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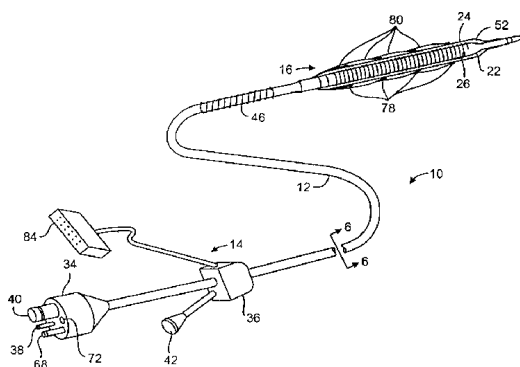
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(54) 【発明の名称】脆弱性プラークを検出および治療するための凍結療法

(57) 【要約】

本発明は、管腔表面を有する血管の脆弱性プラークを検出および/または治療するための方法、装置およびキットを提供する。検出方法は、管腔表面に沿って温度差をその管腔表面に熱的に接続した温度センサ(78)によって感知する工程を有する。治療方法は、急性冠状動脈症候群を抑制するとともに体腔の開通性の維持を補助するために、前記脆弱性プラーク内の保持流体の放出を抑制するべく脆弱性プラークを制御され安全な状態で低温冷却する工程を有する。治療方法は、パッシベーションの一次処置等の追加の治療を含むことができる。



【特許請求の範囲】

【請求項 1】

血管の脆弱性プラークを治療する方法であって、前記脆弱性プラークが、流体を放出可能な状態で保持しており、前記方法は、
前記脆弱性プラークの近傍の前記血管を、前記保持流体の前記血管への放出を抑制するのに十分な温度にまで冷却する工程を包含する、方法。

【請求項 2】

請求項 1 に記載の方法であって、前記冷却工程は、
前記血管の管腔にカテーテルを導入する工程と、
前記脆弱性プラークの近傍の前記血管管腔内に第 1 バルーンを配置する工程と、
前記第 1 バルーンに低温冷却流体を導入する工程と、
前記冷却流体を排出する工程と、
前記第 1 バルーン上に配置された第 2 バルーンを膨張させて前記血管管腔に半径方向から密着させる工程と
を包含する、方法。

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【請求項 3】

請求項 2 に記載の方法であって、前記第 1 バルーンの外面の温度は、約 - 25 ~ - 45 の範囲であり、前記第 2 バルーンの外面の温度は、約 10 ~ - 40 の範囲である、方法。

【請求項 4】

請求項 1 に記載の方法であって、前記血管は動脈である、方法。

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【請求項 5】

請求項 1 に記載の方法であって、前記脆弱性プラークの前記流体は脂質リッチ液体を含む、方法。

【請求項 6】

請求項 5 に記載の方法であって、前記脆弱性プラークは、前記脂質リッチ液体と前記血管の管腔との間の細胞の帽部を含む、方法。

【請求項 7】

請求項 6 に記載の方法であって、さらに、前記脂質リッチ液体の近傍の組織のアポトーシスを抑制する工程を包含する、方法。

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【請求項 8】

請求項 6 に記載の方法であって、前記冷却工程は、前記細胞の帽部の破断を抑制する、方法。

【請求項 9】

請求項 1 に記載の方法であって、前記冷却工程は、前記血管表面の温度を、約 15 秒 ~ 120 秒の時間、約 10 ~ - 40 へ低下させる工程を包含する、方法。

【請求項 10】

請求項 5 に記載の方法であって、さらに、前記脂質リッチ液体を高度に秩序的な六方格子状態へ冷却することによって前記脆弱性プラークを安定化させる工程を包含する、方法。

【請求項 11】

請求項 10 に記載の方法であって、前記脂質リッチ液体は、少なくともゲル状態まで硬化される、方法。

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【請求項 12】

請求項 1 に記載の方法であって、前記冷却工程は、前記脆弱性プラークの炎症を抑制する、方法。

【請求項 13】

請求項 1 に記載の方法であって、前記冷却工程は、前記脆弱性プラークの悪化を抑制する、方法。

【請求項 14】

請求項 1 に記載の方法であって、さらに、前記脆弱性プラークを一次処理によって治療す

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る工程を包含する、方法。

【請求項 15】

請求項 14 に記載の方法であって、前記一次処置は、血管形成術、ステント処理、および関節切除のうちの少なくとも 1 つを含む、方法。

【請求項 16】

請求項 5 に記載の方法であって、前記脂質リッチ液体のサイズを縮小することによって、あるいはその密度または組成を改変することによって前記脆弱性プラークを不活性化する工程をさらに包含する、方法。

【請求項 17】

請求項 16 に記載の方法であって、前記不活性化は、前記脆弱性プラークの化学的性質またはライフサイクルを改変することによって行われる、方法。 10

【請求項 18】

請求項 6 に記載の方法であって、さらに、前記細胞の帽部の厚みを増加させることによって前記脆弱性プラークを不活性化する工程を包含する、方法。

【請求項 19】

血管の脆弱性プラークを治療する方法であって、前記脆弱性プラークが、流体を放出可能な状態で保持しており、前記方法は、前記脆弱性プラークを検出する工程と、前記脆弱性プラークの近傍の前記血管を、前記保持流体の前記血管への放出を抑制するのに十分な温度にまで冷却する工程とを包含する、方法。 20

【請求項 20】

血管の脆弱性プラークを検出する方法であって、前記方法は、プラークの近傍の前記血管管腔内にバルーンを配置する工程と、前記バルーンに貼り付けられた複数の温度センサが前記血管管腔の表面に接続されるように前記バルーンを膨張させる工程と、前記管腔表面に沿った温度差を前記センサによって感知する工程とを包含する、方法。

【請求項 21】

請求項 20 に記載の方法であって、前記複数の温度センサは、熱電対またはサーミスタを含む、方法。 30

【請求項 22】

請求項 20 に記載の方法であって、前記複数の温度センサは、前記バルーンの周部に貼り付けられている、方法。

【請求項 23】

請求項 20 に記載の方法であって、前記複数の温度センサは、約 0.1 より大きい温度差を検出する、方法。

【請求項 24】

請求項 20 に記載の方法であって、前記膨張工程は、流体またはガスによって行うことができる、方法。 40

【請求項 25】

請求項 20 に記載の方法であって、さらに、前記検出された脆弱性プラークを、前記血管を前記脆弱性プラークの近傍で、保持流体の前記血管内への放出を抑制するのに十分な温度にまで冷却することによって治療する工程を包含する、方法。

【請求項 26】

管腔表面を有する血管の脆弱性プラークを検出し治療するための凍結療法カテーテルであって、前記カテーテルは、近端部と遠端部とこれらの間に延出する冷却流体供給管腔および排出管腔とを有するカテーテル本体と、前記カテーテル本体の前記遠端部に配置された第 1 バルーンであって、前記第 1 バルーン 50

は前記供給管腔および前記排出管腔に流体連絡する内面を有する、第1バルーンと、前記第1バルーン上にその間に熱バリアを形成した状態で配置される第2バルーンと、前記管腔表面の温度測定を提供するべく前記第2バルーンに貼り付けられた複数の温度センサと

を備えた、凍結療法カテーテル。

【請求項27】

請求項26に記載の凍結療法カテーテルであって、前記複数の温度センサは、前記第2バルーンの外面に貼り付けられている、凍結療法カテーテル。

【請求項28】

請求項27に記載の凍結療法カテーテルであって、前記複数の温度センサは、前記管腔表面の直接温度測定を提供する、凍結療法カテーテル。 10

【請求項29】

請求項26に記載の凍結療法カテーテルであって、前記複数の温度センサは前記第2バルーンの内面に貼り付けられている、凍結療法カテーテル。

【請求項30】

請求項26に記載の凍結療法カテーテルであって、前記複数の温度センサは、熱電対またはサーミスタである、凍結療法カテーテル。

【請求項31】

請求項26に記載の凍結療法カテーテルであって、前記複数の温度センサは、前記第2バルーンの周部に貼り付けられている、凍結療法カテーテル。 20

【請求項32】

請求項26に記載の凍結療法カテーテルであって、さらに、前記カテーテルの前記近端部に温度読み取り装置へのコネクタを備える、凍結療法カテーテル。

【請求項33】

管腔表面を有する血管の脆弱性プラークを検出するためのカテーテルであって、前記カテーテルは、近端部と遠端部とこれらの間の供給管腔および排出管腔とを有するカテーテル本体と、前記カテーテル本体の前記遠端部に配置されたバルーンであって、前記バルーンは、前記供給管腔および前記排出管腔に流体連絡する内面を有する、バルーンと、前記管腔表面の温度測定を提供するべく前記バルーンによって支持された複数の温度センサと 30

を備えた、カテーテル。

【請求項34】

請求項33に記載のカテーテルであって、前記複数の温度センサは、前記管腔表面の直接温度測定を提供するべく前記バルーンの外面に貼り付けられている、カテーテル。

【請求項35】

請求項33に記載のカテーテルであって、さらに、前記カテーテルの前記近端部に温度読み取り装置に対するコネクタを備える、カテーテル。

【請求項36】

請求項35に記載のカテーテルであって、さらに、前記コネクタに取付けられて温度差を測定する回路を備える、カテーテル。 40

【請求項37】

請求項36に記載のカテーテルであって、さらに、前記コネクタに配置されたインジケータを備える、カテーテル。

【請求項38】

請求項33に記載のカテーテルであって、前記複数の温度センサは、熱電対またはサーミスタを備える、カテーテル。

【請求項39】

請求項33に記載のカテーテルであって、前記複数の温度センサは、第2バルーンの周部に貼り付けられている、カテーテル。 50

【請求項 40】

血管の脆弱性プラークを治療するためのキットであって、前記脆弱性プラークが、流体を放出可能な状態で保持しており、前記キットは、近端部と遠端部と冷却部材とを有するカテーテルと、前記カテーテルの使用取扱説明書であって、前記使用取扱説明書は、前記保持流体の前記血管内への放出を抑制するべく前記脆弱性プラークの近傍の前記血管を冷却するステップを含む、使用取扱説明書とを含む、キット。

【請求項 41】

血管の脆弱性プラークを検出するためのキットであって、前記キットは、近端部と遠端部とその遠端部の近傍に複数の温度センサを備えたバルーン部材とを有するカテーテルと、請求項 20 ~ 25 のいずれかに従って、前記カテーテルを使用するための取扱説明書とを含む、キット。

【発明の詳細な説明】

【0001】

発明の背景

1. 発明の分野

本発明は、一般に、血管を治療するための方法、装置およびキットに関する。より詳細には、本発明は、卒中や不安定狭心症の急性心臓症候群、心筋硬塞、および突然心臓死の原因となり得るもの等の血管内の有害な放出を抑制するために、患者の血管内の病巣、特に脆弱性 (vulnerable) アテローム硬化性プラークを治療するための方法、装置およびキットを提供するものである。

【0002】

アテローム硬化性プラークは、大半の成人においてある程度存在する。プラークは、開放血管管腔を狭めることによって、血管を通る血液流を大幅に限定させ得る。この狭め作用、すなわち狭窄は、多くの場合、乏血性心疾患の原因となる。幸運なことに、患者の血管系のアテローム硬化性プラークを治療するために、多くの経皮血管内処置が開発されている。これらの治療法のうちで最も成功しているものは、経皮経管動脈形成術 (PTA) である。PTA は、狭窄部位を越えて適切な血液流を回復するように血管の狭窄領域を拡張させるために、通常は膨張可能バルーンとして構成される膨張可能な遠端部を備えるカテーテルを使用する。狭窄領域を開放するための他の処置としては、方向性冠動脈じゅく腫切除、レーザ血管形成術、ステント等がある。単体または組み合わせで使用されることにより、これらの経皮血管内処置は、プラークによって引き起こされる狭窄の治療に大きく役立ってきた。

【0003】

プラーク誘発性狭窄の治療は、ここ数十年の間に大きく進歩してきたが、血管プラークに関連する罹患率と死亡率は相変わらず高い。最近の研究は、プラークは、標準的な狭窄プラークと脆弱性プラークとの二つの一般的タイプのいずれかに大きく分類され得ることを示している。時に、耐血栓症性プラークと称される狭窄プラークは、一般に、上述した血管内管腔開放技術によって効果的に処置可能である。それらによって誘発される狭窄は治療が必要であるかもしれないが、これらのアテローム硬化性プラーク自身は多くの場合良性であって、効果的に治療可能な疾患である。

【0004】

残念ながら、プラークが成熟するにつれて、平滑筋細胞の増殖、細胞間質の合成、および脂質蓄積によって血管が狭まる結果、標準的な狭窄プラークと極めて異なるプラークが形成され得る。このようなアテローム硬化性プラークは、血栓症を引き起こしやすく、極めて危険であり得る。この血栓症性または脆弱性プラークは、急性心臓症候群の頻繁な原因となり得る。

【0005】

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これらの脆弱性（そして潜在的に生命を脅かす）プラークの特徴付けが現在研究されている。脆弱性プラークを検出するために多くのストラテジーが提案されている。これらの提案されているストラテジーには、血管造影法、血管内超音波法、血管顕微鏡検査法、磁気共鳴撮像法、磁気共鳴拡散撮像法、分光法、赤外線分光法、シンチグラフィ、光干渉断層撮像法、電子ビーム演算断層撮影スキニング法、およびサーモグラフィがあるが、これらはすべてその有効性に限界があった。特に、提案されているサーモグラフィ法は、脆弱性プラークは通常炎症を起こしており、従って標準的な狭窄性プラークよりも多くの熱を発生することから、温度変化を検出するものである。現在のサーモグラフィ法は、非常にその効果が期待されるものではあるが、それらもまだ温度感度が限定されているという欠点があり、それによって多くの場合、脆弱性プラークの検出の精度が低くなる。

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【0006】

公知のプラーク治療処置法は広く受け入れられており、標準的な狭窄性プラークの治療に良好な有効性を示しているが、それらは血栓状態がアテローム硬化性プラークに重なっている場合は有効でない（そして危険でもあり得る）。具体的には、PTAやステント処置などの一次処置によって引き起こされる機械的応力によって、脆弱性プラークから血液流への流体および/または固体の放出が実際にトリガーされ、それによって心臓血栓閉塞を引き起こす可能性がある。

【0007】

これらの理由により、血管中の脆弱性プラークの検出および治療のための方法、装置およびキットを提供することが望まれている。これらの方法および装置は、好ましくは経皮的方法により、血管内および管内導入用に適したものであるべきである。その新規な方法および装置が、脆弱性プラークを精度良く検出することが可能で、および/または隣接する組織に対する悪影響を最小限にしながらその治療を非常に良好に制御されかつ安全な方法で行うことができることが特に望ましい。さらに、それらの治療法、装置およびキットは、最小限の副作用で脆弱性プラークの放出を抑制するのに有効であるべきである。これらの課題の少なくとも一部が本明細書中に記載される本発明によって達成される。

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【0008】

2. 背景技術の説明

低温外科形成装置および方法がWO98/38934に記載されている。患者の血管内を冷却または加熱するためのバルーンカテーテルが米国特許第5,486,208号とWO91/05528とに記載されている。子宮内摘出を行うための膨張可能ブラダーを備えた冷凍外科用プローブが米国特許第5,501,681号に記載されている。ジュール・トムソン冷却に基づく冷凍外科用プローブが、米国特許第5,275,595号、同第5,190,539号、同第5,147,355号、同第5,078,173号、および同第3,901,241号に記載されている。血管形成術後およびその他の治療用の加熱バルーンを備えたカテーテルが、米国特許第5,196,024号、同第5,191,883号、同第5,151,100号、同第5,106,360号、同第5,092,841号、同第5,041,089号、同第5,019,075号、および同第4,754,752号に記載されている。低温流体源が米国特許第5,644,502号、同第5,617,739号、および同第4,336,691号に記載されている。次の米国特許も本発明に関連し得る（米国特許第5,458,612号、同第5,545,195号、および同第5,733,280号）。

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【0009】

サーモグラフィは、ワード キャッセルズらのザブルネラブルアテロスクレロチックプラーク：アンダースタンディング、アイデンティフィケーション、アンドモディフィケーション（The Vulnerable Atherosclerotic Plaque: Understanding, Identification, and Modification），第13章、pp. 231-242（1999）、およびL. ディアマンポラスらの<http://www.eurekalert.org/releases/aha-at1041499.html>に記載されている。脂質膜に対す

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る低温の影響は、ジャック クループのアドバンスインモレキュラーアンドセルバイオロジ（Advances in Molecular and Cell biology），第19巻、pp. 143 - 192（1997）、P. J. クインのクライオバイオロジ（Cryobiology），第22巻、pp. 128 - 146（1985）；およびマイケル J. テイラー博士のバイオロジオブセルサバイバルインザコールド（ハーウッドアカデミックパブリッシャ、印刷中）（Biology Of Cell Survival In The Cold（Harwood Academic Publishers In Press））に記載されている。

【0010】

上記参考文献それぞれの全開示内容は、本明細書中で参考として援用される。

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【0011】

発明の要旨

本発明は、患者の血管内の脆弱性プラークの検出と凍結療法とを提供する。血管は、静脈、動脈（特に、冠状動脈）を含む患者の血管において、いかなる血管であってもよい。血管は通常、脆弱性プラークから少なくとも部分的に一部狭窄されている。特に本発明は、急性心臓症候群を抑制し、体腔の開通性の維持を補助するために、脆弱性プラーク内の保持流体の放出を抑制することができる。本発明はまた、卒中予防のための頸動脈の脆弱性プラークの治療も提供する。患者の血管系は、脆弱性プラークと標準の狭窄性プラークとの両方を有する場合、本明細書に記載の治療技術は、必要に応じて、標準の狭窄性プラークを実質的に冷却することなく、脆弱性プラークに選択的に向けることができる。別実施形態において、両方のタイプのプラークが治療可能である。

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【0012】

第1の態様において、本発明は、血管の脆弱性プラークを治療するための方法を提供する。この方法は、脆弱性プラークの近傍の血管をこの脆弱性プラーク内の保持流体の血液流への放出を抑制するのに十分な温度にまで冷却する工程を包含する。冷却治療は、多くの場合、血管の管腔の周部表面の全部または一部に対して向けられ、好ましくは脆弱性プラークによって放出可能に保持された脂質リッチ液体が放出されることを抑制する。

【0013】

血管の冷却は、血管の管腔にカテーテルを導入することによって行うことができる。脆弱性プラークの近傍の血管管腔に第1バルーンが配置される。この第1バルーンに低温冷却流体が導入され、そこから排出される。前記第1バルーン上に配置された第2バルーンを膨張させて、血管管腔に半径方向から密着させる。一般に、前記第1バルーンの内面の温度は、約 - 55 ~ - 75 の範囲であり、前記第1バルーンの外表面は、約 - 25 ~ - 45 の範囲である。前記第2バルーンの外表面の温度は、約 10 ~ - 40 の範囲であり、好ましくは、約 10 ~ - 20 、より好ましくは、約 5 ~ - 10 の範囲である。

