R_v \) and \( C_{10} \). In the literature, no data on the relationship between age and venous flow could be found. With respect to venous capacity, the results of the above-mentioned plethysmographic studies by Wijn (1980) and Jagtman (1983) are in accordance with this study. Van den Berg and Barbey (1976), however, found a significant positive correlation between age and calf volume changes due to single venous congestions with high pressures. In first approximation, these findings might seem to be in conflict with the lacking of a correlation between \( C_{10} \) and age. It must be noted, however, that besides on the tangent of the initial part of the \( P_V - V \) relation, these volume changes depend to a great extent on the alinearity of this relation. The findings of Van den Berg and Barbey (1976) might therefore be an indication that - within a certain venous pressure range - the alinearity decreases with age. Such possible decrease might be explained by the decrease with age of the volume fraction of the collagen fibres in the venous wall (Rickenbach 1972). These collagen fibres are the major determinants for the stiffness of the venous wall in cases of high wall stress, as may be induced e.g. by venous congestions with high pressures.
4.4.3 Influence of sex

For several corresponding subgroups, Rv in males was higher than in females, while C10 was lower. Theoretically, there might be two possible explanations. Firstly, these findings might be explained by sex differences in the volume fraction of the venous system relative to the limb volume, and secondly by sex differences in the stiffness of the venous wall and or the effective stiffness of the tissues that surround the venous system.

In the literature, no sex differences with respect to volume fraction and wall stiffness were found. Moreover, no data could be found on sex dependency of venous flow. For the venous capacity in the calf, no sex dependency was found by Wijn (1980) and Jagtman (1983), possibly due to the relatively low number of testees. For calf volume changes due to single venous congestions it was found that these are greater in males than in females (Van den Berg and Barbey 1976). These findings, however, were not confirmed by two (much) smaller studies done by others (Barentsen and Van den Berg 1976, Pointel et al 1981).

4.4.4 Left-right differences

In this study, Rv-calf in the left leg was lower than in the right, while C10-calf in left legs was higher than in right legs. These left-right differences were quite surprising findings, especially for Rv
since the only left-right difference with respect to venous system that was found in the literature concerns an intraluminal venous spur in the left iliac vein which is present in about 21 per cent of the adult population (May and Thurner 1957, Negus et al 1960). However, in such cases the only effect, if any, would have been a higher Rv in left legs as compared to the right.

Left-right differences in limb volume cannot explain the above-mentioned findings since in our material no significant differences were found between the calf circumference in left and right legs (Wilcoxon test). Furthermore, it would be rather far-fetched to explain the differences by a left-right difference in the stiffness of the venous wall within the same subject. However, the results as found in this study might be explained by a greater volume fraction of the venous system in the left leg than in the right. A difference of about 5 per cent in this respect, would be sufficient to explain the findings.

4.4.5 Influence of limb volume

In this study, no significant correlation was found between any of the parameters and limb circumference, which appeared to be significantly greater in males (mean: 35.8 cm) than in females (mean: 33.8 cm) (Wilcoxon test: p < 0.003). As has been explained in section 2.1.4 and 2.2.5-A respectively, Rv and C10 depend on the venous volume as a fraction of the limb volume. Consequently, the lacking of a correla-
tion between calf circumference and these parameters may suggest that generally, the volume of the venous system is largely proportional to the limb volume.

4.4.6 Correlations

The negative correlation as found between $R_v$ and $C_{10}$ at the same site of measurement might be explained by the fact that both parameters depend - in an opposite direction - on the volume of the venous system as a fraction of the limb volume and on the stiffness of the venous wall in the circumferential direction (see 3.3.6). Since $R_v$ depends on the properties of the venous system proximal to the site of measurement, significant correlations might have been expected between $R_v$-dist and the two parameters which depend in part on the properties of the venous system in the calf region, i.e. $R_v$-prox and $C_{10}$-calf. The lack of such correlations in this study, however, might indicate that $R_v$-dist depends mainly on the properties of the venous system in the foot and ankle region and to a far lesser extent on the properties in the calf region.

4.4.7 Alinearity of $P_v$-$V$ relations

Normal values on the coefficient of alinearity ($k$) have been presented as reference values for future studies. The alinearity $k$ depends
on a number of factors, notably on the corresponding venous pressure range and on the compliance of the venous system. A discussion on this complex parameter however, is beyond the scope of this text.

4.5 REFERENCES


CHAPTER 5: VENOUS FLOW RESISTANCE AND VENOUS CAPACITY IN LEGS WITH DEEP VENOUS THROMBOSIS

5.1 INTRODUCTION

This chapter presents the results of a study on $R_v$ and $C_{10}$ in patients with acute and very recent deep venous thrombosis (DVT), in which an increased $R_v$ and a decreased $C_{10}$ may be expected due to the intraluminal obstruction by the thrombotic mass. The study includes a comparison with normals, while in addition, follow-up measurements were done in the post-thrombotic period. Moreover, a retrospective study was done on the sensitivity and specificity of $R_v$, when used as a diagnostic criterion for acute DVT.

5.2 MATERIAL AND METHODS

The material of this study consisted of 76 legs of 70 consecutive patients suspected of having DVT, in which an adequate phlebography was made before the patients were sent to our department, mostly by the Department of Internal Medicine in our University Hospital. The phlebography was classified either as thrombotic ($n=41$, 41 patients) or non-thrombotic ($n=35$, 29 patients). DVT was classified as either
proximal, distal or "both". In this classification, proximal DVT refers to a localization within the popliteal and/or superficial femoral and/or internal iliac vein, while distal refers to a localization in calf veins, distal to the popliteal vein. In the thrombotic limbs (2 exclusively proximal, 2 exclusively distal, 37 both), all first measurements were done within a month after the acute event (mean about 2 weeks).

Calf measurements were carried out in all 41 limbs with DVT and foot measurements were done in 14 legs in which the distal deep veins were involved in the thrombotic process. All parameters were compared to corresponding normal values as presented in chapter 4 (Wilcoxon test). In 22 legs in which the proximal veins were involved in the thrombotic process, a follow-up study was done on Rv-prox and C10-calf (108 measurements).

For a retrospective assessment of the sensitivity and specificity of Rv as a diagnostic criterion for acute DVT, phlebography has been used as the gold standard. Rv-prox was determined in all 35 non-thrombotic and all 41 thrombotic limbs, while Rv-dist was determined in 7 non-thrombotic limbs and 14 limbs in which the distal veins were involved in the thrombotic process. Observer bias due to the previous knowledge of the phlebographic results was excluded by the fact that calculation of Rv-values was carried out solely by a computer program.
5.3 RESULTS

5.3.1 Comparison with normals

Median values for Rv and C10 (absolutely and as a percentage of normal) as well as the statistical significance of abnormality are presented in table 5.1. It follows that both Rv-prox and Rv-dist are significantly higher than normal, while C10-calf is significantly lower than normal. C10-foot however, is significantly lower than normal in only one of the four subgroups.

