Laser-assisted vessel welding: state of the art and future outlook

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1st Editorial decision

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Laser-assisted vessel welding: state of the art and future outlook
Journal of Clinical and Translational Research

Dear Dr. Pabittei,

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Oct 13, 2015.

To submit a revision, go to http://jctres.edmgr.com/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Yao Liu, Msc
Managing Editor
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The authors presented an extensive overview of laser-assisted vessel welding. The article is well written and explores this attractive field.
I support publication.

Reviewer #2: Important issues:
- Point 3.1.1 and others: schematics about how the sealing with laser is conducted would allow to clarify the performance of the technique, for instance, is mechanical pressure requested during use?
- Likewise, P7, L21-26, a schematic including the main elements (tissue, OPD, etc.) would allow to understand easily the proper means.
- Other example: P8, L20-21: when you mention the adventitia, a schematic would provide an idea about the arrangement of the tissues and how they are affected by heat.
- This suggestion is crucial to understand the spatial location of other key elements playing together during using of these techniques, such as protein solders, interface solder-tissue, solder superficial (outer) layer (P28, L22), external irradiation pattern (P26, L8), etc.

Minor comments:
- Introduction. Explain a bit more the meaning of "liquid-tight sealing". Other terms cited in point 2 should be briefly explained, and so their inclusion in the literature search would completely justified (electrospinning, solvent casting, particulate leaching).
- The term "thermal damage" (and its minimization) is broadly used throughout the manuscript. In radiofrequency-based sealing devices the term "thermal spread" is used instead. Is the same issue?
- Point 3.1.1 and others: the terms coagulation and denaturation are used indistinctly to refer modification of the native structure of the collagen. I recommend to point that they are used with the same meaning.
- P6, L40-41: The term "extent of heat generation" is ambiguous in this sentence. Clarify it. Likewise, in L47-48, what do you mean with "dynamics of heat diffusion"?
- P13, L53: LAVW instead of LAWV.
- It also ambiguous the term "narrower temperature gradient" (P15, L3) and the term "steeper thermal gradients". The gradient of a temperature is a vector indicating direction of maximum change, and magnitude of this change respect distance. What do you mean with "narrow" or "steep"? Clarify this.
- I miss some figures including pictures of real surgeries where these techniques are employed.
- P22, L3 and others: days instead of "d"
- I miss some comparison between LAVW and other techniques based on energy, such as radiofrequency. Why is worthy to conduct clinical research on this topic? What drawback associated with RF are you trying to minimize? Why do you think that laser-based methods could improve the current techniques (which would be the rationale)?

Authors' rebuttal

Ms. Yao Liu

Editor, Journal of Clinical and Translational Research

Re: Resubmission revised manuscript

Amsterdam, 22 September 2015

Dear Ms. Liu,

Please find enclosed the resubmission of our manuscript entitled "Laser-assisted vessel welding: state of the art and future outlook." We would like to thank the reviewer for critically reading the manuscript. Several important issues were raised that we have implemented in the manuscript. We have also addressed the reviewers' comments point-by-point in red italics below and used the track changes function in the text to indicate the modifications.

Thank you for the opportunity to resubmit the manuscript.

Kindest regards, also on behalf of the co-authors,

Dara.

Reviewer #1:

The authors presented an extensive overview of laser-assisted vessel welding. The article is well written and explores this attractive field.
I support publication.

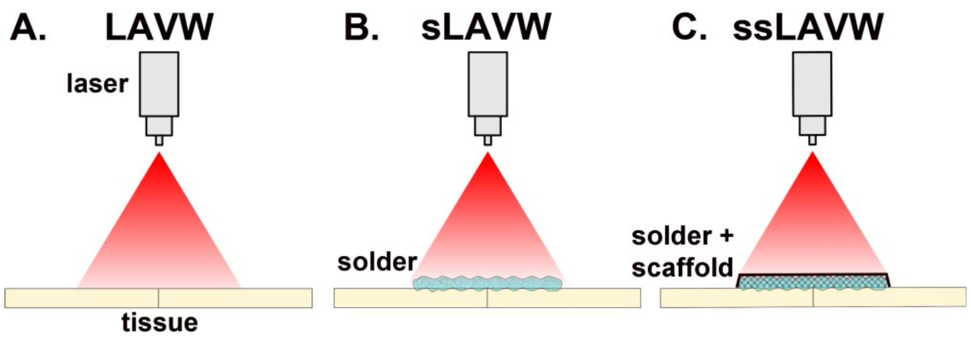
Thank you for your endorsement of our work.

