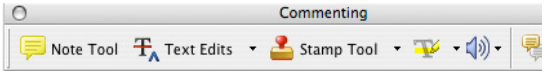
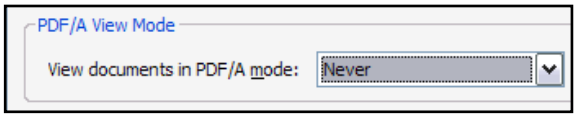
INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

To view, print and annotate your article you will need Adobe Reader version 9 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from http://get.adobe.com/reader/. The exact system requirements are given at the Adobe site: http://www.adobe.com/products/reader/tech-specs.html.

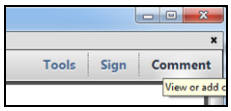
Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file.

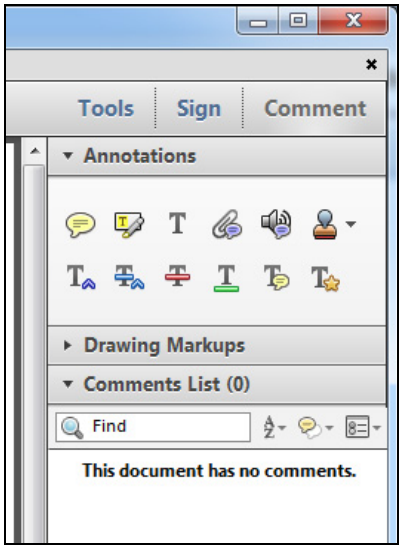
<table>
<tr><th colspan="2">PDF ANNOTATIONS</th></tr>
<tr><th>Adobe Reader version 9</th><th>Adobe Reader version X and XI</th></tr>
<tr><td>When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on ‘Tools’, select ‘Comment & Markup’, then click on ‘Show Comment & Markup tool bar’ (or ‘Show Commenting bar’ on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.
 

(Mac)
PDF ANNOTATIONS (Adobe Reader version 9)

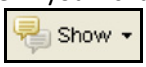
The default for the Commenting tool bar is set to ‘off’ in version 9. To change this setting select ‘Edit | Preferences’, then ‘Documents’ (at left under ‘Categories’), then select the option ‘Never’ for ‘PDF/A View Mode’.
 

(Changing the default setting, Adobe version 9)</td><td>To make annotations in the PDF file, open the PDF file using Adobe Reader XI, click on ‘Comment’.

If this option is not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than XI or the PDF has not been prepared properly.
 

This opens a task pane and, below that, a list of all Comments in the text. These comments initially show all the changes made by our copyeditor to your file.
 
</td></tr>
</table>

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Insert text	Click the 'Text Edits' button  on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon  on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_'  in the top right-hand corner.
Replace text	Click the 'Text Edits' button  on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).	Click the 'Replace (Ins)' icon  on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).
Remove text	Click the 'Text Edits' button  on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon  on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
Highlight text/ make a comment	Click on the 'Highlight' button  on the Commenting tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.	Click on the 'Highlight Text' icon  on the Comment tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.
Attach a file	Click on the 'Attach a File' button  on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.	Click on the 'Attach File' icon  on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.
Leave a note/ comment	Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
Undo/delete change	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.

SEND YOUR ANNOTATED PDF FILE BACK TO ELSEVIER

Save the annotations to your file and return as instructed by Elsevier. Before returning, please ensure you have answered any questions raised on the Query Form and that you have inserted all corrections: later inclusion of any subsequent corrections cannot be guaranteed.

FURTHER POINTS

- Any (grey) halftones (photographs, micrographs, etc.) are best viewed on screen, for which they are optimized, and your local printer may not be able to output the greys correctly.
- If the PDF files contain colour images, and if you do have a local colour printer available, then it will be likely that you will not be able to correctly reproduce the colours on it, as local variations can occur.
- If you print the PDF file attached, and notice some 'non-standard' output, please check if the problem is also present on screen. If the correct printer driver for your printer is not installed on your PC, the printed output will be distorted.

Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

Hemodynamics of 'critical' venous stenosis and stent treatment

Q4 Seshadri Raju, MD, Orla Kirk, BS, Micah Davis, BS, and Jake Olivier, PhD, *Jackson, Miss*

Background: **The concept of 'critical' stenosis at which there is a sharp reduction in forward flow is derived from arterial disease. The critical element in venous stenoses is upstream pressure, not downstream flow. Many venous symptoms and microvascular injury are related to venous hypertension. We studied the effect of venous stenosis on upstream pressure using a mechanical model and with clinical measurements after stenting of iliac vein segments (common and external).**
Methods: **The experimental model consisted of a 'Starling resistor' – Penrose tubing enclosed in a pressurized plastic chamber to simulate abdominal venous flow. Clinical measurements included time averaged velocity, area, rate of flow, and quantified phasic flow volume in the common femoral vein before and after iliac vein stenting. Traditional air plethysmography and occlusion plethysmography were also performed.**
Results: **The mechanical model showed that upstream pressure varied based on (1) volume of venous inflow, (2) abdominal pressure, (3) outflow pressure, and (4) outflow stenosis. Upstream pressure changes were inverse to flow as kinetic energy was converted to pressure as required. A venous stenosis of as little as 10% raised upstream pressure in the model when the abdominal pressure was low, but high grades of stenosis had no contribution when abdominal pressure was high. Stenting of the Penrose moderated or nullified upstream pressure changes related to abdominal pressure. There was significant decompression of the common femoral vein, implying pressure reduction after stenting; median area reduction was 15% and 10% in erect and supine, respectively. Air plethysmography showed improvement in venous volume and in other parameters in confirmation of venous decompression. There was significant prolongation of phasic flow duration and quantitative phasic flow increased (median, 16%) after stenting in the erect position. There was no increase in arterial inflow.**
Conclusion: **The criticality of iliac vein stenosis is based on peripheral venous hypertension, which is controlled by more confounding factors than in arterial stenosis. The experimental model clarifies the interplay of the many variables. Clinical measurements indicate that iliac vein stenting results in decompression of the limb veins and, by inference, a reduction in venous pressure. Venous flow is improved less consistently and, in part, is related to an increase in duration of phasic flow. Limb arterial flow is not increased, and the venous flow changes are likely the result of rearrangement of the velocity and pressure components of venous flow. (J Vasc Surg: Venous and Lym Dis 2013;■:1-8.)**

