

July 2, 2014

Dear Editor,

Thank you for your letter and the reviewers' comments about our manuscript (#10520). The constructive comments on this manuscript by the reviewers are helpful. We appreciate the general comments from the reviewer #1 “.....*The authors should add in the title that the work has been performed on animal model. In the section "Surgical technique" there is a part written in red. Are there particular reasons? .....*” and the reviewer #2 “..... *that authors should specify how they intend to improve the experimental model in the future, so that it could be personalized and extracorporeal blood flow can be changed depending on the parameters measured in vivo in each animal. ....*”. We have modified the manuscript in line with their comments. Hereby we submit the revised manuscript entitled “Severe Thrombocytopenia Complicating Transcatheter Occlusion of a Patent Ductus Arteriosus” for your consideration for publication. We think that we have addressed reviewers' comments to the best degree we could, and we hope this has met the reviewers' and editor's requests. Please find enclosed the edited manuscript in Word format (file name: 10520-review.doc).

**Title: Should temporary extracorporeal continuous portal diversion replace meso/porta-caval shunts in “small-for-size” syndrome in pigs?**

**Author:** Dadong Wang, Yong Xu, Ziman Zhu, Xianglong Tan, Yuliang Tu, Mingming Han, Jing-Wang Tan

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 10520

The manuscript has been improved according to the suggestions of reviewers:

**1. *The authors should add in the title that the work has been performed on animal model. In the section "Surgical technique" there is a part written in red. Are there particular reasons?***

We agree with reviewer 1's comments. The title has been modified to: “**Should temporary extracorporeal continuous portal diversion replace meso/porta-caval shunts in “small-for-size” syndrome in pigs?**” “**The extent of the hepatectomy was referred to bench dissection of 10 pigs,**”, “**the introduction of**” have been changed red color to black color.

**2. *that authors should specify how they intend to improve the experimental model in the future, so that it could be personalized and extracorporeal blood flow can be changed depending on the parameters measured in vivo in each animal. In addition, they must specify which would be the prospects of applying such an approach in human clinical. What risks, features and benefits may it have?***

We have followed reviewer 2's suggestion. We need to use a specified pump and softer catheter in the future, so that this could be personalized and extracorporeal blood flow can be changed depending on the parameters measured *in vivo* in each animal. This approach may cause infection, as the catheter could break or fall off. The feature of the approach is temporary extracorporeal continuous porta-caval diversion (ECPD) to relieve portal hyperperfusion following massive hepatectomy. Finally patients who undergo massive hepatectomy could then be possibly prevented from liver failure or “small-for-size” syndrome.

**3. Note1 :** *Author names should be given first, then the complete name of institution, city, province and postcode.*

We changed the format to “Dadong Wang <sup>a</sup>, Yong Xu <sup>a</sup>, Ziman Zhu <sup>a</sup>, Xianglong Tan <sup>a</sup>, Yuliang Tu <sup>a</sup>, Mingming Han <sup>a</sup>, Jing-Wang Tan <sup>a\*</sup> Department of Hepatobiliary Surgery, the First Affiliated Hospital of Chinese PLA General Hospital 51 FuCheng Road, Haidian District, Beijing, China (100048) ”

**4、 Note2:** *Please provide the title of Jing-Wang Tan*

We changed to “Dr Jing-Wang Tan”

**5. Note3:** *Telephone and fax should consist of +, country number, district number and telephone or fax number*

We changed this to “Telephone +86-10-66848634 Fax: +86-10-66848633”

**6. Notes4:** *For the figures, Please provide one total title. Please list and define all abbreviation appearing in the tables or figures.*

We changed to “Fig 2. ALT to ALT (alanine aminotransferase); Fig 4. PH (post hepatectomy); PCNA (proliferation cell nuclear antigen); TK (thymidine kinase); Fig 5. TUNEL (transferase-mediated dUTP-biotin nick end labeling)

**7、 Note5:** *An informative, structured abstracts of no less than 246 words should accompany each paper. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim in the form: “To investigate/study/...; METHODS (no less than 80 words); RESULTS (no less than 120 words): You should present P values where appropriate and must provide relevant data to illustrate how they were obtained, e.g.  $6.92 \pm 3.86$  vs  $3.61 \pm 1.67$ ,  $P < 0.001$ ; CONCLUSION (no more than 26 words).*