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【0014】

通常、前記血管管腔の細胞表面の温度は、約 10 ~ - 40 、好ましくは、約 10 ~ - 20 、より好ましくは、約 5 ~ - 10 の範囲である。組織は、通常、その所望の温度に、約 15 秒 ~ 120 秒、好ましくは、30 秒 ~ 60 秒の時間維持される。冷却を通常は約 1 ~ 3 サイクル、それらのサイクルを 120 秒毎に約 1 サイクルの速度で繰り返すことによって、脆弱性プラークの安定性を高めることができる。

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【0015】

驚くべきことに、0 より高い冷却温度によって脆弱性プラークの脂質コアを、無秩序な結晶状態の流体から秩序のある結晶状態の固体またはゲルへと転移することができる。従って、脂質リッチ液体を通常約 10 ~ - 10 の範囲の転移温度で、その脂質リッチ液体の状態から高度に秩序のある六方格子状態に通常変化させるのに十分冷却することによって、脆弱性プラークを安定化することができる。冷却によって、前記脂質リッチ液体の近傍の組織、特に脂質リッチ液体と血管の管腔との間の細胞の帽部（cap）を形成している組織の壊死および/またはアポトーシスを抑制しながら、脆弱性プラークを安定化す

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ることができる。冷却処理はまた、脆弱性プラークの炎症および悪化を抑制することができる。冷却処置はさらに、脆弱性プラークの細胞の帽部の破断も抑制することができる。

【0016】

その他の態様において、本発明の脂質リッチ液体の放出を抑制するべく脆弱性プラークを冷却する方法は、追加の治療法と組み合わせることができる。例えば、1つの付属的方法は、冷却された脆弱性プラークを一次処置によって治療する方法を包含し得る。適切な一次処置としては、バルーン血管形成術、じゅく腫切除術、回転じゅく腫切除術、レーザ血管形成術等があり、ここで治療される血管の管腔は、狭窄状態を少なくとも部分的に軽減するために拡張される。前記一次処置は、さらに、ステント配置等の再狭窄を制御するための処置を含んでいてもよい。動脈の場合、一次処置は前記冷却治療の少し前、冷却治療中、好ましくは冷却治療の少し後、好ましくは冷却治療の60秒以内、さらに好ましくは、脂質リッチ液体を所望の温度へ冷却した直後に行われる。あるいは、冷却方法は、さらに、脂質リッチ液体のサイズを縮小し、その脂質リッチ液体の細胞密度または組成を変化させ、前記帽部の構造的完全性 (structural integrity) を促進し (例えば、前記帽部の厚みを増加させる)、脆弱性プラークの化学的性質またはライフサイクルを変化させることによって前記帽部の細胞組成または構造特性等を改変することによって脆弱性プラークを不活性化 (パッシベーション) する工程を包含することができる。

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【0017】

別の態様において、本発明は、流体を放出可能に保持している血管の脆弱性プラークを治療する方法を提供する。この方法は、脆弱性プラークを検出する工程と、脆弱性プラークの近傍において血管を前記保持流体が血管中に放出されることを抑制するのに十分な温度にまで冷却する工程とを包含する。

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【0018】

別の態様において、本発明は、血管の脆弱性プラークを検出する方法を提供する。この方法は、プラーク近傍の血管管腔内にバルーンを配置する工程を包含する。前記バルーンは、このバルーンに貼り付けられた複数の温度センサが血管管腔の表面に接続されるように膨張される。管腔表面に沿った温度差を前記センサによって感知する。

【0019】

別の態様において、本発明は、管腔表面を有する血管の脆弱性プラークを検出し治療するための凍結療法用カテーテルを提供する。このカテーテルは一般に、近端部と、遠端部と、それらの間に延出する冷却流体供給管腔および排出管腔とを備えるカテーテル本体を有する。前記カテーテル本体の前記遠端部の近傍に、前記供給管腔および排出管腔と流体連絡して第1バルーンが配設されている。前記第1バルーン上には、それらの間に熱バリアを形成した状態で第2バルーンが配置されている。前記管腔表面の温度測定を提供するべく前記第2バルーンには複数の温度センサが貼り付けられている。

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【0020】

別の態様において、本発明は、管腔表面を有する血管の脆弱性プラークを検出するためのカテーテルを提供する。このカテーテルは一般に、近端部と、遠端部と、それらの間に延出する供給管腔および排出管腔とを備えるカテーテル本体を有する。前記カテーテル本体の前記遠端部に、前記供給管腔および排出管腔と流体連絡してバルーンが配設されている。前記管腔表面の温度測定を提供するべく前記バルーンには複数の温度センサが支持されている。

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【0021】

別の態様において、本発明はさらに、血管中の脆弱性プラークを治療するためのキットを提供する。このキットは、近端部と、遠端部と、その遠端部の近傍の冷却部材とを備えるカテーテルを有する。前記キットには、前記カテーテルの使用のための取扱説明書が含まれている。これらの取扱説明書は、保持流体が血管に放出されることを防止するために脆弱性プラークの近傍の血管を冷却するステップを含む。このようなキットは、本明細書中に記載される任意の方法のための取扱説明書を含み得る。

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【0022】

さらに別の態様では、本発明は、血管の脆弱性プラークを検出するためのキットを提供する。このキットは、近端部と、遠端部と、その遠端部の近傍の複数の温度センサを有するバルーン部材とを有するカテーテルを備える。取扱説明書は、このカテーテルを使用するためのキットに含まれる。これらの取扱説明書は、プラークの近傍の前記血管管腔内にバルーンを配置するステップと、前記バルーンに貼り付けられた複数の温度センサが前記血管管腔の表面に接続されるように前記バルーンを膨張させるステップと、前記管腔表面に沿って温度差を前記センサによって感知するステップとを有する。このようなキットは、本明細書中に記載したいずれの方法のための取扱説明書を含んでもよい。

【0023】

詳細な実施形態の説明

本明細書中で使用されるように、「脆弱性プラーク」および「ホットプラーク」という用語は、血栓症になり易いアテローム硬化性プラークを指す。図1Aおよび1Bは、その血管の管腔104内に成熟した脆弱性プラーク102を含む血管100の断面を図示している。前記脆弱性プラーク102は一般に軟質で、脂質リッチなアテローム性粥状物質（*gruel*）からなる壊死性コア106と、このコア106をカバーする平滑筋細胞のコラーゲンマトリックスからなる繊維状の硬化帽部108とを含む。前記粥状物質は一般に、前記脆弱性プラーク102によって放出可能な状態で保持されているエステル化コレステロールおよび低濃度リポ蛋白質の液体を含む。前記帽部108の破裂または断裂によって、図2に見られるように、プラーク出血110（破断したプラークを介した高度にトロンボゲンの脂質リッチな液体106の放出）が起こり得る。プラーク出血110により、前記高度にトロンボゲンの脂質リッチな液体106が、血管管腔104の血液流に晒される。図3に図示されているように、前記トロンボゲン液体の放出によって、血管管腔全体の血栓性閉塞112（血塊）が発生し、これによって卒中や急性心臓死等の生命を脅かす状態が発生し得る。

【0024】

脆弱性の三つの決定因子が、図1Aの4-4線に沿った分解断面図である図4に図示されている。脆弱性プラークの破断に対する感受性は、主として、前記アテローム性コアのサイズ114と密度（例えば、コアが大きくなれば破断の可能性が増加する）、前記硬化帽部の厚み116と構造的完全性（例えば、帽部が薄いとき破断の可能性が増大する）、および帽部の炎症（例えば、マクロファージ泡沫細胞118の浸潤によって帽部細胞120が弱体化して破断の可能性が増大する）から決定され得る。さらに、脆弱性プラークの破断は、プラークに対してかかる種々の外的な応力によってもトリガーされ得る。例えば、管内血圧の変動、パルス圧、心臓収縮、血管痙攣等によって脆弱性プラークの破断が促進され得る。あるいは、PTAまたはステント処理などの一次処置によって引き起こされる機械的応力によっても破断がトリガーされ得る。

【0025】

次に、図5および図6を参照して、管腔表面105（図1Aを参照）を有する血管100の脆弱性プラーク102を検出し治療するための凍結療法カテーテル10の一例（これは、2000年7月19日出願の同時係属出願09/619,583（代理人整理番号018468-000610US）により詳細に記載されており、この開示内容が本明細書において参考として開示される）について説明する。このカテーテル10は、近端部14と、遠端部16と、これら間に延出する冷却流体供給管腔18および排出管腔とを備えたカテーテル本体12を含む。前記カテーテル本体12の前記遠端部の近傍には前記供給および排出管腔と流体連絡して、第1バルーン22が配設されている。そしてこの第1バルーン22上に、その間に熱バリア26を形成した状態で第2バルーン24が配設されている。

【0026】

前記両バルーン22, 24は、カテーテル本体12の一体的延出部分として構成することも可能であるが、そのような構造は本発明において必須ではない。これら両バルーン22

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、24は、カテーテル本体12と同じ材料または異なる材料から形成することができ、後者の場合、適切な接着剤、熱溶接等によってカテーテル本体12の前記遠端部16に付着される。カテーテル本体12は、ポリエチレン、ポリイミド、ならびにそれらのコポリマーおよび誘導物等の従来材料から形成することができる。前記両バルーン22、24も、血管形成術用の従来材料、好ましくは、ポリエチレンテレフタレート(PET)、ポリエチレンなどの非弾性材料、または強力な非膨張性バルーンを構成するのに適した他の医用グレードの材料から形成することができる。さらに、これら両バルーン22、24は、より良好な保護を提供するために、互いに異なる材料から形成することも可能である。例えば、第1バルーン22は強度を提供するべくPETから形成し、第2バルーン24は耐久性を提供するべくポリエチレンから形成することができる。これらバルーン22、24の長さは、それぞれ少なくとも1cm、より好ましくは、それぞれ2cm~5cmの範囲である。これらバルーン22、24は、冠状動脈内ではそれぞれ2mm~5mm、そして末梢動脈内ではそれぞれ2mm~10mmの範囲の直径を有する。

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【0027】

前記熱バリア26は、フィラメントによって両バルーン22、24間に維持される空隙として構成することができる。前記フィラメントは、通常は螺旋巻きされた、編み、編成、または結節モノフィラメントを含む。前記モノフィラメントは、PETまたはポリエチレンナフタレート(PEN)から形成して、接着剤結合、熱溶接、ファスナ等によって前記第1バルーン22に固定することができる。前記熱バリア26も、前記第1バルーン22の外面および/または前記第2バルーン24の内面上に形成された複数のこぶによって両バルーン22、24間に維持される空隙を含み得る。前記複数のこぶは、様々な状態で形成することができる。例えば、これらのこぶは、バルーンに本来備えられたものとして形成したり(バルーンの吹出し中に形成される)、またはこれらのこぶを接着剤結合、熱溶接、ファスナ等を使用してバルーンに対して物理的な「ドット」を固定することによって、バルーンの壁の材料を変形することによっても形成することができる。あるいは、前記熱バリア26は、スリーブによって両バルーン22、24間に維持される空隙を含み得る。前記スリーブは、孔あきとし、PETまたはシリコンやポリウレタンなどのゴムから形成することができる。

【0028】

前記カテーテル本体12の近端部14にはハブ34、36が固定されている。ハブ34は、前記流体供給管腔18に凍結療法流体源を接続するためのポート38を提供し、この流体供給管腔18は、前記第1バルーン22の内面と流体連絡している。ハブ34はさらに、前記バルーン22から移動する前記凍結療法流体を前記排出管腔20を通して近位方向に排出するためのポート40を提供する。ハブ36は、カテーテル本体12内のガイドワイヤ管腔44を通して延出するガイドワイヤのためのポート42を提供する。通常、前記ガイドワイヤ管腔44は、図6に図示されているように、前記排出管腔20を通して延出することになる。前記ガイドワイヤ管腔44はまた、このガイドワイヤ管腔44を介して低温冷却流体が血液流に流れ込むことを最小限にするために、前記排出管腔20の外側に軸方向に延出してもよい。必要に応じて、前記ガイドワイヤ管腔44は、第1バルーン22の内面の外側に延出したり、このガイドワイヤ管腔44が、ガイドワイヤが両バルーン22、24の外側に延出することを許容するように構成することもできる。さらに、前記第1バルーン22の近傍でカテーテル本体12に沿って補強コイル46を延出させることができる。この補強コイル46は、カテーテル10が血管内で捻れることを防止するべく、通常6cm~10cmの範囲の長さを有する単純なバネを含み得る。

【0029】

図5の凍結療法カテーテル10はさらに、前記第1および第2バルーン22、24の格納をモニタするための安全機構を示している。前記第1バルーン22は、前記供給および排出管腔と流体連絡する容量を規定している。前記供給管腔18との低温冷却流体供給部には流体遮断装置が接続されている。前記第2バルーン24は、その間に減圧空間52を形成した状態で前記第1バルーン22上に配設されている。前記減圧空間52は、この減圧

空間 5 2 における変化に応答して、前記第 1 バルーン 2 2 への低温冷却流体の流入を阻止するべく前記流体遮断装置に接続されている。

【 0 0 3 0 】

図 7 は、前記自動流体遮断機構 5 4 の作用流れ図を示している。この流体遮断機構 5 4 は通常、バッテリー 6 0 によって駆動される回路によって、遮断バルブ 5 8 に接続された減圧スイッチ 5 6 を含む。前記スイッチ 5 6 は、所定レベルの減圧空間 5 2 が第 2 バルーン 2 4 内に検出される時にのみ閉鎖状態に留まることができる。この閉鎖されたスイッチ 5 6 によって、前記低温冷却流体供給部 6 2 と流体連絡状態で前記遮断バルブ 5 8 は開放することが許容される。あるいは、前記回路は、前記スイッチが開放されている時に前記遮断バルブ 5 8 が開放される状態で、前記所定の減圧空間 5 2 が存在している時にのみ前記スイッチ 5 6 が開放されるように構成することも可能である。前記減圧空間 5 2 は、前記第 1 バルーン 2 2 が穿孔されて、凍結療法流体が減圧空間 5 2 に流入することが許容される場合、または前記第 2 バルーン 2 4 が穿孔されて血液が減圧空間 5 2 に流入することが許容される場合に縮小される。両バルーン 2 2 , 2 4 の格納のモニタリングに加えて、故障発生時に前記減圧スイッチ 5 6 はトリガーされて、追加の凍結療法流体が前記流体供給部 6 2 から供給管腔 1 8 へと供給されることを防止する。前記第 2 バルーン 2 4 も、第 1 バルーン 2 2 から流出し得る任意の低温冷却流体を含むように作用する。

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【 0 0 3 1 】

前記減圧空間 5 2 は、減圧ポート 6 8 (図 5 を参照) を介して、前記本体 1 2 の減圧管腔 6 6 で前記減圧空間 5 2 に接続される単純な固定減圧チャンバ 6 4 によって提供することができる。当該実施形態において、ハンドル 7 4 内には正容積式ポンプ (理想的にはシリンジに類似) が配設され、これは図 8 A に示されているように、アクチュエータ 7 5 によって操作可能である。前記減圧空間 5 2 は、この減圧空間 5 2 が小さいことで少量の流体の漏出が発生した時における減圧量の変化の検出が容易になることから、1 mL ~ 100 mL の範囲、好ましくは 10 mL 以下の小容量を含むべきである。前記凍結療法流体供給部 6 2 と前記回路を駆動するためのバッテリー 6 0 とは、図 8 B に示されているように、1 つのエネルギーパック 7 0 内に共にパッケージ化することができる。このエネルギーパック 7 0 は、カテーテル本体の近位側ハンドル 7 4 から取り外し可能であり、使い捨て式である。複数の別々の交換可能なエネルギーパック 7 0 によって、複数の凍結冷却サイクルを可能にする。さらに、前記ハンドル 7 4 に音声警報またはブザー 7 6 を設けて、このブザーによって前記ハンドルが流体供給部 6 2 からの流れを許容するべく十分に垂直に維持されていない場合に、音声警告を提供するように構成することができる。前記凍結療法カテーテルはさらに、前記第 1 バルーン 2 2 内の流体の圧力および / または温度を測定するために、前記第 1 バルーン 2 2 またはハンドルに配置されたサーミスタ、熱電対等によって前記容量部に接続された側高計 (h y p s o m e t e r) 7 2 を備えることができる。この側高計は、凍結治療の有効性と安全性とに影響する変数 (圧力、温度) の正確なリアルタイム測定を可能にする。

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【 0 0 3 2 】

図 5 の前記デュアルバルーン凍結療法カテーテル 1 0 はさらに、脆弱性プラークのサーモグラフ式検出を提供する温度感知機構も示している。管腔表面 1 0 5 の直接温度測定を提供するべく、前記第 2 バルーン 2 4 には複数の温度センサ 7 8 が貼り付けられている (図 1 A を参照) 。これら温度センサ 7 8 は、複数の 2 0 個以下の熱電対またはサーミスタから構成することができ、0 . 1 より大きい温度差を検出可能に構成することができる。これら温度センサ 7 8 は、一連の軸心および周方向の位置において第 2 バルーン 2 4 に固定することができる。これら複数の温度センサ 7 8 は、図 5 に図示されているように、接着接続、熱溶接、ファスナ等によって、第 2 バルーン 2 4 の外面に固定することができ、あるいは第 2 バルーン 2 4 の内面に固定することも可能である。カテーテル軸 1 2 の長さに沿って、PET またはシリコンやポリウレタンなどのゴムから形成される薄いスリーブ 8 2 内に、温度センサワイヤ 8 0 を固定することができ、後者の場合、これらワイヤ 8 0 は、前記減圧管腔 6 6 を通ってネジ込むことが可能である。前記温度センサワイヤ 8 0

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を、管腔表面に沿った温度マッピングのために温度読み取り装置へ接続するために、カテーテル10の前記近端部14にコネクタ84を設けることも可能である。さらに、図9のブロック図に図示されているように、前記温度センサ78によって感知される温度測定値T1およびT2から前記管腔表面に沿った温度差Tを測定するために、前記コネクタ84に回路77を取り付けても良い。さらに、閾値温度差より上でトリガーされるインジケータを警告目的で前記コネクタに設けてもよい。

【0033】

脆弱性プラークの検出は、前記凍結療法カテーテル10をガイドワイヤを介して血管100の管腔104に導入することによって行うことができる。前記第1バルーン22は、プラークの近傍の血管管腔104内に配置される。この第1バルーン22を膨張させると、第2バルーン24（膨張時に拡張）に貼り付けられた複数の温度センサ78が管腔の表面に熱的に接続される。前記管腔表面105に沿った温度差を前記センサによって感知する。バルーン22の膨張は、約5psi~50psiの範囲の圧力の二酸化炭素、一酸化二窒素等のガスによって行うことができる。前記バルーン22は通常、10秒~120秒の範囲の時間で膨張される。バルーンカテーテルは、静止位置において、またはそれが管腔表面に沿って移動しながら温度差を感知することができる。好適には、管腔表面に沿った特定の位置における直接温度測定を可能にするために、温度センサ78は管腔表面に熱的に接続する。この温度感度の増加によって温度マッピング性が改善され、脆弱性プラーク検出の精度が高まる。次に、図11A-11Cを参照してさらに詳述するように、検出された脆弱性プラークを治療のために凍結療法カテーテル10を使用することができる。