Reviewer #2:

Important issues:

- Point 3.1.1 and others: schematics about how the sealing with laser is conducted would allow to clarify the performance of the technique, for instance, is mechanical pressure requested during use?

Thank you for the suggestion, the following figure has been added to the manuscript. The figure provides a schematic drawing of the difference between laser-assisted vascular welding (LAVW, P. 3.1.1), solderbased LAVW (sLAVW, P. 3.2.1), and scaffold- and solder-enhanced LAVW (ssLAVW, P. 3.3.1).



- Likewise, P7, L21-26, a schematic including the main elements (tissue, OPD, etc.) would allow to understand easily the proper means

This is also a great suggestion. We have added the following figure to clarify the main components of laser-tissue interactions.

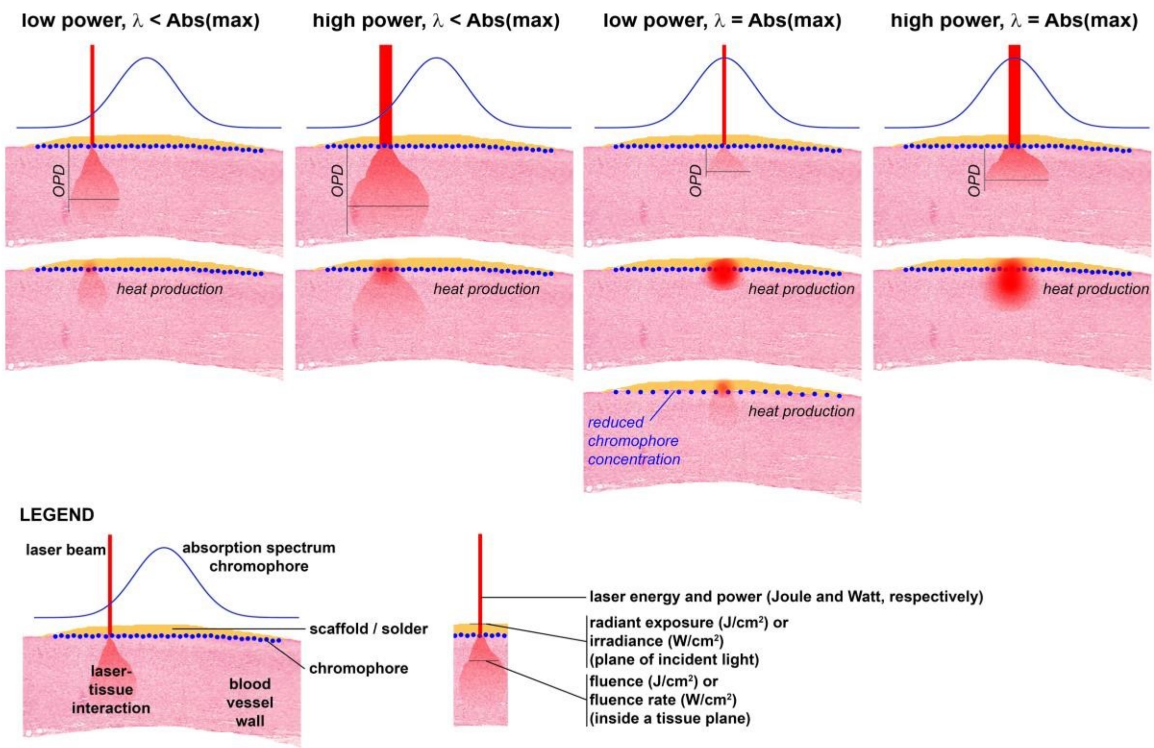
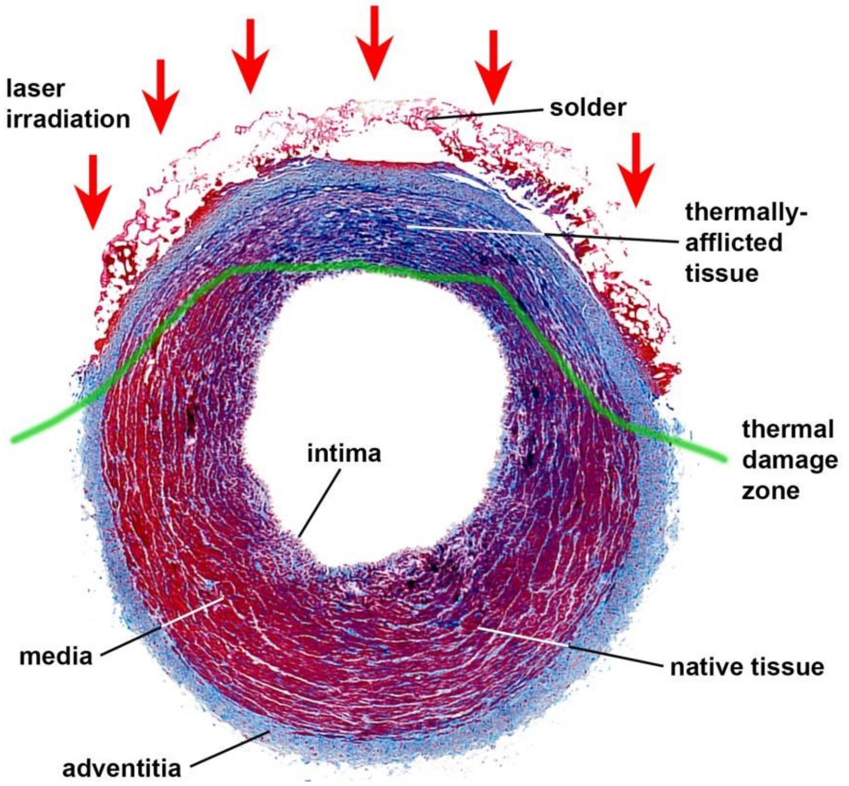


