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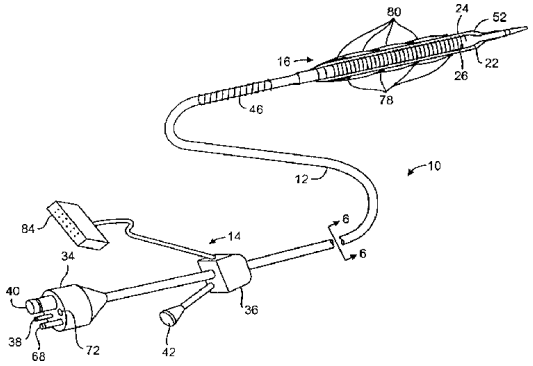
(54)【発明の名称】脆弱性プラークを検出および治療するための凍結療法

(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。
【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。
【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。
【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。
【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

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。
【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。
【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。
【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。
【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

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。
【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。
【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
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。
【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。

【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】

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、シンチグラフィー、光干渉断層撮影法、電子ビーム演算断層撮影スキャニング法、およびサーモグラフィーがあるが、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ー法は、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ー法は、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。

【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、それらは血栓症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。

【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）。

【０００９】

サーモグラフィーは、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．ディアマントポーラスらのｈｔｔｐ：／／ｗｗｗ．ｅｕｒｅｋａｌｅｒｔ．ｏｒｇ／ｒｅｌｅａｓｅｓ／ａｈａ－ａｔｉ０４１４９９．ｈｔｌｍに記載されている。脂質膜に対す

る低温の影響は、ジャック クルーブのアドバンスインモレキュラーアンドセルバイオロジー（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ー（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ー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。

【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。

【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バルーンの外面は、約－２５℃～－４５℃の範囲である。前記第２バルーンの外面の温度は、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。

【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。

【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

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。

【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。

【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。

【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。

【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。

【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、これらの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

，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の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の材料、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。

【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またはシリコー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を通っ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を通っ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を通っ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５２における変化に応答して、前記第１バルーン２２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。

【００３０】

図７は、前記自動流体遮断機構５４の作用流れ図を示している。この流体遮断機構５４は通常、バッテリ６０によって駆動される回路によって、遮断バルブ５８に接続された減圧スイッチ５６を含む。前記スイッチ５６は、所定レベルの減圧空間５２が第２バルーン２４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５６によって、前記低温冷却流体供給部６２と流体連絡状態で前記遮断バルブ５８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５８が開放される状態で、前記所定の減圧空間５２が存在している時にのみ前記スイッチ５６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５２は、前記第１バルーン２２が穿孔されて、凍結療法流体が減圧空間５２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２４が穿孔されて血液が減圧空間５２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２２，２４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５６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６２から供給管腔１８へと供給されることを防止する。前記第２バルーン２４も、第１バルーン２２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。

【００３１】

前記減圧空間５２は、減圧ポート６８（図５を参照）を介して、前記本体１２の減圧管腔６６で前記減圧空間５２に接続される単純な固定減圧チャンバ６４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７４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８Ａに示されているように、アクチュエータ７５によって操作可能である。前記減圧空間５２は、この減圧空間５２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、１ｍＬ～１００ｍＬの範囲、好ましくは１０ｍＬ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６２と前記回路を駆動するためのバッテリ６０とは、図８Ｂに示されているように、１つのエネルギパック７０内に共にパッケージ化することができる。このエネルギパック７０は、カテーテル本体の近位側ハンドル７４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パック７０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７４に音声警報またはブザー７６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６２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２２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２２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（ｈｙｐｓｏｍｅｔｅｒ）７２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。

【００３２】

図５の前記デュアルバルーン凍結療法カテーテル１０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１０５の直接温度測定を提供するべく、前記第２バルーン２４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）。これら温度センサ７８は、複数の２０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７８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２４に固定することができる。これら複数の温度センサ７８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２４の外面に固定することができ、あるいは第２バルーン２４の内面に固定することも可能である。カテーテル軸１２の長さに沿って、ＰＥＴまたはシリコー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８２内に、温度センサワイヤ８０を固定することができ、後者の場合、これらワイヤ８０は、前記減圧管腔６６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８０

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ΔＴ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、これらの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化され、その帽部弱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

において、脂質コアは図１２Ｂに図示されているように、無秩序な結晶状態流体１０６から秩序的な結晶状態固体またはゲル１０６’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１０６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１０６の近傍の組織、特に前記帽部１０８の壊死および／またはアポトーシスを抑制する。

【００４２】

次に図１３Ａおよび１３Ｂ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１３Ａは、脆弱性プラークが脂質リッチ固体／ゲル１０６’状態にまで安定化される冷却された血管１００の断面を図示している。脂質リッチ流体１０６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（ｓｃａｆｆｏｌｄｉｎｇ）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１２４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。場合によっては、冷却方法は図１３Ｂに図示されているように、脂質リッチ液体１０６’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１０８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。

【００４３】

カテーテル１０とその使用のための取扱説明書１２８とが含まれているキット１２６が図１４に図示されている。カテーテル１０は、図１４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１２８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１２８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１０用の殺菌パッケージ１３０上に示される。別実施形態において、使用取扱説明書１２８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１０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１２６のパッケージ１３２上に印刷する等のその他の構成も可能である。