【0034】

図10Aおよび10Bには、管腔表面を有する血管の脆弱性プラークを検出するための別のカテーテル10'が図示されている。この検出カテーテル10'は、近端部14と、遠端部16と、これら間に延出する供給管腔88および排出管腔88とを備えたカテーテル本体12を含む。前記カテーテル本体12の前記遠端部にはバルーン86が配設されている。このバルーン86は、前記供給管腔および排出管腔に流体連絡する内面を有する。前記管腔表面105の直接温度測定を提供するべく、前記バルーン86の外面には複数の温度センサ78が貼り付けられている（図1Aを参照）。

【0035】

脆弱性プラークの検出は、前記検出カテーテル10'をガイドワイヤを介して血管100の管腔104に導入することによって行うことができる。前記バルーン86は、プラークの近傍の血管管腔104内に配置される。このバルーン86を膨張させると、このバルーンに貼り付けられた複数の温度センサ78が管腔の表面に熱的に接続される。前記管腔表面に沿った温度差を前記センサによって感知する。バルーン86は通常、コントラスト、生理食塩水等の標準的な膨張媒体によって膨張させることが可能である。膨張媒体供給および/または排出ポート90が前記供給および/または排出管腔88に接続され、この管腔が前記バルーン86の内面と流体連絡している。前記バルーン86は通常、10秒~120秒の範囲の時間で膨張される。バルーンカテーテルは静止位置において、またはそれが管腔表面に沿って移動しながら温度差を感知することができる。

【0036】

次に、図11A~図11Cを参照して、脆弱性プラーク102の治療用の図5の凍結治療カテーテル10の使用法について説明する。図11Aおよび11Bに図示されているように、カテーテル10はガイドワイヤGWを介して血管100の管腔104に挿入される。第1バルーン22を脆弱性プラーク102の血管管腔104内に配置する。低温冷却流体を第1バルーン22に導入し（そこで、それは多くの場合気化する）、排出する。図11Cに図示されているように、第2バルーン24を膨張させて管壁に半径方向から密着させる。気化した流体は、バルーン22を膨張させる（そしてバルーン24を膨張させる）作用と、これら両バルーン22, 24の外表面を冷却する作用との二つの作用を奏する。前記脆弱性プラーク102の近傍の血管100は、脆弱性プラーク102内から保持流体106が血管100へと放出されることを防止するのに十分な温度にまで冷却される。この冷

却処置は、血管管腔の周面の全部または一部を対象として行われる。好ましくは、冷却によって脂質リッチ液体106を脂質リッチ固体またはゲル106'（これについては後の図12A-12Bを参照して後に詳述する）へと安定化することによって、この脆弱性プラークによって放出可能な状態で保持されている脂質リッチ液体が放出されることを抑制する。脆弱性プラークの冷却を所望の温度プロファイルに限定するべく、前記熱バリア26によって第1バルーン22と第2バルーン24との間の熱伝達も抑制される。さらに、冷却中、前記流体遮断機構によって第1バルーン22および第2バルーン24の格納がモニタリングされる（図7を参照）。

【0037】

適切な低温冷却流体は、好ましくは非毒性のものであって、液体一酸化二窒素、液体二酸化炭素、冷却生理食塩水等が挙げられ得る。低温冷却流体は、昇圧状態で液体として供給管腔18を流れ、第1バルーン22内の低圧状態で気化する。一酸化二窒素の場合、前記供給管腔18内での供給圧は通常、その沸点より低い温度において600psi~1000psiの範囲である。気化後、第1バルーン22内のその中心近くの一酸化二窒素ガスは通常、15psi~100psiの範囲の圧力を有する。好ましくは、一酸化二窒素ガスは、末梢動脈内では50psi~100psiの範囲の圧力を有し、冠状動脈内では約15psi~45psiの範囲の圧力を有する。

【0038】

一般に、前記第1バルーンの内面の温度は約-55~-75の範囲であり、第1バルーンの外面は約-25~-45の範囲である。第2バルーンの外面の温度は約10~40、好ましくは、約10~-20、より好ましくは、約5~-10の範囲である。これによって、約10~-40、好ましくは、約10~-20、より好ましくは、約5~-10の範囲の所望の治療温度が提供される。組織は通常、この所望の温度に約15秒~120秒、好ましくは、30秒~60秒の時間維持される。脆弱性プラークの安定化は、冷却を通常は約1~3サイクル、それらのサイクルを120秒毎に約1サイクルの速度で繰り返すことによって高めることができる。

【0039】

いくつかの場合において、管の冷却は、前記脂質リッチ液体の近傍の組織、特に脂質リッチ液体106と血管104の管腔との間の細胞の帽部108を規定している組織の壊死および/またはアポトーシスの抑制に限定することができる（図1Aを参照）。アポトーシスまたは細胞壊死は、もしもそれによって細胞の帽部が弱体化され、その帽部弱体化によって脆弱性プラークの破断と前記脂質リッチ液体の放出が引き起こされるならば望ましくないかもしれない。従って、本発明は、体腔をライニングしている帽部細胞108とその他の細胞の生存能力に影響を与えることなく、血管内への保持流体の放出を抑制することを可能にするものである。

【0040】

他の適用例において、脆弱性プラーク102の炎症細胞（例えば、マクロファージ118、図4を参照）のアポトーシスおよび/またはプログラムされた細胞死を刺激するために、より低い温度で管を冷却することが望ましいかもしれない。このような炎症細胞の存在によって、帽部の弱体化または腐食がトリガーされ、それによって前記脂質リッチ液体の脆弱性プラーク放出が発生するかもしれないのでアポトーシスは望ましいかもしれない。約0~-15の範囲の温度での冷却によって、脆弱性プラーク、特に細胞帽部108を形成している組織の炎症および悪化を抑制することができる。あるいは、約-20より低い冷却温度での帽部細胞108の壊死を提供することが有用であるかもしれない。帽部壊死によって帽部の細胞増殖と厚み増加を刺激し、それによって帽部の破断を抑制することができる。

【0041】

次に図12Aおよび12Bを参照して、脆弱性プラークの脂質リッチ液体コア106の転移について説明する。図12Aは、脂質コア転移を行う転移温度を図示している。主転移点122は、10~-10の転移温度範囲内のある時点で起こる。この転移点122

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において、脂質コアは図 1 2 B に図示されているように、無秩序な結晶状態流体 1 0 6 から秩序的な結晶状態固体またはゲル 1 0 6 ' への相変化を受け得る。従って、脆弱性プラークは、前記脂質リッチ液体コア 1 0 6 を、その状態を通常無秩序な脂質から高度に秩序的な六方格子状態に変化させるのに十分冷却することによって安定化することができる。好適には、- 5 より高い上の転移温度はさらに、前記脂質リッチ液体 1 0 6 の近傍の組織、特に前記帽部 1 0 8 の壊死および / またはアポトーシスを抑制する。

【 0 0 4 2 】

次に図 1 3 A および 1 3 B を参照して、前記脆弱性プラークの冷却に関連する追加的治療について説明する。図 1 3 A は、脆弱性プラークが脂質リッチ固体 / ゲル 1 0 6 ' 状態にまで安定化される冷却された血管 1 0 0 の断面を図示している。脂質リッチ流体 1 0 6 の長期保持を提供し、さらに可能であれば、組織の内部成長を介した健全な内皮細胞のための構造的骨格 (s c a f f o l d i n g) を提供するべく、プラークを安定化しながら血管管腔内にステント 1 2 4 が配置されている。前記ステントはさらに、プラーク誘発狭窄を軽減し、管腔の開通性を改善することもできる。安定化されたプラークのその他の適切な一次処置としては、バルーン血管形成術、じゅく腫除去術、回転じゅく腫除去術、レーザー血管形成術等が挙げられ、ここで処理された血管の管腔は、狭窄状態を少なくとも部分的に軽減するべく拡大される。動脈の場合、一次処置は、前記冷却治療の少し前、冷却治療中、好ましくは冷却治療の少し後、好ましくは冷却治療の 6 0 秒以内、さらに好ましくは脂質リッチ液体を所望の温度へ冷却した直後に行われる。場合によっては、冷却方法は図 1 3 B に図示されているように、脂質リッチ液体 1 0 6 ' のサイズをおそらく縮小し、またはその脂質リッチ液体の細胞密度もしくは組成を変化させ、および / または脆弱性プラークの化学的性質もしくはライフサイクルを変化させることによって脆弱性プラークを不活性化を行うことができる。不活性化はさらに、帽部 1 0 8 の構造的完全性の促進 (例えば、帽部の厚み、強度、弾性、または硬度の増大) 、傷の形成または脆弱性プラークの化学特性の変化を介した帽部の細胞組成または特性の改変および / または等も含むことができる。

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【 0 0 4 3 】

カテーテル 1 0 とその使用のための取扱説明書 1 2 8 とが含まれているキット 1 2 6 が図 1 4 に図示されている。カテーテル 1 0 は、図 1 4 に図示されているように、図 5 のデュアルバルーンカテーテルであってもよいし、あるいは近端部と遠端部とその遠端部近傍の冷却部材とを備えたカテーテルであってもよい。使用取扱説明書 1 2 8 は、脆弱性プラークの検出および / または治療のための上述した関連方法のステップのセットのいずれかを記載したものとすることができる。使用取扱説明書 1 2 8 は、多くの場合印刷され、必要に応じて少なくとも部分的にバルーンカテーテル 1 0 用の殺菌パッケージ 1 3 0 上に示される。別実施形態において、使用取扱説明書 1 2 8 は、脆弱性プラークの検出および / または治療のためのバルーンカテーテル 1 0 の使用法を図示または例示した機械読み取り可能コード、デジタルまたはアナログデータを含み得る。使用取扱説明書を、キット 1 2 6 のパッケージ 1 3 2 上に印刷する等のその他の構成も可能である。

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【 0 0 4 4 】

以上は本発明の好適実施例の完全な説明であるが、当業者には、様々な代替、改変および均等物が自明であろう。従って、上の説明は、特許請求の範囲によって規定される本発明の範囲を限定するものと解釈されてはならない。

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【 図面の簡単な説明 】

【 図 1 A 】

図 1 A は、成熟した脆弱性プラークを含む血管の断面図を示している。

【 図 1 B 】

図 1 B は、成熟した脆弱性プラークを含む血管の断面図を示している。

【 図 2 】

図 2 は、血管内の脆弱性プラークの破断とプラークの出血の断面図を示している。

【 図 3 】

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図 3 は、血管内の血栓症閉塞部の断面図を示している。

【図 4】

図 4 は、図 1 A の 4 - 4 線に沿った分解断面図を示している。

【図 5】

図 5 は、脆弱性プラークの検出と治療のための凍結療法カテーテルの一例を図示している。

【図 6】

図 6 は、図 5 の 6 - 6 線に沿った前記カテーテルの断面図である。

【図 7】

図 7 は、図 5 のカテーテルの自動流体遮断機構の作動を図示する作用流れ図である。

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【図 8 A】

図 8 A は、図 5 の凍結療法カテーテルに使用されるハンドルと取り外し可能エネルギーパックを図示している。

【図 8 B】

図 8 B は、図 5 の凍結療法カテーテルに使用されるハンドルと取り外し可能エネルギーパックを図示している。

【図 9】

図 9 は、管腔表面の温度差を測定する回路のブロック図を示している。

【図 10 A】

図 10 A は、脆弱性プラークを検出するための別のカテーテルを図示している。

20

【図 10 B】

図 10 B は、図 10 A の 10 B - 10 B 線に沿った前記カテーテルの断面図である。

【図 11 A】

図 11 A は、脆弱性プラークの治療用の図 5 のカテーテルの使用法を図示している。

【図 11 B】

図 11 B は、脆弱性プラークの治療用の図 5 のカテーテルの使用法を図示している。

【図 11 C】

図 11 C は、脆弱性プラークの治療用の図 5 のカテーテルの使用法を図示している。

【図 12 A】

図 12 A は、脆弱性プラークの脂質コア転移を行う転移温度を図示するグラフである。

30

【図 12 B】

図 12 B は、液体の無秩序状態から、固体の秩序状態への脂質コアの転移を図示している。

【図 13 A】

図 13 A は、前記脆弱性プラークの冷却に関連する追加の治療法を図示している。

【図 13 B】

図 13 B は、前記脆弱性プラークの冷却に関連する追加の治療法を図示している。

【図 14】

図 14 は、図 5 の装置と、その使用取扱説明書とを含む脆弱性プラーク治療キットを図示している。

40

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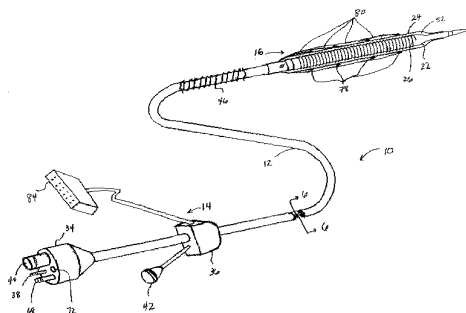
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(54) Title: CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE



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(57) Abstract: The present invention provides methods, apparatus, and kits for detection and/or treatment of vulnerable plaque of a blood vessel having a lumen surface. Detection methods include sensing a temperature differential along a lumen surface with temperature sensors (78) that thermally couple to the lumen surface. Treatment methods include controlled and safe cryogenic cooling of vulnerable plaque to inhibit release of retained fluid within the vulnerable plaque so as to inhibit acute coronary syndrome and to help maintain patency of a body lumen. Treatment methods may include additional treatments, such as primary treatments of passivation.

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Unfortunately, as plaque matures, narrowing of a blood vessel by a proliferation of smooth muscle cells, matrix synthesis, and lipid accumulation may result in formation of a plaque which is quite different than a standard stenotic plaque. Such atherosclerotic plaque becomes thrombosis-prone, and can be highly dangerous. This
5 thrombosis-prone or vulnerable plaque may be a frequent cause of acute coronary syndromes.

The characterization of these vulnerable (and potentially life-threatening) plaques is currently under investigation. A number of strategies have been proposed to detect a vulnerable plaque. Proposed strategies include angiography, intravascular
10 ultrasound, angioscopy, magnetic resonance imaging, magnetic resonance diffusion imaging, spectroscopy, infrared spectroscopy, scintigraphy, optical coherence tomography, electron beam computed tomographic scanning, and thermography, all of which have had limited success. In particular, proposed thermography methods detect temperature variations, as vulnerable plaque is typically inflamed and as such gives off
15 more heat than standard stenotic plaque. While current thermography methods show great promise, they continue to suffer from limited temperature sensitivity which may often result in inaccurate detections of vulnerable plaque.

While the known procedures for treating plaque have gained wide acceptance and shown good efficacy for treatment of standard stenotic plaques, they may
20 be ineffective (and possibly dangerous) when thrombotic conditions are superimposed on atherosclerotic plaques. Specifically, mechanical stresses caused by primary treatments like PTA or stenting may actually trigger release of fluids and/or solids from a vulnerable plaque into the blood stream, thereby potentially causing a coronary thrombotic occlusion.

For these reasons, it would be desirable to provide methods, apparatus, and
25 kits for the detection and treatment of vulnerable plaque in blood vessels. The methods and apparatus should be suitable for intravascular and intraluminal introduction, preferably via a percutaneous approach. It would be particularly desirable if the new methods and apparatus were able to detect the vulnerable plaque accurately and/or deliver
30 the treatment in a very controlled and safe manner, with minimal deleterious effects on adjacent tissues. Treatment methods, apparatus, and kits should further be effective in inhibiting release of the vulnerable plaque with minimum side effects. At least some of these objectives will be met by the invention described herein.

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2. Description of the Background Art

A cryoplasty device and method are described in WO 98/38934. Balloon catheters for intravascular cooling or heating a patient are described in U.S. 5,486,208 and WO 91/05528. A cryosurgical probe with an inflatable bladder for performing
5 intrauterine ablation is described in U.S. 5,501,681. Cryosurgical probes relying on Joule-Thomson cooling are described in U.S. 5,275,595; 5,190,539; 5,147,355; 5,078,713; and 3,901,241. Catheters with heated balloons for post-angioplasty and other treatments are described in U.S. 5,196,024; 5,191,883; 5,151,100; 5,106,360; 5,092,841; 5,041,089; 5,019,075; and 4,754,752. Cryogenic fluid sources are described in U.S.
10 5,644,502; 5,617,739; and 4,336,691. The following U.S. Patents may also be relevant to the present invention: 5,458,612; 5,545,195; and 5,733,280.

Thermography is described by Ward Casscells et al. in The Vulnerable Atherosclerotic Plaque: Understanding, Identification, and Modification, chpt. 13, pp. 231-242 (1999); and L. Diamantopoulos et al. at <http://www.eurcalert.org/releases/aha-ati041499.html>. The impact of low temperatures on lipid membranes is described by Jack Kruuv in *Advances in Molecular and Cell biology*, vol. 19, pp. 143-192 (1997); P.J. Quinn in *Cryobiology*, vol. 22, pp. 128-146 (1985); and Michael J. Taylor, Ph.D. in Biology Of Cell Survival In The Cold, (Harwood Academic Publishers, In Press).
15

The full disclosures of each of the above references are incorporated
20 herein by reference.

SUMMARY OF THE INVENTION

The present invention provides detection and cryotherapy treatment of vulnerable plaque within a blood vessel of a patient. The blood vessel may be any blood vessel in the patient's vasculature, including veins, arteries, and particularly coronary
25 arteries. The vessel will typically be partially stenosed, at least in part from vulnerable plaque. In particular, the present invention may inhibit release of retained fluid within the vulnerable plaque so as to inhibit acute coronary syndrome and to help maintain the patency of a body lumen. The present invention may also provide for the treatment of vulnerable plaque in carotid arteries for stroke prevention. Where the patient's
30 vasculature has both the vulnerable plaque and standard stenotic plaque, the treatment techniques described herein may be selectively directed to the vulnerable plaque, optionally without substantial cooling of the standard stenotic plaque. In other embodiments, both types of plaque may be treated.

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In a first aspect, the present invention provides a method for treating vulnerable plaque of a blood vessel. The method comprises cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of retained fluid from within the vulnerable plaque into the blood stream. The cooling treatment will often be directed against all or a portion of a circumferential surface of a lumen of the blood vessel, and will preferably inhibit release of lipid-rich liquid being releasably retained by the vulnerable plaque.

Cooling of the vessel may be effected by introducing a catheter into a lumen of the blood vessel. A first balloon is positioned within the vessel lumen adjacent the vulnerable plaque. Cryogenic cooling fluid is introduced into the first balloon and exhausted. A second balloon disposed over the first balloon is expanded to radially engage the vessel lumen. Generally, the temperature of an inside surface of the first balloon will be in the range from about -55°C to -75°C and an outside surface of the first balloon will be in the range from about -25°C to -45°C . The temperature of an outside surface of the second balloon will be in the range from about 10°C to -40°C , preferably from about 10°C to -20°C , more preferably from about 5°C to -10°C .

