Venous Flow Velocity, Venous Volume and Arterial Blood Flow

By Jay D. Coffman, M.D., and Jeffrey A. Lempert, M.D.

SUMMARY

The relationship of arterial blood flow and venous volume to venous flow velocity was studied in normal subjects. The effects of current modes of treatment in venous thrombosis and of a vasodilator drug on venous flow velocity were also investigated. Total calf flow and venous volume were measured by venous occlusion plethysmography while venous flow axial velocity was determined by the transit time of $^{131}$I albumin from calf to inguinal region. Local intravenous epinephrine administration induced vasoconstriction and increased venous flow velocity. Intra-arterial isoproterenol and angiotensin increased and decreased arterial flow, respectively, with no change in venous flow velocity or volume, but local heat increased arterial flow and venous flow velocity with no change in venous volume. Local cold, despite vasoconstriction, decreased venous flow velocity accompanied by a decreased arterial flow. Intravenous heparin did not affect venous flow velocity. Intravenous but not oral nylidrin increased venous flow velocity. Therefore venous flow velocity can be significantly increased by vasoconstriction, by large increases in arterial flow (local heat), and by a parenteral vasodilator drug. These experiments indicate that there is a basis for applying heat but not cold in the prevention and treatment of venous thrombosis.

Additional Indexing Words:

Epinephrine  
Heparin  
Nylidrin  
Plethysmography  

Isoproterenol  
Heat  
Venous thrombosis  

Angiotensin  
Cold  
$^{131}$I albumin

ARTERIAL BLOOD FLOW and venous tone in the extremities of man have been the subject of extensive physiologic and pharmacologic study but venous flow velocity has received little attention. Stanton et al. measured linear velocity of venous flow by timing the movement of radio-opaque dye injections; a simpler technique described by Wright et al. using the transit time of a radioisotope, has been used in recent years. It has been shown that head-down tilting and exercise increase, while upright posture and immobilization decrease, venous flow velocity. An increased velocity has also been found with external compression of the limbs. However, the contribution of arterial blood flow and of changes in vein caliber to venous flow velocity have not been determined. Stimuli may affect either the arterial or venous system or both; for instance, epinephrine increases muscle blood flow but constricts veins.

Among the factors precipitating venous thrombosis, a slowing of venous flow is probably one of, if not the most, significant. Although local heat and sometimes local cold have been used for years in the treatment of venous thrombosis, their effect on venous flow velocity has not been studied and has no scientific basis. The hemodynamic actions of heparin, a valuable anticoagulant in treatment, are also unknown except for conflicting reports regarding its effect on limb blood flow.

The present study investigated the physiological factors that affect the velocity of venous blood flow; the effects of therapies currently used in venous thrombosis on venous blood flow velocity, arterial blood flow, and venous volume; and the effect of a vasodilator drug on venous blood flow velocity.

Methods

Total calf blood flow and venous volume were measured by venous occlusion plethysmography on lightly clothed subjects in a 24.5°C constant temperature room. Average age of these normal volunteers was 24 years. The supine subjects were positioned to maintain the posterior aspect of the calf approximately at heart level. The calf was enclosed in a plethysmograph filled with water maintained at a temperature of 34°C. The level of water within the plethysmograph was 10 cm above the calf. A pneumatic cuff, placed on the thigh proximal to the plethysmograph, was used to produce the venous occlusion necessary to measure blood flow and venous volume. The lowest venous occlusion pressure required to obtain the maximum rate of increase in the volume of the calf was determined at the
beginning of each study and averaged 34 mm Hg. During
calf blood flow and venous volume measurements, the foot
was excluded by inflating an 8 cm wide pneumatic cuff on
the ankle at 50 mm Hg above the subject's systolic pressure
as measured in the arm by the auscultatory method. To
measure venous volume, the cuff on the thigh was inflated so
that the effective venous pressure was raised from 1 mm Hg
to a level of 30 mm Hg by 5 mm Hg increments. The
volume of the veins at an effective venous pressure of 30 mm
Hg is reported and is referred to as venous volume. 11
Fluctuations in the level of water in the plethysmograph
were detected by a Sanborn displacement transducer which
sensed the vertical motion of a Lucite float having a
diameter of 4 inches. The transducer was used in conjunc-
tion with a Sanborn strain gauge amplifier and a direct
writing recorder. The recording system was calibrated at the
beginning of each experiment by introducing known quan-
tities of water into the plethysmograph. The volume of the
calf within the plethysmograph was determined by measure-
ment of the water displaced. Blood flow in the calf is
expressed in ml/100 ml of tissue/min. Radial pulse rates and
sphygmomanometric determinations of blood pressure were
obtained with each set of measurements. Mean blood
pressure was calculated by adding one-third of the pulse
pressure to the diastolic pressure.