Figure 3. General fundamentals of laser-tissue interactions. Four main scenarios are presented, each depicted in a column. The top row provides a schematic illustration of optical penetration depth (OPD) for every scenario, whereas the bottom row reflects the corresponding heat production in the solder/scaffold and tissue. The scenarios are the following: (1) low-power laser beam of a wavelength (λ) that is lower than the absorption maximum (Abs(max)) of the chromophore (i.e., moderate heat production at chromophore layer, moderate optical penetration depth, moderate thermal spread in tissue); (2) highpower laser beam of a λ that is lower than the Abs(max) of the chromophore (i.e., moderate-to-high heat production at chromophore layer, large optical penetration depth, high thermal spread in tissue); (3) lowpower laser beam of a λ that is equal to the Abs(max) of the chromophore (i.e., extensive heat production at chromophore layer, low optical penetration depth, thermal spread mainly confined to scaffold/solder- tissue interface); (4) high-power laser beam of a λ that is equal to the Abs(max) of the chromophore (i.e., very profound heat production at chromophore layer, low-to-moderate optical penetration depth, extensive thermal spread at

scaffold/solder- tissue interface with heat diffusion laterally and into tissue).
In the third row of the third column, a scenario is presented in which the chromophore concentration is reduced, accounting for moderate heat production at chromophore layer, moderate optical penetration depth, moderate thermal spread in tissue. The legend in the bottom left corner explains every component in each panel. Moreover, the common nomenclature is provided at the bottom center of the figure.

- Other example: P8, L20-21: when you mention the adventitia, a schematic would provide an idea about the arrangement of the tissues and how they are affected by heat.