5.3.2 Parameter follow-up in the post-thrombotic period

The results of the follow-up study on Rv-prox and C10-calf in the post-thrombotic period are presented graphically in the figures 5.1 and 5.2 respectively. It follows that Rv-prox decreases with time while C10-calf increases. The changes are most pronounced during the first months after the acute event. With few exceptions, Rv returns to high-level normal values within about one year, while during the same period C10 returns to low-level normal values.
<table>
<thead>
<tr>
<th>PARAMETER</th>
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<th>MEDIAN</th>
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<td>C10-calf</td>
<td>L</td>
<td>m</td>
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<td>0.07</td>
<td>0.04</td>
<td>0.05</td>
<td>0.11</td>
<td>47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>f</td>
<td>4</td>
<td>0.05</td>
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<td>0.01</td>
<td>0.12</td>
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<td>0.07</td>
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<td>0.04</td>
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<td>0.002</td>
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<td>C10-foot</td>
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<td>0.06</td>
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<td>C10-foot</td>
<td>L</td>
<td>f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C10-foot</td>
<td>R</td>
<td>m</td>
<td>7</td>
<td>0.09</td>
<td>0.07</td>
<td>0.04</td>
<td>0.13</td>
<td>82</td>
<td>n.s.</td>
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<tr>
<td>C10-foot</td>
<td>R</td>
<td>f</td>
<td></td>
<td></td>
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</table>

Table 5.1: Rv (mmHg.min%) and C10 (%/mmHg) in human legs with deep venous thrombosis. The inter-quartile range (IQR), indicates the difference between the 75th- and the 25th-percentile. Median values are presented also as a percentage of normal (%); p indicates the significance of abnormality.
Fig 5.1: Follow-up study in 22 legs on Rv-prox during the post-thrombotic period.

Fig 5.2: Follow-up study in 22 legs on C10-calf during the post-thrombotic period.
Fig 5.3: $R_v$-prox in legs with acute proximal deep vein thrombosis and in non-thrombotic legs.
5.3.3 Diagnostic accuracy of Rv

In non-thrombotic extremities (n=35), Rv-prox was always lower than 0.54 ru. In limbs with proximal DVT (n=39), two values were lower than 0.54 ru, while the remainder (n=37) were higher than 0.72 ru (fig 5.3). So retrospectively, legs with proximal DVT's may be separated from non-thrombotic limbs with a sensitivity of 95% (95% confidence limits: 83-99%) and a specificity of 100% (95% confidence limits: 90-100%).

In non-thrombotic extremities Rv-dist was always lower than 0.52 ru, while in legs with distal DVT (n=14), 9 values were lower than 0.52 ru and 5 were higher than 0.76 ru. So retrospectively, legs with distal DVT may be separated from non-thrombotic legs with a sensitivity of 36% (95% confidence limits: 13-65%) and a specificity of 100% (95% confidence limits: 59-100%).

5.4 DISCUSSION

5.4.1 Comparison with normals

In legs with DVT, Rv is higher than normal, while C10-calf is lower than normal. These findings may be explained by the intraluminal thrombotic mass, which results in a functional elimination of some
part of the venous system, thereby causing impediment of venous flow and preventing veins from distension. The fact that - except for one subgroup - C10-foot is not significantly different from normal, might indicate that generally the veins within the foot are spared from the thrombotic process. Apart from the above-mentioned functional elimination of some part of the venous system as an explanation for the increased Rv and the decreased C10, several other factors may come into play in this respect.

1) Generally in cases of DVT, the limb volume is increased due to the development of edema. This implies that the volume of the venous system, relative to the limb volume will be smaller than before. As has been explained in the sections 2.1.4 and 2.2.5 respectively, this causes an increase in Rv and a decrease in C10. These changes are in about the same proportion as the limb volume increase which generally will be within about 20-30 per cent.

2) In legs with DVT, the edema is located in part within the stiff fascia (Lofferer and Mostbeck 1967), which may explain the increased intrafascial pressure as was demonstrated by Quarfordt et al (1983). Moreover, since the fascia is likely to be strained in these cases, there will be an increase in the effective stiffness of the tissues that surround the venous system. The increased intrafascial (i.e. extraluminal) pressure is likely to be associated with a relatively small caliber of the deep veins and hence tends to increase Rv. Moreover, this increase may still be amplified by the increased stiffness of the tissues that surround the venous system (see 2.1.4). With respect to C10, it has already been emphasized in section 2.2.5 that
the potentially capacity-increasing effect of an increased extra-luminal pressure may well be over-ruled by the capacity-decreasing effect of an increased stiffness of the tissues that surround the venous system.

3) \( R_v \) may be increased by an increased whole blood viscosity. A "slight increase" could be demonstrated in 16 of 20 patients with DVT (Volker and Trübestein 1983). Unfortunately, no quantitative data were given in this report but these findings might explain at least in part our experience that it is not unusual that in the limbs contralateral to the DVT, \( R_v \) is increased up to values that are within the "warning zone" as presented in the chapter on normal values (chapter 4).

5.4.2 Parameter changes in the post-thrombotic period

The relative normalization of \( R_v \) and \( C_{10} \), as presented in Fig. 5.1 and 5.2 respectively, may be explained by a process of recanalization and/or collateralization as well as a relative normalization of the other factors as mentioned in the previous section. In two cases, a striking decrease of \( R_v \)-prox by tens of per cents was found, together with an increase in \( C_{10} \)-calf up to twice the original values, following a two days treatment with elastic bandages. These examples have drawn our attention with respect to the apparently great potential influence of factors other than recanalization and/or collateralization which are unlikely to occur in such short notice. An explanation for these short-term changes might be a rapid reduction of the intra-
<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR</th>
<th>SPECIFICITY (%)</th>
<th>PROX DVT (%)</th>
<th>DIST DVT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallböök</td>
<td>1971</td>
<td>100 (95-100)</td>
<td>100 (89-100)</td>
<td>0 (0-52)</td>
</tr>
<tr>
<td>Johnston</td>
<td>1974</td>
<td>92 (79-88)</td>
<td>100 (77-100)</td>
<td>25 (5-57)</td>
</tr>
<tr>
<td>Hull</td>
<td>1976</td>
<td>97 (95-99)</td>
<td>93 (87-97)</td>
<td>17 (10-27)</td>
</tr>
<tr>
<td>Benedict</td>
<td>1977</td>
<td>96 (92-99)</td>
<td>97 (91-100)</td>
<td>22 (9-42)</td>
</tr>
<tr>
<td>Hull</td>
<td>1977</td>
<td>95 (88-98)</td>
<td>98 (91-100)</td>
<td>19 (7-39)</td>
</tr>
<tr>
<td>Flanigan</td>
<td>1978</td>
<td>95 (88-98)</td>
<td>96 (87-100)</td>
<td>71 (44-90)</td>
</tr>
<tr>
<td>Boccolon</td>
<td>1981</td>
<td>-</td>
<td>100 (87-100)</td>
<td>87 (60-98)</td>
</tr>
<tr>
<td>Cramer</td>
<td>1983</td>
<td>91 (59-100)</td>
<td>100 (74-100)</td>
<td>-</td>
</tr>
<tr>
<td>Wheeler</td>
<td>1982</td>
<td>92 (87-95)</td>
<td>98 (92-100)</td>
<td>48 (32-63)</td>
</tr>
<tr>
<td>Peters</td>
<td>1983</td>
<td>93 (86-97)</td>
<td>92 (79-98)</td>
<td>68 (45-86)</td>
</tr>
<tr>
<td>Pini</td>
<td>1984</td>
<td>94 (88-97)</td>
<td>96 (91-99)</td>
<td>60 (34-80)</td>
</tr>
<tr>
<td>Voorhoeve</td>
<td>1986</td>
<td>88 (78-95)</td>
<td>90 (80-96)</td>
<td>7 (1-23)</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td>100 (90-100)</td>
<td>95 (83-99)</td>
<td>36 (13-65)</td>
</tr>
</tbody>
</table>

Table 5.2: Sensitivity and specificity of various criteria for phlebographically proven deep venous thrombosis as found in plethysmographic studies. For these values we have calculated the 95% confidence limits (between brackets).
fascial edema, and hence a reduction of both intrafascial pressure and effective stiffness of the tissues that surround the venous system. The effects of these changes (i.e. a decrease of \( R_v \) and an increase of \( C_{IO} \)) have been pointed out in 5.4.1 as well as in 2.1.4 and 2.2.5.