Venous flow axial velocity was measured by the transit
time of a bolus of 131I albumin from the calf to the inguinal
region. A catheter was inserted via a 17 gauge needle into
the saphenous vein at the ankle and threaded to lie proximal
to the ankle pneumatic cuff. A slow intravenous saline drip
ensured patency of the catheter. A scintillation probe was
centered over the femoral vein located medially to the
femoral artery pulsation. Lead shielding was placed on the
thigh distal to the probe. One ml of 131I albumin in saline
was injected as rapidly as possible into the catheter via a
three way stopcock and then the intravenous saline was
opened; the ankle cuff was inflated at suprasystolic pressure
during all injections. Time of injection was marked on a
direct writing recorder which received the radioactive
counts from the scintillation probe via a ratemeter (time
constant set at 0.1 sec). The length from the tip of the
 catheter in the calf to the scintillation probe at the groin was
measured. The speed of venous blood flow was determined
during the time of injection of the initial rise in radioactive
counts at the probe and expressed in cm/sec. The initial rise
in radioactivity was clear cut and usually rapid. In 13 sub-
jects, two venous flow velocities were performed in suc-
cession to determine the reproducibility of the method.
The two venous flow velocities averaged 15.9 and 15.3 cm/sec
and did not differ significantly. However, individual venous
flow velocities showed a wide range among the subjects un-
der the same conditions.

In each experiment, calf blood flows and venous volumes
were determined at 15 min intervals until stable and then a
venous flow velocity was measured. The following
procedures were performed after control values were ob-
tained:

1. In ten normal subjects, 0.25 to 0.5 \(\mu g/min\) of
epinephrine was infused by a constant infusion pump into
the saphenous vein catheter for 8 min and calf blood flow,
venous volume, and venous flow velocity were repeated.
The dose was chosen to produce a decrease in venous
volume without changes in blood pressure, pulse rate, or calf
blood flow. Histamine (2 \(\mu g/min\)), bradykinin (10 \(\mu g/min\)),
or sodium nitroprusside (12–30 mg/min) was infused into
the saphenous vein in two subjects.

2. In 21 subjects, a catheter was also inserted into the
femoral artery for infusion by a constant infusion pump of
0.2 to 1.5 \(\mu g/min\) of isoproterenol in 11 subjects or 0.125 to
0.25 \(\mu g/min\) of angiotensin in ten subjects. The doses were
adjusted to increase or decrease calf blood flow with no
change in venous volume, pulse rate, or blood pressure.
Before and following drug administration at a rate of 1 to 2
ml/min, normal saline was infused at the same rate. After a
stable increase or decrease in calf blood flow was obtained
during drug administration, venous volume and flow
velocity were determined.

3. In 20 subjects, controls were determined with 34° C
water in the plethysmograph. The water was changed to 42°
C and measurements repeated at 10 and 25 minutes. The
water was then changed to 10° C and the studies repeated at
10 and 25 minutes.

4. In ten subjects, after controls were determined, 10,000
units of heparin were given intravenously. Calf blood flow,
venous volume, and venous flow velocity were obtained at
30, 60, and 90 minutes.

