Ultrasound system to measure esophageal varix pressure: an in vitro validation study

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Bleeding from esophageal varices is a major complication of liver cirrhosis and portal hypertension. Approximately one-third of patients with varices will experience an episode of bleeding over a 2-yr period. Mortality from the first bleeding episode ranges from 30 to 50%. The major predictors of bleeding are the hepatic venous pressure gradient (HVPG), severity of underlying liver disease, varix size, and stigmata of variceal bleed (red color sign) (North Italian Endoscopic Club) (6). The least subjective of these parameters is the HVPG.

Esophageal varices bleed only when the HVPG is 12 mmHg or when the balloon pressure required to obliterate the varix to 50% of its original size correlates with the varix pressure. We describe our experience with a ultrasound system to measure varix pressure in a novel in vitro model. We tested several variables that may affect the varix pressure measurement by the ultrasound system technique in this in vitro model. Our observations indicate that the ultrasound system is a valid system to measure varix pressure and has the potential to be useful for in vivo use in humans.

MATERIALS AND METHODS

Bag ultrasound occlusion system. Our ultrasound system consists of three catheters, a 2.3-mm ultrasound probe (model UM-3R; Olympus, Tokyo, Japan) equipped with a 12.5-MHz transducer, a water infusion catheter, a manometric catheter, and a bag. The three catheters were placed in the bag through a specially designed silicone coupling, to which the bag was attached by using surgical sutures (Fig. 1). The infusion catheter inflated the bag with water while the ultrasound probe and manometric channel obtained ultrasound images and bag pressure simultaneously. The ultrasound probe was anchored at the proximal and distal ends of the bag to ensure that the ultrasound transducer remained in the center of the bag during distension. The latter is critical for the proper focal length of the ultrasound transducer that permits adequate imaging of the entire circumference of the esophagus. The distensibility of the latex bag was measured to determine the maximal volume of water used for the distension. The maximal bag volume was that amount of water that caused the varix wall thickness to decrease by 50% of its original size. We report that balloon pressure required to obliterate the varix to 50% of its original size correlates with the varix pressure. We describe our experience with a ultrasound system to measure varix pressure in a novel in vitro model. We tested several variables that may affect the varix pressure measurement by the ultrasound system technique in this in vitro model. Our observations indicate that the ultrasound system is a valid system to measure varix pressure and has the potential to be useful for in vivo use in humans.

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Esophagus, vein, and bag preparation. The esophagus and left external jugular vein were excised from five freshly killed pigs. The study protocol was approved by the Subcommittee on Animal Studies of Veterans Affairs San Diego Healthcare System. The first three excised veins were used in the hydrodynamic bag occlusion experiments. The fourth vein was used in the experiment examining the effects of esophageal wall properties on occlusion pressure, and the fifth was used in the hydrostatic occlusion experiments. Immediately after dissection, the vein and esophagus were placed in room temperature saline to prevent dehydration and preserve the biomechanical properties of the tissues. The vein was mounted between the two pieces of silicone tubing and placed inside the esophagus. In all vein occlusion experiments, one side of the vein was connected with a water reservoir to generate a pressure gradient and an in-line manometric channel to record vein pressure. The other end of the vein was connected to two separate reservoirs positioned at the same vertical height. The exit end of the vein was further connected to a thin catheter equipped with an intravenous drip-rate monitor that allowed observation of the continuity and cessation of fluid flow through the vein. The height of the reservoir determined the vein pressure and was the driving force for the hydrodynamic system. For the hydrostatic vein model, the two ends of the vein were connected to two separate reservoirs positioned at the same vertical height.

Occlusion of the vein was performed by using two bag inflation techniques: 1) a rapid infusion (~5 ml/min) with a hand-held syringe and 2) a slow infusion technique (0.5 ml/min) using a pneumohydraulic pump (Armdorfer Medical Specialties, Milwaukee, WI) (1). Bag inflations were continued until there was complete occlusion of the vein lumen as seen on ultrasound images and cessation of fluid flow through the vein. The accuracy of the ultrasound system was tested at vein pressures of 10, 15, 20, 25, 30, 35, 40, 45, and 50 mmHg. At each vein pressure, both methods (rapid and slow) of bag inflation were used. Four bag occlusion experiments, one slow and three rapid influsions, were performed at each vein pressure. In some experiments, the bag pressure was raised to 20 mmHg higher than the vein pressure, and then the bag was allowed to deflate slowly (~5 ml/min) to determine the vein opening pressure.