Usually, the temperature at the cell surface of the blood vessel lumen is in the range from about 10°C to -40°C , preferably from about 10°C to -20°C , more preferably from about 5°C to -10°C . The tissue is typically maintained at the desired temperature for a time period in the range from about 15 seconds to 120 seconds, preferably from 30 seconds to 60 seconds. Vulnerable plaque stabilization may be enhanced by repeating cooling in cycles, typically with from about 1 to 3 cycles, with the cycles being repeated at a rate of about one cycle every 120 seconds.

Surprisingly, cooling temperatures above 0°C can effect a transition of the vulnerable plaque's lipid core from a disordered crystalline state fluid to an ordered crystalline state solid or gel. Thus, vulnerable plaque can be stabilized by cooling the lipid-rich liquid sufficiently to change a state of the lipid-rich liquid, typically to a highly ordered hexagonal lattice at transition temperatures generally in the range from about 10°C to -10°C . Cooling may stabilize the vulnerable plaque while inhibiting necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid, particularly of the tissues defining a cap of cells between the lipid-rich liquid and the lumen of the blood vessel. Cooling may also inhibit inflammation and deterioration of the vulnerable plaque. The cooling treatment may further inhibit rupture of the cap of cells of the vulnerable plaque.

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In other aspects, the present invention of cooling the vulnerable plaque to inhibit release of lipid-rich liquid may be combined with additional treatments. For example, one adjunctive method may comprise treating the cooled vulnerable plaque with a primary treatment. Suitable primary treatments may include balloon angioplasty, 5 atherectomy, rotational atherectomy, laser angioplasty, or the like, where the lumen of the treated blood vessel is enlarged to at least partially alleviate a stenotic condition. The primary treatment may also include procedures for controlling restenosis, such as stent placement. In the case of arteries, the primary treatment will be effected shortly before, during, or preferably very shortly after the cooling treatment, preferably within 60 10 seconds of the cooling treatment, more preferably immediately following the cooling of the lipid-rich liquid to a desired temperature. Alternatively, cooling methods may additionally comprise passivating the vulnerable plaque by reducing a size of the lipid-rich liquid, changing a cellular consistency or composition of the lipid-rich liquid, enhancing a structural integrity of the cap (e.g. increasing a thickness of the cap), 15 modifying a cellular composition or structural properties of the cap, and/or the like by altering the chemistry or life cycle of the vulnerable plaque.

In another aspect, the present invention provides a method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid. The method includes detecting the vulnerable plaque and cooling the blood vessel adjacent the 20 vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

In another aspect, the present invention provides a method for detecting vulnerable plaque of a blood vessel. The method includes positioning a balloon within the vessel lumen adjacent a plaque. The balloon is inflated so that a plurality of 25 temperature sensors affixed to the balloon are coupled a surface of the vessel lumen. A temperature differential along the lumen surface is sensed with the sensors.

In another aspect, the present invention provides a cryotherapy catheter for detecting and treating vulnerable plaque of a blood vessel having a lumen surface. The catheter generally comprises a catheter body having a proximal end and a distal end with 30 a cooling fluid supply lumen and an exhaust lumen extending therebetween. A first balloon is disposed near the distal end of the catheter body in fluid communication with the supply lumen and exhaust lumen. A second balloon is disposed over the first balloon with a thermal barrier therebetween. A plurality of temperature sensors are affixed to the second balloon so as to provide temperature measurements of the lumen surface.

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In another aspect, the present invention provides a catheter for detecting a vulnerable plaque of a blood vessel having a lumen surface. The catheter generally comprises a catheter body having a proximal end and a distal end with a supply lumen and an exhaust lumen extending therebetween. A balloon is disposed on the distal end of the catheter body in fluid communication with the supply lumen and exhaust lumen. A plurality of temperature sensors are supported by the balloon so as to provide temperature measurements of the lumen surface.

In another aspect, the invention also provides a kit for treating vulnerable plaque in a blood vessel. The kit comprises a catheter having a proximal end, a distal end, and a cooling member near its distal end. Instructions are included in the kit for use of the catheter. These instructions comprise the step of cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained fluid into the blood vessel. Such a kit may include instructions for any of the methods described herein.

In yet another aspect, the invention provides a kit for detecting vulnerable plaque of a blood vessel. The kit comprises a catheter having a proximal end, a distal end, and a balloon member with a plurality of temperature sensors near its distal end. Instructions are included in the kit for use of the catheter. These instructions comprise the steps of positioning a balloon within the vessel lumen adjacent a plaque, inflating the balloon so that a plurality of temperature sensors affixed to the balloon are coupled to a surface of the vessel lumen, and sensing a temperature differential along the lumen surface with the sensors. Such a kit may include instructions for any of the methods described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A and 1B are cross-sectional views of a blood vessel containing a mature vulnerable plaque.

Fig. 2 illustrates a cross-sectional view of a vulnerable plaque rupture and plaque hemorrhage in the blood vessel.

Fig. 3 illustrates a cross-sectional view of a thrombotic occlusion in the blood vessel.

Fig. 4 illustrates an exploded cross-sectional view of Fig. 1A taken along line 4-4.

Fig. 5 illustrates an exemplary cryotherapy catheter for detecting and treating vulnerable plaque.

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Fig. 6 is a cross-sectional view of the catheter taken along line 6-6 in Fig. 5.

Fig. 7 is a functional flow diagram illustrating the operation of an automatic fluid shutoff mechanism of the catheter of Fig. 5.

5 Figs. 8A and 8B illustrate a handle and removable energy pack for use in the cryotherapy catheter of Fig. 5.

Fig. 9 illustrates a block diagram of a circuit which measures a temperature differential of the lumen surface.

Fig. 10A illustrates an alternative catheter for detecting vulnerable plaque.

10 Fig. 10B is a cross-sectional view of the catheter taken along line 10B-10B in Fig. 10A.

Figs. 11A-11C illustrate use of the catheter of Fig. 5 for treatment of vulnerable plaque.

Fig. 12A is a graph illustrating a transition temperature which effects a lipid core transition of the vulnerable plaque.

15 Fig. 12B illustrates the lipid core transition from a liquid, disordered state to a solid, ordered state.

Fig. 13A and 13B illustrate additional treatments in conjunction with cooling of the vulnerable plaque.

20 Fig. 14 illustrates a vulnerable plaque treatment kit including the apparatus of Fig. 5 and instructions for use.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

As used herein, the terms "vulnerable plaque" and "hot plaque" refer to atherosclerotic plaque that is thrombosis-prone. Figs. 1A and 1B illustrate cross-sectional
25 views of a blood vessel 100 containing a mature vulnerable plaque 102 within a lumen 104 of the vessel. The vulnerable plaque 102 generally comprises a necrotic core 106 of soft, lipid-rich, atheromatous gruel and a fibrous, sclerotic cap 108 of a collagen matrix of smooth muscle cells that covers the core 106. The gruel generally comprises a liquid of esterified cholesterol and low density lipoproteins which is releasably retained by the
30 vulnerable plaque 102. Disruption or fissuring of the cap 108 may cause plaque hemorrhage 110 (release of the highly thrombogenic lipid-rich liquid 106 through the ruptured plaque), as seen in Fig. 2. As a result of plaque hemorrhage 110, the highly thrombogenic lipid-rich liquid 106 is exposed to flowing blood of the vessel lumen 104. As illustrated in Fig. 3, release of the thrombogenic liquid may cause a thrombotic

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occlusion 112 (blood clot) of the entire vessel lumen, which in turn may be lead to life-threatening conditions, such as a stroke or sudden cardiac death.

Three determinants of vulnerability are illustrated in Fig. 4, which is an exploded cross-sectional view of Fig. 1A taken along line 4-4. Susceptibility of a vulnerable plaque to rupture may be primarily determined from the size 114 and consistency of the atheromatous core (e.g. a larger core increases chances for rupture), the thickness 116 and structural integrity of the sclerotic cap (e.g. a thinner cap increases chances for rupture), and cap inflammation (e.g. macrophage foam cell 118 infiltration weakens the cap cells 120 and increases chances for rupture). Additionally, vulnerable plaque disruption may be triggered by numerous extrinsic stresses imposed on the plaque. For example, fluctuations in intraluminal blood pressure, pulse pressure, heart contraction, vasospasm, and the like may precipitate disruption of a vulnerable plaque. Alternatively, mechanical stresses caused by primary treatments like PTA or stenting may trigger rupture as well.

Referring now to Figs. 5 and 6, an exemplary cryotherapy catheter 10 (which is more fully described in co-pending application no. 09/619,583 filed July 19, 2000 (Attorney Docket No. 018468-000610US)), the full disclosure of which is incorporated herein by reference) for detecting and treating vulnerable plaque 102 of a blood vessel 100 having a lumen surface 105 (see Fig. 1A) will be described. The catheter 10 comprises a catheter body 12 having a proximal end 14 and a distal end 16 with a cooling fluid supply lumen 18 and an exhaust lumen 20 extending therebetween. A first balloon 22 is disposed near the distal end of the catheter body 12 in fluid communication with the supply and exhaust lumens. A second balloon 24 is disposed over the first balloon 22 with a thermal barrier 26 therebetween.

The balloons 22, 24 may be an integral extension of the catheter body 12, but such a structure is not required by the present invention. The balloons 22, 24 could be formed from the same or a different material as the catheter body 12 and, in the latter case, attached to the distal end 16 of the catheter body 12 by suitable adhesives, heat welding, or the like. The catheter body 12 may be formed from conventional materials, such as polyethylenes, polyimides, and copolymers and derivatives thereof. The balloons 22, 24 may also be formed from conventional materials used for angioplasty, preferably being inelastic, such as polyethylene terephthalate (PET), polyethylene, or other medical grade material suitable for constructing a strong non-distensible balloon. Additionally, balloons 22 and 24 could be formed from different material to provide improved

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protection. For example, the first balloon 22 could be formed from PET to provide strength while the second balloon 24 could be formed from polyethylene to provide durability. The balloons 22, 24 have a length of at least 1 cm each, more preferably in the range from 2 cm to 5 cm each. The balloons 22, 24 will have diameters in the range from
5 2 mm to 5 mm each in a coronary artery and 2 mm to 10 mm each in a peripheral artery.

The thermal barrier 26 may comprise a gap maintained between the balloons 22, 24 by a filament. The filament typically comprises a helically wound, braided, woven, or knotted monofilament. The monofilament may be formed from PET or polyethylene naphthlate (PEN), and affixed to the first balloon 22 by adhesion bonding,
10 heat welding, fasteners, or the like. The thermal barrier 26 may also comprise a gap maintained between the balloons 22, 24 by a plurality of bumps on an outer surface of the first balloon 22 and/or an inner surface of the second balloon 24. The plurality of bumps may be formed in a variety of ways. For example, the bumps may be intrinsic to the balloon (created during balloon blowing), or the bumps could be created by deforming the
15 material of the balloon wall, by affixing mechanical "dots" to the balloon using adhesion bonding, heat welding, fasteners, or the like. Alternatively, the thermal barrier 26 may comprise a gap maintained between the balloons 22, 24 by a sleeve. The sleeve may be perforated and formed from PET or rubbers such as silicone and polyurathane.

Hubs 34 and 36 are secured to the proximal end 14 of the catheter body 12.
20 Hub 34 provides a port 38 for connecting a cryogenic fluid source to the fluid supply lumen 18 which is in turn in fluid communication with the inner surface of the first balloon 22. Hub 34 further provides a port 40 for exhausting the cryogenic fluid which travels from balloon 22 in a proximal direction through the exhaust lumen 20. Hub 36 provides a port 42 for a guidewire which extends through a guidewire lumen 44 in the
25 catheter body 12. Typically, the guidewire lumen 44 will extend through the exhaust lumen 20, as shown in Fig. 6. The guidewire lumen 44 may also extend axially outside the exhaust lumen 20 to minimize the occurrence of cryogenic fluid entering the blood stream via the guidewire lumen 44. Optionally, the guidewire lumen 44 may extend outside the inner surface of the first balloon 22 or the guidewire lumen 44 may allow for a
30 guidewire to extend outside both balloons 22, 24. Additionally, a reinforcing coil 46 may extend along the catheter body 12 proximal the first balloon 22. The reinforcing coil 46 may comprise a simple spring having a length typically in the range from 6 cm to 10 cm to prevent the catheter 10 from kinking up inside the blood vessel.

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The cryotherapy catheter 10 in Fig. 5 additionally illustrates a safety mechanism that monitors the containment of the first and second balloons 22, 24. The first balloon 22 defines a volume in fluid communication with the supply and exhaust lumens. A fluid shutoff is coupled to a cryogenic fluid supply with the supply lumen 18. 5 The second balloon 24 is disposed over the first balloon 22 with a vacuum space 52 therebetween. The vacuum space 52 is coupled to the fluid shutoff so as to inhibit flow of cryogenic fluid into the first balloon 22 in response to a change in the vacuum space 52.

Fig. 7 illustrates a functional flow diagram of the automatic fluid shutoff mechanism 54. The fluid shutoff 54 typically comprises a vacuum switch 56 connected 10 to a shutoff valve 58 by a circuit, the circuit being powered by a battery 60. The switch 56 may remain closed only when a predetermined level of vacuum space 52 is detected in the second balloon 24. The closed switch 56 allows the shutoff valve 58, in fluid communication with the cryogenic fluid supply 62, to be open. Alternatively, the circuit may be arranged so that the switch 56 is open only when the predetermined vacuum space 15 52 is present, with the shutoff valve 58 being open when the switch is open. The vacuum space 52 is reduced when either the first balloon 22 is punctured, allowing cryogenic fluid to enter the vacuum space 52, or the second balloon 24 is punctured, allowing blood to enter the vacuum space 52. In addition to monitoring the containment of both balloons 22, 24, in the event of a failure, the vacuum switch 56 will be triggered to prevent the 20 delivery of additional cryogenic fluid from the fluid supply 62 into the supply lumen 18. The second balloon 24 also acts to contain any cryogenic fluid that may have escaped the first balloon 22.

The vacuum space 52 may be provided by a simple fixed vacuum chamber 64 coupled to the vacuum space 52 by a vacuum lumen 66 of the body 12 via a vacuum 25 port 68 (See Fig. 5). In the exemplary embodiment, a positive displacement pump (ideally being similar to a syringe) is disposed within handle 74 and may be actuated by actuator 75, as seen in Fig. 8A. The vacuum space 52 should comprise a small volume of vacuum in the range from 1 mL to 100 mL, preferably 10 mL or less, as a smaller vacuum space 52 facilitates detection of a change in the amount of vacuum when a small amount 30 of fluid leakage occurs. The cryogenic fluid supply 62 and battery 60 for powering the circuit may be packaged together in an energy pack 70, as seen in Fig 8B. The energy pack 70 is detachable from a proximal handle 74 of the catheter body and disposable. A plurality of separate replaceable energy packs 70 allow for multiple cryogenic cooling cycles. Additionally, an audio alert or buzzer 76 may be located on the handle 74, with

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the buzzer providing an audio warning unless the handle is maintained sufficiently upright to allow flow from the fluid supply 62. The cryotherapy catheter may additionally comprise a hypsometer 72 coupled to the volume by a thermistor, thermocouple, or the like located in the first balloon 22 or handle to determine the pressure and/or temperature of fluid in the first balloon 22. The hypsometer allows for accurate real time measurements of variables (pressure, temperature) that effect the efficacy and safety of cryotherapy treatments.

The dual balloon cryotherapy catheter 10 in Fig. 5 also illustrates a temperature sensing mechanism that provides for thermographic detection of vulnerable plaque. A plurality of temperature sensors 78 are affixed to the second balloon 24 so as to provide direct temperature measurements of the lumen surface 105 (see Fig. 1A). The temperature sensors 78 may comprise a plurality of up to 20 thermocouples or thermistors and may be capable of detecting temperature differences greater than 0.1 °C. The temperature sensors 78 may be secured to the second balloon 24 at a series of axial and circumferential locations. The plurality of temperature sensors 78 may be affixed by adhesion bonding, heat welding, fasteners, or the like to an outer surface of the second balloon 24, as shown in Fig. 5, or may be alternatively affixed to an inner surface of the second balloon 24. Temperature sensor wires 80 may be secured along the length of the catheter shaft 12 within a thin sleeve 82 formed from PET or rubbers such as silicone and polyurathane, or in the latter case the wires 80 may be threaded through the vacuum lumen 66. A connector 84 at the proximal end 14 of the catheter 10 may also be provided to connect the temperature sensor wires 80 to a temperature readout device for temperature mapping along the lumen surface. Additionally, a circuit 77 may be attached to the connector 84 for measuring a temperature differential ΔT along the lumen surface from temperature measurement T1 and T2 sensed by the temperature sensors 78, as illustrated in the block diagram of Fig. 9. An indicator which is triggered above a threshold temperature differential may also be located on the connector for alerting purposes.

Detection of vulnerable plaque may be carried out by introducing the cryotherapy catheter 10 into a lumen 104 of the blood vessel 100 over a guidewire. The first balloon 22 is positioned within the blood vessel lumen 104 adjacent a plaque. The first balloon 22 is inflated so that the plurality of temperature sensors 78 affixed to the second balloon 24 (which expands upon inflation) thermally couple a surface of the vessel lumen. A temperature differential along the lumen surface 105 is sensed with the

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sensors. Inflation of balloon 22 may be effected by a gas, such as carbon dioxide, nitrous oxide, or the like, at a pressure in the range from about 5 psi to 50 psi. The balloon 22 will typically be inflated for a time period in the range from 10 to 120 seconds. The balloon catheter may sense for a temperature differential in a static position or as it moving along the lumen surface. Advantageously, temperature sensors 78 thermally engage the lumen surface to allow for direct temperature measurements to be made at specific locations along the lumen surface. This increased temperature sensitivity may in turn lead to improved temperature mapping and accurate vulnerable plaque detections. Cryotherapy catheter 10 may then be used for treating the detected vulnerable plaque as described in more detail below with reference to Figs. 11A-11C.

An alternative catheter 10' for detecting a vulnerable plaque of a blood vessel having a lumen surface is illustrated in Figs. 10A and 10B. Detection catheter 10' comprises a catheter body 12 having a proximal end 14 and a distal end 16 with a supply lumen 88 and an exhaust lumen 88 extending therebetween. A balloon 86 is disposed on the distal end of the catheter body 12. Balloon 86 has an inner surface in fluid communication with the supply lumen and exhaust lumen. A plurality of temperature sensors 78 are affixed to an outer surface of the balloon 86 so as to provide direct temperature measurements of the lumen surface 105 (see Fig. 1A).

