Letters to the Editors

On the lung injury and disseminated intravascular clotting seen after liver trauma

To the Editors:

One has the impression that the effect of cryosurgery of the liver, as reported by Blackwell et al (and evidently seen mainly if the frozen liver section's size is substantial) (Surgery 1999;126:518-26), is similar if not identical to what we saw in hepatic resections after using the finger fracture technique.

Long before SIRS or the cytokines became part of the vocabulary, we found convincing evidence of pulmonary insufficiency and disseminated intravascular clotting after liver resections with the finger fracture technique. These changes were attributed to liver cell embolism or the release of proteolytic enzymes after cell membrane rupture (Surg Gynecol Obstet: 1974;138: 885) since they were absent if the hepatic veins were occluded prior to the resection.

We always felt that these changes occur in varying degrees during every liver resection because of the unique anatomical arrangement of the human liver, characterized as it is by a tight interdigitation of the portal (or Glissonian) and hepatic venous systems, an arrangement that's absent in the dog! This feature turns an anatomical resection based on the Glissonian system into an opportunity for debris (or cytokines) to become dislodged into the most distal branches of the hepatic veins since these vessels naturally cross the transecting plane and are opened invariably during the procedure.

This suggests a simple way to evaluate the role of liver "cell embolism" as a cause for the changes the authors have observed so far, namely by occluding the hepatic veins before attacking the area drained by these vessels again with a freezing probe.

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Reply

To the Editors:

We would like to thank Dr Gans for his thoughtful comments and for the opportunity to respond to his letter.

Dr Gans points out that the adverse effects of cryoablation may be related to embolization of particulate matter, including cellular debris, at the time of the cryoablation procedure. While adverse effects do not seem to be significant with small-volume cryoablation, it is important to note that the side effects of cryotherapy do occur in a step-wise fashion and some degree of side effects (eg, thrombocytopenia) can be seen clinically even with small-volume cryoablation.[1] Furthermore, while our model utilizes an approximately 35% cryoablation, this should not be considered "large volume" from the standpoint of liver parenchymal loss, since up to 70% of normal parenchyma can be routinely removed without serious adverse effects.[2] Clearly, there are systemic effects from cryoablation that extend far beyond the parenchymal loss itself.

Dr Gans has raised an important concept regarding possible embolization of cellular material during the cryoablation procedure. Cryoablation involves the placement of large probes either into the center of hepatic tumors or on the liver surface, followed by circulation of liquid nitrogen with generation of temperatures to -180°C, followed by a slow thawing phase. This technique is reported to cause solute-solvent shifts, small vessel obliteration, and membrane damage in addition to other mechanisms of cell death. Recent data from our laboratory demonstrate that cryoablation induces rupture of the hepatocyte plasma membrane with release of cellular contents into the space of Disse. Furthermore, preliminary data suggest that resection of the cryoablated liver prior to the thawing phase prevents NF-κB activation, cytokine upregulation, and lung inflammation. Thus it seems plausible that cryoablation induces distant damage by release of injurious agents from the site of injury in the liver and that this process may occur during the thawing phase of cryoablation.

Of note, under most circumstances, cytokines are not stored in a pre-activated form within macrophages (or other cells). Thus cytokine production requires active gene transcription of messenger RNA unique to each cytokine, a process closely upregulated by activation of NF-κB within the cell.[3] In our rat model of cryoablation, we have measured activated NF-κB by 30 minutes in the nonablated liver tissue and in distant sites (ie, lung) by 1 hour.[4] Thus some aspect of the ablative process or release of injurious mediators causes activation of NF-κB and subsequent increased circulating serum cytokines, including TNF-α . Whether the use of vascular isolation techniques including ligation of hepatic veins could limit or prevent the systemic effects of cryoablation is an intriguing idea. While vascular isolation techniques may confirm that a soluble mediator is responsible for both the liver and lung NF-κB activation and lung inflammation, this has not been combined with cryoablation clinically as far as we are aware, possibly due to the following reasons: (1) isolated venous outflow occlusion will cause