5. In six subjects, flow and volume parameters were deter-
mined 5 and 20 minutes after the intravenous administra-
tion of 7.5 mg of nitroprusside. In eight fasting subjects, venous
flow velocities were measured 30, 60, and 90 minutes after 12 mg of
nitroprusside were ad-
ministered orally. No plethysmograph was used in these
eight experiments and the lower extremity was not elevated
above heart level.

Statistical analyses were performed using the Wilcoxon
signed ranks test. Mainland discusses the advantages of
signed ranks test compared to other statistical methods,
depending upon Gaussian distribution. 19

Results

Local Intravenous Epinephrine

In ten experiments, epinephrine infused into the
saphenous vein decreased venous volume and in-
creased venous flow velocity \((P < 0.01)\) while calf
blood flow did not change significantly (table 1).
Postinfusion measurements obtained 15 minutes later
demonstrated an increase in venous volume \((4.0 to 4.5
ml, P < 0.01)\) and slowing of venous flow velocity
\((27.5 to 12.4 \text{ cm/sec}, P < 0.05)\). No significant
changes occurred in pulse rate or mean blood pressure
during these experiments. Histamine, bradykinin, and
sodium nitroprusside were infused into the saphenous
vein of two subjects each but no changes in venous
volume occurred. Therefore, we were not able to
determine the effect of dilating the veins on venous
flow velocity.

Intra-arterial Isoprotenerol or Angiotensin

In 11 subjects, intra-arterial isoprotenerol increased
calf blood flow \((P < 0.01)\) but did not significantly
affect venous volume or venous flow velocity (table 1).
No significant change occurred in mean blood
pressure while pulse rate showed a small increase
\((P < 0.05)\). In ten subjects, intra-arterial angiotensin
decreased calf blood flow \((P < 0.01)\) but did not
significantly affect venous volume or venous flow

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The Effect of Intravenous Epinephrine and Intra-arterial Isoproterenol and Angiotensin on Flow Parameters (Means ± sd)

<table>
<thead>
<tr>
<th></th>
<th>Calf flow (ml/100 ml/min)</th>
<th>Venous volume (ml/100 ml)</th>
<th>Venous velocity (cm/sec)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Pulse rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.1 ± 1.0</td>
<td>4.6 ± 0.8</td>
<td>9.8 ± 3.4</td>
<td>82 ± 6</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>3.0 ± 1.1</td>
<td>4.0 ± 0.7*</td>
<td>27.5 ± 11.8*</td>
<td>82 ± 5</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Control</td>
<td>2.8 ± 0.7</td>
<td>4.4 ± 0.9</td>
<td>20.7 ± 18.5</td>
<td>77 ± 8</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>4.5 ± 1.0*</td>
<td>4.3 ± 0.9</td>
<td>21.7 ± 14.6</td>
<td>76 ± 9</td>
<td>71 ± 12*</td>
</tr>
<tr>
<td>Control</td>
<td>2.4 ± 0.7</td>
<td>4.3 ± 0.9</td>
<td>15.1 ± 4.8</td>
<td>80 ± 8</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>1.3 ± 0.5*</td>
<td>4.4 ± 1.0</td>
<td>13.0 ± 5.6</td>
<td>81 ± 10</td>
<td>67 ± 10</td>
</tr>
</tbody>
</table>

*P ≤ 0.05.

velocity. No changes occurred in mean blood pressure or pulse rate.

Local Temperature

Table 2 shows the effects of changes in local temperature on calf blood flow, venous volume, and venous flow velocity for the 20 experiments. When the water temperature in the plethysmograph was changed from 34 to 42° C, calf blood flow and venous flow velocity increased significantly (P<0.01) but there was no change in venous volume. On changing the local temperature to 10° C, calf blood flow, venous volume, and venous flow velocity significantly decreased (P<0.01). The only significant change in blood pressure or pulse rate in these experiments was a small decrease in pulse rate (P<0.05) when the water temperature was changed from 42 to 10° C.