Detection of vulnerable plaque may be carried out by introducing the detection catheter 10' into a lumen 104 of the blood vessel 100 over a guidewire. The balloon 86 is positioned within the vessel lumen adjacent a plaque. The balloon 86 is inflated so that a plurality of temperature sensors 78 affixed to the balloon thermally couple a surface of the vessel lumen. A temperature differential along the lumen surface is sensed with the sensors. Balloon 86 is generally inflatable with standard inflation media, such as contrast, saline, or the like. An inflation media supply and/or exhaust port 90 is connected to the supply and/or exhaust lumen 88 which is in turn in fluid communication with the inner surface of balloon 86. Balloon 86 will typically be inflated for a time period in the range from 10 to 120 seconds. The balloon catheter may sense for a temperature differential in a static position or as it moving along the lumen surface.

Referring now to Figs. 11A through 11C, use of cryotherapy catheter 10 of Fig. 5 for treatment of vulnerable plaque 102 will be described. As illustrated in Fig. 11A and 11B, catheter 10 will be introduced into a lumen 104 of the blood vessel 100 over a guidewire GW. The first balloon 22 is positioned within the blood vessel lumen 104 adjacent the vulnerable plaque 102. Cryogenic cooling fluid is introduced into the first

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balloon 22 (in which it often vaporizes) and exhausted. The second balloon 24 expands to radially engage the vessel wall, as illustrated by Fig. 11C. The vaporized fluid serves both to inflate balloon 22 (and expand balloon 24) and to cool the exterior surface of the balloons 22, 24. The blood vessel 100 adjacent the vulnerable plaque 102 is cooled to a temperature sufficient to inhibit release of retained fluid 106 from within the vulnerable plaque 102 into the blood vessel 100. The cooling treatment will be directed at all or a portion of a circumferential surface the vessel lumen. Preferably cooling will inhibit release of lipid-rich liquid being releasably retained by the vulnerable plaque by stabilizing the lipid-rich liquid 106 to a lipid-rich solid or gel 106' (which is described in more detail in Figs. 12A-12B below). Heat transfer will also be inhibited between the first and second balloons 22, 24 by the thermal barrier 26 so as to limit cooling of the vulnerable plaque to a desired temperature profile. Additionally, containment of the first and second balloons 22, 24 will be monitored during cooling by the fluid shutoff mechanism (see Fig. 7).

Suitable cryogenic fluids will preferably be non-toxic and may include liquid nitrous oxide, liquid carbon dioxide, cooled saline and the like. The cryogenic fluid will flow through the supply lumen 18 as a liquid at an elevated pressure and will vaporize at a lower pressure within the first balloon 22. For nitrous oxide, a delivery pressure within the supply lumen 18 will typically be in the range from 600 psi to 1000 psi at a temperature below the associated boiling point. After vaporization, the nitrous oxide gas within the first balloon 22 near its center will have a pressure typically in the range from 15 psi to 100 psi. Preferably, the nitrous oxide gas will have a pressure in the range from 50 psi to 100 psi in a peripheral artery and a range from about 15 psi to 45 psi in a coronary artery.

Generally, the temperature of an inside surface of the first balloon will be in the range from about -55° C to -75° C and an outside surface of the first balloon will be in the range from about -25° C to -45° C. The temperature of an outside surface of the second balloon will be in the range from about 10° C to -40° C, preferably from about 10° C to -20° C, more preferably from about 5° C to -10° C. This will provide a desired treatment temperature in a range from about 10° C to -40° C, preferably from about 10° C to -20° C, more preferably from about 5° C to -10° C. The tissue is typically maintained at the desired temperature for a time period in the range from about 15 to 120 seconds, preferably being from 30 to 60 seconds. Vulnerable plaque stabilization may be

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enhanced by repeating cooling in cycles, typically with from about 1 to 3 cycles, with the cycles being repeated at a rate of about one cycle every 120 seconds.

In some instances, cooling of the vessel may be limited to inhibiting necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid, particularly of the tissues defining a cap of cells 108 between the lipid-rich liquid 106 and the lumen of the blood vessel 104 (see Fig. 1A). Apoptosis or cell necrosis may be undesirable if it weakens the cap of cells as cap weakening may likely incite rupture of the vulnerable plaque and release of the lipid-rich liquid. Thus, the present invention may inhibit release of the retained fluid into the blood vessel without affecting the viability of the cap cells 108 and other cells which line the body lumen.

In other applications, cooling of the vessel at cooler temperatures may be desirable to provide for apoptosis and/or programmed cell death stimulation of inflammatory cells (e.g. macrophages 118, see Fig. 4) in the vulnerable plaque 102. Apoptosis may be desirable as the presence of such inflammatory cells may trigger cap weakening or erosion which in turn may lead to vulnerable plaque release of the lipid-rich liquid. Cooling at temperatures in the range from about 0° C to -15° C may inhibit inflammation and deterioration of the vulnerable plaque, particularly of the tissues defining the cap of cells 108. Alternatively, it may be beneficial to provide for necrosis in the cap cells 108 at cooling temperatures below about -20° C. Cap necrosis may stimulate cellular proliferation and thickening of the cap which in turn may inhibit cap rupture.

Referring now to Figs. 12A and 12B, transition of the vulnerable plaque's lipid-rich liquid core 106 will be described. Fig. 12A illustrates the transition temperature which effects a lipid core transition. The main transition point 122 occurs at some point between the transition temperature range of 10° C to -10° C. At this transition point 122, the lipid core may undergo a phase change from a disordered crystalline state fluid 106 to a ordered crystalline state solid or gel 106', as shown in Fig. 12B. Thus, vulnerable plaque can be stabilized by cooling the lipid-rich liquid core 106 sufficiently to change its state, typically from a disordered lipid to a highly ordered hexagonal lattice. Advantageously, a transition temperature above -5° C also inhibits necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid 106, particularly of the cap 108.

With reference now to Figs. 13A and 13B, additional treatments in conjunction with cooling of the vulnerable plaque will be illustrated. Fig. 13A illustrates a cross section of a blood vessel 100 that has been cooled so that the vulnerable plaque

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has been stabilized to lipid-rich solid/gel 106'. A stent 124 has been placed within the vessel lumen while the plaque is stabilized to provide a long-term restraint of lipid-rich fluid 106, and possibly to provide a structural scaffolding for healthy endothelial cells via tissue ingrowth. The stent may also alleviate plaque-induced stenosis and to improve the

5 . patency of the lumen. Other suitable primary treatments of the stabilized plaque may include balloon angioplasty, atherectomy, rotational atherectomy, laser angioplasty, or the like, where the lumen of the treated blood vessel is enlarged to at least partially alleviate a stenotic condition. In the case of arteries, the primary treatment will be effected shortly before, during, or preferably very shortly after the cooling treatment, preferably within 60

10 seconds of the cooling treatment, more preferably immediately following the cooling of the lipid-rich liquid to a desired temperature. In some instances, cooling may effect passivation of the vulnerable plaque, possibly reducing a size of the lipid-rich liquid 106", as illustrated in Fig. 13B, or modifying a cellular consistency or composition of the lipid-rich liquid, and/or the like by altering the chemistry or life cycle of the vulnerable plaque.

15 Passivation may also include enhancing a structural integrity of cap 108 (e.g. increasing the thickness, strength, elasticity, or hardness of the cap), modifying a cellular composition or property of the cap, and/or the like via scar formation or alteration of the chemistry of the vulnerable plaque.

A kit 126 including a catheter 10 and instructions for use 128 is illustrated

20 in Fig. 14. Catheter 10 may comprise the dual balloon catheter of Fig. 5, as illustrated in Fig. 14, or a catheter having a proximal end, a distal end, and a cooling member near its distal end. Instructions for use 128 may describe any of the associated method steps set forth above for detection and/or treatment of vulnerable plaque. Instructions for use 128 will often be printed, optionally appearing at least in part on a sterile package 130 for

25 balloon catheter 10. In alternative embodiments, instructions for use 128 may comprise a machine readable code, digital or analog data graphically illustrating or demonstrating the use of balloon catheter 10 to detect and/or treat vulnerable plaque. Still further alternatives are possible, including printing of the instructions for use on packaging 132 of kit 126, and the like.

30 While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents will be obvious to those of skill in the art. Hence, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

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WHAT IS CLAIMED IS:

- 1 1. A method for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, said method comprising:
3 cooling the blood vessel adjacent the vulnerable plaque to a
4 temperature sufficient to inhibit release of the retained fluid into the blood vessel.
- 1 2. A method as in claim 1, wherein the cooling step comprises:
2 introducing a catheter into a lumen of the blood vessel;
3 positioning a first balloon within the vessel lumen adjacent the
4 vulnerable plaque;
5 introducing a cryogenic cooling fluid into the first balloon;
6 exhausting the cooling fluid; and
7 expanding a second balloon disposed over the first balloon to
8 radially engage the vessel lumen.
- 1 3. A method as in claim 2, wherein the temperature of an outer
2 surface the first balloon is in the range from about -25° C to -45° C and the temperature
3 of an outer surface the second balloon is in the range from about 10° C to -40° C.
- 1 4. A method as in claim 1, wherein the blood vessel is an artery.
- 1 5. A method as in claim 1, wherein the fluid of the vulnerable plaque
2 comprises a lipid-rich liquid.
- 1 6. A method as in claim 5, wherein the vulnerable plaque comprises a
2 cap of cells between the lipid-rich liquid and a lumen of the blood vessel.
- 1 7. A method as in claim 6, further comprising inhibiting apoptosis of
2 tissue adjacent the lipid-rich liquid.
- 1 8. A method as in claim 6, wherein the cooling step inhibits rupture of
2 the cap of cells.
- 1 9. A method as in claim 1, wherein the cooling step comprises
2 lowering the temperature of the blood vessel surface from about 10° C to -40° C for a
3 time period in the range from about 15 to 120 seconds.

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- 1 10. A method as in claim 5, further comprising stabilizing the
2 vulnerable plaque by cooling the lipid-rich liquid to a highly ordered hexagonal lattice.
- 1 11. A method as in claim 10, wherein the lipid-rich liquid is hardened
2 to at least a gel-state.
- 1 12. A method as in claim 1, wherein the cooling inhibits inflammation
2 of the vulnerable plaque.
- 1 13. A method as in claim 1, wherein the cooling inhibits deterioration
2 of the vulnerable plaque.
- 1 14. A method as in claim 1, further comprising treating the vulnerable
2 plaque with a primary treatment.
- 1 15. A method as in claim 14, wherein the primary treatment comprises
2 at least one of angioplasty, stenting, and arthrectomy.
- 1 16. A method as in claim 5, further comprising passivating the
2 vulnerable plaque by reducing a size or modifying a consistency or composition of the
3 lipid-rich liquid.
- 1 17. A method as in claim 16, wherein passivation is carried out by
2 altering the chemistry or life cycle of the vulnerable plaque.
- 1 18. A method as in claim 6, further comprising passivating the
2 vulnerable plaque by increasing a thickness of the cap of cells.
- 1 19. A method for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, said method comprising:
3 detecting the vulnerable plaque; and
4 cooling the blood vessel adjacent the vulnerable plaque to a temperature
5 sufficient to inhibit release of the retained fluid into the blood vessel.
- 1 20. A method for detecting vulnerable plaque of a blood vessel, said
2 method comprising:
3 positioning a balloon within the vessel lumen adjacent a plaque;

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4 inflating the balloon so that a plurality of temperature sensors affixed to
5 the balloon are coupled to a surface of the vessel lumen; and
6 sensing a temperature differential along the lumen surface with the
7 sensors.

1 21. A method as in claim 20, wherein the plurality of temperature
2 sensors comprise thermocouples or thermistors.

1 22. A method as in claim 20, wherein the plurality of temperature
2 sensors are affixed circumferentially about the balloon.

1 23. A method as in claim 20, wherein the plurality of temperature
2 sensors detect temperature differences greater than about 0.1 ° C.

1 24. A method as in claim 20, wherein the inflating step may be
2 effected by a fluid or a gas.

1 25. A method as in claim 20, further comprising treating the detected
2 vulnerable plaque by cooling the blood vessel adjacent the vulnerable plaque to a
3 temperature sufficient to inhibit release of a retained fluid into the blood vessel.

1 26. A cryotherapy catheter for detecting and treating vulnerable plaque
2 of a blood vessel having a lumen surface, said catheter comprising:
3 a catheter body having a proximal end and a distal end with a cooling fluid
4 supply lumen and an exhaust lumen extending therebetween;
5 a first balloon disposed at the distal end of the catheter body, the first
6 balloon having an inner surface in fluid communication with the supply lumen and
7 exhaust lumen;
8 a second balloon disposed over the first balloon with a thermal barrier
9 therebetween; and
10 a plurality of temperature sensors affixed to the second balloon so as to
11 provide temperature measurements of the lumen surface.

1 27. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed to an outer surface of the second balloon.

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- 1 28. A cryotherapy catheter as in claim 27, wherein the plurality of
2 temperature sensors provide direct temperature measurements of the lumen surface.
- 1 29. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed to an inner surface of the second balloon.
- 1 30. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors comprise thermocouples or thermistors.
- 1 31. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed circumferentially about the second balloon.
- 1 32. A cryotherapy catheter as in claim 26, further comprising a
2 connector to a temperature readout device on the proximal end of the catheter.
- 1 33. A catheter for detecting a vulnerable plaque of a blood vessel
2 having a lumen surface, said catheter comprising:
3 a catheter body having a proximal end and a distal end with a supply
4 lumen and an exhaust lumen therebetween;
5 a balloon disposed on the distal end of the catheter body, the balloon
6 having an inner surface in fluid communication with the supply lumen and the exhaust
7 lumen; and
8 a plurality of temperature sensors supported by the balloon so as to provide
9 temperature measurements of the lumen surface.
- 1 34. A catheter as in claim 33, wherein the plurality of temperature
2 sensors are affixed to an outer surface of the balloon so as to provide direct temperature
3 measurements of the lumen surface.
- 1 35. A catheter as in claim 33, further comprising a connector to a
2 temperature readout device on the proximal end of the catheter.
- 1 36. A catheter as in claim 35, further comprising a circuit attached to
2 the connector which measures a temperature differential.
- 1 37. A catheter as in claim 36, further comprising an indicator located
2 on the connector.

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1 38. A catheter as in claim 33, wherein the plurality of temperature
2 sensors comprise thermocouples or thermistors.

1 39. A catheter as in claim 33, wherein the plurality of temperature
2 sensors are affixed circumferentially about the second balloon.

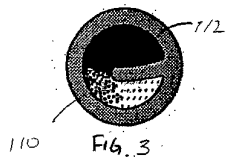
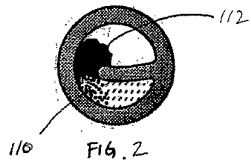
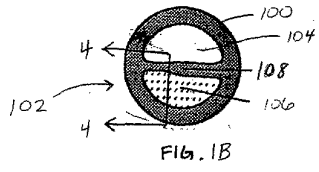
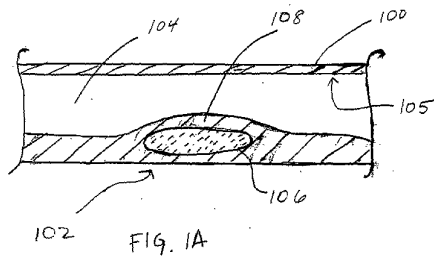
1 40. A kit for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, the kit comprising:
3 a catheter having a proximal end, a distal end, and a cooling member; and
4 instructions for use of the catheter, said instructions comprising the step of
5 cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained
6 fluid into the blood vessel.

1 41. A kit for detecting vulnerable plaque of a blood vessel, the kit
2 comprising:
3 a catheter having a proximal end, a distal end, and a balloon member with
4 a plurality of temperature sensors near its distal end; and
5 instructions for use of the catheter according to any of claims 20-25.

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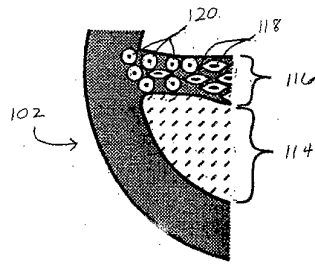
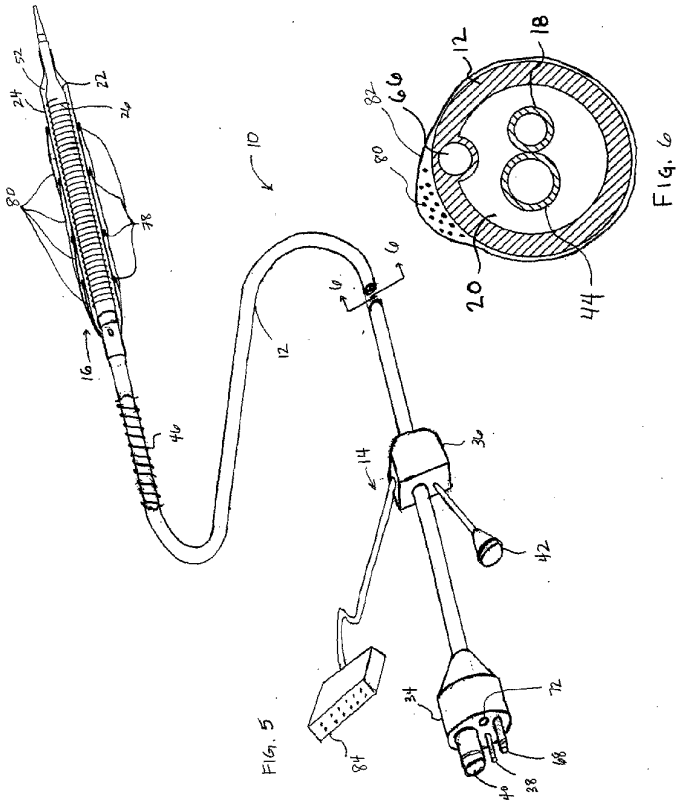


FIG. 4

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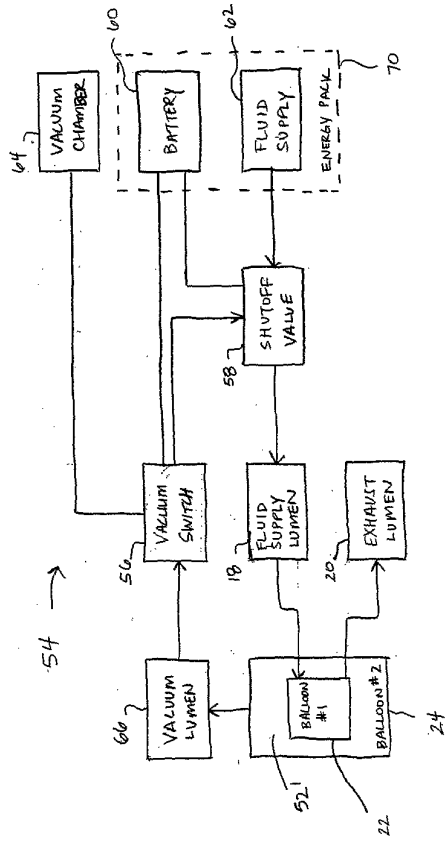