5.4.3 Notions on sensitivity

The sensitivity of \( R_v \) as a DVT-criterion may be defined as the percentage "thrombotic" \( R_v \)-values in legs with DVT. Table 5.2 presents sensitivity-values of various other plethysmographic DVT-criteria as presented in the literature. For optimum comparability of these values we have calculated their corresponding 95% confidence limits. It follows that the sensitivity values in the present study are in agreement with those in the literature.

For distal DVT, measurement at the foot-level (i.e. the measurement of \( R_v\)-dist) provides no better results than the results of calf measurements in other studies. Some studies however present a relatively high sensitivity in cases of distal DVT (Flanigan et al 1978, Boccalon et al 1981, Peters et al 1983). However, this might be well explained by the definition of "distal" since in these studies a possible DVT in the popliteal vein has not been excluded properly. In this study, \( R_v\)-prox in the two cases with exclusively distal DVT showed non-thrombotic values.

In all plethysmographic methods, the sensitivity of a DVT-criterion depends on the hemodynamic significance of the thrombus. In this
respect, the discrepancy between the high sensitivity values in cases of proximal DVT and the low sensitivity in cases of distal DVT is fully understandable in view of the different venous anatomy in the upper and lower leg. Theoretically, various other factors may influence this sensitivity. In the literature, false negative results have been reported also in cases of non-occlusive proximal DVT (Hallböök and Ling 1973, Wheeler et al 1974, Brown et al 1987). Moreover, some authors have supposed that e.g. in cases of DVT, an impaired venous emptying through the deep venous system might become masked by a bypass effect of superficial varicose veins (Boyssen and Eiriksson 1968, Hallböök and Gothling 1971, Brown et al 1987). From own studies however, it is concluded that the sensitivity for DVT of Rv is unlikely to be influenced by primary truncal varicosis of the great saphenous vein (chapter 6). Theoretically, false negative results might be found also in cases of DVT, located in only one of multiple superficial femoral veins, in which the incidence of DVT seems to be even higher than normal (Liu et al 1986). In limbs with double popliteal veins no such higher incidence was found by the same authors. Moreover, in the case of DVT most often both these popliteal veins will be affected.

A very special source of false negative plethysmographic results - especially if emptying rates, deduced from the steepest part of the emptying curves are used -, may be formed by isolated DVT's located proximally to the congestion cuff. In these cases, the emptying curves may be biphasic with an initial rapid phase, changing distinctly into
a slower phase (Zetterquist et al 1975, Partsch 1976, Bergqvist and Hallböök 1977, Bocale 1982, Wuppermann 1984). The rapid phase can be explained by the initially unimpeded venous outflow into the previously compressed (normal) veins underneath the congestion cuff (Brakkee and Kuiper 1982) as well as into the unobstructed part of the venous system proximal to the congestion cuff (Bergqvist and Hallböök 1977).

For this reason it was decided to omit the initial .5s of the emptying curves in the calculation of Rv. If necessary, the delay time may be adjusted at will up to at least 0.9s.

Biphasic emptying curves might explain the lower sensitivity for isolated iliac vein DVT's as compared to femoropopliteal DVT's as was reported in one study (Niederle and Prerovsky 1976). In one patient with an isolated iliac vein thrombosis an expected high Rv-value (1.24 ru) was found. However, when in the calculation of Rv the steepest parts of the emptying rates were taken into account, Rv was in the non-thrombotic range (0.43 ru). In order to avoid such potential influence of biphasic emptying curves, the initial 0.5s of the emptying curves is omitted also by others (Cramer et al 1983, Voorhoeve 1986). Note however that with isolated obstructions within the iliac vein, the rapid phase of venous emptying may very well exceed 0.5s (Bergqvist and Hallböök 1977).

The low sensitivity of Rv in cases of distal DVT does not necessarily interfere with the management of DVT. Although in cases of distal DVT pulmonary embolisation (PE) can be demonstrated by serial lung-scanning in 16-40 per cent of the patients (Kistner et al 1972, Yao et
al 1974, Mostbeck et al 1975, Moreno Cabral et al 1977), symptomatic PE is found only in up to 1.6 per cent without any associated deaths (Kakkar et al 1969, Browse and Clemenson 1972, Doous 1976). So, if the thrombus remains within the distal venous system, false negative results would have no serious short-term consequences. However, since distal DVT may propagate proximally, thereby increasing the risk of potentially lethal PE, serial plethysmographic investigations are advocated by various authors. In studies using impedance plethysmography, it was found in this respect that it is safe to withhold anticoagulant treatment from "symptomatic" outpatients (Hull et al 1983, Büller et al 1984, Hull et al 1985, Huisman et al 1986, Huisman et al 1987), when repeated investigations show non-thrombotic results. It may still be noted here that although exclusively distal DVT is not associated with serious short-term consequences, long-term sequellae in the sense of a post-thrombotic syndrome may still develop in these cases (Partsch et al 1981).

5.4.4 Notions on specificity

The specificity of Rv as a DVT-criterion may be defined as the percentage "non-thrombotic" Rv-values in non-thrombotic legs. The high specificity of Rv is in agreement with the high specificity of various other plethysmographic DVT-criteria as presented in the literature (table 5.2).

It must be emphasized that "thrombotic" Rv-values do not provide
definite proof for the existence of DVT. As in all plethysmographic methods, also the specificity of Rv may be influenced by several factors. Note e.g. that all factors that may cause venous compression (see 2.3.3) may be responsible in this respect. Three such factors, however, can be eliminated by an adequate measurement technique. Firstly, the deflation of the congestion cuff must be sufficiently fast in order to avoid an artificial impairment of venous flow. Secondly, during calf measurements the knees of the subject must be slightly bent, since stretching of the knees may result in a substantial increase in Rv-prox (3.3.4). Thirdly, an increased venous tone e.g. due to a low temperature may increase Rv-dist by hundreds of per cents (3.3.3) and may thereby account for false positive results.

In the literature, there are some indications that the presence of lymphedema might influence the specificity of plethysmographic methods (Kriessmann 1978). However, for Rv, no indication for such an influence was found (chapter 7).

Finally, it is important to realize that in post-thrombotic limbs it is difficult to establish whether or not "thrombotic results" are due to recurrent recent DVT or are still due to an old thrombus. However, a clear increase of Rv within the post-thrombotic period is very likely to be associated with recurrent DVT. In a systematic study done by others, it was found that after 3, 6, 9 and 12 months after the onset of DVT, plethysmograms showed non-thrombotic results in 67%, 85%, 92% and 95% of the patients respectively (Huisman et al 1988). The present follow-up study and the study of Jay et al (1984) are grossly in line with these findings. For Rv, however, it must be noted
that these "non-thrombotic results" may not be considered as entirely normalized since generally, $R_v$ remains increased up to values that are within the "warning zone" (see 4.3). Correspondingly, clear left-right differences for $R_v$-prox often remain for a period of at least several years.

