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(54) Title: TESTING LUMENECTOMY SAMPLES FOR MARKERS OF NON-VASCULAR DISEASES

(57) Abstract: Lumenectomy material is tested to determine the presence or likelihood of a condition of a patient. The lumenectomy material is in the form of at least one continuous tissue strand collected *in vivo* from an inner surface of a body lumen of the patient. The presence of at least one marker of a disease is determined. The disease may be hypertension, hyperlipidemia, depression, obesity, metabolic syndrome, insulin resistance, kidney damage, or diabetes. The patient is identified as having or as likely to develop the disease if a marker of the disease is identified in the lumenectomy material of the patient.

TESTING LUMENECTOMY SAMPLES FOR MARKERS OF NON-VASCULAR DISEASES

TECHNICAL FIELD

0001 This invention is related to the area of disease diagnosis and prognosis. In particular, it relates to testing for disease markers in lumenectomy samples, such as samples from a blood vessel.

BACKGROUND OF THE INVENTION

0002 Cardiovascular disease frequently arises from the accumulation of atheromatous material on the inner walls of vascular lumens, particularly arterial lumens of the coronary and other vasculature, resulting in a condition known as atherosclerosis. Atherosclerosis occurs naturally as a result of aging, but may also be aggravated by factors such as diet, hypertension, heredity, vascular injury, and the like. Atheromatous and other vascular deposits restrict blood flow and can cause ischemia which, in acute cases, can result in myocardial infarction. Atheromatous deposits can have widely varying properties, with some deposits being relatively soft and others being fibrous and/or calcified. In the latter case, the deposits are frequently referred to as plaque.

0003 One conventional treatment for cardiovascular disease is the use of stents. Endolumenal stents are commonly used to treat obstructed or weakened body lumens, such as blood vessels and other vascular lumens. Once deployed in the blood vessel, the stent can remain in the body lumen where it will maintain the patency of the lumen and/or support the walls of the lumen which surround it. One factor impeding the success of stent technology in endolumenal treatments is the frequent occurrence of in-stent restenosis, characterized by proliferation and migration of smooth muscle cells within and/or adjacent to the implanted stent, causing reclosure or blockage of the body lumen.

0004 Atherosclerosis and restenosis can be treated in a variety of ways, including drugs, bypass surgery, and a variety of catheter-based approaches which rely on intravascular debulking or removal of the atheromatous or other material occluding a blood vessel. Of particular interest to the present invention, a variety of methods for cutting or dislodging

material and removing such material from the blood vessel have been proposed, generally being referred to as atherectomy procedures. Atherectomy catheters intended to excise material from the blood vessel lumen generally employ a rotatable and/or axially translatable cutting blade which can be advanced into or past the occlusive material in order to cut and separate such material from the blood vessel lumen. In particular, side-cutting atherectomy catheters generally employ a housing having an aperture on one side, a blade which is rotated or translated by the aperture, and a balloon to urge the aperture against the material to be removed.

0005 Although atherectomy catheters have proven very successful in treating many types of atherosclerosis and in-stent restenosis, improved atherectomy catheters and methods are continuously being pursued. For example, many currently available side-cutting atherectomy catheters have difficulty in capturing occluding material in the cutting aperture. To facilitate material capture, the cutting aperture is frequently elongated to increase the area into which the material can penetrate. Such elongation typically requires an equivalent lengthening of the cutter housing. Since most cutter housings are rigid, such lengthening makes it more difficult to introduce the distal end of the catheter through tortuous regions of the vasculature.

0006 Another shortcoming of many currently available atherectomy catheters is that they typically require a balloon positioned opposite the cutting window to urge the cutting window into contact with occluding material. Such balloons, however, unduly increase the size of the distal portion of the catheter. Even with the balloon, the amount of material that can be removed by conventional atherectomy catheters is limited by the size of the cutting window. Other disadvantages of some catheters include cutting elements with less than ideal hardness, inadequate storage space within the catheter for containing removed material, sub-optimal guide wire lumens, and/or the like. In addition, the available atherectomy catheters generally provide material insufficient in quantity and/or quality for testing by many histological, array, proteomic or other biochemical or molecular methods. For example, in one report a device and method available to the artisan collected less than about 50 mg of tissue. (Safian et al., *Circulation* 82: 305-307 (1990)). This amount of material is not typically enough to carry out more than one test, or is insufficient to successfully carry out a number of diagnostic tests available to the physician or researcher.