【００４４】

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。

【図面の簡単な説明】

【図１Ａ】

図１Ａ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１Ｂ】

図１Ｂ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。

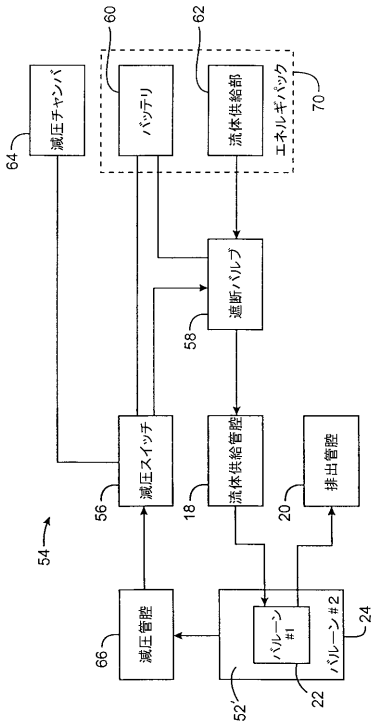
【図２】

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。

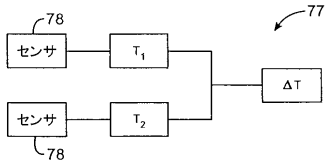
【図３】

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１Ａ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。
【図８Ａ】
図８Ａ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パックを図示している。
【図８Ｂ】
図８Ｂ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１０Ａ】
図１０Ａ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。
【図１０Ｂ】
図１０Ｂは、図１０Ａの１０Ｂ－１０Ｂ線に沿った前記カテーテルの断面図である。
【図１１Ａ】
図１１Ａ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１１Ｂ】
図１１Ｂ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１１Ｃ】
図１１Ｃ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１２Ａ】
図１２Ａ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。
【図１２Ｂ】
図１２Ｂ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１３Ａ】
図１３Ａ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１３Ｂ】
図１３Ｂ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。

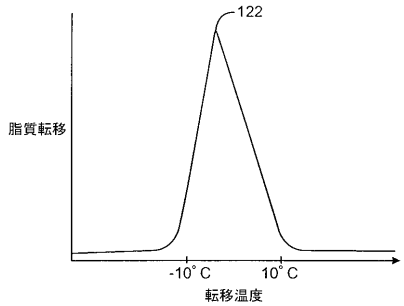
【図７】



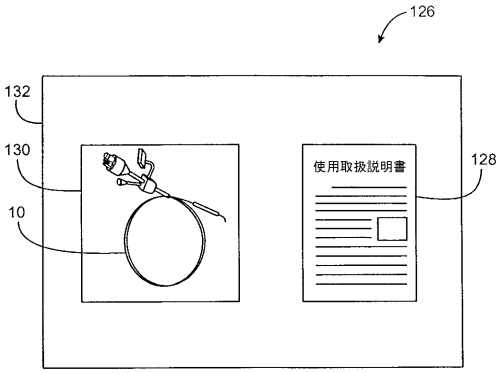
【図９】



【図１２Ａ】



【図１４】



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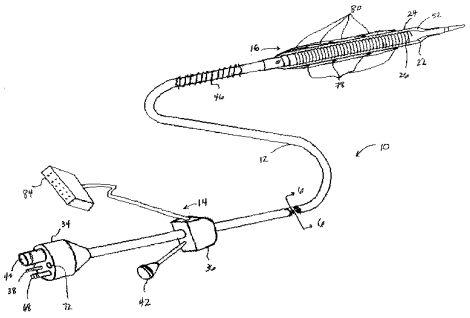
(54) Title: CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE



(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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CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods, apparatus, and kits for treating blood vessels. More particularly, the present invention provides methods, apparatus, and kits for treating a lesion, and particularly a vulnerable atherosclerotic plaque, within a patient's vasculature to inhibit harmful releases within the vasculature, such as those which may be responsible for strokes or acute coronary syndromes of unstable angina, myocardial infarction, and sudden cardiac death.

Atherosclerotic plaque is present to some degree in most adults. Plaques can severely limit the bloodflow through a blood vessel by narrowing the open vessel lumen. This narrowing effect or stenosis is often responsible for ischemic heart disease. Fortunately, a number of percutaneous intravascular procedures have been developed for treating atherosclerotic plaque in a patient's vasculature. The most successful of these treatments is percutaneous transluminal angioplasty (PTA). PTA employs a catheter having an expansible distal end, usually in the form of an inflatable balloon, to dilate a stenotic region in the vasculature to restore adequate blood flow beyond the stenosis. Other procedures for opening stenotic regions include directional arthrectomy, laser angioplasty, stents, and the like. Used alone or in combination, these percutaneous intravascular procedures have provided significant benefits for treatment of stenoses caused by plaque.

While treatments of plaque-induced stenoses have advanced significantly over the last few decades, the morbidity and mortality associated with vascular plaques have remained significant. Recent work suggests that plaque may generally fall into one of two different general types: standard stenotic plaques and vulnerable plaques. Stenotic plaque, which is sometimes referred to as thrombosis-resistant plaque, can generally be treated effectively by the known intravascular lumen opening techniques mentioned above. Although the stenoses they induce may require treatment, these atherosclerotic plaques themselves are often a benign and effectively treatable disease.

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.

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.

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 cystalline 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.

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, 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 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), 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 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 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 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.