Fig. 7

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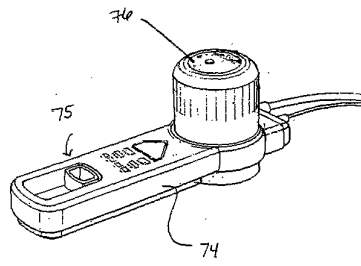


FIG. 8A

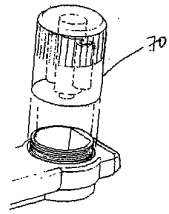


FIG. 8B

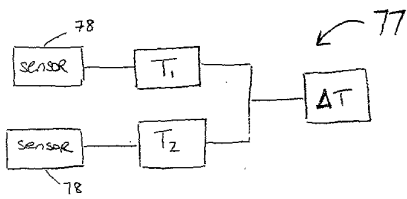
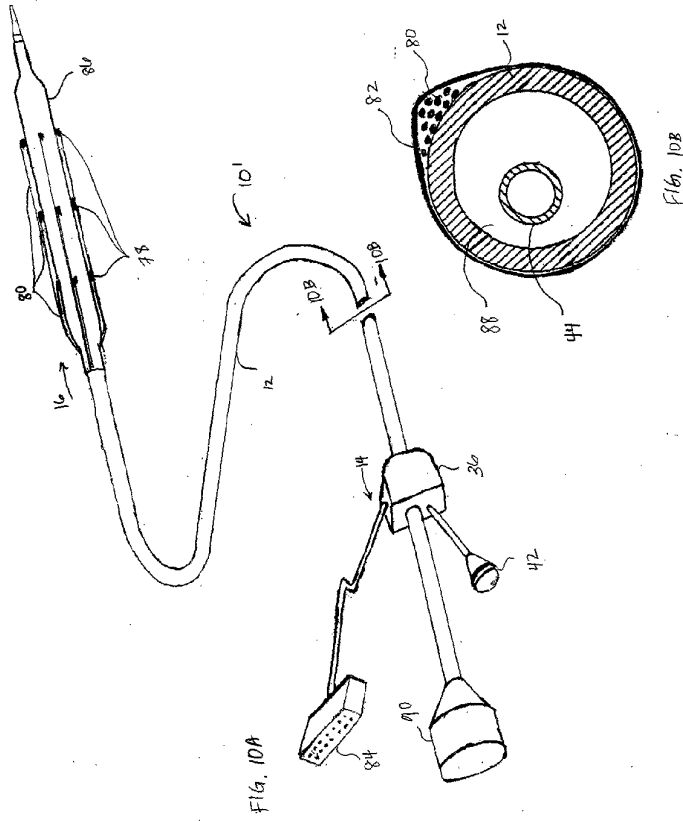


FIG. 9

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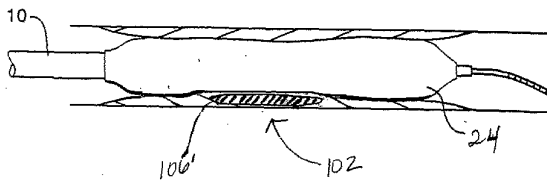
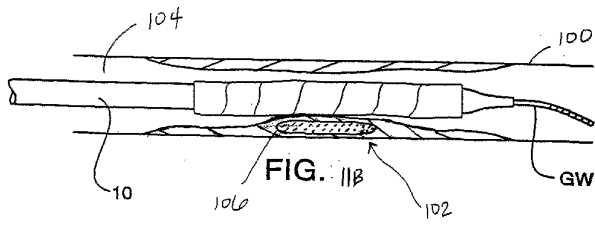
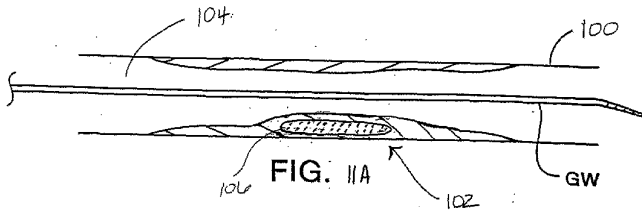


FIG. 11C

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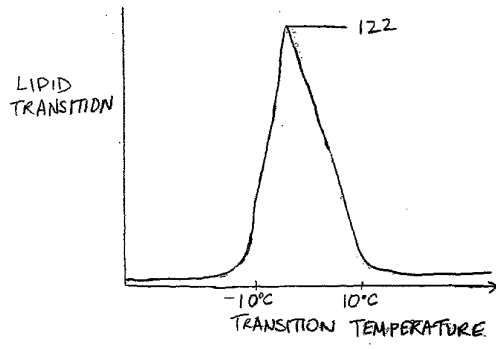


FIG. 12A

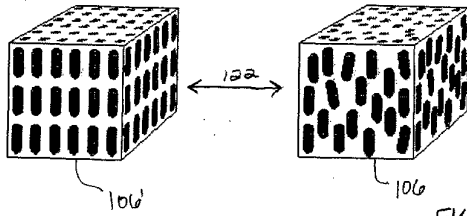
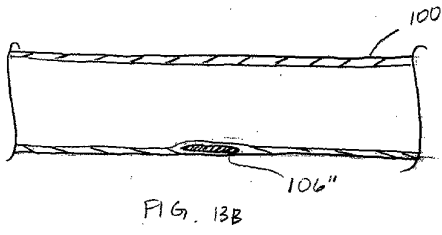
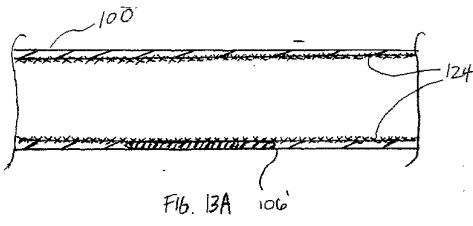


FIG. 12B

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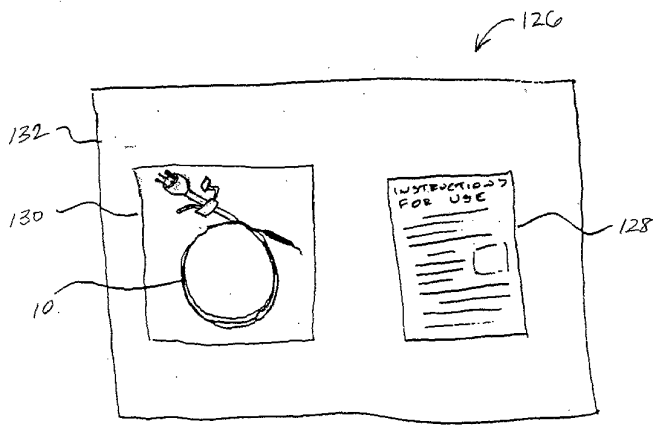


FIG. 14

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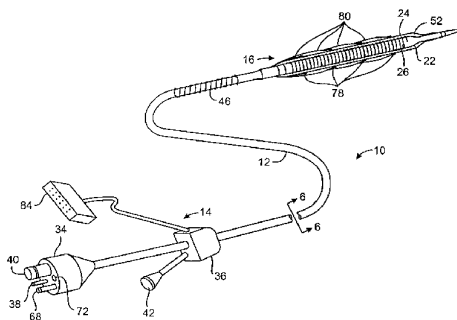
(71) Applicant: CRYOVASCULAR SYSTEMS, INC. [US/US]; 105 Copper Court, Los Gatos, CA 95032 (US).

(15) Information about Correction: see PCT Gazette No. 13/2003 of 27 March 2003, Section II

(72) Inventors: JOYE, James; 16175 Andrews Court, Monte Sereno, CA 95030 (US). TATSUTANI, Kristine; 353 Newton Avenue #3, Oakland, CA 94606 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE



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(57) Abstract: The present invention provides methods, apparatus, and kits for detection and/or treatment of vulnerable plaque of a blood vessel having a lumen surface. Detection methods include sensing a temperature differential along a lumen surface with temperature sensors (78) that thermally couple to the lumen surface. Treatment methods include controlled and safe cryogenic cooling of vulnerable plaque to inhibit release of retained fluid within the vulnerable plaque so as to inhibit acute coronary syndrome and to help maintain patency of a body lumen. Treatment methods may include additional treatments, such as primary treatments of passivation.

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Unfortunately, as plaque matures, narrowing of a blood vessel by a proliferation of smooth muscle cells, matrix synthesis, and lipid accumulation may result in formation of a plaque which is quite different than a standard stenotic plaque. Such atherosclerotic plaque becomes thrombosis-prone, and can be highly dangerous. This thrombosis-prone or vulnerable plaque may be a frequent cause of acute coronary syndromes.

The characterization of these vulnerable (and potentially life-threatening) plaques is currently under investigation. A number of strategies have been proposed to detect a vulnerable plaque. Proposed strategies include angiography, intravascular ultrasound, angioscopy, magnetic resonance imaging, magnetic resonance diffusion imaging, spectroscopy, infrared spectroscopy, scintigraphy, optical coherence tomography, electron beam computed tomographic scanning, and thermography, all of which have had limited success. In particular, proposed thermography methods detect temperature variations, as vulnerable plaque is typically inflamed and as such gives off more heat than standard stenotic plaque. While current thermography methods show great promise, they continue to suffer from limited temperature sensitivity which may often result in inaccurate detections of vulnerable plaque.

While the known procedures for treating plaque have gained wide acceptance and shown good efficacy for treatment of standard stenotic plaques, they may be ineffective (and possibly dangerous) when thrombotic conditions are superimposed on atherosclerotic plaques. Specifically, mechanical stresses caused by primary treatments like PTA or stenting may actually trigger release of fluids and/or solids from a vulnerable plaque into the blood stream, thereby potentially causing a coronary thrombotic occlusion.

For these reasons, it would be desirable to provide methods, apparatus, and kits for the detection and treatment of vulnerable plaque in blood vessels. The methods and apparatus should be suitable for intravascular and intraluminal introduction, preferably via a percutaneous approach. It would be particularly desirable if the new methods and apparatus were able to detect the vulnerable plaque accurately and/or deliver the treatment in a very controlled and safe manner, with minimal deleterious effects on adjacent tissues. Treatment methods, apparatus, and kits should further be effective in inhibiting release of the vulnerable plaque with minimum side effects. At least some of these objectives will be met by the invention described herein.

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2. Description of the Background Art

A cryoplasty device and method are described in WO 98/38934. Balloon catheters for intravascular cooling or heating a patient are described in U.S. 5,486,208 and WO 91/05528. A cryosurgical probe with an inflatable bladder for performing intrauterine ablation is described in U.S. 5,501,681. Cryosurgical probes relying on Joule-Thomson cooling are described in U.S. 5,275,595; 5,190,539; 5,147,355; 5,078,713; and 3,901,241. Catheters with heated balloons for post-angioplasty and other treatments are described in U.S. 5,196,024; 5,191,883; 5,151,100; 5,106,360; 5,092,841; 5,041,089; 5,019,075; and 4,754,752. Cryogenic fluid sources are described in U.S. 5,644,502; 5,617,739; and 4,336,691. The following U.S. Patents may also be relevant to the present invention: 5,458,612; 5,545,195; and 5,733,280.

Thermography is described by Ward Casscells et al. in The Vulnerable Atherosclerotic Plaque: Understanding, Identification, and Modification, chpt. 13, pp. 231-242 (1999); and L. Diamantopoulos et al. at <http://www.eurekalert.org/releases/aha-ati041499.html>. The impact of low temperatures on lipid membranes is described by Jack Kruuv in *Advances in Molecular and Cell biology*, vol. 19, pp. 143-192 (1997); P.J. Quinn in *Cryobiology*, vol. 22, pp. 128-146 (1985); and Michael J. Taylor, Ph.D. in Biology Of Cell Survival In The Cold, (Harwood Academic Publishers, In Press).

The full disclosures of each of the above references are incorporated herein by reference.

SUMMARY OF THE INVENTION

The present invention provides detection and cryotherapy treatment of vulnerable plaque within a blood vessel of a patient. The blood vessel may be any blood vessel in the patient's vasculature, including veins, arteries, and particularly coronary arteries. The vessel will typically be partially stenosed, at least in part from vulnerable plaque. In particular, the present invention may inhibit release of retained fluid within the vulnerable plaque so as to inhibit acute coronary syndrome and to help maintain the patency of a body lumen. The present invention may also provide for the treatment of vulnerable plaque in carotid arteries for stroke prevention. Where the patient's vasculature has both the vulnerable plaque and standard stenotic plaque, the treatment techniques described herein may be selectively directed to the vulnerable plaque, optionally without substantial cooling of the standard stenotic plaque. In other embodiments, both types of plaque may be treated.

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In a first aspect, the present invention provides a method for treating vulnerable plaque of a blood vessel. The method comprises cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of retained fluid from within the vulnerable plaque into the blood stream. The cooling treatment will often be directed against all or a portion of a circumferential surface of a lumen of the blood vessel, and will preferably inhibit release of lipid-rich liquid being releasably retained by the vulnerable plaque.

Cooling of the vessel may be effected by introducing a catheter into a lumen of the blood vessel. A first balloon is positioned within the vessel lumen adjacent the vulnerable plaque. Cryogenic cooling fluid is introduced into the first balloon and exhausted. A second balloon disposed over the first balloon is expanded to radially engage the vessel lumen. Generally, the temperature of an inside surface of the first balloon will be in the range from about -55° C to -75° C and an outside surface of the first balloon will be in the range from about -25° C to -45° C. The temperature of an outside surface of the second balloon will be in the range from about 10° C to -40° C, preferably from about 10° C to -20° C, more preferably from about 5° C to -10° C.

Usually, the temperature at the cell surface of the blood vessel lumen is in the range from about 10° C to -40° C, preferably from about 10° C to -20° C, more preferably from about 5° C to -10° C. The tissue is typically maintained at the desired temperature for a time period in the range from about 15 seconds to 120 seconds, preferably from 30 seconds to 60 seconds. Vulnerable plaque stabilization may be enhanced by repeating cooling in cycles, typically with from about 1 to 3 cycles, with the cycles being repeated at a rate of about one cycle every 120 seconds.

Surprisingly, cooling temperatures above 0° C can effect a transition of the vulnerable plaque's lipid core from a disordered crystalline state fluid to a ordered crystalline state solid or gel. Thus, vulnerable plaque can be stabilized by cooling the lipid-rich liquid sufficiently to change a state of the lipid-rich liquid, typically to a highly ordered hexagonal lattice at transition temperatures generally in the range from about 10° C to -10° C. Cooling may stabilize the vulnerable plaque while inhibiting necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid, particularly of the tissues defining a cap of cells between the lipid-rich liquid and the lumen of the blood vessel. Cooling may also inhibit inflammation and deterioration of the vulnerable plaque. The cooling treatment may further inhibit rupture of the cap of cells of the vulnerable plaque.

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In other aspects, the present invention of cooling the vulnerable plaque to inhibit release of lipid-rich liquid may be combined with additional treatments. For example, one adjunctive method may comprise treating the cooled vulnerable plaque with a primary treatment. Suitable primary treatments may include balloon angioplasty, 5 atherectomy, rotational atherectomy, laser angioplasty, or the like, where the lumen of the treated blood vessel is enlarged to at least partially alleviate a stenotic condition. The primary treatment may also include procedures for controlling restenosis, such as stent placement. In the case of arteries, the primary treatment will be effected shortly before, during, or preferably very shortly after the cooling treatment, preferably within 60 10 seconds of the cooling treatment, more preferably immediately following the cooling of the lipid-rich liquid to a desired temperature. Alternatively, cooling methods may additionally comprise passivating the vulnerable plaque by reducing a size of the lipid-rich liquid, changing a cellular consistency or composition of the lipid-rich liquid, enhancing a structural integrity of the cap (e.g. increasing a thickness of the cap), 15 modifying a cellular composition or structural properties of the cap, and/or the like by altering the chemistry or life cycle of the vulnerable plaque.

In another aspect, the present invention provides a method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid. The method includes detecting the vulnerable plaque and cooling the blood vessel adjacent the 20 vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

In another aspect, the present invention provides a method for detecting vulnerable plaque of a blood vessel. The method includes positioning a balloon within the vessel lumen adjacent a plaque. The balloon is inflated so that a plurality of 25 temperature sensors affixed to the balloon are coupled a surface of the vessel lumen. A temperature differential along the lumen surface is sensed with the sensors.

In another aspect, the present invention provides a cryotherapy catheter for detecting and treating vulnerable plaque of a blood vessel having a lumen surface. The catheter generally comprises a catheter body having a proximal end and a distal end with 30 a cooling fluid supply lumen and an exhaust lumen extending therebetween. A first balloon is disposed near the distal end of the catheter body in fluid communication with the supply lumen and exhaust lumen. A second balloon is disposed over the first balloon with a thermal barrier therebetween. A plurality of temperature sensors are affixed to the second balloon so as to provide temperature measurements of the lumen surface.

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In another aspect, the present invention provides a catheter for detecting a vulnerable plaque of a blood vessel having a lumen surface. The catheter generally comprises a catheter body having a proximal end and a distal end with a supply lumen and an exhaust lumen extending therebetween. A balloon is disposed on the distal end of the catheter body in fluid communication with the supply lumen and exhaust lumen. A plurality of temperature sensors are supported by the balloon so as to provide temperature measurements of the lumen surface.

In another aspect, the invention also provides a kit for treating vulnerable plaque in a blood vessel. The kit comprises a catheter having a proximal end, a distal end, and a cooling member near its distal end. Instructions are included in the kit for use of the catheter. These instructions comprise the step of cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained fluid into the blood vessel. Such a kit may include instructions for any of the methods described herein.

In yet another aspect, the invention provides a kit for detecting vulnerable plaque of a blood vessel. The kit comprises a catheter having a proximal end, a distal end, and a balloon member with a plurality of temperature sensors near its distal end. Instructions are included in the kit for use of the catheter. These instructions comprise the steps of positioning a balloon within the vessel lumen adjacent a plaque, inflating the balloon so that a plurality of temperature sensors affixed to the balloon are coupled to a surface of the vessel lumen, and sensing a temperature differential along the lumen surface with the sensors. Such a kit may include instructions for any of the methods described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A and 1B are cross-sectional views of a blood vessel containing a mature vulnerable plaque.

Fig. 2 illustrates a cross-sectional view of a vulnerable plaque rupture and plaque hemorrhage in the blood vessel.

Fig. 3 illustrates a cross-sectional view of a thrombotic occlusion in the blood vessel.

Fig. 4 illustrates an exploded cross-sectional view of Fig. 1A taken along line 4-4.

Fig. 5 illustrates an exemplary cryotherapy catheter for detecting and treating vulnerable plaque.

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Fig. 6 is a cross-sectional view of the catheter taken along line 6-6 in Fig. 5.

Fig. 7 is a functional flow diagram illustrating the operation of an automatic fluid shutoff mechanism of the catheter of Fig. 5.

5 Figs. 8A and 8B illustrate a handle and removable energy pack for use in the cryotherapy catheter of Fig. 5.

Fig. 9 illustrates a block diagram of a circuit which measures a temperature differential of the lumen surface.

Fig. 10A illustrates an alternative catheter for detecting vulnerable plaque.