The concept of 'critical' stenosis is derived from arterial work. It is the particular degree of stenosis when there is a sharp drop in pressure and flow curves in the stenotic segment and in the perfusion downstream. Since flow and pressure are tightly interconnected, 'critical' stenosis varies with flow but is generally in the 60% to 80% range for many clinical arterial stenoses. However, these values cannot be extrapolated to venous stenosis because numerous governing factors such as collapsibility, velocity/pressure profiles, and pulsatility are different and Reynold's number is lower. Most importantly, the critical element relevant to venous symptoms is elevation of upstream pressure, not deprivation of downstream flow. Venous edema is related to elevated pressure. Microvascular damage, which underlies chronic venous disease, is now known to be triggered or sustained by venous hypertension.[1-5] In addition, lower limb venous outflow is susceptible to external compression ('Starling Resistor') as it transits through the abdomen. The purpose of this article is to clarify the many variables that determine 'criticality' of iliac vein stenoses using a mechanical venous model. We also analyzed clinical measurements in patients undergoing iliac vein stenting to confirm that pressure related parameters improve after stenting as suggested by model results.

METHODS

The basic model described by Starling[6] and later Holt[7] (Fig 1A, B) consisted of a 'venous conduit' of 10-inch-long Penrose drain (1/2 inch inside diameter [ID], similar in size to the iliac vein) positioned horizontally between short large bore (1/2 inch ID) rigid connectors (to minimize end effects) and enclosed within an airtight transparent rigid PVC cylinder capped by rubber stoppers on either end. Pressurization ('Starling pressure') to the cylinder was provided by water fed by gravity from a reservoir. Inflow to the Penrose was also from a gravity-fed reservoir constantly replenished to maintain a constant level and pressure head. Water, a Newtonian fluid (viscoscity independent of shear rate), was the flow medium; Blood, a particulate suspension that exhibits anomalous viscous properties in certain flow regimens, nevertheless behaves like a Newtonian fluid in large conduit flows,[8-10] meaning that model results will qualitatively reflect biologic flow. Volumetric flow at constant input pressure from the reservoir into the

From The Rane Center.
Q1 Author conflict of interest: Dr Raju owns stock in Veniti.
Reprint requests: Dr Seshadri Raju, The Rane Center, 971 Lakeland Dr., East Tower, Ste. 401, Jackson, MS 39216 (e-mail: rajumd@earthlink.net).
The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
2213-333X/$36.00

http://dx.doi.org/10.1016/j.jvsv.2013.01.005

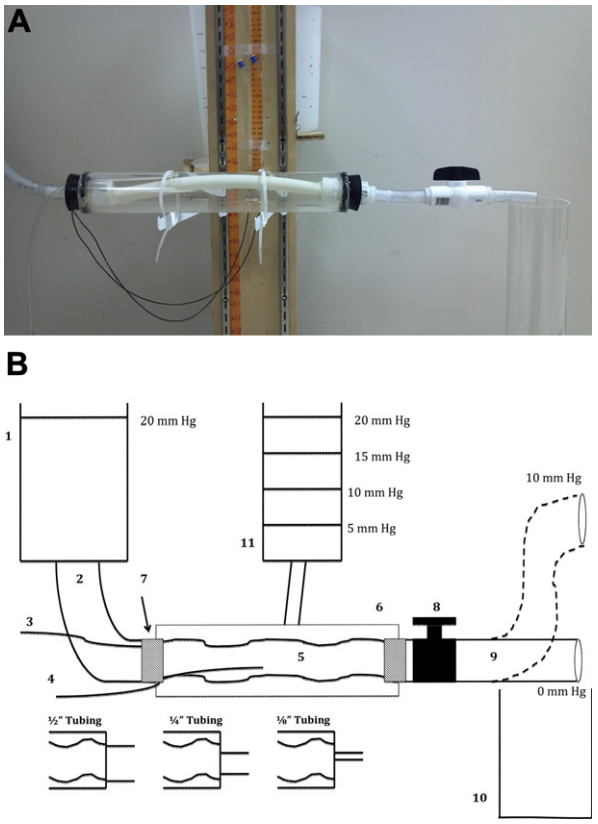


Fig 1. Mechanical venous model. **(A)** Shows the Penrose enclosed within a Plexiglas cylinder. Various parts are shown in the schematic **(B)**, 1. Inflow reservoir, 2. Inflow tubing, 3. Upstream pressure monitoring catheter, 4. Penrose pressure-monitoring catheter, 5. Penrose tubing, 6. Plexiglas cylinder, 7. Short connector in between Penrose and tubing, 8. Ball valve used to simulate outflow stenosis, 9. Outflow tubing; level of outflow orifice could be varied; 0 mm Hg and 10 mm Hg are shown; outflow tubing size varied from 1/2 inch to 1/8 inch (shown at the bottom) to simulate outflow stenosis, 10. Outflow tank, 11. Pressurizing reservoir for the Starling resistor.