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.

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.

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.

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.

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.

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 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 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

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

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 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 napthlate (PEN), and affixed to the first balloon 22 by adhesion bonding, 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 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. 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 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 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.

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. 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 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 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 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 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 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

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

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

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

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 inflamatory cells (e.g. macrophages 118, see Fig. 4) in the vulnerable plaque 102. Apoptosis may be desirable as the presence of such inflamatory 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

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.

WHAT IS CLAIMED IS:

1. A method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, said method comprising:

cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

2. A method as in claim 1, wherein the cooling step comprises:

introducing a catheter into a lumen of the blood vessel;

positioning a first balloon within the vessel lumen adjacent the vulnerable plaque;

introducing a cryogenic cooling fluid into the first balloon;

exhausting the cooling fluid; and

expanding a second balloon disposed over the first balloon to radially engage the vessel lumen.

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

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

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

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

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

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

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

10. A method as in claim 5, further comprising stabilizing the vulnerable plaque by cooling the lipid-rich liquid to a highly ordered hexagonal lattice.

11. A method as in claim 10, wherein the lipid-rich liquid is hardened to at least a gel-state.

12. A method as in claim 1, wherein the cooling inhibits inflammation of the vulnerable plaque.

13. A method as in claim 1, wherein the cooling inhibits deterioration of the vulnerable plaque.

14. A method as in claim 1, further comprising treating the vulnerable plaque with a primary treatment.

15. A method as in claim 14, wherein the primary treatment comprises at least one of angioplasty, stenting, and arthrectomy.

16. A method as in claim 5, further comprising passivating the vulnerable plaque by reducing a size or modifying a consistency or composition of the lipid-rich liquid.

17. A method as in claim 16, wherein passivation is carried out by altering the chemistry or life cycle of the vulnerable plaque.

18. A method as in claim 6, further comprising passivating the vulnerable plaque by increasing a thickness of the cap of cells.

19. A method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, said method comprising:
detecting the vulnerable plaque; and
cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

20. A method for detecting vulnerable plaque of a blood vessel, said method comprising:
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.

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

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

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

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

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

26. A cryotherapy catheter for detecting and treating vulnerable plaque of a blood vessel having a lumen surface, said catheter comprising:

a catheter body having a proximal end and a distal end with a cooling fluid supply lumen and an exhaust lumen extending therebetween;

a first balloon disposed at the distal end of the catheter body, the first balloon having an inner surface in fluid communication with the supply lumen and exhaust lumen;

a second balloon disposed over the first balloon with a thermal barrier therebetween; and

a plurality of temperature sensors affixed to the second balloon so as to provide temperature measurements of the lumen surface.

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

28. A cryotherapy catheter as in claim 27, wherein the plurality of temperature sensors provide direct temperature measurements of the lumen surface.

29. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors are affixed to an inner surface of the second balloon.

30. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors comprise thermocouples or thermistors.

31. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors are affixed circumferentially about the second balloon.

32. A cryotherapy catheter as in claim 26, further comprising a connector to a temperature readout device on the proximal end of the catheter.

33. A catheter for detecting a vulnerable plaque of a blood vessel having a lumen surface, said catheter comprising:

a catheter body having a proximal end and a distal end with a supply lumen and an exhaust lumen therebetween;

a balloon disposed on the distal end of the catheter body, the balloon having an inner surface in fluid communication with the supply lumen and the exhaust lumen; and

a plurality of temperature sensors supported by the balloon so as to provide temperature measurements of the lumen surface.

34. A catheter as in claim 33, wherein the plurality of temperature sensors are affixed to an outer surface of the balloon so as to provide direct temperature measurements of the lumen surface.

35. A catheter as in claim 33, further comprising a connector to a temperature readout device on the proximal end of the catheter.

36. A catheter as in claim 35, further comprising a circuit attached to the connector which measures a temperature differential.

37. A catheter as in claim 36, further comprising an indicator located on the connector.

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

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

40. A kit for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, the kit comprising:

a catheter having a proximal end, a distal end, and a cooling member; and

instructions for use of the catheter, said instructions comprising the step of cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained fluid into the blood vessel.

41. A kit for detecting vulnerable plaque of a blood vessel, the kit comprising:

a catheter having a proximal end, a distal end, and a balloon member with a plurality of temperature sensors near its distal end; and

instructions for use of the catheter according to any of claims 20-25.

