Abstract Text:

DESCRIPTION (provided by applicant): Saphenous vein graft (SVG) closure after coronary artery bypass grafting (CABG) is an underreported and poorly understood problem. Imperfect surgical technique is frequently blamed but this can be detected using flow measurement technology, allowing us to focus on other causal factors. We have developed clinical tools to show that endothelial cell (EC) disruption in the saphenous vein graft (SVG) and aspirin resistance (ASA-R) after CABG are significant predictors of graft failure. Analysis of coronary sinus (CS) blood samples obtained from these patients revealed that the level of F1.2, a marker of thrombin formation, relates to ASA-R and abnormalities of blood flow and EC integrity in the SVG (i.e. Virchow’s triad). On the basis of this and other observations, we hypothesize that a dysregulated burst of thrombin within the SVG is a common pathway in the development of graft failure. This hypothesis will be tested first with an animal model in order to establish that controlled manipulations in SVG thrombogenicity and the other components of Virchow’s triad have a consistent and measurable impact of thrombin within the SVG. We have developed a comprehensive strategy for analyzing the role of thrombin in our porcine CABG model by monitoring its stimulus (tissue factor), formation (F1.2 peptide release), deposition (activity assessed directly on the SVG lumen), effects (imaging of mural thrombus and analysis of platelet derived microparticles) and inhibition (TAT complex). Novel approaches to prevent thrombin production within the high risk SVG will be tested. Because it is difficult to model ASA-R and other common clinical risk factors for SVG thrombosis in animals, a sufficiently powered clinical trial will be required to establish the link between a burst in thrombin production within the SVG and early graft failure. Lay Description: Familiarity, concerns about the safety of alternatives, and acceptable intermediate-term results have led to established practice patterns such as use of aspirin as the sole antiplatelet agent and routine use of the SVG as a conduit for most bypass cases. Definitive alterations in management strategies after CABG await a clear understanding of why grafts fail and the elucidation of treatable risk factors, e.g. regional thrombin dysregulation. Because anticoagulation is not harmless in these patients, reliable identification of the risk of SVG failure would provide a rationale basis to selectively intervene and optimize graft patency without increasing bleeding in the population as a whole.

Project Terms:

Accounting; Animal Model; Animals; Anticoagulation; Antiplatelet Drugs; Aspirin; base; Biological Assay; Blood; Blood flow; Blood Platelets; Blood specimen; Bypass; catalyst; cell injury; Clinical; Clinical Research; Clinical Trials; Closure; Coagulation Process; Complex; Coronary Artery Bypass; Coronary sinus structure; day; Defect; Deposition; Development; Disruption; Endothelial Cells; Exclusion; Familiarity; Family suidae; Feedback; Fibrinolytic Agents; Future; graft failure; Hemorrhage; Hour; Human; Image; Intravascular Thrombus Formation; Lead; Link; Measurable; Measurement; Mediating; Modeling; Monitor; novel; novel strategies; Operative Surgical Procedures; Pathway interactions; Patients; Pattern; Peptides; Platelet Function Tests; Population; Postoperative Period; prevent; Production; programs; Prothrombin; Regulation; Research Personnel; Resistance; Risk; Risk Factors; Role; Safety; Saphenous Vein; Stimulus; Stress; Sus scrofa; Techniques; Technology; Testing; Thrombin; Thromboplastin; Thrombosis; Thrombus; Time; tool; Translating; Translations; Triad Acrylic Resin; Work

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Department / Educational Institution Type:

SURGERY
SCHOOLS OF MEDICINE

Congressional District:

State Code: MD
District: 07

Other Information:

FOA:

Study Section: Clinical and Integrative Cardiovascular Sciences Study Section (CICS)
Fiscal Year: 2007 Award Notice Date: 31-JAN-2007

Project Start Date: 1-FEB-2007
Budget Start Date: 1-FEB-2007

DUNS Number: 188435911

Project End Date: 31-JAN-2012
Budget End Date: 31-JAN-2008

CFDA Code: 837

Administering Institutes or Centers:

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Project Funding Information for 2007:

Total Funding: $545,579

Year: 2007
Funding IC: NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
FY Total Cost by IC: $545,579
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No Subprojects information available for 1R01HL084080-01A1