10 Fig. 10B is a cross-sectional view of the catheter taken along line 10B-10B in Fig. 10A.

Figs. 11A-11C illustrate use of the catheter of Fig. 5 for treatment of vulnerable plaque.

Fig. 12A is a graph illustrating a transition temperature which effects a lipid core transition of the vulnerable plaque.

15 Fig. 12B illustrates the lipid core transition from a liquid, disordered state to a solid, ordered state.

Fig. 13A and 13B illustrate additional treatments in conjunction with cooling of the vulnerable plaque.

20 Fig. 14 illustrates a vulnerable plaque treatment kit including the apparatus of Fig. 5 and instructions for use.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

As used herein, the terms "vulnerable plaque" and "hot plaque" refer to atherosclerotic plaque that is thrombosis-prone. Figs. 1A and 1B illustrate cross-sectional
25 views of a blood vessel 100 containing a mature vulnerable plaque 102 within a lumen 104 of the vessel. The vulnerable plaque 102 generally comprises a necrotic core 106 of soft, lipid-rich, atheromatous gruel and a fibrous, sclerotic cap 108 of a collagen matrix of smooth muscle cells that covers the core 106. The gruel generally comprises a liquid of esterified cholesterol and low density lipoproteins which is releasably retained by the
30 vulnerable plaque 102. Disruption or fissuring of the cap 108 may cause plaque hemorrhage 110 (release of the highly thrombogenic lipid-rich liquid 106 through the ruptured plaque), as seen in Fig. 2. As a result of plaque hemorrhage 110, the highly thrombogenic lipid-rich liquid 106 is exposed to flowing blood of the vessel lumen 104. As illustrated in Fig. 3, release of the thrombogenic liquid may cause a thrombotic

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occlusion 112 (blood clot) of the entire vessel lumen, which in turn may be lead to life-threatening conditions, such as a stroke or sudden cardiac death.

Three determinants of vulnerability are illustrated in Fig. 4, which is an exploded cross-sectional view of Fig. 1A taken along line 4-4. Susceptibility of a vulnerable plaque to rupture may be primarily determined from the size 114 and consistency of the atheromatous core (e.g. a larger core increases chances for rupture), the thickness 116 and structural integrity of the sclerotic cap (e.g. a thinner cap increases chances for rupture), and cap inflammation (e.g. macrophage foam cell 118 infiltration weakens the cap cells 120 and increases chances for rupture). Additionally, vulnerable plaque disruption may be triggered by numerous extrinsic stresses imposed on the plaque. For example, fluctuations in intraluminal blood pressure, pulse pressure, heart contraction, vasospasm, and the like may precipitate disruption of a vulnerable plaque. Alternatively, mechanical stresses caused by primary treatments like PTA or stenting may trigger rupture as well.

Referring now to Figs. 5 and 6, an exemplary cryotherapy catheter 10 (which is more fully described in co-pending application no. 09/619,583 filed July 19, 2000 (Attorney Docket No. 018468-000610US)), the full disclosure of which is incorporated herein by reference) for detecting and treating vulnerable plaque 102 of a blood vessel 100 having a lumen surface 105 (see Fig. 1A) will be described. The catheter 10 comprises a catheter body 12 having a proximal end 14 and a distal end 16 with a cooling fluid supply lumen 18 and an exhaust lumen 20 extending therebetween. A first balloon 22 is disposed near the distal end of the catheter body 12 in fluid communication with the supply and exhaust lumens. A second balloon 24 is disposed over the first balloon 22 with a thermal barrier 26 therebetween.

The balloons 22, 24 may be an integral extension of the catheter body 12, but such a structure is not required by the present invention. The balloons 22, 24 could be formed from the same or a different material as the catheter body 12 and, in the latter case, attached to the distal end 16 of the catheter body 12 by suitable adhesives, heat welding, or the like. The catheter body 12 may be formed from conventional materials, such as polyethylenes, polyimides, and copolymers and derivatives thereof. The balloons 22, 24 may also be formed from conventional materials used for angioplasty, preferably being inelastic, such as polyethylene terephthalate (PET), polyethylene, or other medical grade material suitable for constructing a strong non-distensible balloon. Additionally, balloons 22 and 24 could be formed from different material to provide improved

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protection. For example, the first balloon 22 could be formed from PET to provide strength while the second balloon 24 could be formed from polyethylene to provide durability. The balloons 22, 24 have a length of at least 1 cm each, more preferably in the range from 2 cm to 5 cm each. The balloons 22, 24 will have diameters in the range from
5 2 mm to 5 mm each in a coronary artery and 2 mm to 10 mm each in a peripheral artery.

The thermal barrier 26 may comprise a gap maintained between the balloons 22, 24 by a filament. The filament typically comprises a helically wound, braided, woven, or knotted monofilament. The monofilament may be formed from PET or polyethylene naphthlate (PEN), and affixed to the first balloon 22 by adhesion bonding,
10 heat welding, fasteners, or the like. The thermal barrier 26 may also comprise a gap maintained between the balloons 22, 24 by a plurality of bumps on an outer surface of the first balloon 22 and/or an inner surface of the second balloon 24. The plurality of bumps may be formed in a variety of ways. For example, the bumps may be intrinsic to the
15 balloon (created during balloon blowing), or the bumps could be created by deforming the material of the balloon wall, by affixing mechanical "dots" to the balloon using adhesion bonding, heat welding, fasteners, or the like. Alternatively, the thermal barrier 26 may comprise a gap maintained between the balloons 22, 24 by a sleeve. The sleeve may be perforated and formed from PET or rubbers such as silicone and polyurathane.

Hubs 34 and 36 are secured to the proximal end 14 of the catheter body 12.
20 Hub 34 provides a port 38 for connecting a cryogenic fluid source to the fluid supply lumen 18 which is in turn in fluid communication with the inner surface of the first balloon 22. Hub 34 further provides a port 40 for exhausting the cryogenic fluid which travels from balloon 22 in a proximal direction through the exhaust lumen 20. Hub 36 provides a port 42 for a guidewire which extends through a guidewire lumen 44 in the
25 catheter body 12. Typically, the guidewire lumen 44 will extend through the exhaust lumen 20, as shown in Fig. 6. The guidewire lumen 44 may also extend axially outside the exhaust lumen 20 to minimize the occurrence of cryogenic fluid entering the blood stream via the guidewire lumen 44. Optionally, the guidewire lumen 44 may extend outside the inner surface of the first balloon 22 or the guidewire lumen 44 may allow for a
30 guidewire to extend outside both balloons 22, 24. Additionally, a reinforcing coil 46 may extend along the catheter body 12 proximal the first balloon 22. The reinforcing coil 46 may comprise a simple spring having a length typically in the range from 6 cm to 10 cm to prevent the catheter 10 from kinking up inside the blood vessel.

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The cryotherapy catheter 10 in Fig. 5 additionally illustrates a safety mechanism that monitors the containment of the first and second balloons 22, 24. The first balloon 22 defines a volume in fluid communication with the supply and exhaust lumens. A fluid shutoff is coupled to a cryogenic fluid supply with the supply lumen 18.

5 The second balloon 24 is disposed over the first balloon 22 with a vacuum space 52 therebetween. The vacuum space 52 is coupled to the fluid shutoff so as to inhibit flow of cryogenic fluid into the first balloon 22 in response to a change in the vacuum space 52.

Fig. 7 illustrates a functional flow diagram of the automatic fluid shutoff mechanism 54. The fluid shutoff 54 typically comprises a vacuum switch 56 connected

10 to a shutoff valve 58 by a circuit, the circuit being powered by a battery 60. The switch 56 may remain closed only when a predetermined level of vacuum space 52 is detected in the second balloon 24. The closed switch 56 allows the shutoff valve 58, in fluid communication with the cryogenic fluid supply 62, to be open. Alternatively, the circuit may be arranged so that the switch 56 is open only when the predetermined vacuum space

15 52 is present, with the shutoff valve 58 being open when the switch is open. The vacuum space 52 is reduced when either the first balloon 22 is punctured, allowing cryogenic fluid to enter the vacuum space 52, or the second balloon 24 is punctured, allowing blood to enter the vacuum space 52. In addition to monitoring the containment of both balloons 22, 24, in the event of a failure, the vacuum switch 56 will be triggered to prevent the

20 delivery of additional cryogenic fluid from the fluid supply 62 into the supply lumen 18. The second balloon 24 also acts to contain any cryogenic fluid that may have escaped the first balloon 22.

The vacuum space 52 may be provided by a simple fixed vacuum chamber 64 coupled to the vacuum space 52 by a vacuum lumen 66 of the body 12 via a vacuum

25 port 68 (See Fig. 5). In the exemplary embodiment, a positive displacement pump (ideally being similar to a syringe) is disposed within handle 74 and may be actuated by actuator 75, as seen in Fig. 8A. The vacuum space 52 should comprise a small volume of vacuum in the range from 1 mL to 100 mL, preferably 10 mL or less, as a smaller vacuum space 52 facilitates detection of a change in the amount of vacuum when a small amount

30 of fluid leakage occurs. The cryogenic fluid supply 62 and battery 60 for powering the circuit may be packaged together in an energy pack 70, as seen in Fig 8B. The energy pack 70 is detachable from a proximal handle 74 of the catheter body and disposable. A plurality of separate replaceable energy packs 70 allow for multiple cryogenic cooling cycles. Additionally, an audio alert or buzzer 76 may be located on the handle 74, with

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the buzzer providing an audio warning unless the handle is maintained sufficiently upright to allow flow from the fluid supply 62. The cryotherapy catheter may additionally comprise a hypsometer 72 coupled to the volume by a thermistor, thermocouple, or the like located in the first balloon 22 or handle to determine the pressure and/or temperature of fluid in the first balloon 22. The hypsometer allows for accurate real time measurements of variables (pressure, temperature) that effect the efficacy and safety of cryotherapy treatments.

The dual balloon cryotherapy catheter 10 in Fig. 5 also illustrates a temperature sensing mechanism that provides for thermographic detection of vulnerable plaque. A plurality of temperature sensors 78 are affixed to the second balloon 24 so as to provide direct temperature measurements of the lumen surface 105 (see Fig. 1A). The temperature sensors 78 may comprise a plurality of up to 20 thermocouples or thermistors and may be capable of detecting temperature differences greater than 0.1 °C. The temperature sensors 78 may be secured to the second balloon 24 at a series of axial and circumferential locations. The plurality of temperature sensors 78 may be affixed by adhesion bonding, heat welding, fasteners, or the like to an outer surface of the second balloon 24, as shown in Fig. 5, or may be alternatively affixed to an inner surface of the second balloon 24. Temperature sensor wires 80 may be secured along the length of the catheter shaft 12 within a thin sleeve 82 formed from PET or rubbers such as silicone and polyurathane, or in the latter case the wires 80 may be threaded through the vacuum lumen 66. A connector 84 at the proximal end 14 of the catheter 10 may also be provided to connect the temperature sensor wires 80 to a temperature readout device for temperature mapping along the lumen surface. Additionally, a circuit 77 may be attached to the connector 84 for measuring a temperature differential ΔT along the lumen surface from temperature measurement T1 and T2 sensed by the temperature sensors 78, as illustrated in the block diagram of Fig. 9. An indicator which is triggered above a threshold temperature differential may also be located on the connector for alerting purposes.

Detection of vulnerable plaque may be carried out by introducing the cryotherapy catheter 10 into a lumen 104 of the blood vessel 100 over a guidewire. The first balloon 22 is positioned within the blood vessel lumen 104 adjacent a plaque. The first balloon 22 is inflated so that the plurality of temperature sensors 78 affixed to the second balloon 24 (which expands upon inflation) thermally couple a surface of the vessel lumen. A temperature differential along the lumen surface 105 is sensed with the

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sensors. Inflation of balloon 22 may be effected by a gas, such as carbon dioxide, nitrous oxide, or the like, at a pressure in the range from about 5 psi to 50 psi. The balloon 22 will typically be inflated for a time period in the range from 10 to 120 seconds. The balloon catheter may sense for a temperature differential in a static position or as it moving along the lumen surface. Advantageously, temperature sensors 78 thermally engage the lumen surface to allow for direct temperature measurements to be made at specific locations along the lumen surface. This increased temperature sensitivity may in turn lead to improved temperature mapping and accurate vulnerable plaque detections. Cryotherapy catheter 10 may then be used for treating the detected vulnerable plaque as described in more detail below with reference to Figs. 11A-11C.

An alternative catheter 10' for detecting a vulnerable plaque of a blood vessel having a lumen surface is illustrated in Figs. 10A and 10B. Detection catheter 10' comprises a catheter body 12 having a proximal end 14 and a distal end 16 with a supply lumen 88 and an exhaust lumen 88 extending therebetween. A balloon 86 is disposed on the distal end of the catheter body 12. Balloon 86 has an inner surface in fluid communication with the supply lumen and exhaust lumen. A plurality of temperature sensors 78 are affixed to an outer surface of the balloon 86 so as to provide direct temperature measurements of the lumen surface 105 (see Fig. 1A).

Detection of vulnerable plaque may be carried out by introducing the detection catheter 10' into a lumen 104 of the blood vessel 100 over a guidewire. The balloon 86 is positioned within the vessel lumen adjacent a plaque. The balloon 86 is inflated so that a plurality of temperature sensors 78 affixed to the balloon thermally couple a surface of the vessel lumen. A temperature differential along the lumen surface is sensed with the sensors. Balloon 86 is generally inflatable with standard inflation media, such as contrast, saline, or the like. An inflation media supply and/or exhaust port 90 is connected to the supply and/or exhaust lumen 88 which is in turn in fluid communication with the inner surface of balloon 86. Balloon 86 will typically be inflated for a time period in the range from 10 to 120 seconds. The balloon catheter may sense for a temperature differential in a static position or as it moving along the lumen surface.

Referring now to Figs. 11A through 11C, use of cryotherapy catheter 10 of Fig. 5 for treatment of vulnerable plaque 102 will be described. As illustrated in Fig. 11A and 11B, catheter 10 will be introduced into a lumen 104 of the blood vessel 100 over a guidewire GW. The first balloon 22 is positioned within the blood vessel lumen 104 adjacent the vulnerable plaque 102. Cryogenic cooling fluid is introduced into the first

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balloon 22 (in which it often vaporizes) and exhausted. The second balloon 24 expands to radially engage the vessel wall, as illustrated by Fig. 11C. The vaporized fluid serves both to inflate balloon 22 (and expand balloon 24) and to cool the exterior surface of the balloons 22, 24. The blood vessel 100 adjacent the vulnerable plaque 102 is cooled to a temperature sufficient to inhibit release of retained fluid 106 from within the vulnerable plaque 102 into the blood vessel 100. The cooling treatment will be directed at all or a portion of a circumferential surface the vessel lumen. Preferably cooling will inhibit release of lipid-rich liquid being releasably retained by the vulnerable plaque by stabilizing the lipid-rich liquid 106 to a lipid-rich solid or gel 106' (which is described in more detail in Figs. 12A-12B below). Heat transfer will also be inhibited between the first and second balloons 22, 24 by the thermal barrier 26 so as to limit cooling of the vulnerable plaque to a desired temperature profile. Additionally, containment of the first and second balloons 22, 24 will be monitored during cooling by the fluid shutoff mechanism (see Fig. 7).

Suitable cryogenic fluids will preferably be non-toxic and may include liquid nitrous oxide, liquid carbon dioxide, cooled saline and the like. The cryogenic fluid will flow through the supply lumen 18 as a liquid at an elevated pressure and will vaporize at a lower pressure within the first balloon 22. For nitrous oxide, a delivery pressure within the supply lumen 18 will typically be in the range from 600 psi to 1000 psi at a temperature below the associated boiling point. After vaporization, the nitrous oxide gas within the first balloon 22 near its center will have a pressure typically in the range from 15 psi to 100 psi. Preferably, the nitrous oxide gas will have a pressure in the range from 50 psi to 100 psi in a peripheral artery and a range from about 15 psi to 45 psi in a coronary artery.

Generally, the temperature of an inside surface of the first balloon will be in the range from about -55°C to -75°C and an outside surface of the first balloon will be in the range from about -25°C to -45°C . The temperature of an outside surface of the second balloon will be in the range from about 10°C to -40°C , preferably from about 10°C to -20°C , more preferably from about 5°C to -10°C . This will provide a desired treatment temperature in a range from about 10°C to -40°C , preferably from about 10°C to -20°C , more preferably from about 5°C to -10°C . The tissue is typically maintained at the desired temperature for a time period in the range from about 15 to 120 seconds, preferably being from 30 to 60 seconds. Vulnerable plaque stabilization may be

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enhanced by repeating cooling in cycles, typically with from about 1 to 3 cycles, with the cycles being repeated at a rate of about one cycle every 120 seconds.

In some instances, cooling of the vessel may be limited to inhibiting necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid, particularly of the tissues defining a cap of cells 108 between the lipid-rich liquid 106 and the lumen of the blood vessel 104 (see Fig. 1A). Apoptosis or cell necrosis may be undesirable if it weakens the cap of cells as cap weakening may likely incite rupture of the vulnerable plaque and release of the lipid-rich liquid. Thus, the present invention may inhibit release of the retained fluid into the blood vessel without affecting the viability of the cap cells 108 and other cells which line the body lumen.

In other applications, cooling of the vessel at cooler temperatures may be desirable to provide for apoptosis and/or programmed cell death stimulation of inflammatory cells (e.g. macrophages 118, see Fig. 4) in the vulnerable plaque 102. Apoptosis may be desirable as the presence of such inflammatory cells may trigger cap weakening or erosion which in turn may lead to vulnerable plaque release of the lipid-rich liquid. Cooling at temperatures in the range from about 0° C to -15° C may inhibit inflammation and deterioration of the vulnerable plaque, particularly of the tissues defining the cap of cells 108. Alternatively, it may be beneficial to provide for necrosis in the cap cells 108 at cooling temperatures below about -20° C. Cap necrosis may stimulate cellular proliferation and thickening of the cap which in turn may inhibit cap rupture.

Referring now to Figs. 12A and 12B, transition of the vulnerable plaque's lipid-rich liquid core 106 will be described. Fig. 12A illustrates the transition temperature which effects a lipid core transition. The main transition point 122 occurs at some point between the transition temperature range of 10° C to -10° C. At this transition point 122, the lipid core may undergo a phase change from a disordered crystalline state fluid 106 to a ordered crystalline state solid or gel 106', as shown in Fig. 12B. Thus, vulnerable plaque can be stabilized by cooling the lipid-rich liquid core 106 sufficiently to change its state, typically from a disordered lipid to a highly ordered hexagonal lattice. Advantageously, a transition temperature above -5° C also inhibits necrosis and/or apoptosis of tissue adjacent the lipid-rich liquid 106, particularly of the cap 108.