Penrose setup ('Starling resistor') could be varied by using rigid plastic tubing of variable known diameters connecting them. Though static pressure at the Penrose when flow is stopped will be the same (reservoir input pressure) for all tubing sizes, smaller tubing will carry smaller flows with lower pressures (Poiseulle equation) into the Penrose, simulating vasoconstriction. The outflow tubing emptied above the water level (no siphon effect) into an effluent tank. Outflow 'stenosis' could be simulated by using smaller outflow tubing. Rate of flow through the conduit was manually measured outflow into the graduated effluent tank. Lateral pressures within the Penrose (Penrose pressure) and immediately upstream (upstream pressure) were measured by water manometers through appropriately positioned catheters inserted through small side holes in the rigid end connectors. The heights of the input reservoir, the pressurizing reservoir, and the end orifice of the outflow tube were each adjusted relative to the Penrose to provide the range of pressures tested. Pressures are shown as mm Hg using standard conversion from water pressure in cm. They approximate known physiological ranges (resting, vasoconstriction, hyperemia) in lower limb venous flow. Resting lower limb flow approximates ≈1000 mL/minute, often increasing up to four times with peripheral vasodilatation and decreasing by 80% with vasoconstriction.[9] Peripheral supine venous pressure is in the 10 to 12 mm range.[8] Capillary pressure at the venular end is estimated to be 15 to 20 mm Hg.[11]

In some experiments, a high precision adjustable ball valve, graduated by timed volumetric flows to simulate varying degrees of 'stenosis,' was mounted between the Starling resistor and the outflow tube.

In a final set of experiments, 14 mm diameter Wallstents (Boston Scientific, Natick, MA) were inserted into the Penrose to cover 1/3 and 2/3 of its length from the inflow connector or its entire length to assess their effect on upstream pressure.

Each 'run' was repeated two or more times, and the results were averaged. Variance within each run set was <1%.

Patients and clinical measurements. Preoperative and postoperative duplex measurements were extracted from clinical records of patients who underwent iliac vein stenting in the last 2 years (11 years for air plethysmography [APG; ACI Medical, Los Angeles, CA]) for relief of obstruction. All patients in whom both preoperative and postoperative data sets were available were included. Ninety-six of 230 and 551 of 1980 stented limbs were available for analysis of duplex and air plethysmography data, respectively. The ratio of non-thrombotic to post-thrombotic limbs in the data set was 1:3.

Flow data was obtained with a duplex scanner (Logiq9, GE Medical Systems, Waukesha, WI). Time averaged flow velocity (TAV), vessel diameter, and duration of forward flow during the respiratory cycle (T) were recorded in the supine and erect positions in the common femoral vein 1 cm above the sapheno-femoral junction before and after stenting; this site is at least 1 to 3 cm below the lower end of the stent. Calculated parameters from the above basic data included area of the vessel ($A = \pi r^2$), volumetric rate of flow ($Q = A^*TAV$), and absolute phasic flow volume (Q^*T) in the common femoral vein that egressed out during each respiratory cycle (Fig 2).

APG. Standard parameters including venous volume (VV), ejection volume, ejection fraction, residual volume, and residual volume fraction were measured. The APG instrument was also used to obtain the following parameters with occlusion plethysmography[12]: (1) The rate of arterial inflow calculated from the slope of the initial steep segment of the volumetric curve; (2) duration of arterial inflow curve to plateau; and (3) outflow fraction (OF) at 1 and 2 seconds. All are supine measurements.

All postoperative measurements were made at least 6 weeks after the procedure to mitigate any related short-term perturbation such as hematoma, limb edema, and cardiovascular effects of perioperative medications.

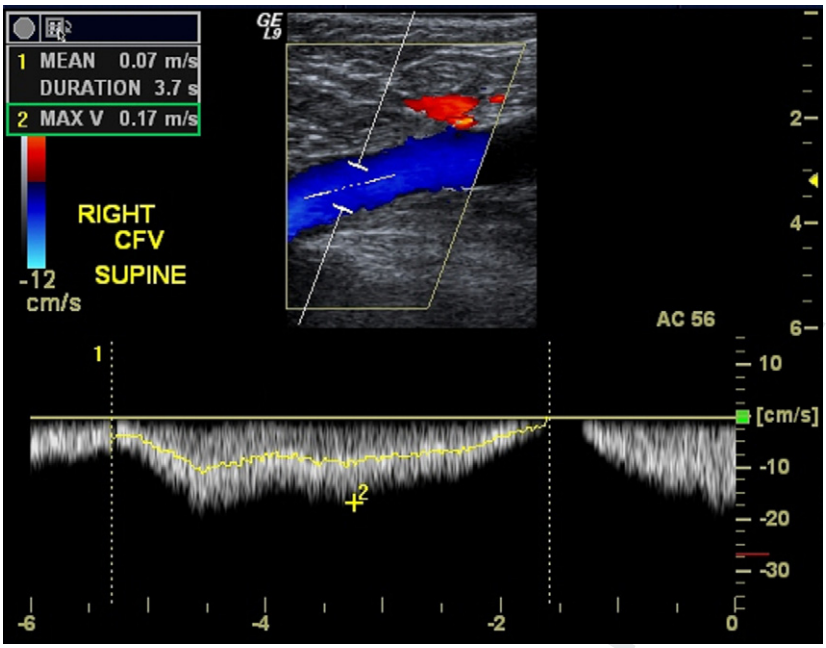


Fig 2. Color flow with phasic waveform in the common femoral vein (CVF). Phase duration is marked by technologist. Time average velocity is machine-calculated based on phase duration.

Statistics. Individual data are given as median with range, unless otherwise indicated. Paired values were analyzed by nonparametric, two-tailed Wilcoxon rank test. Statistical significance was defined as a *P* value less than .05. All analysis was performed using Prism software (Irvine, CA). Graphics were generated using Prism software and Microsoft Excel (Redmond, WA).