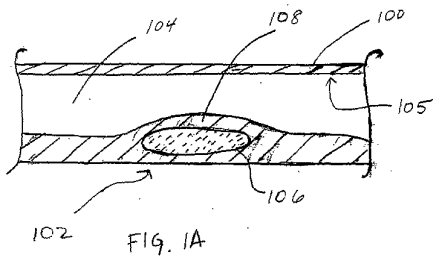

FIG. 1A

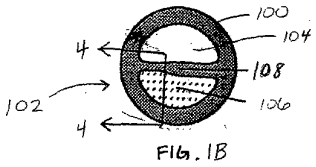

FIG. 1B

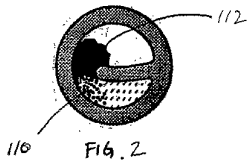

FIG. 2

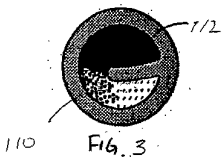

FIG. 3

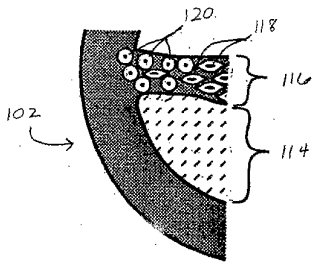

FIG. 4

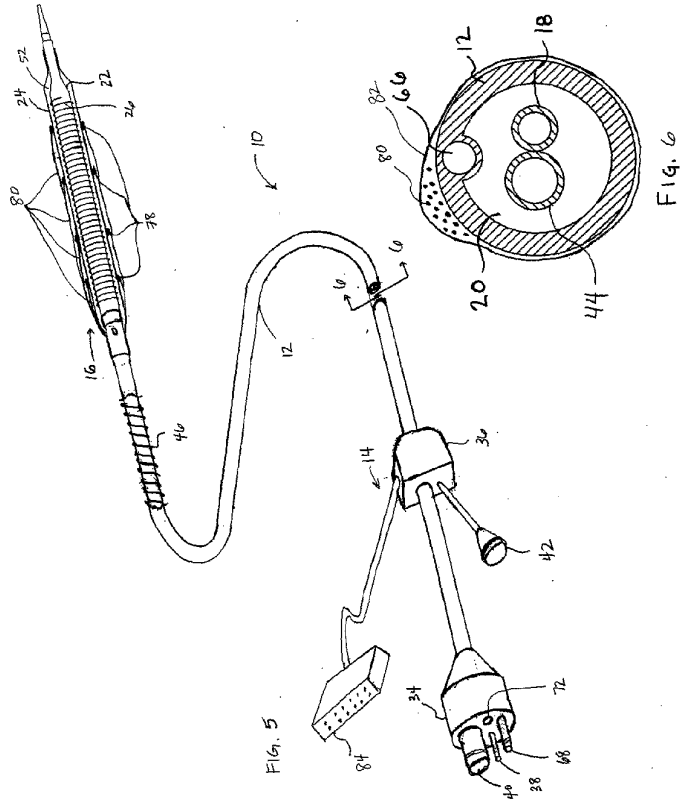
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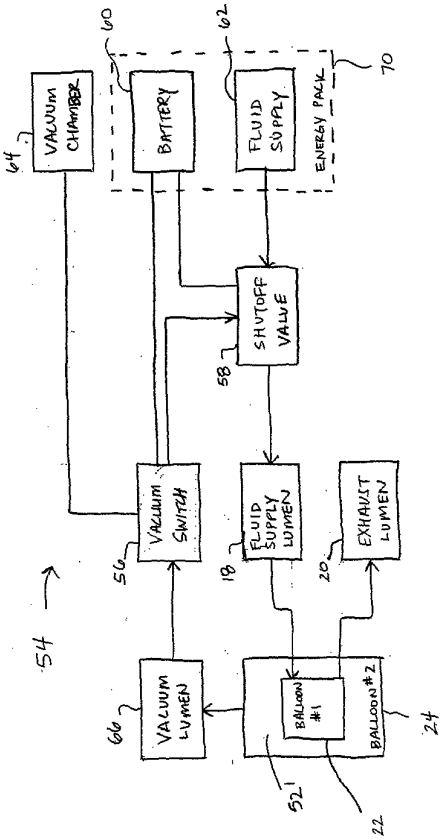
Fig. 5

Fig. 6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62
70
64
VACUUM CHAMBER
BATTERY
FLUID SUPPLY
ENERGY PACK
SHUTOFF VALVE
58
VACUUM SWITCH
FLUID SUPPLY LUMEN
EXHAUST LUMEN
56
18
20
54
VACUUM LUMEN
BALLOON #1
BALLOON #2
24
66
52
22