Heparin

In ten normal subjects, no significant changes were found in venous flow velocity at 30, 60, and 90 minutes following 10,000 units of intravenous heparin (table 2). Calf blood flow did not change but a small significant increase in venous volume (P<0.05) occurred at the 90 minute determination. No significant changes occurred in pulse rate or mean blood pressure in these experiments.

Nylidrin

In six subjects, intravenous nylidrin increased calf blood flow, decreased venous volume, and increased venous flow velocity (all P<0.05) at both the 5 and 20 minute determinations compared to the control measurements (table 3). An increase in pulse rate (P=0.05) occurred in these experiments but the decrease in blood pressure was not significant. In the eight subjects whose legs were not elevated in a plethysmograph, oral administration of nylidrin did not significantly increase venous flow velocity although the mean blood pressure was significantly decreased at the 30 minute and 60 minute (P=0.01) intervals.

Discussion

In this study, we attempted to separate the effects of venous and arterial hemodynamics on venous flow axial velocity. We expected that an increase or decrease in arterial blood flow would induce corresponding changes in venous flow velocity while an increase or decrease in the cross-sectional area of veins would slow or increase venous velocity, respectively. Since the hormones were infused into the saphenous vein, only the larger veins and not the postcapillary venules were affected. Venous flow would be directed

Table 2

The Effect of Local Heat, Cold, and Heparin on Flow Parameters (Means ± sd)

<table>
<thead>
<tr>
<th></th>
<th>Calf flow (ml/100 ml/min)</th>
<th>Venous volume (ml/100 ml)</th>
<th>Venous velocity (cm/sec)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Pulse rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34° C</td>
<td>3.9 ± 1.7</td>
<td>4.8 ± 1.1</td>
<td>13.5 ± 11.9</td>
<td>80 ± 6</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>42° C</td>
<td>7.7* ± 2.5</td>
<td>4.7 ± 1.1</td>
<td>16.3* ± 5.9</td>
<td>80 ± 6</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>10° C</td>
<td>2.2* ± 0.8</td>
<td>3.8* ± 0.8</td>
<td>8.2* ± 4.1</td>
<td>81 ± 6</td>
<td>74* ± 8</td>
</tr>
<tr>
<td>Control</td>
<td>2.4 ± 0.9</td>
<td>4.2 ± 0.9</td>
<td>14.4 ± 3.9</td>
<td>77 ± 6</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>Heparin 30 min</td>
<td>2.4 ± 1.0</td>
<td>4.3 ± 0.9</td>
<td>12.1 ± 2.6</td>
<td>79 ± 6</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>Heparin 60 min</td>
<td>2.4 ± 0.7</td>
<td>4.3 ± 0.9</td>
<td>13.4 ± 2.1</td>
<td>80 ± 9</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>Heparin 90 min</td>
<td>2.3 ± 0.7</td>
<td>4.4* ± 0.9</td>
<td>12.1 ± 2.8</td>
<td>80 ± 8</td>
<td>68 ± 7</td>
</tr>
</tbody>
</table>

*P ≤ 0.05.
Table 3

The Effect of Intravenous and Oral Nylidrin on Flow Parameters (Means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Calf flow (ml/100 ml/min)</th>
<th>Venous volume (ml/100 ml)</th>
<th>Venous velocity (cm/sec)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Pulse rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.8 ± 0.9</td>
<td>4.1 ± 0.8</td>
<td>5.4 ± 1.9</td>
<td>85 ± 14</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>I.v. nylidrin (5 min)</td>
<td>5.1 ± 1.9*</td>
<td>3.6 ± 0.7*</td>
<td>11.6 ± 4.3*</td>
<td>78 ± 17</td>
<td>102 ± 18*</td>
</tr>
<tr>
<td>I.v. nylidrin (20 min)</td>
<td>5.6 ± 1.9*</td>
<td>3.8 ± 0.7*</td>
<td>8.9 ± 2.6*</td>
<td>81 ± 15</td>
<td>89 ± 13*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral nylidrin (30 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral nylidrin (60 min)</td>
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<td></td>
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<tr>
<td>Oral nylidrin (90 min)</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*P < 0.05.

from superficial to deep veins, for the water level in the plethysmograph was above venous pressure in the elevated limb. These facts are important because the volume of the postcapillary venules is very large and the superficial veins of the limbs are reported to be more reactive than the deep veins. More dramatic results may have been obtained if these areas had been affected.