Distension of the bag inside the esophagus results in an increase in the esophageal circumference, which causes axial lengthening of the vein. The axial lengthening of the vein will cause a decrease in the vein cross-sectional area (CSA) in accordance with the law of volume and mass conservation. The decrease in the vein CSA related to axial lengthening of the vein is unrelated to the occlusive effects of the bag on the vein. To separate the effects of bag distension on vein CSA as a result of axial lengthening and bag occlusion we conducted studies in which vein and bag were placed inside a rigid cylinder (nondistensible, 60-ml plastic syringe) instead of the distensible esophagus. The vein pressure in this experiment was kept constant at 25 mmHg.

Hydrodynamic and hydrostatic esophageal varix occlusion model. To determine the effects of fluid flow inside the vein on the occlusion pressure, we tested a hydrodynamic and a hydrostatic model of esophageal vein (Fig. 1). In the hydrodynamic model, the fluid was allowed to flow through the vein by connecting the vein to the reservoir at one end and letting the fluid from the vein exit at the other end, lower than the reservoir. The exit end of the vein was further connected to a thin catheter equipped with an intravenous drip-rate monitor that allowed observation of the continuity and cessation of fluid flow through the vein. The height of the reservoir determined the vein pressure and was the driving force for the hydrodynamic system. For the hydrostatic vein model, the two ends of the vein were connected to two separate reservoirs positioned at the same vertical height.

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Data measurements. All pressures were measured in reference to the atmospheric pressure. The bag pressure required to obliterate the lumen of the vein completely was determined. Identification of the complete obliteration of the vein lumen was made visually from the ultrasound images (Fig. 2). To determine the reproducibility of the vein occlusion on ultrasound images, two investigators blinded to the bag pressure independently recorded vein occlusion during one of the hydrodynamic vein occlusion experiments. Similarly, the vein opening pressure was also determined in a blinded fashion by two investigators. To determine the relationship between bag pressure and vein CSA, the ultrasound images were digitized and analyzed by using a commercially available image analysis software program (Sigma Scan Pro; Jandel Scientific, San Rafael, CA). Ultrasound images were magnified $\times 8$ to improve the measurement accuracy. Intraluminal CSA of the vein was determined from the ultrasound images during the period of bag distension. The bag pressure required to cause a 100% reduction in the vein CSA was determined during all trials. In all 108 trials, the vein occlusion was observed when the bag pressure was slightly greater ($1.4 \pm 0.7 \text{ mmHg}$) than the vein pressure. Coincident with the disappearance of the vein lumen on the ultrasound images, there was cessation of fluid flow through the vein. The rate of bag inflation, rapid or slow, had no effect on the ultrasound measurement of vein pressure. We found an excellent correlation between vein occlusion pressure and intrabag pressure at all vein pressures tested. For each vein pressure examined, at 10, 15, 20, 25, 30, 35, 40, 45 and 50 mmHg, the respective bag occlusion pressures (means $\pm$ SD) are shown in Table 1.

<table>
<thead>
<tr>
<th>Vein Pressure (mmHg)</th>
<th>Mean Occlusion Pressure (mmHg)</th>
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<tbody>
<tr>
<td>10</td>
<td>$11.6 \pm 0.5$</td>
</tr>
<tr>
<td>15</td>
<td>$16.7 \pm 0.6$</td>
</tr>
<tr>
<td>20</td>
<td>$21.6 \pm 0.7$</td>
</tr>
<tr>
<td>25</td>
<td>$26.3 \pm 0.6$</td>
</tr>
<tr>
<td>30</td>
<td>$31.4 \pm 0.8$</td>
</tr>
<tr>
<td>35</td>
<td>$36.0 \pm 0.9$</td>
</tr>
<tr>
<td>40</td>
<td>$41.5 \pm 0.2$</td>
</tr>
<tr>
<td>45</td>
<td>$46.4 \pm 0.2$</td>
</tr>
<tr>
<td>50</td>
<td>$51.4 \pm 0.7$</td>
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Values are in millimeters of mercury and mean pressures are $\pm$ SD; $n = 108$. 

RESULTS

Relationship of bag pressure, vein pressure, and vein CSA in the hydrodynamic model. A total of 108 trials in three different veins (obtained from 3 different animals) were performed for the study. At each vein pressure, 10, 15, 20, 25, 30, 35, 40, 45 and 50 mmHg, four trials were conducted. The vein pressure remained unchanged throughout the bag distension procedure. The ultrasound images were adequate to visualize the geometry of the esophagus and vein during the entire period of distension. An increase in the vein pressure resulted in an increase in the vein CSA (Fig. 3). At zero bag pressure, the shape of the esophagus was irregular, and the vein was fully distended. As the bag volume increased, the esophagus became circular and changes in the shape and CSA of the vein were observed. The bag pressure required to cause a 100% reduction in the vein CSA was determined during all trials. In all 108 trials, the vein occlusion was observed when the bag pressure was slightly greater ($1.4 \pm 0.7 \text{ mmHg}$) than the vein pressure. Coincident with the disappearance of the vein lumen on the ultrasound images, there was cessation of fluid flow through the vein. The rate of bag inflation, rapid or slow, had no effect on the ultrasound measurement of vein pressure. We found an excellent correlation between vein occlusion pressure and intrabag pressure at all vein pressures tested. For each vein pressure examined, at 10, 15, 20, 25, 30, 35, 40, 45 and 50 mmHg, the respective bag occlusion pressures (means $\pm$ SD) are shown in Table 1.
Because the complete vein occlusion was determined visually, there was the possibility of observer bias. To eliminate observer bias, off-line determination of the timing of the vein occlusion was conducted in a blinded fashion by two investigators for one vein occlusion protocol. There was a close agreement between the two individuals as to the timing of complete vein occlusion (correlation coefficients: observer 1, $R^2 = 0.99$; observer 2, $R^2 = 0.99$) (Fig. 4).

Relationship between changes in the vein CSA with the changes in bag pressure. To better understand the mechanics of the vein occlusion process, the relationship of bag pressure, vein intraluminal CSA, and vein pressure was analyzed during a slow and continuous infusion of the bag. Initially, the vein CSA begins to decrease slowly as the bag pressure increases. An $\sim 50\%$ reduction in the vein CSA occurs when the bag pressure was $\sim 5$ mmHg less than the vein pressure. As the bag pressure approached to within 2 mmHg of the vein pressure, there was a rapid decrease in the vein CSA. Complete vein occlusion coincides with the bag pressure equal to or slightly greater than the vein pressure. The relationship between bag pressure and vein CSA was analyzed at three different vein pressures: 25, 35, and 40 mmHg. There was no difference in the dynamics of vein occlusion at the three pressures tested (Fig. 5).

Relationship between vein CSA and bag pressure in the distensible esophagus compared with nondistensible cylinder. The vein was placed inside a syringe instead of the esophagus for these experiments, and the vein pressure was kept constant at 25 mmHg. The CSA of the vein during bag distension in the syringe experiments was numerically higher than the esophageal experiments but not statistically different (Fig. 6).

Occlusion pressures in the hydrodynamic vs. hydrostatic model of the esophageal varix. The relationship between vein occlusion and fluid flow through the vein was investigated in these experiments. The vein was kept at a constant pressure of 25 mmHg, and experiments were conducted under hydrostatic and hydrodynamic conditions (Fig. 7). There were no significant differences in the bag pressure that caused occlusion of the vein under two experimental conditions.

Opening vs. closing vein pressure. The relationship between the bag pressure required to completely occlude the vein and the bag pressure at the instance of vein opening was examined in the hydrostatic system. Slow bag deflation revealed that the vein opening pressure is actually closer to the true vein pressure than the vein closing pressure. Five vein occlusion and opening experiments were performed with the vein pressure maintained at a constant 25 mmHg. The average occlusion and opening pressures were $27 \pm 0.2$ and $25.7 \pm 0.3$ mmHg, respectively, ($P < .05$).

DISCUSSION

The data generated from our novel in vitro model show that the ultrasound technique is a reliable and reproducible technique to measure the true vein pressure objectively. The vein opening pressure is better than the vein closure pressure in predicting the true vein pressure by the ultrasound technique.
The increase in the axial length of the vein caused by distention of the esophagus does not affect the vein CSA and measurement accuracy significantly. Finally, the vein occlusion pressure is not affected by the fluid flow in the vein.

We developed a novel in vitro model of esophageal varix that allowed us to assess several potential factors that may affect the accuracy of varix pressure measurement by the ultrasound system. Miller et al. (12), using a ultrasound system “somewhat like ours,” reported that the balloon pressure that causes a 50% reduction in the varix CSA is equal to the varix pressure. However, Miller did not study the dynamic relationship between balloon pressure and vein CSA, and therefore it appears that their selection of the 50% value is arbitrary. Our in vitro model allowed us to study the precise and dynamic relationship between the changes in bag pressure and vein CSA. We found that the vein CSA decreases slowly as the bag is inflated and that it reaches 50% of its original value when the bag pressure is ~5 mmHg less than the vein pressure. As the bag pressure is allowed to increase further, the vein CSA decreases rapidly, and the complete vein occlusion occurs when bag pressure is slightly higher than the vein pressure. Complete occlusion of the vein correlates closely with the true vein pressure.