FIG. 7

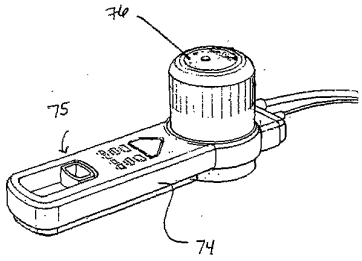

FIG. 8A

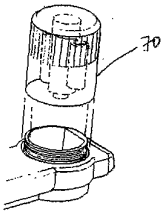

FIG. 8B

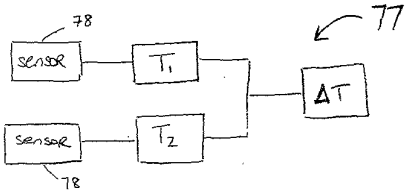

FIG. 9

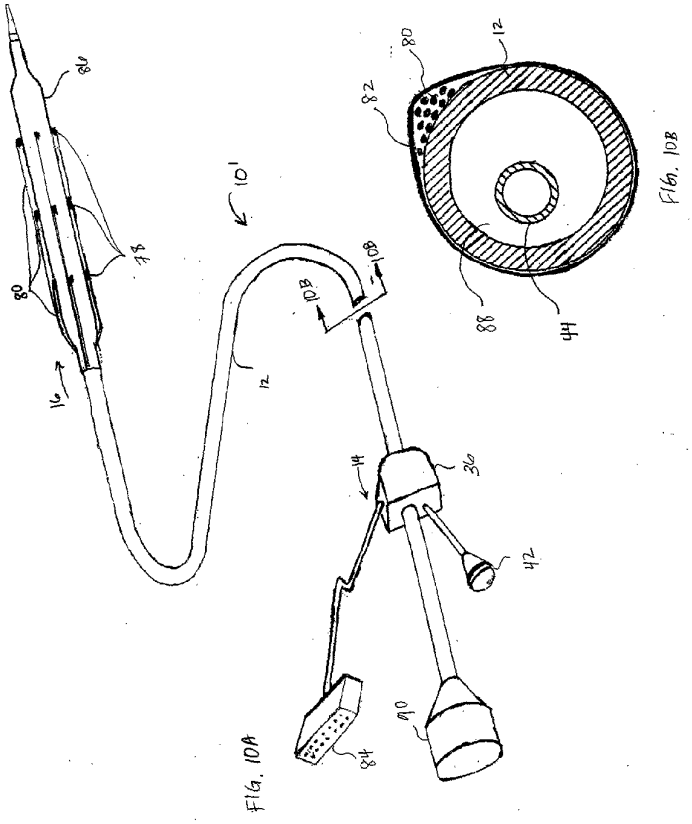

Fig. 10B

Fig. 10A

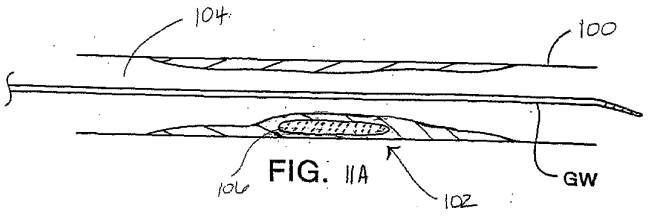

FIG. 11A

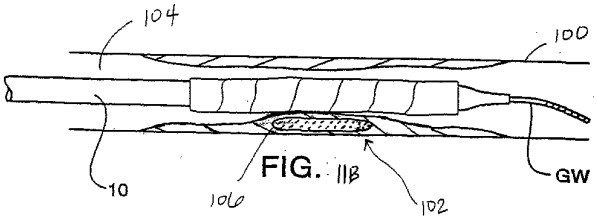

FIG. 11B

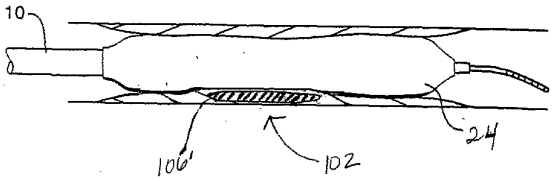

FIG. 11C

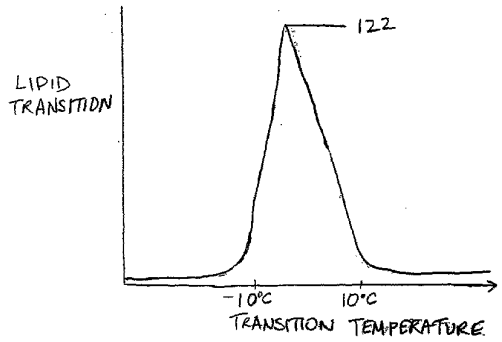

FIG. 12A

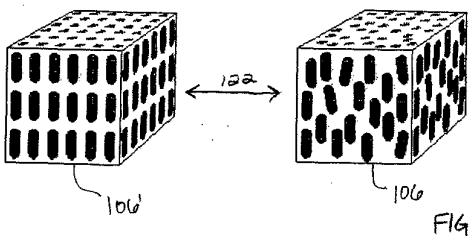

FIG. 12B

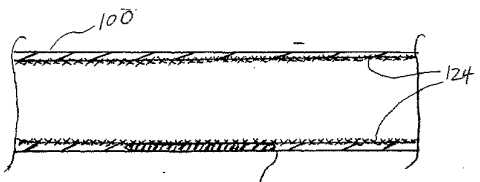

FIG. 13A

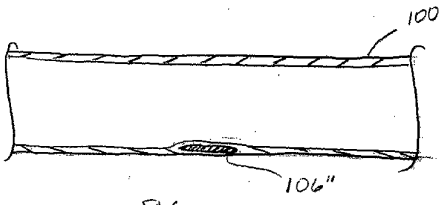

FIG. 13B

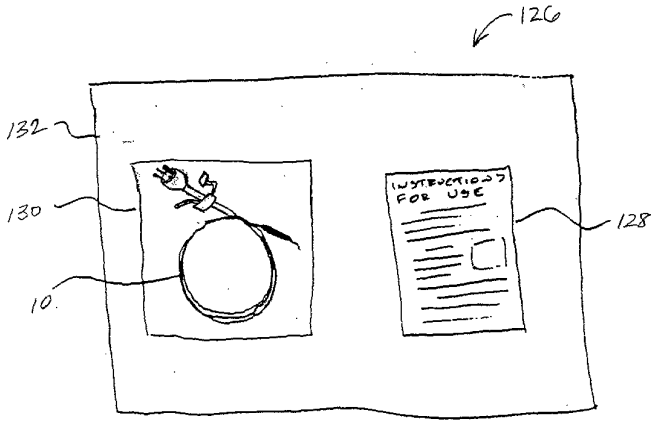

FIG. 14

【国際公開パンフレット（コレクトバージョン）】

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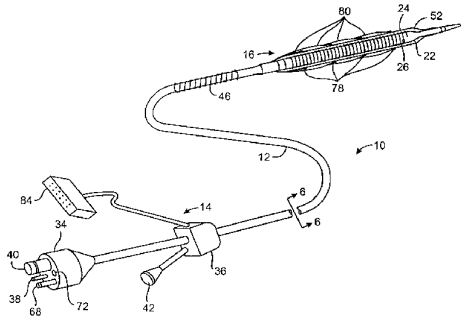
(54) Title: CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE



(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.