With reference now to Figs. 13A and 13B, additional treatments in conjunction with cooling of the vulnerable plaque will be illustrated. Fig. 13A illustrates a cross section of a blood vessel 100 that has been cooled so that the vulnerable plaque

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has been stabilized to lipid-rich solid/gel 106'. A stent 124 has been placed within the vessel lumen while the plaque is stabilized to provide a long-term restraint of lipid-rich fluid 106, and possibly to provide a structural scaffolding for healthy endothelial cells via tissue ingrowth. The stent may also alleviate plaque-induced stenosis and to improve the patency of the lumen. Other suitable primary treatments of the stabilized plaque may include balloon angioplasty, atherectomy, rotational atherectomy, laser angioplasty, or the like, where the lumen of the treated blood vessel is enlarged to at least partially alleviate a stenotic condition. In the case of arteries, the primary treatment will be effected shortly before, during, or preferably very shortly after the cooling treatment, preferably within 60 seconds of the cooling treatment, more preferably immediately following the cooling of the lipid-rich liquid to a desired temperature. In some instances, cooling may effect passivation of the vulnerable plaque, possibly reducing a size of the lipid-rich liquid 106", as illustrated in Fig. 13B, or modifying a cellular consistency or composition of the lipid-rich liquid, and/or the like by altering the chemistry or life cycle of the vulnerable plaque. Passivation may also include enhancing a structural integrity of cap 108 (e.g. increasing the thickness, strength, elasticity, or hardness of the cap), modifying a cellular composition or property of the cap, and/or the like via scar formation or alteration of the chemistry of the vulnerable plaque.

A kit 126 including a catheter 10 and instructions for use 128 is illustrated in Fig. 14. Catheter 10 may comprise the dual balloon catheter of Fig. 5, as illustrated in Fig. 14, or a catheter having a proximal end, a distal end, and a cooling member near its distal end. Instructions for use 128 may describe any of the associated method steps set forth above for detection and/or treatment of vulnerable plaque. Instructions for use 128 will often be printed, optionally appearing at least in part on a sterile package 130 for balloon catheter 10. In alternative embodiments, instructions for use 128 may comprise a machine readable code, digital or analog data graphically illustrating or demonstrating the use of balloon catheter 10 to detect and/or treat vulnerable plaque. Still further alternatives are possible, including printing of the instructions for use on packaging 132 of kit 126, and the like.

While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents will be obvious to those of skill in the art. Hence, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

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WHAT IS CLAIMED IS:

- 1 1. A method for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, said method comprising:
3 cooling the blood vessel adjacent the vulnerable plaque to a
4 temperature sufficient to inhibit release of the retained fluid into the blood vessel.

- 1 2. A method as in claim 1, wherein the cooling step comprises:
2 introducing a catheter into a lumen of the blood vessel;
3 positioning a first balloon within the vessel lumen adjacent the
4 vulnerable plaque;
5 introducing a cryogenic cooling fluid into the first balloon;
6 exhausting the cooling fluid; and
7 expanding a second balloon disposed over the first balloon to
8 radially engage the vessel lumen.

- 1 3. A method as in claim 2, wherein the temperature of an outer
2 surface the first balloon is in the range from about -25° C to -45° C and the temperature
3 of an outer surface the second balloon is in the range from about 10° C to -40° C.

- 1 4. A method as in claim 1, wherein the blood vessel is an artery.

- 1 5. A method as in claim 1, wherein the fluid of the vulnerable plaque
2 comprises a lipid-rich liquid.

- 1 6. A method as in claim 5, wherein the vulnerable plaque comprises a
2 cap of cells between the lipid-rich liquid and a lumen of the blood vessel.

- 1 7. A method as in claim 6, further comprising inhibiting apoptosis of
2 tissue adjacent the lipid-rich liquid.

- 1 8. A method as in claim 6, wherein the cooling step inhibits rupture of
2 the cap of cells.

- 1 9. A method as in claim 1, wherein the cooling step comprises
2 lowering the temperature of the blood vessel surface from about 10° C to -40° C for a
3 time period in the range from about 15 to 120 seconds.

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- 1 10. A method as in claim 5, further comprising stabilizing the
2 vulnerable plaque by cooling the lipid-rich liquid to a highly ordered hexagonal lattice.
- 1 11. A method as in claim 10, wherein the lipid-rich liquid is hardened
2 to at least a gel-state.
- 1 12. A method as in claim 1, wherein the cooling inhibits inflammation
2 of the vulnerable plaque.
- 1 13. A method as in claim 1, wherein the cooling inhibits deterioration
2 of the vulnerable plaque.
- 1 14. A method as in claim 1, further comprising treating the vulnerable
2 plaque with a primary treatment.
- 1 15. A method as in claim 14, wherein the primary treatment comprises
2 at least one of angioplasty, stenting, and arthrectomy.
- 1 16. A method as in claim 5, further comprising passivating the
2 vulnerable plaque by reducing a size or modifying a consistency or composition of the
3 lipid-rich liquid.
- 1 17. A method as in claim 16, wherein passivation is carried out by
2 altering the chemistry or life cycle of the vulnerable plaque.
- 1 18. A method as in claim 6, further comprising passivating the
2 vulnerable plaque by increasing a thickness of the cap of cells.
- 1 19. A method for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, said method comprising:
3 detecting the vulnerable plaque; and
4 cooling the blood vessel adjacent the vulnerable plaque to a temperature
5 sufficient to inhibit release of the retained fluid into the blood vessel.
- 1 20. A method for detecting vulnerable plaque of a blood vessel, said
2 method comprising:
3 positioning a balloon within the vessel lumen adjacent a plaque;

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4 inflating the balloon so that a plurality of temperature sensors affixed to
5 the balloon are coupled to a surface of the vessel lumen; and
6 sensing a temperature differential along the lumen surface with the
7 sensors.

1 21. A method as in claim 20, wherein the plurality of temperature
2 sensors comprise thermocouples or thermistors.

1 22. A method as in claim 20, wherein the plurality of temperature
2 sensors are affixed circumferentially about the balloon.

1 23. A method as in claim 20, wherein the plurality of temperature
2 sensors detect temperature differences greater than about 0.1 ° C.

1 24. A method as in claim 20, wherein the inflating step may be
2 effected by a fluid or a gas.

1 25. A method as in claim 20, further comprising treating the detected
2 vulnerable plaque by cooling the blood vessel adjacent the vulnerable plaque to a
3 temperature sufficient to inhibit release of a retained fluid into the blood vessel.

1 26. A cryotherapy catheter for detecting and treating vulnerable plaque
2 of a blood vessel having a lumen surface, said catheter comprising:
3 a catheter body having a proximal end and a distal end with a cooling fluid
4 supply lumen and an exhaust lumen extending therebetween;
5 a first balloon disposed at the distal end of the catheter body, the first
6 balloon having an inner surface in fluid communication with the supply lumen and
7 exhaust lumen;
8 a second balloon disposed over the first balloon with a thermal barrier
9 therebetween; and
10 a plurality of temperature sensors affixed to the second balloon so as to
11 provide temperature measurements of the lumen surface.

1 27. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed to an outer surface of the second balloon.

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- 1 28. A cryotherapy catheter as in claim 27, wherein the plurality of
2 temperature sensors provide direct temperature measurements of the lumen surface.
- 1 29. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed to an inner surface of the second balloon.
- 1 30. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors comprise thermocouples or thermistors.
- 1 31. A cryotherapy catheter as in claim 26, wherein the plurality of
2 temperature sensors are affixed circumferentially about the second balloon.
- 1 32. A cryotherapy catheter as in claim 26, further comprising a
2 connector to a temperature readout device on the proximal end of the catheter.
- 1 33. A catheter for detecting a vulnerable plaque of a blood vessel
2 having a lumen surface, said catheter comprising:
3 a catheter body having a proximal end and a distal end with a supply
4 lumen and an exhaust lumen therebetween;
5 a balloon disposed on the distal end of the catheter body, the balloon
6 having an inner surface in fluid communication with the supply lumen and the exhaust
7 lumen; and
8 a plurality of temperature sensors supported by the balloon so as to provide
9 temperature measurements of the lumen surface.
- 1 34. A catheter as in claim 33, wherein the plurality of temperature
2 sensors are affixed to an outer surface of the balloon so as to provide direct temperature
3 measurements of the lumen surface.
- 1 35. A catheter as in claim 33, further comprising a connector to a
2 temperature readout device on the proximal end of the catheter.
- 1 36. A catheter as in claim 35, further comprising a circuit attached to
2 the connector which measures a temperature differential.
- 1 37. A catheter as in claim 36, further comprising an indicator located
2 on the connector.

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1 38. A catheter as in claim 33, wherein the plurality of temperature
2 sensors comprise thermocouples or thermistors.

1 39. A catheter as in claim 33, wherein the plurality of temperature
2 sensors are affixed circumferentially about the second balloon.

1 40. A kit for treating vulnerable plaque of a blood vessel, the
2 vulnerable plaque releasably retaining fluid, the kit comprising:
3 a catheter having a proximal end, a distal end, and a cooling member; and
4 instructions for use of the catheter, said instructions comprising the step of
5 cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained
6 fluid into the blood vessel.

1 41. A kit for detecting vulnerable plaque of a blood vessel, the kit
2 comprising:
3 a catheter having a proximal end, a distal end, and a balloon member with
4 a plurality of temperature sensors near its distal end; and
5 instructions for use of the catheter according to any of claims 20-25.

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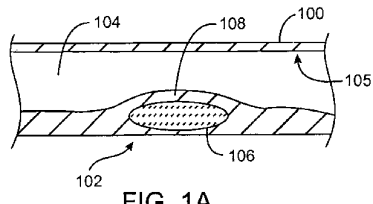


FIG. 1A

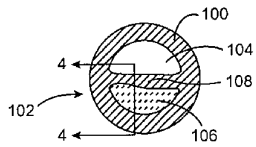


FIG. 1B

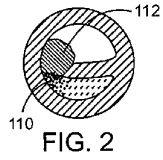


FIG. 2

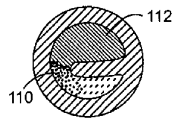


FIG. 3

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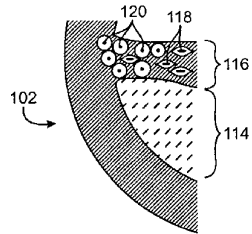


FIG. 4

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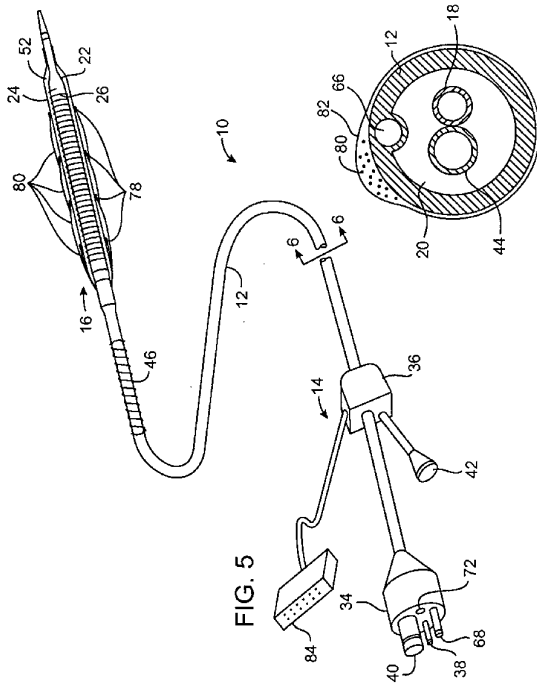


FIG. 5

FIG. 6

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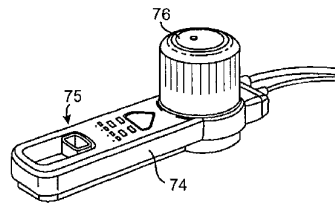


FIG. 8A

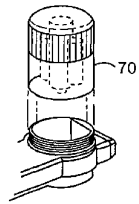


FIG. 8B

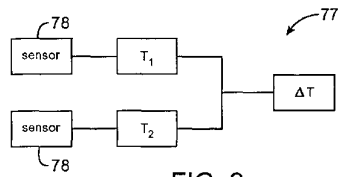


FIG. 9

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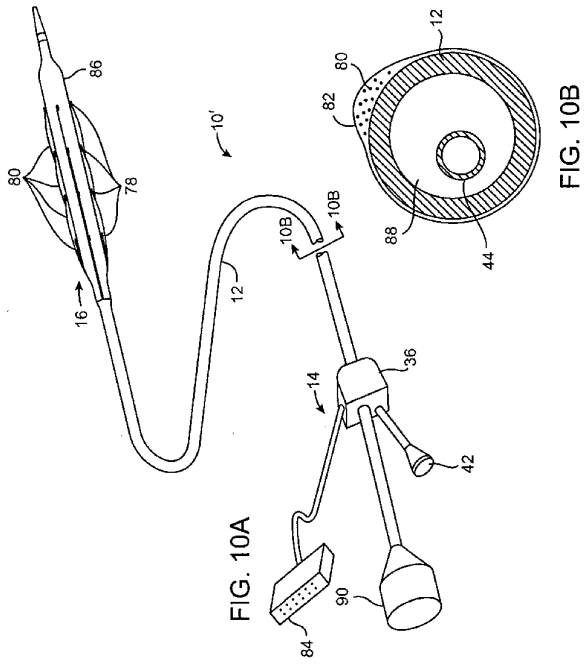


FIG. 10B

FIG. 10A

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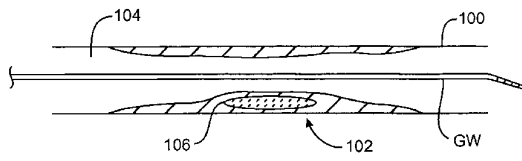


FIG. 11A

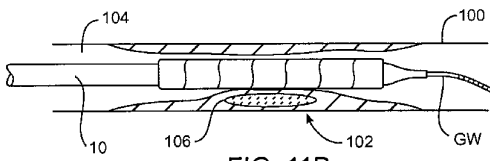


FIG. 11B

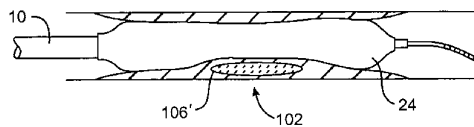


FIG. 11C

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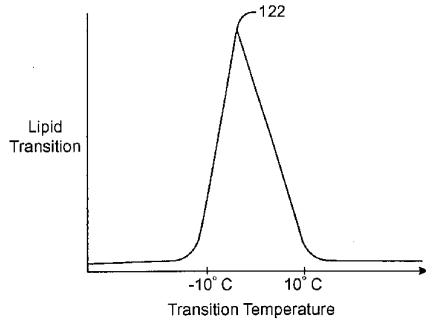


FIG. 12A

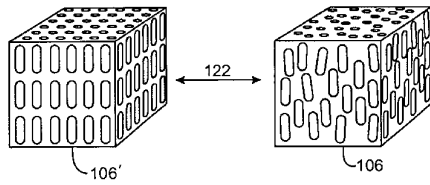


FIG. 12B

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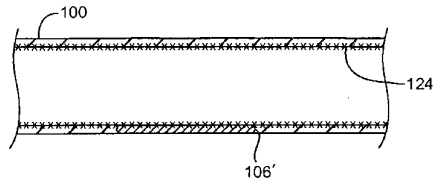


FIG. 13A

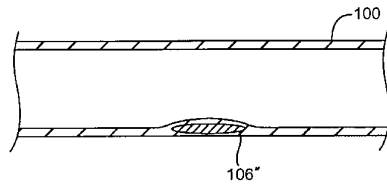


FIG. 13B

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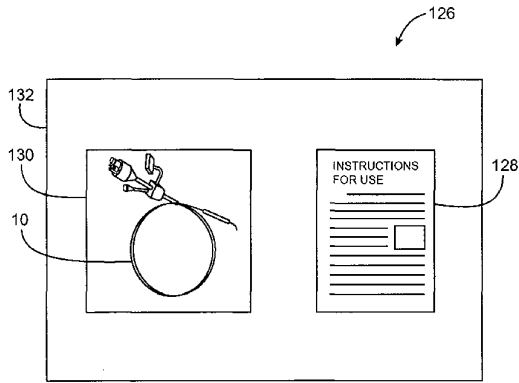


FIG. 14

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【 国際調査報告 】

INTERNATIONAL SEARCH REPORT		International application No. PCT/US01/26817
A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61B 18/18 US CL. : 606/21		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
U.S. : 606/20-26; 128/898		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EAST search terms: <u>plaque, balloon, cryos, temperature sensors</u>		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,868,735 A (Lafontaine) 09 February 1999, whole document.	1-4,9, 12-15, 19-21, 24-28, 30, 32-38 ----- 5-8, 16-18, 22, 23, 29, 31, 39
Y	US 5,899,899 A (Arless et al) 04 May 1999, whole document.	5-8, 16-18, 22, 23, 29, 31, 39
A	US 5,902,299 A (Jayaraman) 11 May 1999, whole document.	1-39
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "A" document defining the general state of the art which is not considered to be of particular relevance "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "E" earlier document published on or after the international filing date "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Z" document published prior to the international filing date but later than the priority date claimed "O" document referring to an oral disclosure, use, exhibition or other means "a" document member of the same patent family "P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 16 NOVEMBER 2001		Date of mailing of the international search report 25 JAN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20251 Facsimile No. (703) 305-3280		Authorized officer MICHAEL PEFFLEY <i>Diana Smith f</i> Telephone No. (703) 305-0658

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No. PCT/US01/95817

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(a) for the following reasons:

1. Claims Nos.: 40 AND 41
because they relate to subject matter not required to be searched by this Authority, namely:
these claims included recitation of written subject matter (i.e. instructions) which is non-statutory subject matter.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

フロントページの続き

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, 3

Fターム(参考) 4C060 JJ02

专利名称(译)	用于检测和治疗易损斑块的冷冻疗法		
公开(公告)号	JP2004506470A	公开(公告)日	2004-03-04
申请号	JP2002520722	申请日	2001-08-17
[标]申请(专利权)人(译)	克里欧科尔多瓦青蟹在系统公司		
申请(专利权)人(译)	克里欧科尔多瓦青蟹在系统公司		
[标]发明人	ジョイジェイムズ タツタニクリスティン		
发明人	ジョイ,ジェイムズ タツタニ,クリスティン		
IPC分类号	A61B5/00 A61B17/00 A61B17/22 A61B18/02		
CPC分类号	A61B5/01 A61B5/6853 A61B18/02 A61B2017/00101 A61B2017/22001 A61B2017/22002 A61B2017/22051 A61B2018/0022 A61B2018/0212 A61B2018/0262		
FI分类号	A61B17/36.310		
F-TERM分类号	4C060/JJ02		
优先权	09/641462 2000-08-18 US		
其他公开文献	JP4845330B2 JP2004506470A5		
外部链接	Espacenet		

摘要(译)

方法，装置和试剂盒检测和/或治疗血管的易损斑块。可以在充满热气体的气球上使用温度传感器沿管腔表面感测温度差。治疗方法包括对易损斑块进行受控和安全的低温冷却，以抑制易损斑块内滞留液的释放，从而抑制急性冠状动脉综合征并帮助维持体腔通畅。