RESULTS

Mechanical venous model. Upstream pressure was found to be related to (1) volume of inflow, and for any given inflow, (2) Starling pressure, (3) outflow pressure, and (4) outflow stenosis. This is illustrated in experiments where only the tested variable changed with others set at zero or basal settings. Upstream pressure is defined (and named) as the pressure at the Penrose inlet and would broadly reflect peripheral venous pressure; pressure gradient in the limb venous flow is estimated to be very small (<5 mm Hg).[8,13] In the experimental setup, the pressure head at the inflow tank (20 mm Hg) simulates the pressure at the venular end of the capillary. This pressure never can exceed 20 mm Hg in the setup and in the quiescent resting limb as no new energy is added. In vivo, calf, and foot muscle pumps can impart additional motive energy (and pressure).

Inflow volume. Upstream pressures are shown for a range of volumetric inflows (Fig 3). Upstream pressure increases non-linearly with inflow volume represented in the figure by cross-sectional area of inflow tubing.

Outflow pressure. Upstream pressures are shown for a range of outflow pressures (Fig 4). It is a gentle curve. The inflow/outflow pressure gradient remains roughly constant. Flow volume decreases as upstream pressure increases due to conversion of part of the flow velocity to pressure energy.

Starling pressure. Upstream pressures are shown for a range of Starling pressures (Fig 5). Upstream pressure increases in a linear fashion as the flow decreases in a curvilinear fashion elevating the upstream pressure. As a result, the transmural pressure (upstream pressure - Starling pressure) remains at a near constant level.

Outflow stenosis. Upstream pressures are shown for a range of outflow stenoses (Fig 6). Outflow tubing size of 1/2 inch ID represented 0% stenosis as inflow tubing was also the same size. Ten percent to 30% stenoses (volumetric) values were obtained with the ball valve setup at the outflow end. For 45% to 95% stenosis, outflow tubing varying from 3/8 inch to 1/8 inch ID provided calculated area stenosis. Since diameter/flow relationship is non-linear, the two stenosis scales are different, but yielded empirically stepwise reduction in flows.

Combinations. Upstream pressures are shown for various combinations of Starling pressure, outflow pressure and outflow stenosis (Table I). 'Reference pressure' is upstream pressure and is derived data in Figures 3 to 6, where individual components of the various combinations were tested against zero setting for other components of the various combinations. It can be seen that the upstream pressure is largely influenced by the highest reference pressure in the combination mix (ie, upstream pressure is not additive but reflects the value of that single component with the highest reference pressure).

Effect of stenting. The effect of stenting on the influence of Starling pressure on upstream pressure is shown

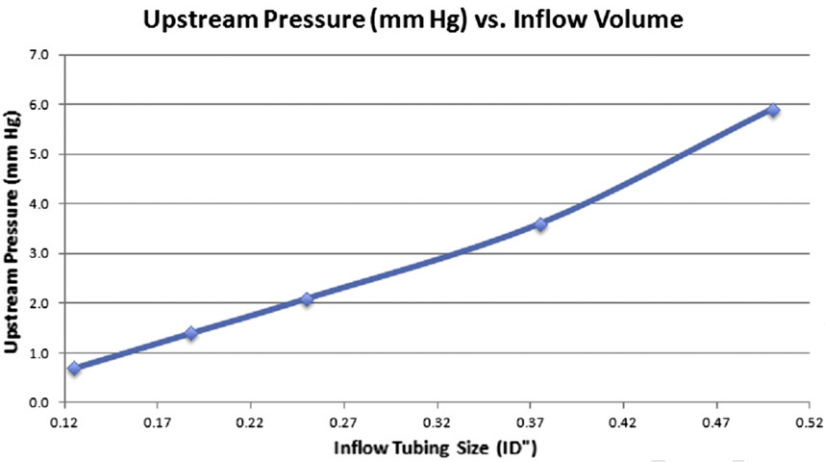


Fig 3. Relationship between upstream pressure and inflow volume. In this graph, volume is indicated by inflow tubing size (X axis). *ID,* Inside diameter.

(Fig 7). Partial stenting of 1/3 length of the Penrose had no effect; stenting 2/3 length prevented upstream pressure rise with Starling pressure rise of up to 10 mm Hg, and stenting the full length of the Penrose was protective up to 20 mm Hg Starling pressures. Full length stenting in effect converts the collapsible Penrose into a rigid tube, rendering it immune to Starling pressure effects on upstream pressure.

There were no experiments to correct outflow stenosis with stents because of the nature of mechanical simulation of outflow stenosis. The effect of stent correction of outflow stenosis can be assumed to yield pressure values similar to zero stenosis in Figure 6.

Clinical studies

Duplex measurements. Common femoral vein flows are shown before and after iliac vein stenting in the supine and erect positions (Table II). The most striking change is in reduction in common femoral vein area (decompression), of median 15% and 10% in erect and supine, respectively, after stenting. Median velocities (TAV) increased significantly as a result, by 25% in erect and 37% in supine position. Rate of flow/sec is unchanged ($P =$ NS) after stenting in either position. However, duration of phasic flow (T) and phasic flow volume increased significantly by median 18% and 16%, respectively, after stenting in the erect position. T and phasic flow volume showed a trend towards increase (median, 11% and 14%, respectively) in the supine position after stenting, which did not reach statistical significance in the sample size.

Veno-arteriolar reflux. There are significant (Table I footnote) decreases in flow parameters on changing the position from supine to erect. Preoperatively, duration of phasic flow (T), rate of flow, and phasic flow volume declined on postural change by median 28%, 37%, and 52%, respectively, all of which were significant decreases.

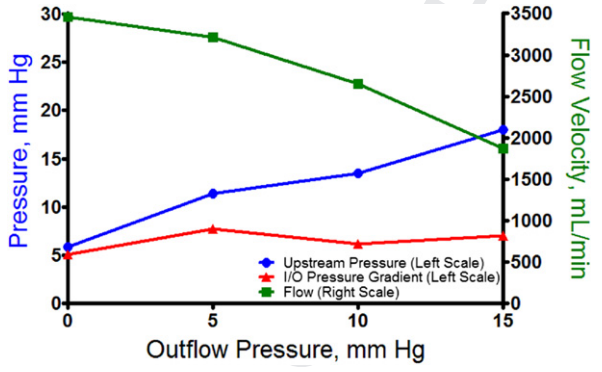


Fig 4. Relationship between outflow pressure (X axis), upstream pressure with I/O pressure gradient (left Y axis), and flow velocity (right Y axis). Upstream pressure increases with increasing outflow pressure, and flow declines. I/O pressure gradient remains nearly the same. *I/O,* Inflow/outflow pressure.

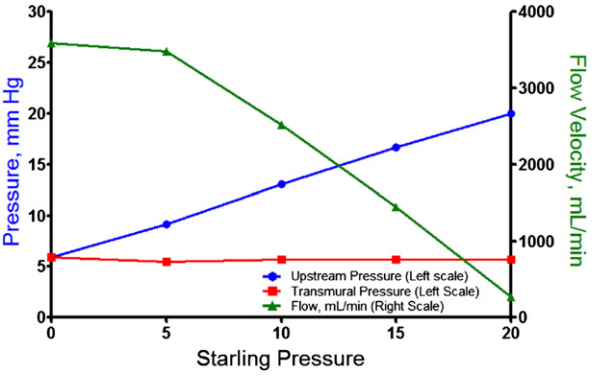


Fig 5. Relationship between Starling pressure (X axis), upstream pressure with transmural pressure (left Y axis), and flow velocity (right Y axis). With increasing Starling pressure, upstream pressure increases in a linear fashion, as flow declines in a curvilinear fashion. Transmural pressure remains constant.

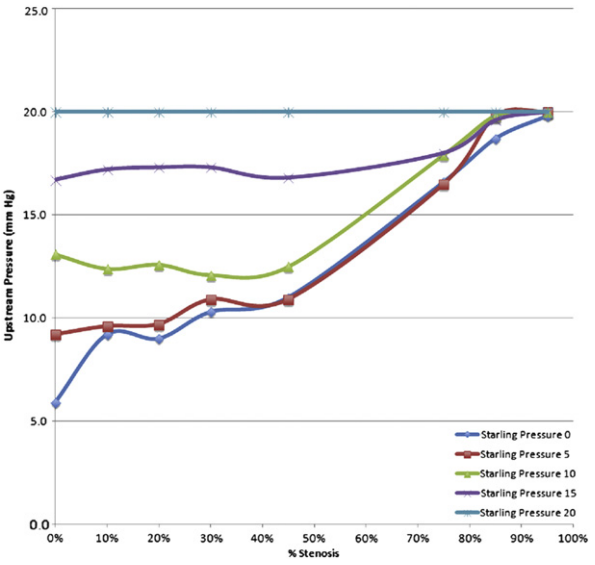


Fig 6. Relationship between outflow stenosis and upstream pressure for a variety of Starling pressures. Note sharp increase in upstream pressure with as little as 10% stenosis when Starling pressure is 0 mm Hg. Outflow stenoses of ≥42% show progressive increase in upstream pressure when Starling pressure is 1to 10 mm Hg. When Starling pressures are ≥15 mm Hg, the upstream pressure curve is flat (ie, increasing the degree of stenosis has little effect on the already high upstream pressure [see text]).

Post-stent, these postural declines were similar, and there was no improvement in veno-arteriolar reflux (P = NS).

APG. APG parameters are given before and after stenting showing improvement in all of the displayed parameters (Table III).

Occlusion plethysmography. Occlusion plethysmographic data was obtained in the supine position (Table IV). There is no change in arterial flow parameters after venous stenting. Volumetric outflow fractions also did not change.

DISCUSSION

Pressure, specifically upstream pressure, is the critical element in venous stenoses. Flow may be related to venous claudication but is not critical and seldom leads to tissue loss.

Upstream pressure is influenced by (1) outflow stenosis, (2) volume of inflow, (3) Starling pressure, and (4) atrial pressures. Clinical analogues resulting in limb edema from the last three biomechanical factors in whole or part are high cardiac output states such as septicemia or arteriovenous fistula, venous edema from increased abdominal pressure in morbid obesity, and edema of congestive heart failure respectively. When there is a combination of these factors, the model results suggest that the highest contributing factor (not an additive combination) sets the upstream pressure. Of the four factors, stenosis, specifically iliac vein stenosis, is important as it appears to be a ubiquitous lesion.[14,15] Significant stenosis (≥50%) is present in one-third, and lesser degrees of stenosis in an additional third of the general population in silent form. Therefore, a diagnostic search is worthwhile even if one of the other three causative factors is clinically apparent. This approach has yielded clinical relief in selected symptomatic patients.[16]

What degree of stenosis should be considered critical? In Figure 6, there is a sharp rise in upstream pressure with as little as 10% stenosis when Starling pressure is at 0 mm Hg and at 45% stenosis when Starling pressure is 10 mm Hg. At higher Starling pressures, increasing stenosis has little effect on upstream pressure as the former sets the pressure. While these quantitative stenotic thresholds cannot be precisely extrapolated to clinical practice, this means there is no single 'critical stenosis,' and all of the factors contributing to venous hypertension have to be considered. Of these, only the intra-abdominal pressure/stenosis combination was adequately studied in the model.[11]