WO 02/015807 A1

CRYOTHERAPY METHOD FOR DETECTING AND TREATING VULNERABLE PLAQUE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods, apparatus, and kits for treating blood vessels. More particularly, the present invention provides methods, apparatus, and kits for treating a lesion, and particularly a vulnerable atherosclerotic plaque, within a patient's vasculature to inhibit harmful releases within the vasculature, such as those which may be responsible for strokes or acute coronary syndromes of unstable angina, myocardial infarction, and sudden cardiac death.

Atherosclerotic plaque is present to some degree in most adults. Plaques can severely limit the bloodflow through a blood vessel by narrowing the open vessel lumen. This narrowing effect or stenosis is often responsible for ischemic heart disease. Fortunately, a number of percutaneous intravascular procedures have been developed for treating atherosclerotic plaque in a patient's vasculature. The most successful of these treatments is percutaneous transluminal angioplasty (PTA). PTA employs a catheter having an expansible distal end, usually in the form of an inflatable balloon, to dilate a stenotic region in the vasculature to restore adequate blood flow beyond the stenosis. Other procedures for opening stenotic regions include directional arthrectomy, laser angioplasty, stents, and the like. Used alone or in combination, these percutaneous intravascular procedures have provided significant benefits for treatment of stenoses caused by plaque.

While treatments of plaque-induced stenoses have advanced significantly over the last few decades, the morbidity and mortality associated with vascular plaques have remained significant. Recent work suggests that plaque may generally fall into one of two different general types: standard stenotic plaques and vulnerable plaques. Stenotic plaque, which is sometimes referred to as thrombosis-resistant plaque, can generally be treated effectively by the known intravascular lumen opening techniques mentioned above. Although the stenoses they induce may require treatment, these atherosclerotic plaques themselves are often a benign and effectively treatable disease.

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.

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.

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 cystalline 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.

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, 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 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), 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 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 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 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.

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.

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.

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.

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.

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.

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 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 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

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

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 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 napthlate (PEN), and affixed to the first balloon 22 by adhesion bonding, 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 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. 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 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 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.

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. 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 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 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 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 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 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

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

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

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

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 inflamatory cells (e.g. macrophages 118, see Fig. 4) in the vulnerable plaque 102. Apoptosis may be desirable as the presence of such inflamatory 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

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.

WHAT IS CLAIMED IS:

1. A method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, said method comprising:

cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

2. A method as in claim 1, wherein the cooling step comprises:

introducing a catheter into a lumen of the blood vessel;

positioning a first balloon within the vessel lumen adjacent the vulnerable plaque;

introducing a cryogenic cooling fluid into the first balloon;

exhausting the cooling fluid; and

expanding a second balloon disposed over the first balloon to radially engage the vessel lumen.

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

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

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

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

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

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

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

10. A method as in claim 5, further comprising stabilizing the vulnerable plaque by cooling the lipid-rich liquid to a highly ordered hexagonal lattice.

11. A method as in claim 10, wherein the lipid-rich liquid is hardened to at least a gel-state.

12. A method as in claim 1, wherein the cooling inhibits inflammation of the vulnerable plaque.

13. A method as in claim 1, wherein the cooling inhibits deterioration of the vulnerable plaque.

14. A method as in claim 1, further comprising treating the vulnerable plaque with a primary treatment.

15. A method as in claim 14, wherein the primary treatment comprises at least one of angioplasty, stenting, and arthrectomy.

16. A method as in claim 5, further comprising passivating the vulnerable plaque by reducing a size or modifying a consistency or composition of the lipid-rich liquid.

17. A method as in claim 16, wherein passivation is carried out by altering the chemistry or life cycle of the vulnerable plaque.

18. A method as in claim 6, further comprising passivating the vulnerable plaque by increasing a thickness of the cap of cells.

19. A method for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, said method comprising:

detecting the vulnerable plaque; and

cooling the blood vessel adjacent the vulnerable plaque to a temperature sufficient to inhibit release of the retained fluid into the blood vessel.

20. A method for detecting vulnerable plaque of a blood vessel, said method comprising:

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.

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

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

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

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

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

26. A cryotherapy catheter for detecting and treating vulnerable plaque of a blood vessel having a lumen surface, said catheter comprising:

a catheter body having a proximal end and a distal end with a cooling fluid supply lumen and an exhaust lumen extending therebetween;

a first balloon disposed at the distal end of the catheter body, the first balloon having an inner surface in fluid communication with the supply lumen and exhaust lumen;

a second balloon disposed over the first balloon with a thermal barrier therebetween; and

a plurality of temperature sensors affixed to the second balloon so as to provide temperature measurements of the lumen surface.

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

28. A cryotherapy catheter as in claim 27, wherein the plurality of temperature sensors provide direct temperature measurements of the lumen surface.

29. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors are affixed to an inner surface of the second balloon.

30. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors comprise thermocouples or thermistors.

31. A cryotherapy catheter as in claim 26, wherein the plurality of temperature sensors are affixed circumferentially about the second balloon.

32. A cryotherapy catheter as in claim 26, further comprising a connector to a temperature readout device on the proximal end of the catheter.

33. A catheter for detecting a vulnerable plaque of a blood vessel having a lumen surface, said catheter comprising:

a catheter body having a proximal end and a distal end with a supply lumen and an exhaust lumen therebetween;

a balloon disposed on the distal end of the catheter body, the balloon having an inner surface in fluid communication with the supply lumen and the exhaust lumen; and

a plurality of temperature sensors supported by the balloon so as to provide temperature measurements of the lumen surface.

34. A catheter as in claim 33, wherein the plurality of temperature sensors are affixed to an outer surface of the balloon so as to provide direct temperature measurements of the lumen surface.

35. A catheter as in claim 33, further comprising a connector to a temperature readout device on the proximal end of the catheter.

36. A catheter as in claim 35, further comprising a circuit attached to the connector which measures a temperature differential.

37. A catheter as in claim 36, further comprising an indicator located on the connector.

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

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

40. A kit for treating vulnerable plaque of a blood vessel, the vulnerable plaque releasably retaining fluid, the kit comprising:

a catheter having a proximal end, a distal end, and a cooling member; and

instructions for use of the catheter, said instructions comprising the step of cooling the blood vessel adjacent the vulnerable plaque to inhibit release of the retained fluid into the blood vessel.

41. A kit for detecting vulnerable plaque of a blood vessel, the kit comprising:

a catheter having a proximal end, a distal end, and a balloon member with a plurality of temperature sensors near its distal end; and

instructions for use of the catheter according to any of claims 20-25.

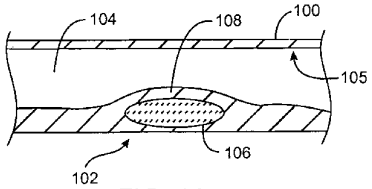


FIG. 1A

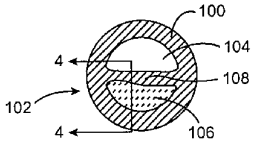


FIG. 1B

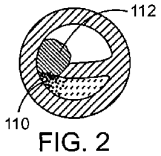


FIG. 2

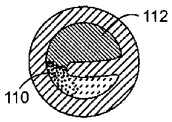


FIG. 3

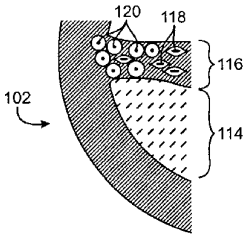
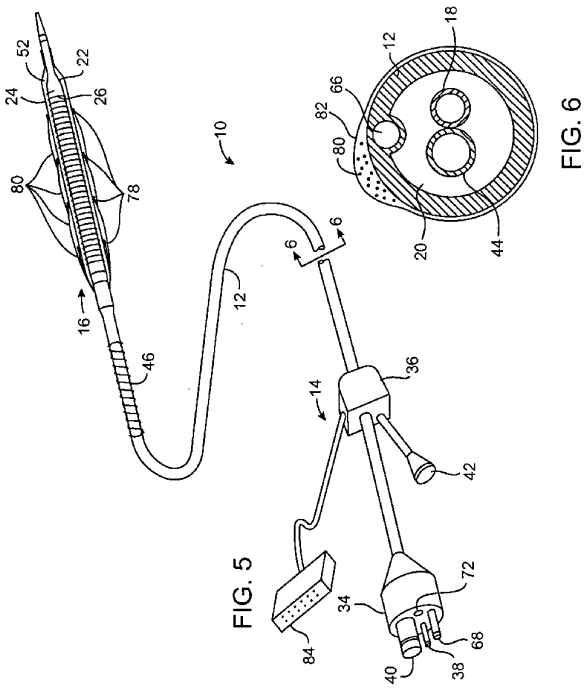


FIG. 4


52
22
24
26
80
78
10
16
46
12
6
6
36
14
42
72
34
84
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38
68
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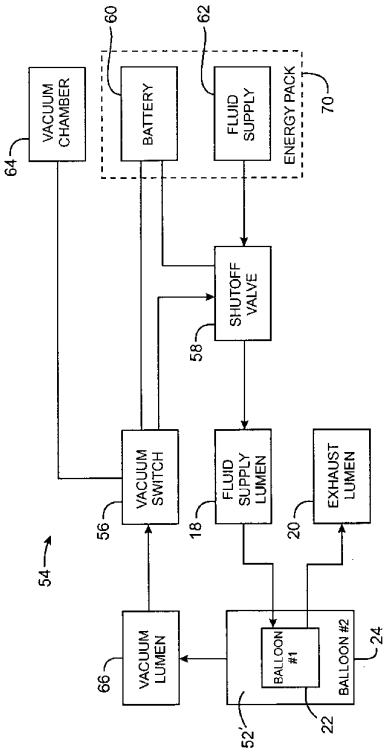
20
44

FIG. 5

FIG. 6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62
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BATTERY
FLUID SUPPLY
ENERGY PACK
70
64
SHUTOFF VALVE
58
VACUUM SWITCH
FLUID SUPPLY LUMEN
EXHAUST LUMEN
56
18
20
54
VACUUM LUMEN
BALLOON #1
BALLOON #2
24
66
52
22