In accordance with your suggestion, the following histology image of an ssLAVW-treated porcine carotid artery, showing the vascular layers, area of laser irradiation, thermally afflicted tissue, thermal damage zone and the non-affected native tissue has been added to the manuscript.



- This suggestion is crucial to understand the spatial location of other key elements playing together during using of these techniques, such as protein solders, interface solder-tissue, solder superficial (outer) layer (P28, L22), external irradiation pattern (P26, L8), etc.

We agree, and hope that the anatomical picture we added, which includes sections of native tissue and afflicted tissue, provides sufficient elucidation.

Minor comments:

- Introduction. Explain a bit more the meaning of "liquid-tight sealing". Other terms cited in point 2 should be briefly explained, and so their inclusion in the literature search would completely justified (electrospinning, solvent casting, particulate leaching).

The term liquid-tight sealing has been explained ("i.e., immediate closure of the incision or wound that prevents bleeding or seeping of fluids from the perfused blood vessel"). Also, we added brief explanations on electrospinning and solvent casting particulate leaching techniques.

- The term "thermal damage" (and its minimization) is broadly used throughout the manuscript. In radiofrequency-based sealing devices the term "thermal spread" is used instead. Is the same issue?

Yes; basically the same essence is implied. However, thermal spread fundamentally refers to heat diffusion, which does not necessarily have to translate to damage (i.e., in the regions where the temperature is just a few degrees above the native temperature). Thermal damage is more concrete and therefore used in this manuscript.

- Point 3.1.1 and others: the terms coagulation and denaturation are used indistinctly to refer modification of the native structure of the collagen. I recommend to point that they are used with the same meaning.

Thank you for the recommendation. To provide uniformity we have used the term protein denaturation throughout the text.

- P6, L40-41: The term "extent of heat generation" is ambiguous in this sentence. Clarify it. Likewise, in L47-48, what do you mean with "dynamics of heat diffusion"?

We changed the term "extent of heat generation" to "degree of heat build-up".

What we meant with "dynamics of heat diffusion" is the temporal changes in thermal profile within the tissue. This has been changed accordingly.

- P13, L53: LAVW instead of LAWV.

Good eye - this has been corrected.

- It also ambiguous the term "narrower temperature gradient" (P15, L3) and the term "steeper thermal gradients". The gradient of a temperature is a vector indicating direction of maximum change, and magnitude of this change respect distance. What do you mean with "narrow" or "steep"? Clarify this.

What we meant by narrower temperature gradient is small temperature difference between the area where heat absorption occurs (i.e., the chromophore molecules) and the non-absorbing regions (where heat diffuses upon absorption). The more efficient and homogenous the heating process the smaller the temperature gradient.

- I miss some figures including pictures of real surgeries where these techniques are employed.

At this stage the technique is applied in vitro and not yet on animal. Therefore we don't have any picture of real surgery.

- P22, L3 and others: days instead of "d"

We used d to abbreviate days throughout the paper.

- I miss some comparison between LAVW and other techniques based on energy, such as radiofrequency. Why is worthy to conduct clinical research on this topic? What drawback associated with RF are you trying to minimize? Why do you think that laser-based methods could improve the current techniques (which would be the rationale)?

Indeed the comparison with RF is not made in this paper. However, we compared this technique with suture-based anastomosis, the gold standard and widely used technique currently used in the clinical setting. The comparison has been stated in the introduction. Many researchers have investigated the outcome parameters of laser-assisted vascular anastomosis technique to suture anastomosis.

Moreover, in this paper we highlighted the current status of LAVW, what the drawbacks are, and how the technique can be improved further. We believe that focusing on RF would take away from the central message related to the different LAVW modalities and cloud the essence of the paper. We therefore respectfully omitted information about RF.

2nd Editorial decision

Date: 23-September-2015

Ref.: Ms. No. JCTRes-D-15-00005R1
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Journal of Clinical and Translational Research

Dear Dr. Pabittei,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

Comments from the editor and reviewers can be found below.

Thank you for submitting your work to JCTR.

Kindest regards,

Yao Liu
Managing Editor
Journal of Clinical and Translational Research

Comments from the editors and reviewers: