

SSC Subcommittee Project Template

Subcommittee Name: Models of Thrombosis & Hemostasis

Project Name: Evaluating procedural and reporting variability in the inferior vena cava stenosis thrombosis model

Project Lead/PI: Steven Grover

Template Form Date: 10/17/2022

Project Description/Abstract:

State the project's broad, long-term objectives and specific aims, making reference to the proposed health/scientific impact as a result of the project. Suggested length is 2-3 paragraphs.

The murine inferior vena cava stenosis model of venous thrombus formation is a commonly used procedure to investigate mechanisms of venous thrombus formation and resolution. Studies using this model have provided important insights into the contribution of a number of pathways including coagulation and immune cell mediated processes. As with many preclinical models the specific procedure used to induce thrombus formation with this approach varies between investigators. Examples of procedural variables include the type of spacer used to generate the stenosis, if side branches are ligated, if back branches are cauterized and if vascular clips are applied. In line with the observed variability in the procedure used to induce thrombus formation, marked variability in thrombus incidence and weight are also apparent. This project intends to evaluate the procedural and reporting variability in the inferior vena cava stenosis model. A literature review-based approach will be used to synthesize information on the spectrum of procedural and reporting variables. Members of the field will be actively engaged in a complementary investigator survey-based approach. Through these efforts we intend to identify commonly used procedures and elements of commonality that may be shared between approaches. We further intend to compile a set of recommendations on reporting of procedural variables and outcome measures.

Project Design and Methodology:

List the data expected to collect, sample size and statistical analysis. Concisely describe the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

Phase 1: Literature Review

Aim: Identify commonly used IVC stenosis approaches in the literature

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In the first phase of the project a systematic literature review will be conducted to establish the spectrum of approaches used in the IVC stenosis model. Suitable articles for inclusion in the literature review will be identified in literature databases including Embase, MEDLINE and Web of Science and eligibility for inclusion adjudicated by two independent reviewers. Data on the IVC stenosis procedure will be extracted from the full text of papers identified in the systematic review. The literature review will include data on articles published up to September 2022.

Phase 2: Investigator Questionnaire

Aim: Identify commonly used IVC stenosis approaches via self-reporting of investigators

An investigator questionnaire has been drafted to collect data on procedural details of the IVC stenosis model in a unified manner. The Questionnaire will be circulated to corresponding authors of papers identified in Phase 1 and will also be made more widely available to the field on the SSC Models of Thrombosis & Hemostasis section of the myISTH community website.

Phase 3: Experimental Evaluation

Aim: Evaluate reproducibility of a standardized IVC stenosis procedure

To better understand the reproducibility of the IVC stenosis model a multi-investigator study will be initiated. 5-6 investigators with established expertise with the IVC stenosis model will be provided with a standardized protocol integrating common approaches identified in the systematic review and investigator questionnaire. Investigators will conduct 10-12 of these IVC stenosis procedures and record the incidence of thrombus formation and thrombus weight at 48 hours after induction. Intra- and inter-investigator variation will be determined with respect to thrombus incidence and thrombus weight as an indication of reproducibility.

Study Population:

List the inclusion and exclusion criteria, eligibility, patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number.
Suggested length 2-3 paragraphs

Not Applicable

Infrastructure:

Description of project set-up, management, operational requirements and resources.

Phase 1: Covidence systematic review software is available to the PI and will be used to search the literature. Computational resources are available in the PI's laboratory to conduct the proposed work. The project PI will serve as the coordinator and point of contact for this phase of the study.

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Phase 2: Computational resources necessary to integrate responses from the investigator questionnaire. Assistance from the SSC may be needed to facilitate distribution of the investigator questionnaire to interested parties. The project PI will serve as the coordinator and point of contact for this phase of the study.

Phase 3: Experimental evaluation will require dissemination of a standardized protocol to study investigators. Funds will be required to facilitate study investigators obtaining mice suitable for use in the evaluation. Funds may also be required to support purchasing of surgical consumables to be sent to study investigators. The project PI will serve as the coordinator and point of contact for this phase of the study.

Timeline and Milestones:

Project stage/set up: July 2022

Launch: October 2022

Duration: 2 years

Finalization/analysis: October 2024

Reporting (annual at minimum): Annually

Publication:

Manuscript 1 - Systematic Review and Investigator Questionnaire Analysis, October 2023

Manuscript 2 - Experimental Evaluation of standardized procedure, October 2024

Expected Outcomes:

Describe potential for future collaboration, funded research grant, publication (specify type – SSC Communications, Guidance Document, Original Article, etc.):

1. This project will establish a network of study investigators with expertise in the IVC stenosis models of thrombosis that may lead to future collaborations on aspects of venous thrombosis research.
2. This project should lead directly to the submission of 2 manuscripts for publication (1xSSC communication, 1x Original Article). It is hoped that bringing together study investigators on this project may also facilitate drafting of an additional review on insights gained from the IVC stenosis model.

Possible References:

1. Geddings J, Aleman MM, Wolberg A, von Bruhl ML, Massberg S, Mackman N. Strengths and weaknesses of a new mouse model of thrombosis induced by inferior vena cava stenosis:

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communication from the SSC of the ISTH. J Thromb Haemost. 2014;12:571-573. doi: 10.1111/jth.12510

2. Diaz JA, Obi AT, Myers DD, Jr., Wroblewski SK, Henke PK, Mackman N, Wakefield TW. Critical review of mouse models of venous thrombosis. Arterioscler Thromb Vasc Biol. 2012;32:556-562. doi: 10.1161/ATVBAHA.111.244608

3. Diaz JA, Saha P, Cooley B, Palmer OR, Grover SP, Mackman N, Wakefield TW, Henke PK, Smith A, Lal BK. Choosing a mouse model of venous thrombosis: a consensus assessment of utility and application. J Thromb Haemost. 2019;17:699-707. doi: 10.1111/jth.14413

4. Grover SP, Evans CE, Patel AS, Modarai B, Saha P, Smith A. Assessment of Venous Thrombosis in Animal Models. Arterioscler Thromb Vasc Biol. 2016;36:245-252. doi: 10.1161/ATVBAHA.115.306255