FIG. 7

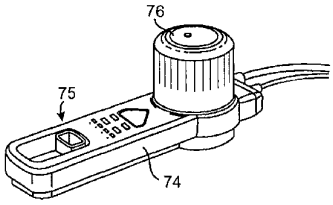

FIG. 8A

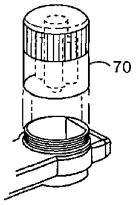

FIG. 8B

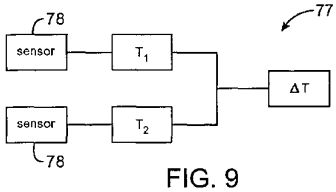

FIG. 9

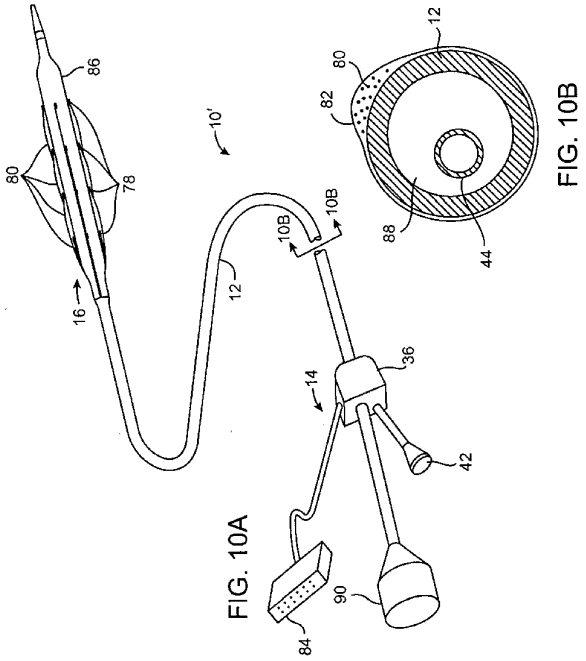

FIG. 10A

FIG. 10B

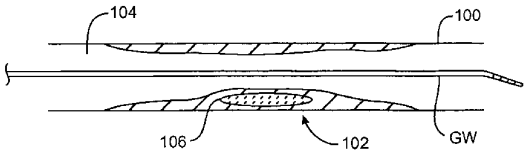

FIG. 11A

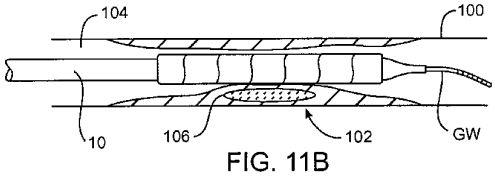

FIG. 11B

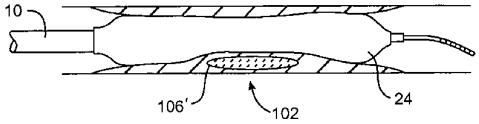

FIG. 11C

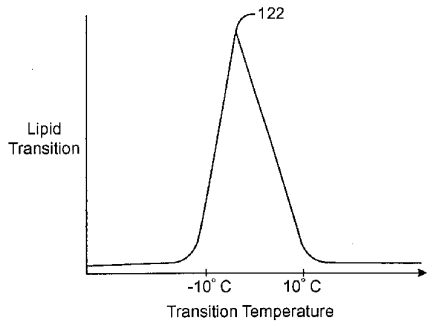

FIG. 12A

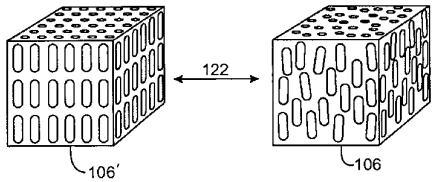

FIG. 12B

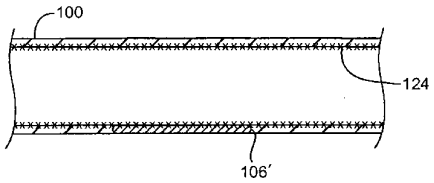

FIG. 13A

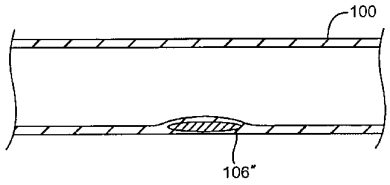

FIG. 13B

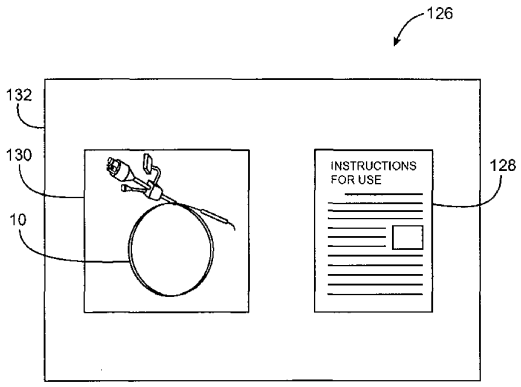

FIG. 14

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/25817

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: plaque, balloon, cryo$, temperature sensors

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

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 NOVEMBER 2001	25 JAN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL PEFFLEY Telephone No. (703) 308-0858

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/25817

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(2)(a) for the following reasons:

1. [X] 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.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)★

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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。