Furthermore, identifying a complete collapse of the vein on the ultrasound images is less subjective than a 50% reduction in the vein CSA. The major advantage of the ultrasound method is that it allows precise determination of the complete occlusion and reopening of the vein during bag inflation and deflation, respectively. We believe that measuring vein pressure by the ultrasound technique is similar to measuring blood pressure by an inflatable bag. The blood pressure is measured during the opening rather than closure of the artery. Along the same principles, we found that the opening pressure of the vein during bag deflation was more accurate than the closing pressure of the vein. The reason for the latter observation is not clear. One possibility is that it is easier to visualize a small opening from a totally occluded vein on the ultrasound images rather than vice versa.

Pressure gauge measurement of varix pressure is dependent on the principle that the pressure gauge, when applied to the surface of the varix, results in collapse of the gauge membrane, thereby causing cessation of the airflow in the gauge (2). The gauge pressure continues to increase until the airflow resumes, which occurs at the same pressure as the varix pressure. The assumption in the pressure gauge technique is that the thin wall of the varix and the surrounding tissue do not offer intrinsic resistance to the displacement of the pressure-sensitive membrane of the pressure gauge. There is no occlusion of the varix in the pressure gauge system. The endoscopic balloon technique of varix pressure measurement relies on the principle that distending a balloon against the varix results in a change in the shape of the varix from the circular to a relatively flat configuration (8). It is assumed that change in the varix shape occurs when the bag pressure is equal to varix pressure. The latter implies that a partial collapse of the vein occurs when the bag pressure and varix pressures are equal. Our studies show that the true vein pressure is that bag pressure at which there is complete collapse of the lumen of the vein. The disadvantage of the endoscopic balloon technique is that it cannot determine the degree of closure of the varix. Furthermore, ultrasound technique can detect small-sized varices more accurately than endoscopy (11, 13). Therefore, in contrast to the endoscopic balloon and endoscopic pressure gauge technique, the ultrasound technique may be able to measure pressure in the small varix as accurately as in the large-sized varix in vivo. Polio et al. (18) found that the vein wall thickness and vein diameter affect the pressure measurement by the pressure gauge technique. In our system, the vein CSA was directly related to the vein pressure. We could not measure changes in vein wall thickness in our experiment, because our ultrasound system is

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**Fig. 6.** Intraluminal CSA of the vein in the distensible esophagus and nondistensible cylinder during slow and continuous bag inflation. The vein CSA during bag distension was somewhat higher when it was located in the nondistensible cylinder compared with a distensible esophagus; however, the differences are not statistically significant.

**Fig. 7.** Intraluminal CSA of the vein in the hydrodynamic and hydrostatic occlusion models during a slow and continuous bag inflation. Fluid flow within the vein had no significant effect on the vein occlusion process or vein occlusion pressure.
not sensitive to detect such small changes. However, one may predict that with an increase in the vein CSA there will be a proportional decrease in the vein wall thickness. Our finding that the measurement accuracy was not related to the vein pressure suggests that the vein wall thickness and diameter may not affect the vein pressure measurement accuracy by the ultrasound technique.

It may seem that the bag is entirely responsible for causing compression of the vein during bag inflation in our system. To the contrary, the viscoelastic properties of the esophagus are equally important for the genesis of bag pressure and occlusion of the vein. In fact, if the bag is inflated outside the esophagus, it does not generate any pressure at the volumes of distension used in the study. We found that the vein pressure measurement accuracy was the same whether it was placed inside a nondistensible cylinder or a distensible esophagus. The difference, however, is that the volume of fluid required to achieve bag pressure to cause vein occlusion is lower in the nondistensible cylinder compared with the distensible esophagus. In an in vivo situation, other factors, i.e., spontaneous or bag distension-induced contraction of the esophagus, may increase the bag pressure rapidly and can cause occlusion of the vein. Several investigators have suggested use of atropine to inhibit esophageal contractions when measuring vein pressure by the pressure gauge technique or endoscopic bag distension technique (16, 18).

We believe that the rapidity of pressure increases in the bag may be affected by the viscoelastic properties of the esophagus and contractions of the esophagus, but it is unlikely that the pressure measurement accuracy is compromised by these properties.

In summary, the ultrasound method has the potential to measure varix pressure in vivo independently of varix size and viscoelastic properties of the esophageal wall. Studies are in progress in our laboratory to determine the accuracy of the ultrasound technique to determine the varix pressure in vivo. Furthermore, the ultrasound technique can determine varix wall thickness and radius, two other variables required to determine varix wall stress, the parameter likely to be the most important predictor of variceal rupture (21).

GRANTS
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REFERENCES