5.4.5 Notions on positive and negative predictive values

The positive predictive value (PPV) of $R_v$ as a DVT-criterion may be defined as the percentage thrombotic legs in all legs with "thrombotic" $R_v$-values. The negative predictive value (NPV) then indicates the percentage non-thrombotic legs in all legs with "non-thrombotic" $R_v$-values. In this study however, values for PPV, NPV as well as for the percentage false positives and false negatives have been omitted on purpose. Besides the sensitivity and the specificity, these values greatly depend on the mean "a priori" chance for having DVT within the population that was under investigation. Table 5.3 clearly illustrates this potentially dramatic influence. Based on the known sensitivity and specificity of $R_v$ as a DVT-criterion, values for PPV, NPV and percentages of false positive or false negative results may be estimated for each patient individually, provided one is able to estimate correctly the a priori chance for having DVT. Generally, since "textbook clinical signs" of DVT are rather common but largely unspecific, this a priori chance for having DVT will be smaller in symptomatic outpatients as compared to symptomatic hospitalized patients, in which
<table>
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<th>SITUATION A</th>
<th>SITUATION B</th>
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<td>mean a priori chance = 1%</td>
<td>mean a priori chance = 90%</td>
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</table>

GOLD STANDARD

<table>
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<tr>
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<th>-</th>
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<tr>
<td>TEST +</td>
<td>9</td>
<td>99</td>
</tr>
<tr>
<td>TEST -</td>
<td>1</td>
<td>891</td>
</tr>
</tbody>
</table>

Table 5.3:
Numerical example to illustrate the great influence of the a priori chance, e.g. for having thrombosis, on the positive and negative predictive values (PPV and NPV) of a certain diagnostic test as well as on the percentage false positives (false pos.) and false negatives (false neg.). In the situations A and B, these a priori chances are 1% and 90% respectively. In both situations, the sensitivity and specificity of the test are assumed to be 90%.

PPV = 8% (9/108)  PPV = 99% (810/820)
NPV = 100% (891/892)  NPV = 50% (90/180)
false pos. = 10% (99/1000)  false pos. = 1% (10/1000)
false neg. = 0% (1/1000)  false neg. = 9% (90/1000)
risk factors (Coon 1977, Briet et al 1985) are relatively common.

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6.1 INTRODUCTION

Venous flow resistance in human legs with primary truncal varicosis of the great saphenous vein (PTV) might be lower than normal, because of the relatively great caliber of such PTV. Some authors have even suggested that in cases of deep vein thrombosis, the reduced flow through the deep veins might become masked by the collateral function of the PTV (Boyssen and Eiriksson 1968, Hallböök and Gothlin 1971, Brown et al 1987).

This chapter presents the results of a study on Rv and C10 in legs with PTV, including a comparison with normals and an evaluation of the contribution of PTV to total venous outflow. Abnormalities in limbs with PTV with relevance to Rv and C10 are discussed. Moreover, the influence of PTV on the sensitivity of Rv - when used as a diagnostic criterion for proximal deep venous thrombosis - is discussed.
Table 6.1: \( R_v \) (mmHg.min/%) and \( C_{10} \) (\%/mmHg) in human legs with primary truncal varicosis of the great saphenous vein: The inter-quartile range (IQR), indicates the difference between the 75th- and the 25th-percentile. Median values are presented also as a percentage of normal (%); \( p \) indicates the significance of abnormality.
6.2 MATERIAL AND METHODS

The material for this study, consisted of human legs with PTV, in which reflux was demonstrable by means of Doppler ultrasound examination from the femoro-saphenal junction down to at least below the level of the knee joint. None of the subjects had signs of chronic venous insufficiency exceeding grade I (slight edema, slight corona phlebectatica), lymphedema or a history of deep venous thrombosis. Calf measurements were done in 41 limbs (28 patients) and foot measurements in 26 limbs (17 patients). All parameters were compared with corresponding normal values (Wilcoxon test). In some cases a combination of Wilcoxon tests was done over both sexes.

To evaluate the contribution of PTV to the total venous outflow, Rv-prox values before and after local compression of the PTV against the medial femoral condyle were compared in 11 limbs (Wilcoxon test). Venous flow arrest was tested by Doppler ultrasound examination.

6.3 RESULTS

6.3.1 Comparison with normals

For Rv and C10, median values (absolutely and as a percentage of normal) as well as the statistical significance of abnormality are presented in table 6.1. It follows that Rv in legs with PTV tends to
<table>
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<th>Rv-uncompressed</th>
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<tr>
<td>0.18</td>
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</tr>
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<td>0.24</td>
<td>0.22</td>
</tr>
</tbody>
</table>

mean: 0.21 0.23
SD: 0.06 0.06
difference: + 9.5%
p (Wilcoxon): 0.045

Table 6.2: Rv-prox values before and during local compression of PTV against the medial femoral condyle.
be somewhat lower than normal. For $Rv$-prox, the differences are (dubiously) significant only in the female subgroups. When both sexes are taken together (combination of Wilcoxon tests), the differences for $Rv$-prox are significant for right legs ($p = 0.02$). For $Rv$-dist, the differences are significant, notably in left legs.

$C_{10}$-calf is higher than normal, with significant differences in three of the four subgroups. $C_{10}$-foot tends to be lower than normal but significant differences are found in the largest subgroup only.

6.3.2 The contribution of PTV to total venous outflow

$Rv$-prox before compression of the PTV against the medial femoral condyle was found to be significantly lower than afterwards ($P < 0.05$). As a result of this compression, mean values for $Rv$-prox increased by about 10 per cent (table 6.2).

6.4 DISCUSSION

In limbs with PTV, $Rv$ tends to be lower than normal. The slight decrease in $Rv$ as found in this study, seems to be smaller than might have been expected in view of the greatly increased - even doubled - venous emptying rates following the release of venous congestion as have been reported in the literature (Ziriksson and Dahn 1968,
Gundersen et al 1971, Wille et al 1982). This discrepancy can be explained by the fact that these emptying rates are obtained with relatively high congestion pressures (more than 40 mmHg). For such pressure values, the Pv-VER relation becomes concave to the pressure axis. In patients with PTV, this concavity appeared to be less pronounced. This may explain that emptying rates that correspond to these high congestion pressures may show much greater differences than the initial slope of the Pv-VER relation from which Rv is deduced.

In this study, functional elimination of PTV causes an increase in Rv by about 10%. This means that the mean flow resistance in these PTVs is approximately a factor ten greater than that of the remaining veins. Consequently, the mean contribution of PTV to total venous outflow is about 10%. Since generally, Rv in legs with acute deep venous thrombosis (DVT) is increased by hundreds of per cents (chapter 5), it is considered unlikely that the sensitivity of Rv as a DVT-criterion will be influenced by PTV.

CI0 in legs with PTV was found to be higher than in normals, notably at the calf. These results are in accordance with the abnormally steep pressure-volume relationships of the calf in patients with PTV as reported by others (Van den Berg et al 1982, Van den Berg 1983, Jagtman 1983). Although difficult to compare, the results of the present study are also in line with reports on abnormally great calf-volume changes in legs with PTV, resulting from single venous congestions (Eriksson and Dahn 1968, Gundersen et al 1971, D'Inverno 1981, Schander 1982).
Based on measurements of the calf circumference, it was found that the mean calf volume in patients with PTV is about 10% greater than in normals. Provided that the configuration of the venous system would remain unaltered, this increased calf volume would result in an increased $R_v$-prox (see 2.2.4) and a decreased $C_{10}$-calf (see 2.3.5). However, the differences as found in this study are in an opposite direction. Two factors might account for this:

a) In the literature, it has been reported that the diameter of PTV is abnormally great and may be several times its original value (Zsoter et al 1967, Laszt 1972, Bocking and Roach 1974, Mellmann 1981). Moreover, in patients with PTV, the mean diameters of the deep veins are significantly greater than normal and increase with the severity of the PTV (Mellmann 1981). The mean diameter increase as was found in this respect was greatest in calf veins (up to about 40%), smaller for popliteal and femoral veins (up to about 25%) and not significant for the external iliac veins. When compared with normals, this greater diameter of the deep veins may account for some decrease in the (absolute) venous flow resistance (see 2.1.2) and an increase in the (absolute) compliance of the venous system (see 2.2.3). Because of the relatively great venous "caliber" in legs with PTV, there may be an abnormally great volume of the venous system, even relative to the above-mentioned abnormally great calf volume in these patients. As has been explained in the sections 2.1.4 and 2.2.5 respectively, this might explain in part the tendency to a low $R_v$-prox and an abnormally high $C_{10}$-calf in the legs in patients with PTV. The greater significance of these differences for $C_{10}$ than for $R_v$ might be explained in
part by the above-mentioned greater mean diameter increase of the deep veins in the calf (important to C10-calf) than in the more proximal veins (important to Rv-prox).

b) As has been explained earlier, a decrease in Rv and an increase in C10 may be caused by an abnormally low stiffness of the venous wall in the circumferential direction (see 2.1.4 and 2.2.5). Such abnormally low wall stiffness has been found in PTV (Zsoter et al 1976, Laszt 1971), especially for small deformations (Bocking and Roach 1974) as are most likely to occur at Pv = 10 mmHg (see 3.3.6). With respect to the morphological substrate of this abnormal stiffness, it may be noted that for these small circumferential deformations, the elastic properties of the venous wall are determined predominantly by its smooth muscle (Azuma and Hasgawa 1973, Hasegawa 1983). In PTV this smooth muscle shows distinct qualitative rather than quantitative abnormalities (Prerovski 1981). According to Staubesand (1978 & 1983), the smooth muscle cells in PTV change from a "contractile" into a "metabolically modified" type which can be distinguished e.g. by a reduction of its contractile filaments. Moreover, the smooth muscle cells in PTV are markedly separated from each other by an increased amount of connective tissue in which many of the collagen fibres show an "atypical" appearance (Staubesand 1978 & 1983, Niebes 1983, Rose 1986). Fibrotic replacement of smooth muscle represents a late stage of varicosis (Leu et al 1979). The findings of the present study, notably on C10, might indicate that the majority of the patients were in the "pre-fibrotic" phase.


CHAPTER 7: VENOUS FLOW RESISTANCE AND VENOUS CAPACITY IN HUMAN LEGS
WITH PRIMARY LYMPHEDEMA

7.1 INTRODUCTION

In the literature, there are sparse indications that in non-thrombotic limbs with edema, there may be some impairment of venous flow, while in addition the limb distension resulting from venous congestion is smaller than normal (Hallböök and Ling 1973, Kriessmann 1978).

This chapter presents the results of a study on $R_v$ and $C_{10}$ in legs with primary lymphedema, including a comparison with normals and an evaluation of the influence of the clinical severity of the edema on the parameters. Abnormalities in limbs with primary lymphedema with relevance to $R_v$ and $C_{10}$ are discussed. In addition, the influence of primary lymphedema on the specificity of $R_v$ as a DVT-criterion is discussed.

7.2 MATERIAL AND METHODS

The material for this study consisted of human legs with primary lymphedema in which the diagnosis was made on clinical grounds (see e.g. Brunner et al, 1984). None of the subjects had signs of secundary
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SIDE</th>
<th>SEX</th>
<th>n</th>
<th>MEDIAN</th>
<th>IQR</th>
<th>MIN</th>
<th>MAX</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rv-prox</td>
<td>L</td>
<td>m</td>
<td>9</td>
<td>0.22</td>
<td>0.14</td>
<td>0.13</td>
<td>0.42</td>
<td>138</td>
<td>0.02</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>L</td>
<td>f</td>
<td>12</td>
<td>0.24</td>
<td>0.09</td>
<td>0.19</td>
<td>0.40</td>
<td>120</td>
<td>0.055</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>R</td>
<td>m</td>
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<td>0.32</td>
<td>0.14</td>
<td>0.26</td>
<td>0.43</td>
<td>160</td>
<td>0.003</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>R</td>
<td>f</td>
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<td>0.33</td>
<td>0.16</td>
<td>0.24</td>
<td>0.53</td>
<td>143</td>
<td>0.01</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>L</td>
<td>m+f</td>
<td>16</td>
<td>0.32</td>
<td>0.17</td>
<td>0.19</td>
<td>0.51</td>
<td>123</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rv-dist</td>
<td>R</td>
<td>m+f</td>
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<td>0.31</td>
<td>0.14</td>
<td>0.19</td>
<td>0.48</td>
<td>107</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>m</td>
<td>9</td>
<td>0.12</td>
<td>0.08</td>
<td>0.07</td>
<td>0.19</td>
<td>80</td>
<td>0.08</td>
</tr>
<tr>
<td>C10-calf</td>
<td>L</td>
<td>f</td>
<td>12</td>
<td>0.10</td>
<td>0.02</td>
<td>0.06</td>
<td>0.13</td>
<td>91</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-calf</td>
<td>R</td>
<td>m</td>
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<td>0.10</td>
<td>0.04</td>
<td>0.08</td>
<td>0.13</td>
<td>77</td>
<td>0.03</td>
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<tr>
<td>C10-calf</td>
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<td>0.08</td>
<td>0.04</td>
<td>0.04</td>
<td>0.12</td>
<td>73</td>
<td>0.03</td>
</tr>
<tr>
<td>C10-foot</td>
<td>L</td>
<td>m</td>
<td>6</td>
<td>0.11</td>
<td>0.07</td>
<td>0.06</td>
<td>0.19</td>
<td>100</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-foot</td>
<td>L</td>
<td>f</td>
<td>10</td>
<td>0.08</td>
<td>0.03</td>
<td>0.06</td>
<td>0.13</td>
<td>80</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-foot</td>
<td>R</td>
<td>m</td>
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<td>0.10</td>
<td>0.03</td>
<td>0.08</td>
<td>0.11</td>
<td>91</td>
<td>n.s.</td>
</tr>
<tr>
<td>C10-foot</td>
<td>R</td>
<td>f</td>
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<td>0.08</td>
<td>0.05</td>
<td>0.04</td>
<td>0.15</td>
<td>89</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 7.1: Rv (mmHg.min/%) and C10 (%/mmHg) in human legs with primary lymphedema: The inter-quartile range (IQR), indicates the difference between the 75th- and the 25th-percentile. Median values are presented also as a percentage of normal (%); p indicates the significance of abnormality.
lymphedema, varicose veins, chronic venous insufficiency or a history of deep venous thrombosis. Based on the clinical severity of the edema at the calf level, the limbs were classified as either grade I (light/medium) or grade II (severe) lymphedema. Calf measurements were done in 38 legs (33 patients) and foot measurements in 29 legs (24 patients). All parameters have been compared with corresponding normal values (Wilcoxon test). In some cases a combination of Wilcoxon tests was done over both sexes.