0007 Recently atherectomy catheters have been developed which can access small, tortuous regions of the vasculature and remove atheromatous and other occluding materials from within blood vessels and stents in a controlled fashion. In particular, these atherectomy catheters facilitate capturing and invagination of atheromatous materials. Particularly, these catheters are capable of in vivo capturing and removing of continuous tissue strands of sufficient quantity and quality for testing in vitro. These catheters and methods of their use are adaptable for use in a variety of body lumens, including but not limited to coronary and other arteries.

0008 There is a continuing need in the art to develop new methods for accurate and early assessments of disease states and incipient or imminent disease states.

DISCLOSURE OF THE INVENTION

0009 One aspect of the invention provides a method of determining the presence or likelihood of a condition of a patient. A lumenectomy material comprising at least one continuous tissue strand collected in vivo from an inner surface of a body lumen of a subject is tested for the presence of at least one marker of a disease selected from the group consisting of hypertension, hyperlipidemia, depression, obesity, metabolic syndrome, insulin resistance, kidney damage, and diabetes. The patient is identified as having or as likely to develop the disease if a marker of the disease is identified in the lumenectomy material of the subject.

0010 This and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with methods for detection, diagnosis, and prognosis of diseases.

DETAILED DESCRIPTION OF THE INVENTION

0011 The inventors have developed methods for testing for the presence or likelihood of certain diseases. Rather than testing for certain disease markers in serum, for example, the present methods test for disease markers in lumenectomy samples, such as atherectomy samples.

00012 Diseases which can be evaluated using the method of the invention include, but are not limited to, hypertension, hyperlipidemia, depression, obesity, diabetes, insulin resistance, metabolic syndrome, kidney disease, and kidney damage. Lumens from which the test sample can be harvested include blood vessels, such as the coronary artery, the gastrointestinal tract, such as the intestine, airways, such as the bronchi and the trachea, tear ducts, mammary ducts, kidney tubules, ureters, bladders, urethras, vas deferens, epididymis, and fallopian tubes.

00013 Lumenectomy catheters which can be used to collect the samples of the present invention are described in U.S. application publication no. 20050177068, the disclosure of which is expressly incorporated herein. Other lumenectomy catheters which provide sufficient material for testing may also be used. In certain embodiments the amount of material collected can be about 1 mg to about 2000 mg, more typically the amount of material can be about 1 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 500 mg to about 600 mg, about 600 mg to about 700 mg, about 700 mg to about 800 mg, or about 800 mg up to about 2000 mg.

00014 The material excised from the body lumen will vary in length and will depend on the catheter configuration, the type of material removed, the body lumen, and the like. However, in certain embodiments, the material will be in the form of continuous strands that have a substantially consistent depth and width of tissue cuts. The material is typically longer than the length of the cutting window (but it may be shorter), and typically as a length of at least about 2.0 mm, although the length may be between about 0.5 cm up to about 10 cm or longer in length. Advantageously, the planning action of the catheter provides a material tissue structure that reflects the actual in vivo tissue structure, and provides information about larger portions of the disease state of the body lumen.

00015 Markers which can be tested are any for which an association has been established between the marker and the disease or imminent onset of the disease. Markers can be, for example, proteins, enzymes, or RNAs. The marker can be the presence or absence of a substance or an increased or decreased level of the substance. The material collected from the body lumen is typically a continuous strip of tissue that may be longer than the cutting window of the lumenectomy catheter. This material can provide a sufficient amount of

sample material of a quality and quantity that can be used for one or more of genomic screening, DNA hybridization, RNA hybridization, gene expression analysis, PCR amplifications, proteomic testing, drug efficacy screening, protein marker detection, DNA marker detection, RNA marker detection, histological testing, histopathology, cytopathology, cell and tissue type analysis, biopsy, or the like. In addition, the material collected may be sufficient in amount and quality for testing for one or more of the presence of a DNA, and RNA, or a protein marker.

00016 Generally the markers may be in the category of apoptotic markers, cell cycle proteins, transcriptional factors, proliferative markers, endothelial growth factors, adhesion molecules, cytokines, chemokines, chemokine receptors, inflammation markers, coagulation factors, fibrinolytic factors, oxidative stress related molecules, extracellular matrix molecules, interleukins, growth factors, glycoproteins, proteoglycans, cell-surface markers, serum markers, or immune factors. Other types of markers which are established as associated with the diseases may be used as well.

00017 Specific markers which may be used include C-reactive protein, interleukin-6, and/or intracellular adhesion molecule-1 for depression; angiotensin II, aldosterone, and/or atrial natriuretic factor for hypertension; tissue factor pathway inhibitor, plasminogen activator inhibitor-1, triglycerides, and/or apolipoprotein B for hyperlipidemia; triglycerides for insulin resistance; low density lipoprotein, Remnant-like particles-cholesterol and/or triglycerides for diabetes; triglycerides-rich lipoproteins for kidney damage. Other markers as are known in the art and which are associated with specific diseases can be used as well, without limitation.

