Reviewer's report

Title: Impact of Cytokine Release on Ventricular Function after Hepatic Reperfusion: A Prospective Observational Echocardiographic Study with Tissue Doppler Imaging

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Reviewer: Paolo Feltracco

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Comment for Authors

The authors correlated cardiac performance measured by TEE and TDI with cytokines release at different points during liver transplantation; any hemodynamic instability after the reperfusion stage was also evaluated. They concluded that cytokine release might not be the major cause of circulatory derangement at reperfusion.

The methods are quite appropriate, the results well reported, the discussion understandable, but sometimes slightly supported by data obtained.

The content of the paper is of scientific interest, even though the main message (no link between cytokines release and PRS) may not be valid for the whole range of cirrhotic patients undergoing OLT.

Some issues and concerns with this paper:

Main message: No observed impairment of LV function, no changes in MAP as a consequence of an increase in pro-inflammatory mediators after reperfusion.

Issue with definition of baseline cardiac performance and MELD score of candidates

Authors only mention at the end of paper a rather low MELD, and report a mean value of 15 on tab 1.

They should emphasize the low MELD, the fact that none of recipients at baseline displayed a LV-EF <50% (average 72%), and the extremely low cardiovascular risk factor of their case series. That 11 patients tolerated a complete cross-clamping of IVC without veno-venous bypass indirectly suggests that they underwent surgery with a “well-maintained” cardiovascular function at baseline. This may be one important factor for not observing PRS.

The non-occurrence of hemodynamic impairment cannot be true for the population of candidates with high MELD, and represents a limitation that deserves mentioning. The development of a clinically relevant PRS (manifested not only with >30% reduction in MAP) could be facilitated by a reduced cardiac reserve. A reduced myocardial performance (systolic and diastolic dysfunction) is almost always present in the late cirrhosis, where, despite a normal to increased cardiac output and contractility at rest, an abnormal and blunted response to pathologic stress may occur.
The assertion that significant cytokines liberation is not coincident with hemodynamic instability and impaired cardiac function might be therefore true only for these low-risk, not advanced liver recipients (conclusion not applicable to all end-stage cirrhotic patients currently included in the modern liver transplant programs).

Amount of Vasoactive drug infused

Another issue to be clarified is the rate of infusion of noradrenaline. High dose noradrenaline, a sudden consistent increase in venous return (liberation of total clamp of IVC), and an optimal myocardial reserve may have accounted for the non-reduction of MAP after reperfusion, despite cytokines liberation. Based on how noradrenaline is reported (mcg/min) it is very difficult to appreciate the exact dose/per patient/per stage.

Was the hemodynamic status immediately before reperfusion prophylactically “assisted” “reinforced” by an increase in catecholamine administration, vasoconstrictors, or fluid infusion? It does not emerge… It is difficult to assert “no myocardial depression” if an incremental dosage of amines had been given.

The 2nd statement of discussion underlines that echocardiographic parameters reflected the hemodynamic changes due to administration of catecholamines, and volemia changes.

A desirable, common goal of anesthesia conduction during clamping in OLT is to maintain MAP with vasoconstrictors or amines (or fluids). How can we differentiate the primary spontaneous variations of myocardial fibers function from those influenced by catecholamines?

Importance of the quality of the grafts

Also the quality of implanted graft may be of importance in determining PRS, both as regard the amount of cytokines released and vasoregulation of tone of systemic circulation and pulmonary artey. The fact that IL6 and IL8 increased significantly both during clamping and after reperfusion does not necessarily mean that the measured increase be clinically relevant. TNF alpha was below the detection level. Marginal graft and high-risk patients would potentially show far greater levels than those observed.

Statistically significant does not always mean clinically significant.

Good grafts, adequate filling pressure in PA after reperfusion (sudden massive increase in venous return), and optimal basal cardiac reserve (plus amines) may act synergically to mask PRS manifestations. The reduction in SVR after reperfusion may be not only due to cytokines but also to the “doubling” of CO (mathematical result).

Methods of evaluation of cardiac performance, TEE and TDI

Where there difficulties in recording clear images in the transgastric short-axis while the stomach was pushed away during liver dissection and grafting?

Some “minor” doubts in interpreting the TEE measurement of some parameters: FAC in transgastric short-axis may not well define systolic function of LV,
depending on momentary LV filling. Even FAC and EF% may consistently reflect the changes in volume loading and/or the administration of catecholamines, and not necessarily the variations of fiber function (i.e. dp/dt). A reduction in CO is reported after clamping, with a “compensatory” increase in SVR….however, LV-EF% increased at this stage…..

- How was INRT easily measured with transmitral Doppler?
- Line 23 on pag9 .....mitral annulus on the lateral position… better than on the medial aspects
- Line 9- 10 pag 10 E/A ratio >1.5 ????... likely 1?

Minor Errors or imprecisions
Abstract : Line 17 2-5 minutes after….? lines 19-20 MPAP CVP and CO unchanged…when??
Line 16 on pag 9 indice ?
Line 23 on pag 7 inversion better.. to respect chronological sequence
Lines 5-6 on pag 16…pertinent statement, citation and reference?
Line 16 on pag 16 fortified ?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: no