To evaluate the influence of the clinical severity of the edema on Rv-prox and C10-calf, the parameters in 17 legs with grade I and 15 legs with grade II edema have been compared (Wilcoxon test).

7.3 RESULTS

7.3.1 Comparison with normals

Median values for Rv and C10 (absolutely and as a percentage of normal) as well as the statistical significance of abnormality are presented in table 7.1. It follows that Rv-prox is significantly higher than normal. Rv-dist tends to be lower than normal but no significant differences were found in our material.

C10-calf is significantly lower than normal, notably in right legs. However, if both sexes are taken together (combination of Wilcoxon tests), significant differences can be demonstrated also in left legs.
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>SIDE</th>
<th>SEX</th>
<th>n(I)</th>
<th>n(II)</th>
<th>II/I(%)</th>
<th>p (II &gt; I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rv-prox</td>
<td>L</td>
<td>m</td>
<td>3</td>
<td>6</td>
<td>156</td>
<td>n.s.</td>
</tr>
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<td>f</td>
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<td>4</td>
<td>136</td>
<td>0.04</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>L</td>
<td>comb.</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>R</td>
<td>m</td>
<td>2</td>
<td>2</td>
<td>135</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rv-prox</td>
<td>R</td>
<td>f</td>
<td>4</td>
<td>3</td>
<td>159</td>
<td>0.02</td>
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<tr>
<td>Rv-prox</td>
<td>R</td>
<td>comb.</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 7.2: Rv-prox in grade II (severe) lymphedema as compared to grade I (light/medium) lymphedema; the factor II/I(%) indicates mean values in grade II expressed as a percentage of mean values in grade I; p indicates the significance of the differences (n.s. = not significant; comb. = combination of Wilcoxon tests).
(p = 0.04). C10-foot tends to be lower than normal but the differences were not significant in this material.

7.3.2 Influence of the clinical severity of the edema

Rv-prox in grade I and grade II lymphedema are compared in table 7.2. It follows that Rv-prox in grade II edema is significantly higher than in grade I edema, notably in the female subgroups. However, if both sexes are taken together (combination of Wilcoxon tests), the differences are highly significant for both left and right legs.

C10-calf in grade II edema tends to be lower than in grade I lymphedema in all four subgroups (ratio of mean values ranging from 68-78%) but no significant differences were found in this material.

7.4 DISCUSSION

Rv-prox in human legs with primary lymphedema was found to be higher than normal and to increase with the clinical severity of the lymphedema. In addition, C10-calf is lower than normal. Several factors might account for these differences.

1) The development of edema results in an increased limb volume, although the configuration of the venous system remains unchanged. As
has been explained in the sections 2.1.4 en 2.2.5 respectively, this will be associated with an increase in \( R_v \) and a decrease in \( C_{10} \) in about the same proportion as the limb volume increase at the site of measurement. In order to estimate the influence of this effect, the statistical comparison with normals was repeated with capacity and resistance values based on the absolute instead of the relative venous volume. As a reasonable approach for such values, \( C_{10}\)-calf was multiplied and \( R_v\)-prox was divided by the square of the local limb circumference. These in this way converted parameter values were compared to similarly converted normal values. Then it appeared that the calf capacity was not significantly different from normals but for the resistance (dubiously) significantly differences remained in two of the four subgroups.

2) In legs with primary lymphedema, the edema is located in part within the stiff fascia (Lofferer et al 1972). If, by increasing amounts of edema, the fascia becomes strained, this is likely to be associated with both an increased intrafascial pressure and an increase in the effective stiffness of the tissues that surround the venous system. That this actually may happen might be suggested by the experience of surgeons that following cleavage of the fascia in patients with primary lymphedema, fluid is pressed out. The increased intrafascial (i.e. extraluminal) pressure is then likely to be associated with a relatively small diameter of the deep veins. The tendency to a relatively low \( R_v \) that may result from such decreased caliber may still be amplified by the increased stiffness of the tissues that surround the venous system (see 2.1.4). With respect to
C10, it has already been emphasized in section 2.2.5 that the potentially capacity-increasing effect of an increased extraluminal pressure may very well be over-ruled by the capacity-decreasing effect of an increased stiffness of the tissues that surround the venous system.

3) There are some phlebographical experiences that a "fragile and poorly developed system" may exist in human legs with primary lymphedema (Fischer and May, cited by Kuiper and Brakkee, 1975). If so (and the findings were not simply due to the above-mentioned increased intrafascial pressure), this might provide an additional explanation for an increased Rv and a decreased C10 in cases of primary lymphedema.

In legs with primary lymphedema, both Rv-prox and Rv-dist appeared to be within the "non-thrombotic" range (i.e. below 0.54 ru and 0.52 ru respectively, see chapter 5). Consequently, in this material there is no indication that the specificity of Rv as a thrombosis criterion is influenced by the presence of primary lymphedema.

7.5 REFERENCES


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Measurement of venous flow resistance $R_v$ and venous capacity $C_{10}$ by means of strain-gauge plethysmography provides quantitative venous parameters that are essentially independent of congestion pressure(s). Notably $R_v$ may be considered an almost "universal" hemodynamic parameter. In the hands of the phlebologist, measurement of $R_v$ and $C_{10}$ may serve a dual purpose. Firstly of course, the method is very suitable for basic phlebological research, while in addition it may be used for several specific clinical purposes.

With respect to future basic phlebological research, it would be interesting e.g. to evaluate the connections between both $R_v$ and $C_{10}$ and the calf muscle pump function, as measured also by means of strain-gauge plethysmography (Kuiper 1966, Kuiper and Van de Staak 1970). This might be done in a prospective study starting with children of about ten years of age, since it is our experience that in this age group, the calf muscle pump function seems to be impaired. Another study might be focused on the venous system in the human arm. Probably, arm-measurements will have their own specific methodic problems. From own experiences in this respect, it has become obvious that e.g. tissue displacement as has been described in section 3.3.1 may be a problem in this respect.

With respect to the clinical applicability of $R_v$-measurements, the diagnosis of deep venous thrombosis (DVT) might seem the most obvious choice. For this purpose, the method might prove to be of value,
probably also in cases of axillary vein thrombosis. However, if the method is needed only for the diagnosis of DVT, other - less complicated - plethysmographic methods may be more suitable. On the other hand, in view of the universal and quantitative character of Rv, this parameter may serve as an aid for the diagnosis of recurrent DVT, for which even the interpretation of the diagnostic gold standard (i.e. phlebography), is not always easy. If in the post-thrombotic period, Rv shows a clear increase, this is likely to be due to recurrent DVT. Moreover, in the post-thrombotic period, persistently elevated Rv-values beyond a certain level and a certain duration might be used as an indication for venous bypass operations. These are clear advantages over plethysmographic methods that only provide thrombosis yes-or-no decisions rather than showing any quantitative insight into local venous hemodynamics. Finally, in another study it might still be evaluated to what extent Rv-values might aid in choosing high or low elastic stockings during the post-thrombotic period.
This study presents an investigation of methodical and clinical aspects of the measurement of the venous flow resistance $R_v$ and the venous capacity $C_{10}$ in human legs. Essentially, the method is based upon an advanced analysis of volume changes in a limb segment as measured by strain gauge plethysmography. The volume changes are obtained by a series of venous congestions with different pressures. Following the instantaneous release of each venous congestion, values for the venous emptying rates ($VER$) and the corresponding venous pressure ($P_v$) are calculated. By analogy to Ohm's law, $R_v$ proximal to the site of the strain-gauges is deduced from the slope of the linearly approximated relationship between pressure ($P_v$) and flow ($VER$). $R_v$ is expressed in mmHg.min/%. With strain-gauges around the calf (i.e. calf measurements) or the foot (i.e. foot measurements) respectively, $R_v$ is referred to as $R_v$-prox and $R_v$-dist. In addition, $C_{10}$ of the limb segment underneath the strain-gauges (i.e. $C_{10}$-calf or $C_{10}$-foot) is deduced from the slope of the relationship between the applied congestion pressure and the corresponding maximum volume change of the limb at 10 mmHg venous pressure.

In the INTRODUCTION, the history and the purpose of this study are described, while in CHAPTER 1, a brief survey is presented on morphology and physiology of the venous system as far as it pertains to the present study. CHAPTER 2 presents some important aspects of venous flow resistance and venous capacity. With regard to venous flow resistance, some elementary notions on fluid dynamics are presented at
first, followed by a discussion on various factors that may influence venous flow resistance in the human leg. Finally, the principles of the plethysmographic measurement of Rv are explained, together with some specific influencing factors. With respect to venous capacity, a brief disclosure is given on (vascular wall-) elasticity, on which the capacity depends in part. Moreover, the terms distensibility and compliance are explained, since these terms are important to the understanding of the term capacity as it is used in this thesis. Then, the principles of the capacity-measurement are pointed out as well as some important influencing factors.

In CHAPTER 3, the measurement-procedures for Rv and C10 are presented in detail. This is followed by a study on methodic factors that may influence the measurement results. It was found that in subjects, well-acclimatized to a room temperature of 28-30 degrees centigrade, the measurements are reproducible within 10 per cent. Inadequate acclimatization may result in relatively great variations in Rv and C10, notably in measurements at the foot. The potential influence of the congestion cuff on the parameter values is discussed. Furthermore, it was demonstrated that Rv-calf may be increased by hundreds of per cents due to stretching of the knee joint, while it may be increased also by excessive bending of the knee joint. In addition, it was found that an increased extravascular pressure - e.g. due to a high passive calf muscle tension - may be associated with a decrease in Rv-prox and an increase in C10-calf.

CHAPTER 4 presents normal values for Rv and C10. Both quantities are related to sex and the site of measurement. No significant age depen-
dency was found. Rv was found to be lower in males than in females and lower in left legs than in right legs. C10 was found to be higher in males than in females and higher in left than in right legs. Correlations between selected parameters are presented. The left-right and the sex dependency as found for various parameters implies that a statistically sound comparison with patient groups can be made only for corresponding subgroups and not for a patient group as a whole.

CHAPTER 5 presents a study on Rv and C10 in human legs with deep venous thrombosis (DVT). It was found that Rv is significantly higher than in normals, while C10 is significantly lower, notably in measurements at the calf-level. In a follow-up study it was demonstrated that generally, Rv-prox decreases sharply within the first few months after the acute event, while C10-calf increases. With few exceptions, Rv eventually returns to (high-level) non-thrombotic values within about one year, while in the same time C10 returns to (low-level) non-thrombotic values. The sensitivity of Rv when used as a diagnostic criterion for recent DVT was assessed retrospectively. For proximal DVT, the sensitivity of Rv-prox was 95% (95% confidence limits 83-99%) and for distal DVT, the sensitivity of Rv-dist was 36% (95% confidence limits 13-65%). The specificity for Rv was 100% (95% confidence limits Rv-prox: 90-100%; Rv-dist: 59-100%). Influencing factors for the sensitivity and specificity are discussed.

CHAPTER 6 presents a study on Rv and C10 in human limbs with primary truncal varicosis of the great saphenous vein (PTV). It was found that Rv tends to be lower than normal, notably for Rv-dist but significant differences are hardly demonstrable. C10-calf is significantly higher
than normal, while for C10-foot the differences are less significant.
Physical and morphological abnormalities of PTV with relevance to Rv
and C10 are discussed. It was demonstrated that the contribution of
PTV in venous hemodynamics amounts to about 10 per cent. It is consi-
dered unlikely that the sensitivity of Rv-prox - when used as a
diagnostic criterion for recent deep venous thrombosis - is influenced
by PTV.

CHAPTER 7 presents a study on Rv and C10 in human legs with primary
lymphedema. It was found that Rv-prox is significantly higher than
normal and increases with the clinical severity of the edema, while
C10-calf is significantly lower than normal. For Rv-dist and C10-foot,
no significant abnormalities were found. No indications were found
that the specificity of Rv - when used as a thrombosis criterion - is
influenced by primary lymphedema.

Finally, in the EPILOGUE some suggestions are done for possible
future studies, with regard to basic phlebological research as well as
specific clinical applications.
SAMENVATTING

In deze studie wordt een onderzoek beschreven naar methodische en klinische aspecten van de in vivo meting van de veneuze stromingsweerstand Rv in menselijke benen. Het gaat hierbij om een geavanceerde analyse van volumeveranderingen in een been, welke worden gemeten met behulp van ‘kwiktouwtjes’-plethysmografie. De volumeveranderingen worden verkregen door een reeks veneuze stuwingen met verschillende stuwdrukken. Na momentaan opheffen van iedere veneuze stuwing wordt een waarde voor de veneuze uitstroomsterkte (VER) en de bijbehorende veneuze druk (Pv) bepaald. Naar analogie met de wet van Ohm wordt dan uit de helling van de lineair benaderde relatie tussen druk (Pv) en stroomsterkte (VER) een waarde voor Rv berekend (uitgedrukt in mmHg.min/%), welke bij meting aan de kuit betrekking heeft op het bovenbeenstraject (Rv-prox) en bij meting aan de voet op het onderbeenstraject (Rv-dist). Tevens wordt uit de relatie tussen de volumetoename van de meetplaats en de toegepaste stuwdruk een waarde berekend voor de volume distensibiliteit van de meetplaats bij een veneuze druk van 10 mmHg, in deze studie aangeduid als veneuze capaciteit C10 (C10-kuit of C10-voet, uitgedrukt in %/mmHg).

In de INLEIDING wordt de historie en het doel van het onderzoek beschreven, waarna in HOOFDSTUK 1 wordt ingegaan op enkele structurele en functionele aspecten van het veneuze systeem voor zover deze van belang zijn voor deze studie. In HOOFDSTUK 2 wordt ingegaan op enkele aspecten van de veneuze stromingsweerstand en de veneuze capaciteit. Voor wat de veneuze stromingsweerstand betreft, wordt eerst kort
ingegaan op enige elementaire aspecten van de vloeistofdynamica in buizen en buizensystemen. Daarnaast worden diverse factoren besproken, welke in menselijke benen van invloed kunnen zijn op de veneuze stromingsweerstand in menselijke benen in het algemeen. Tenslotte worden de principes van de plethysmografische meting van $Rv$ uiteengezet met de daarbij behorende specifieke beïnvloedende factoren. Voor wat betreft de veneuze capaciteit wordt eerst ingegaan op o.a. het begrip (vaatwand-) elasticiteit, waarvan het voor een deel afhankelijk is. Daarna worden de begrippen distensibiliteit en compliantie besproken, daar deze van belang zijn voor het begrip van de term capaciteit zoals deze in dit proefschrift wordt gebruikt. Vervolgens worden de principes van de capaciteits-meting uiteengezet alsmede enkele belangrijke factoren welke hierop van invloed kunnen zijn.