Epinephrine was used to constrict the veins and was found to significantly increase venous flow velocity; arterial blood flow was not affected. No change in venous volume was found with histamine; previous investigators have reported that venous volume was decreased or unaffected. We failed to dilate the veins without a change in arterial blood flow, using substances reported to be venodilators, perhaps because the venules were unaffected or more likely because veins have little resting tone. The absence of basal tone would also explain the failure of local heat to change venous volume. An increase or decrease in arterial blood flow by isoproterenol and angiotensin respectively with no changes in venous volume did not affect venous flow velocity. However an increase in arterial flow during local heat application was accompanied by an increase in venous flow velocity while venous volume remained the same. The decrease in arterial flow with local cooling was accompanied by a slower venous flow velocity despite a significant decrease in venous volume. Since heat and cold did affect venous flow velocity in the direction expected from the change in arterial flow, it may be that the flow changes caused by isoproterenol and angiotensin were not great enough to affect venous flow velocity. Larger doses of these hormones could not be used without causing systemic hemodynamic effects which induce reflex changes in the peripheral circulation. These experiments do demonstrate that venoconstriction increases venous flow velocity and that large changes in arterial flow will produce parallel effects in venous flow velocity.

The significant increases in venous flow velocity which occurred with local heat indicate that there is a basis for applying heat in the prevention and treatment of venous thrombosis. This conclusion presupposes that venous stasis is a major factor in the formation or extension of venous thrombosis, and that the data obtained in normal young people can be extrapolated to the patient population. Since local cold significantly decreased venous flow velocity, its use would be contraindicated. In the hepatic experiments, venous flow velocity was not affected; the mode of action of heparin is probably only through its anticoagulant effect. We also failed to find an effect of heparin on arterial blood flow, although a small but significant increase in venous volume occurred 90 minutes after heparin administration. In a previous study, only small changes in calf blood flow and venous volume occurred over a 90 to 120 minute period following placebo ingestion. No previous studies are available concerning heparin and venous volume. Although Abrahams and Howarth reported that heparin increased forearm blood flow, Burt and Lambert found no effect of intravenous heparin on hand or forearm blood flow.

In an attempt to find a means to maximally increase venous flow velocity, we studied nylidrin which is chemically related to epinephrine. We had previously shown that nylidrin increases arterial blood flow while decreasing venous volume; both actions would increase venous flow velocity. With intravenous nylidrin, a significant increase in venous flow velocity was found with the expected increase in arterial blood flow and decrease in venous volume. With oral administration of nylidrin, we attempted to duplicate the clinical setting of patients predisposed to venous thrombosis by not elevating the limbs above heart level; arterial flow and venous volume were therefore not measured. In this situation, no change in venous flow velocity was obtained. The significant decrease in blood pressure probably indicates that the oral drug was acting systemically. In the nonelevated limb, it may be that the flow velocity was slowed in the

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caused by the rise in postcapillary resistance caused by the venoconstriction.

In summary, venous flow velocity can be significantly increased by venoconstriction, by large increases in arterial blood flow, such as occur with local heating, and by parenteral nylidrin administration with elevated limbs. Since intensive postoperative care including elastic support, limb elevation, and physical therapy does not prevent venous thrombosis measured by the 125I fibrinogen tagging method, a trial of local heating of the limbs would appear valuable. As with minidose heparin, the local heat should be instituted preoperatively or as early as possible in medical patients for an adequate study. The advantages of a simple, noninvasive, and nontoxic prophylactic method are obvious.

Acknowledgment

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