We changed the abstract to “**AIM:** To investigate the feasibility of temporary extracorporeal continuous porta-caval diversion (ECPD) to relieve portal hyperperfusion in “small-for-size” syndrome following massive hepatectomy in pigs. **METHODS:** Fourteen pigs underwent 85-90% liver resection and were then randomly divided into control (n=7) and diversion groups (n=7). In the diversion group, portal venous blood was aspirated through the portal catheter and into a tube connected to a centrifugal pump. After filtration, the blood was returned to the pig through a double-lumen catheter inserted into the internal jugular or subclavian vein. With the conversion pump, portal venous inflow was partially diverted to the inferior vena cava through a catheter inserted via the gastroduodenal vein at 100-130 mL/min. Portal hemodynamics, injury, and regeneration in the liver remnant were compared between the two groups. **RESULTS:** Compared to the control group, porta-caval diversion via ECPD significantly mitigated excessive portal venous flow and portal vein pressure (PVP); the PVF, HAF, and PVP in the two groups were not significantly different at baseline; however, the PVF ( $431.8 \pm 36.6$  vs

238.8±29.3 P<0.01, 210.3±23.4 vs 122.3±20.6 P<0.01) and PVP (13.8±2.6 vs. 8.7±1.4 P<0.01, 15.6±2.110.1±1.3 P<0.05) in the control group were significantly higher than those in the diversion group. The HAF in the control group was significantly lower than that in the diversion group at 2h and 48h of PH, and ECPD significantly attenuated injury to the sinusoidal lining and hepatocytes, increased the regeneration index of the liver remnant, and relieved damage that the liver remnant suffered from endotoxin and bacterial translocation. **CONCLUSIONS:** ECPD, which can dynamically modulate portal inflow, can reduce injury to liver remnant and facilitate liver regeneration, and therefore should replace permanent meso/porta-caval shunts in SFSS” .

**8、Notes 6: write a summary of less than 100 words to outline the most innovative and important arguments and core.**

We wrote the Core tip ” Meso/porta-caval shunts have usually been adopted to relieve portal hyperperfusion in “small-for-size” syndrome (SFSS) or postoperative liver failure (PLF); however, these methods cannot dynamically adjust portal inflow to affect “functional competition”. In this study, extracorporeal continuous porta-caval diversion (ECPD) was temporarily adopted to relieve hyperperfusion, dynamically adjust the effect of portal inflow towards functional competition, and preserve optimal portal inflow. This also reduces injury to the sinusoidal endothelium, decreases endotoxin/bacterial translocation, and facilitates liver regeneration in SFSS after massive hepatectomy, and therefore could replace permanent meso/porta-caval shunts, which have no benefit or harm towards liver regeneration in late stages”

**9. Notes 7: Comments:**

We added the comments “ **Background:** Portal hypertension and splanchnic pooling following major hepatectomy or a small graft have been reported to contribute to high postoperative morbidity and mortality rates associated with these procedures. The placement of a portal-systemic shunt or splenic artery ligation improves survival following subtotal hepatectomy or a small graft, probably as a result of decompression of portal blood flow. However, excessive diversion or hypoperfusion by a portal-systemic shunt retards regeneration of the liver remnant or small graft, and meso/porta-caval shunts are permanent, having no benefit or harm to liver regeneration in late stages. **Research frontiers:** A portal-systemic shunt is adopted to relieve portal hyperperfusion following subtotal hepatectomy or a small graft, however, it can not avoid “functional competition” between the portal vein and systemic circulation. **Innovations and breakthroughs:** Meso/porta-caval shunts cannot dynamically adjust portal inflow to affect “functional competition”. In this study, extracorporeal continuous

porta-caval diversion (ECPD) was temporarily adopted to relieve hyperperfusion, dynamically adjusted portal inflow to affect functional competition, and preserved optimal portal inflow, which could perhaps replace permanent meso/porta-caval shunts that have no benefit or harm towards liver regeneration in late stages.

**Applications:** Continuous hemofiltration/hemodiafiltration is a routine clinical treatment used as a renal replacement. The placement of a catheter in the portal vein also makes ECPD feasible and safe, and could be personalized so that extracorporeal blood flow can be dynamically changed depending on parameters measured in real time.”

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Jing-Wang Tan

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