00018 Particular types of tests that can be carried out successfully on the excised lumenectomy material removed by the methods of the present invention include, but are not limited to, enzyme histochemistry, immunohistology, immunocytochemistry, immunoassays, immunofluorescent assays, immunoprecipitation assays, ELISA, flow cytometry, fluorescent activated cell sorting, radioimmunochemistry, electrophoresis, two-dimensional gel electrophoresis, Western blotting, protein sequencing, mass spectrometry, proteomic analysis, and protein microarray analysis. Further, Northern blotting, RNase protection assays, in situ hybridization assays, DNA microarray testing, reverse transcription polymerase chain reaction PCR (RT-PCR), Southern blotting, DNA sequencing, PCR amplification, single strand conformational polymorphism assays, single strand polymorphism (SNP) assays, and

serial analysis of gene expression (SAGE) assays can be successfully carried out with the lumenectomy material compositions collected by the disclosed methods.

00019 Prior to using the harvested material, the material can optionally be placed in a preserving agent, a tissue fixative, or a preparation agent compatible with a particular test to be run. Agents known in the art for preserving, fixing or preparing the material for later use include, for example, saline, heparinized saline, liquid nitrogen, formalin, a membrane lysis agent, an RNA or DNA preparation agent, and the like. The material can be collected in a single access or can be collected in multiple transluminal accesses in the same patient. Further, the material is typically at least one substantially consistent, continuous strip of material that maintains the structure of the material as it was removed from the inner surface of the lumen of the patient. Also, sample material can be collected from one, two, or more sites in the same or a different body lumen of a patient.

00020 The lumenectomy catheters can achieve selective plaque excision, *i.e.*, they can specifically target diseased areas. Thus the samples are enriched in disease markers, relative to serum samples, in which disease markers are diluted with other substances from non-diseased tissues. Nonetheless, serum testing may be performed in conjunction with the lumenectomy evaluation, and the results used, for example, to confirm each other.

00021 The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

References

00022 The disclosure of each reference cited is expressly incorporated herein.

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CLAIMS:

1. A method of determining the presence or likelihood of a condition of a patient comprising:
testing lumenectomy material comprising at least one continuous tissue strand
collected *in vivo* from an inner surface of a body lumen of a subject for the presence of at
least one marker of a disease selected from the group consisting of hypertension,
hyperlipidemia, depression, obesity, metabolic syndrome, insulin resistance, kidney damage,
and diabetes; and

identifying the patient as having or as likely to develop the disease if a marker of the
disease is identified in the lumenectomy material of the subject.

2. The method of claim 1 wherein the disease is hypertension.
3. The method of claim 1 wherein the disease is hyperlipidemia.
4. The method of claim 1 wherein the disease is depression.
5. The method of claim 1 wherein the disease is obesity.
6. The method of claim 1 wherein the disease is diabetes.
7. The method of claim 1 wherein the disease is insulin resistance.
8. The method of claim 1 wherein the disease is metabolic syndrome.
9. The method of claim 1 wherein the disease is kidney disease.
10. The method of claim 4 wherein the marker is C-reactive protein.
11. The method of claim 4 wherein the marker is interleukin-6.
12. The method of claim 4 wherein the marker is intracellular adhesion molecule-1.
13. The method of claim 2 wherein the marker is angiotensin II.
14. The method of claim 9 wherein the marker is intracellular adhesion molecule-1.
15. The method of claim 9 wherein the marker is vascular adhesion molecule-1.

16. The method of claim 9 wherein the marker is monocyte chemoattractant protein-1.
17. The method of claim 2 wherein the marker is aldosterone.
18. The method of claim 2 wherein the marker is atrial natriuretic factor.
19. The method of claim 3 wherein the marker is tissue factor pathway inhibitor.
20. The method of claim 3 wherein the marker is plasminogen activator inhibitor-1.
21. The method of claim 3 wherein the marker is triglycerides.
22. The method of claim 3 wherein the marker is apolipoprotein B.
23. The method of claim 7 wherein the marker is triglycerides.
24. The method of claim 6 wherein the marker is triglycerides.
25. The method of claim 6 wherein the marker is low density lipoprotein (LDL) particles.
26. The method of claim 6 wherein the marker is Remnant-like particles-cholesterol (RLP-C).
27. The method of claim 9 wherein the marker is triglyceride-rich lipoproteins (TRL).
28. The method of claim 1 further comprising testing serum of the subject for the presence of the at least one marker.