'Normal' intra-abdominal pressure averages about 6.5 mm Hg,[11] with a wide range from <1 mm Hg to 16 mm Hg with a positive correlation to body mass.[17] Lesser degrees of stenosis may be symptomatic in patients with low intra-abdominal pressure than in patients with higher pressures. Intra-abdominal pressure can be clinically monitored via bladder pressure.[17] Elevated intra-abdominal pressure in obese patients has been implicated in chronic venous disease.[18] Most obese patients with advanced venous disease harbor iliac vein stenosis, but increased abdominal pressure alone may be the main factor in a small fraction.[18,19] Though the model suggests that

Table I. Upstream pressure for various combinations of setup pressures

Setup Pressure Combinations				*Reference Pressure*		
Inflow (mm Hg)	*Starling (mm Hg)*	*Stenosis (%)*	*Upstream Pressure (mm Hg)*	*Inflow (mm Hg)*	*Starling (mm Hg)*	*Stenosis (%)*
20	15	0	**16.7**	5.9	**16.7**	5.9
20	15	95	**20.0**	5.9	16.7	**19.8**
20	10	0	**13.1**	5.9	**13.1**	5.9
20	20	30	**20.0**	5.9	**20.0**	10.3
20	5	79	**16.5**	5.9	9.2	**16.6**
20	5	42	**10.9**	5.9	9.2	**11.0**
20	10	10	**12.4**	5.9	**13.1**	9.2
20	15	89	**19.6**	5.9	16.7	**18.7**

Reference pressure is for particular setup parameter when others are zero. Upstream pressure approximates highest reference pressure (bold).

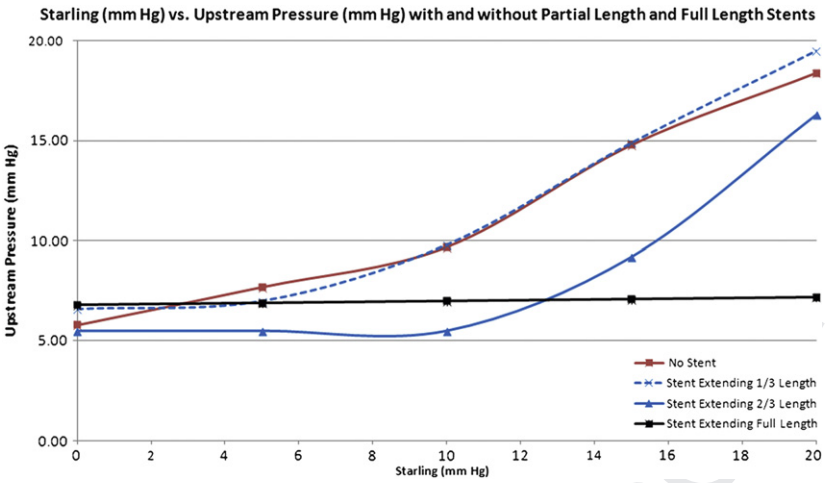


Fig 7. The effect of stenting the Penrose in the Starling resistor on upstream pressure. Stenting the full length of the Penrose keeps upstream pressure low and nearly constant, despite increasing Starling pressures. Stenting 2/3 of the length of the Penrose is effective for Starling pressure ≤ 10 mm Hg. Stenting only 1/3 of the length of the penrose has little pressure-shielding effect.

stenting may be helpful even in the latter subset, the extent of stenting required is unclear as there is no provision for differential wall thickness of vena cava (thicker) and iliac veins (thinner) in the model design.

In postthrombtic and non-thrombotic limbs with symptoms, the stenosis itself is likely the dominant factor in peripheral venous hypertension. Three-quarters of limbs in the data set were postthrombotic. In our clinical practice, symptomatic iliac vein stenoses in these subsets have averaged ≥50% on intravascular ultrasound,[20] though stenting lesser degrees of stenoses have led to clinical relief occasionally.

The various flow/pressure relationships are best understood from flow energetics. Peripheral venous flow energy (E) is the sum of pressure (P) and velocity components (v) according to Bernoulli theorem: $E = P + 1/2\ pv^2$. The gravity component need not be considered in the supine subject. Since velocity is near zero at the venular end of the capillary, all of the energy is represented by pressure estimated to be 15 to 20 mm Hg. Depending upon downstream flow conditions, some portion of the pressure energy is converted to velocity. For conversion, 1 mm Hg = 1330 dynes/cm^2 (using velocity in cm per second).[8] When there is an increase in Starling pressure, outflow pressure, or stenosis, the upstream pressure increases with a slowing of the flow (ie, velocity is converted to pressure energy). The pressure will raise enough from energy conversion to overcome the highest of the three impediments to flow (no additive effect) as illustrated in Table I. There is a ceiling on how high the pressure can

Table II. Common femoral vein flow velocity data before and after stenting (erect and supine positions)

Erect Duplex: n = 96	*Erect Pre-stent*	*Erect Post-stent*	*% Change (+/−)*	P *Value*
Time averaged velocity (TAV, cm/sec)	0.04 (0.01-0.12)	0.05 (0.01-0.10)	+25	.006[a]
Diameter (mm)	13.60 (8.90-19.20)	12.55 (7.50-22.50)	−8	.0001[a]
Area (mm^2)	145.28 (62.21-289.53)	123.70 (44.18-397.61)	−15	.0001[a]
Phasic duration (T, sec)[b]	1.95 (0.19-4.10)	2.30 (0.30-5.30)	+18	.02[a]
Flow volume rate (mL/min)[b]	5.90 (1.54-16.66)	5.98 (0.65-19.88)	+1	.8
Phasic flow volume (mL)[b]	11.15 (0.92-43.30)	12.89 (0.92-53.68)	+16	.049[a]
Supine Duplex: n = 61	*Supine Pre-stent*	*Supine Post-stent*	*% Change (+/−)*	P *Value*
Time averaged velocity (TAV, cm/sec)	0.08 (0.02-0.18)	0.11 (0.05-0.25)	+38	.0009[a]
Diameter (mm)	11.90 (5.70-18.10)	11.30 (5.30-19.30)	−5	.05
Area (mm^2)	111.22 (25.52-257.30)	100.29 (22.06-292.55)	−10	.045[a]
Phasic duration (T, sec)[b]	2.70 (0.15-5.10)	3.10 (0.60-5.10)	+15	.1
Flow volume rate (mL/min)[b]	9.29 (1.79-94.77)	9.29 (2.64-35.11)	0	.1
Phasic flow volume (mL)[b]	23.17 (1.19-94.77)	26.47 (6.04-137.62)	+14	.1

[a]Significant.
[b]Values for phasic duration, flow volume rate and phasic flow volume were all significantly different ($P < .0001$) between supine and erect positions (veno-arteriolar reflux) before stenting. It remained the same after stenting.

Table III. Air plethysmography data

n = 551	*Pre-stent*	*Post-stent*	*95% Confidence Interval*	P *Value*
Ejection volume	68 (4-287)	69 (6-302)	−6.14, .1.39	.0007[a]
Venous volume	49 (1-215)	48 (0-192)	7.12, .2.21	.0001[a]
Residual volume fraction	13 (0-128)	12 (0-153)	3.00, −0.07	.0009[a]
Ejection fraction	50.7 (4-118.8)	53.4 (2-128.1)	0.96, 5.11	.0005[a]

[a]Significant.

rise in the resting limb. That ceiling is the prevailing capillary pressure, which represents all of the fluid energy available. Only vasodilatation (relaxation of precapillary sphincters) can allow for additional fluid energy in the resting limb.

There are no collaterals or heart pump in the flow model. Collaterals may moderate the described pressure changes as they function as pressure relief (surge) valves,[21] opening up only after a set pressure is exceeded. After iliac vein stenting, collaterals often dramatically 'disappear,' indicating that higher pressure had prevailed despite collateral function. The influence of abdominal pressure on collaterals is unknown. There is no heart pump in the model. It can increase or decrease central venous pressure. However, there will be opposite effects in the periphery. The model does not allow for modulation of microcirculation by precapillary sphincters (see later).

The duplex findings show that there is decompression of the common femoral vein (meaning lowered pressure) following iliac vein stenting. This is evident in the supine and erect positions. We have previously shown that supine foot venous pressure decreases after iliac vein stenting.[20] In the erect position, peripheral venous decompression will be less evident as a gravity component of about 70 to 85 mm Hg is superimposed on resting venous pressure at the calf and foot levels, respectively. Therefore, APG measures VV in the erect position at a higher point in the volume pressure curve, which is sharply non-linear (much less unit volume per unit pressure than in supine). Nevertheless, a small but significant improvement in VV was noticed (Table III). We interpret this as restoration of venous tone not only from decompression but also from improved calf function (ejection volume, ejection fraction, residual volume fraction) from unobstructed iliac vein flow. Resting venous flow rate (volume flow/minute) remains unchanged after stenting both in the supine and erect positions (ie, the same volume of flow per minute is carried through a smaller aggregate flow channel at a lower pressure but faster velocity). Outflow fractions (Table III), which are volumetric rate of flow indices in the supine position, remain unchanged in confirmation. Phasic flow volume, which takes into account duration of flow during the respiratory cycle, is increased in the erect position with possibly a trend (non-significant) in the supine position. The phasic flow increase in the erect position is related to prolongation of the flow phase (T). Assuming an 18/minute respiratory rate, the respiratory flow phase is about 2 seconds flow, with 1 second cessation in the erect position before stenting (Table II). In the supine position, inspiratory flow occurs much longer (2.7 seconds) with a very brief cessation of only ≈0.3 seconds, which is one-third of the erect value. T increases significantly in erect but not supine position after iliac vein stenting. Nevertheless, the ratio of erect to supine flow parameters (Arteriolar-venous reflux) remained unchanged after venous stenting. This, however, relates only to postural velocity changes. Postural change in pressure component of flow was not measured and is not measurable because it is obscured by the gravity component in the erect position.

The question arises if iliac vein stenting increases arterial inflow. There is no increase in the supine arterial inflow measured by occlusion plethysmography (Table IV) after stenting. Erect measurements were not taken. For reasons mentioned below, it seems likely that increment in venous phasic flow volume is due to rearrangement of pressure and flow components (and possibly recruitment of prior collateral flow) rather than a true increase in arterial inflow.

The arterial flow (hence, pressure) to the post-capillary venules is primarily set by the precapillary sphincters in response to local tissue metabolism.[11] There is a view that the arterial and venous circulations are separated by a "vascular waterfall" at the capillary level.[22,23] Like in a waterfall, the river level at the bottom will have little influence on the waterfall discharge. Even if there is no such

Table IV. Occlusive plethysmography data

n = 110	*Pre-stent*	*Post-stent*	P *Value*
Arterial inflow (mL/min)	2 (0.03-16.2)	2 (0.5-10)	.23
Duration to plateau (sec)	55 (0.7-396)	54 (2.4-342)	.92
Outflow fraction 1 second (%)	37.5 (3-86)	39 (8-92)	.69
Outflow fraction 2 seconds (%)	67 (7-131)	70 (14-128)	.56

waterfall break, venous stenoses are in tandem with the powerful precapillary constrictors. In line with flow principles across tandem stenosis,[13] such venous stenosis will have very little influence on arterial inflow unless the resistance of the venous stenosis exceeds that of the precapillary sphincters. Because of the large network of veins, this seldom happens except rarely (phlegmasia cerula dolens, for example). Iliac vein stenting for chronic stenoses therefore will only have a minor impact, if any, in improving arterial inflow.

On assuming orthostasis, the precapillary sphincters undergo powerful vasoconstriction[23,24] to maintain homeostasis. As a result, arterial inflow is reduced from supine levels,[24] which is reflected in halving of the common femoral vein phasic flow from supine to erect (Table II). The marked reduction in rate of flow and phasic flow duration (T) when erect is likely due to this as well. There is evidence that orthostatic venous pressure increase triggers the arteriolar constriction (veno-arteriolar reflux).[25,26] The dose-response curve, however, appears highly nonlinear.[24] The venous pressure reduction after iliac vein stenting is dwarfed by the gravity component in the erect position, and therefore appears unlikely to relieve the arteriolar vasoconstriction to increase arterial inflow.

The experimental and clinical findings suggest that the main effect of iliac vein stenting is venous decompression, with secondary changes in the character of the flow pattern likely due to reapportioning between pressure and velocity components of flow energy.

The authors wish to acknowledge helpful review of the biomechanical aspects of this manuscript by Roger D. Kamm (MIT), Geert Schmid-Schonbein (UCSD) and Ghassan S. Kassab (IUPUI).

AUTHOR CONTRIBUTIONS

Conception and design: SR
Analysis and interpretation: SR, MD
Data collection: SR, OK, MD
Writing the article: SR
Critical revision of the article: SR
Final approval of the article: SR
Statistical analysis: OK, JO
Obtained funding: SR
Overall responsibility: SR

REFERENCES

1. Pascarella L, Schonbein GW, Bergan JJ. Microcirculation and venous ulcers: a review. Ann Vasc Surg 2005;19:921-7.
2. Coleridge Smith PD. The microcirculation in venous hypertension. Vasc Med 1997;2:203-13.
3. Saharay M, Shields DA, Porter JB, Scurr JH, Coleridge Smith PD. Leukocyte activity in the microcirculation of the leg in patients with chronic venous disease. J Vasc Surg 1997;26:265-73.
4. Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. Physiol Rev 2011;91:327-87.
5. Takase S, Lerond L, Bergan JJ, Schmid-Schonbein GW. Enhancement of reperfusion injury by elevation of microvascular pressures. Am J Physiol Heart Circ Physiol 2002;282:H1387-94.
6. Knowlton FP, Starling EH. The influence of variations in temperature and blood-pressure on the performance of the isolated mammalian heart. J Physiol 1912;44:206-19.
7. Holt JP. Flow of liquids through collapsible tubes. Circ Res 1959;7:342-53.
8. Burton AC. Physiology and biophysics of the circulation. Year Book Medical Publishers: Chicago; 1972.
9. Nichols WW, O'Rourke MF, Hartley C, McDonald DA. McDonald's blood flow in arteries: Theoretic, experimental, and clinical principles. 4th ed. Arnold, Oxford University Press: London, New York; 1998.
10. Whitmore RL. Rheology of the circulation. Pergamon Press: London; 1968.
11. Hall JE. Guyton and Hall textbook of medical physiology. Saunders/Elsevier: Philadelphia; 2011.
12. Neglen P, Raju S. Detection of outflow obstruction in chronic venous insufficiency. J Vasc Surg 1993;17:583-9.
13. Strandness DE Jr, Sumner DS. Hemodynamics for Surgeons. Grune & Stratton: New York; 1975.
14. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic patient population. J Vasc Surg 2004;39:937-43.
15. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136-43; discussion: 44.
16. Raju S, Oglesbee M, Neglen P. Iliac vein stenting in postmenopausal leg swelling. J Vasc Surg 2011;53:123-30.
17. Sanchez NC, Tenofsky PL, Dort JM, Shen LY, Helmer SD, Smith RS. What is normal intra-abdominal pressure? Am Surg 2001;67:243-8.
18. Danielsson G, Eklof B, Grandinetti A, Kistner RL. The influence of obesity on chronic venous disease. Vasc Endovasc Surg 2002;36:271-6.
19. Raju S, Darcey R, Neglen P. Iliac-caval stenting in the obese. J Vasc Surg 2009;50:1114-20.
20. Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007;46:979-90.
21. Larock BE, Jeppson RW, Watters GZ. Hydraulics of pipeline systems. CRC Press: Boca Raton, FL; 2000.
22. Fung YC, Sobin SS. Pulmonary alveolar blood flow. Circ Res 1972;30:470-90.
23. Permutt S, Riley RL. Hemodynamics of collapsible vessels with tone: the vascular waterfall. J Appl Physiol 1963;18:924-32.
24. Raju S, Sanford P, Herman S, Olivier J. Postural and ambulatory changes in regional flow and skin perfusion. Eur J Vasc Endovasc Surg 2012;43:567-72.
25. Gauer OHT, H.L. Postural changes in the circulation. In: Hamilton WF, editor. Handbook of physiology. Williams & Wilkins: Baltimore; 1965. p. 2409-39. Q3
26. Rushmer RF. Cardiovascular Dynamics. W.B. Saunders: Philadelphia; 1976.

Submitted Nov 29, 2012; accepted Jan 29, 2013.

AUTHOR QUERY FORM

ELSEVIER	**Journal:** JVSV **Article Number:** 66	**Please e-mail or fax your responses and any corrections to:** **E-mail: a.obrien@elsevier.com** **Fax: 215-239-3388**

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof.

Location in article	Query / Remark: Click on the Q link to find the query's location in text Please insert your reply or correction at the corresponding line in the proof
	If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query
Q1	Please confirm that this statement is true, or edit for clarification. Conflict of interest statement was unclear, and stated "Stock in Veniti."
Q2	Please indicate in which section this "see later" occurs rather than this vague reference.
Q3	Please provide given-name for second author in reference 25.
Q4	Please confirm that given names and surnames have been identified correctly.
Q5	Figure 6 and 7 resolution is good enough, but the image quality is insufficient. Pleae provide better quality image.
	Please check this box or indicate your approval if you have no corrections to make to the PDF file ☐

Thank you for your assistance.