In HOOFDSTUK 3 wordt beschreven hoe in dit onderzoek de veneuze stromingsweerstand $Rv$ en de veneuze capaciteit $C10$ worden bepaald. Tevens wordt aangegeven welke methodische factoren van invloed kunnen zijn op het resultaat van de metingen. In dit kader werd o.a. ingegaan op de mogelijke invloed van de gebruikte stuwmanchet op de uitkomst van de metingen. Voorts bleek dat strekken van het kniegewricht bij kuitmetingen kan leiden tot een aanzienlijke verhoging van $Rv$ doordat de V. poplitea hierdoor kan worden gecomprimeerd. Er dient derhalve te worden gemeten bij een lichte flexiestand van de knie. Verhoging van de extraluminale druk (bijv. door een hoge passieve kuitspierspanning) kan bij kuitmetingen resulteren in een verhoging van $C10$, gepaard aan een op het eerste gezicht verrassende verlaging van $Rv$. Er dient derhalve gemeten te worden bij maximaal ontspannen kuitmusculatuur. Na
een adequate acclimatisatie aan een omgevingstemperatuur van ca. 30°C is de veneuze tonus verwaarloosbaar klein. De reproduceerbaarheid van zowel Rv als C10 in kuit- en voetmetingen ligt dan binnen de 10 procent. Indien aan deze voorwaarde niet wordt voldaan, bleken met name bij voetmetingen grote variaties in de parameterwaarden het gevolg te kunnen zijn.

In HOOFDSTUK 4 wordt het onderzoek beschreven naar de normaalwaarden van Rv en C10 in zowel kuit- als voetmetingen. Leeftijdsafhankelijkheid van de parameters werd hierbij niet aangetoond. Geslachtsafhankelijkheid van de parameters was aantoonbaar in een aantal gevallen waarbij voor de mannen een lagere Rv en een hogere C10 werd gevonden. Links-rechts afhankelijkheid was eveneens aantoonbaar in een aantal gevallen waarbij in linker benen een lagere Rv-prox en een hogere C10 werd gevonden. De geslachtsafhankelijkheid van de parameters, alsmede de gevonden links-rechts verschillen, impliceert dat voor een statistisch verantwoorde vergelijking met de hierna beschreven patiënten-groepen geen uitspraken kunnen worden gedaan voor een populatie als geheel, maar dat deze afzonderlijk moet worden bezien voor de diverse subpopulaties.

In HOOFDSTUK 5 wordt een onderzoek beschreven naar Rv en C10 in extremiteiten met een flebografisch bevestigde (acute) diepe veneuze trombose. In alle subgroepen bleek dat Rv duidelijk is verhoogd t.o.v. normalen, zowel in kuitmetingen als in voetmetingen. C10 is duidelijk verlaagd t.o.v. normalen in kuitmetingen. Bij meting aan de voet zijn de verschillen veel minder duidelijk. Bij het vervolgen van de parameterwaarden in de tijd bleek dat, met name in de eerste
maanden na het optreden van de trombose, Rv-prox over het algemeen een forse daling vertoont, terwijl C10-kuit groter wordt. Met weinig uitzonderingen daalde Rv binnen ongeveer een jaar tot hoog-non-trombotische waarden terwijl in dezelfde tijd C10 steeg tot laag-non-trombotische waarden. De sensitiviteit en specificiteit van Rv voor recente diepe veneuze trombosen werd retrospectief bepaald. De sensitiviteit van Rv-prox voor bovenbeenstrombosen bedroeg 95% (95% betrouwbaarheidsgrenzen 83-99%), terwijl de sensitiviteit van Rv-dist voor onderbeenstrombosen 35% bedroeg (95% betrouwbaarheidsgrenzen 13-65%). De specificiteit van Rv bedroeg 100% (95% betrouwbaarheidsgrenzen voor Rv-prox: 90-100%; voor Rv-dist, na adequate acclimatisatie (1): 59-100%). De factoren welke de sensitiviteit en de specificiteit van Rv (en andere plethysmografische meetmethoden) kunnen beïnvloeden, worden besproken.

In HOOFDSTUK 6 wordt een onderzoek beschreven naar Rv en C10 in extremiteiten met een primaire stamvaricosis van de vena saphena magna. Hoewel in vergelijking met normalen een gemiddeld enigszins lagere Rv aantoonbaar was in zowel kuit- als voetmetingen, zijn signifi- cancante verschillen nauwelijks aantoonbaar. Bij onderzoek naar de bijdrage van de varix aan de totale veneuze uitstroom bleek dat functionele uitschakeling van de varix d.m.v. locale compressie tegen de epicondylus femoralis medialis bij kuitmetingen een weliswaar significante verhoging van Rv ten gevolge had, maar dat deze gemiddeld minder dan 10% bedroeg. Het wordt onwaarschijnlijk geacht dat het bestaan van een primaire vena saphena magna stamvaricosis een bedreiging vormt voor de sensitiviteit van Rv als criterium voor de diagnos-
tiep van diepe veneuze trombosen. C10-kuit was verhoogd t.o.v. normalen, terwijl de verschillen voor C10-voet minder uitgesproken waren. De fysische en morfologische veranderingen in varices worden uiteengezet.

In HOOFDSTUK 7 wordt een onderzoek beschreven naar Rv en C10 in extremiteiten met primair lymfoedeem. Hierbij was Rv-prox duidelijk verhoogd ten opzichte van normalen, waarbij de waarden bij een ernstig lymfoedeem hoger waren dan bij een als minder ernstig gekwalificeerd oedeem. De Rv-waarden vielen binnen de waarden welke werden gevonden bij de niet-trombotische extremiteiten (hoofdstuk 4). Derhalve werden geen aanwijzingen gevonden dat het bestaan van primair lymfoedeem een bedreiging vormt voor de specificiteit van Rv als criterium voor de diagnostiek van diepe veneuze trombose. C10-kuit was duidelijk verlaagd ten opzichte van de normalen. Bij voetmetingen zijn voor Rv en C10 geen verschillen t.o.v. normalen aantoonbaar.

In de EPILOOG worden tenslotte nog enkele suggesties gedaan voor eventueel vervolg-onderzoek, zowel op basaal-wetenschappelijk gebied als voor specifiek klinische toepassing.

Vanaf april 1982 was hij werkzaam op de afdeling Dermatologie van het Sint Radboudziekenhuis te Nijmegen. De eerste drie jaren was dit in het kader van een door de Nederlandse Hartstichting gesubsidieerd onderzoeks-project uitsluitend binnen de sectie flebologie (Hoofd: Prof. Dr. J. P. Kuiper), alwaar de basis voor deze studie werd gelegd.

De opleiding tot dermatoloog werd gestart op 1 maart 1985, eveneens in het Sint Radboudziekenhuis (Opleider: Prof. Dr. R. Happle). Sinds 1 februari 1989 is hij als dermatoloog-fleboloog werkzaam in het Medisch Spectrum Twente (Oldenzaal/Enschede).

En last but not least: sinds 1981 is hij gehuwd met Gonnie Steenman en hij is de trotse vader van Lisette (3 jaar) en Stefan (2 jaar).