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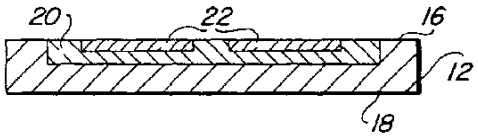
(71)出願人　501344371
アドバンスト・バイオ・プロスゼティック・サーフィスズ・リミテッド
アメリカ合衆国テキサス州７８２４０，サン・アントニオ，リサーチ・ドライブ　４７７８
(74)代理人　100089705
弁理士　社本　一夫
(74)代理人　100076691
弁理士　増井　忠弐
(74)代理人　100075270
弁理士　小林　泰
(74)代理人　100080137
弁理士　千葉　昭男

最終頁に続く

(54)【発明の名称】生体内センサ及びその製造方法

(57)【要約】
身体内の物理的、化学的又は電気的パラメータを監視するために使用される移植可能な生体内センサである。生体内センサは、移植可能な医療装置と一体であり、外部から又は内部から付与されたエネルギに応答可能である。エネルギを付与したとき、センサは、装置の材料の少なくとも一部にて相変化し、次に、放射線撮影法、超音波撮影法、核磁気共鳴映像法、高周波映像法等のような従来の技術によって身体外部にてその相変化が検知される。ステント又はその他の形式の管腔内導管のような管腔内インプラントの管腔内における沈着物の程度及び形式を測定し、又は体積測定、流量測定、圧力測定、電気的測定、生物化学的測定、温度測定を行なうために、本発明の生体内センサを採用することができる。生体内センサは、感知又は監視されたパラメータに応答して管腔内インプラントの機械的及び（又は）物理的性質を調整し得るよう治療目的のためにも使用することができる。



【特許請求の範囲】
【請求項１】
移植可能な医療装置において、
ａ．移植可能な基材担持部材と、
ｂ．少なくとも一つの形状記憶材料又は超弾性材料によって作られ、移植可能な基材担持部材に結合されたセンサ部材とを備える、移植可能な医療装置。
【請求項２】
請求項１に記載の移植可能な医療装置において、
移植可能な基材担持部材が、ステンレス鋼、タンタル、金、白金、チタン、ニッケル、それらのバナジウム金属合金、ニッケル－チタン、エルジロイ及びそれらの組合せから成る群から選ばれた生体適合性材料によって作られている、移植可能な医療装置。
【請求項３】
請求項１に記載の移植可能な医療装置において、
移植可能な基材担持部材が基本的に金属合金から成る、移植可能な医療装置。
【請求項４】
請求項１に記載の移植可能な医療装置において、
移植可能な基材担持部材が基本的にニッケル－チタン合金から成る、移植可能な医療装置。
【請求項５】
請求項２に記載の移植可能な医療装置において、
センサ部材が基本的に金属合金から成る、移植可能な医療装置。
【請求項６】
請求項４に記載の移植可能な医療装置において、
センサ部材が基本的にニッケル－チタン合金から成る、移植可能な医療装置。
【請求項７】
請求項１に記載の移植可能な医療装置において、
センサ部材が複数の片持ち梁部材を更に備える、移植可能な医療装置。
【請求項８】
請求項７に記載の移植可能な医療装置において、
複数の片持ち梁部材が、形状記憶材料、超弾性材料、弾性的に変形可能な材料又は塑性変形可能な材料の少なくとも１つによって作られている、移植可能な医療装置。
【請求項９】
請求項８に記載の移植可能な医療装置において、
複数の片持ち梁部材が、第一の位置である「不作動」位置及び第二の位置である「作動」位置を有する二元機能を備える、移植可能な医療装置。
【請求項１０】
請求項７に記載の移植可能な医療装置において、
複数の片持ち梁部材が、ある量のエネルギが付与されたときに変化する電気機械的応答曲線を有する形態とされる、移植可能な医療装置。
【請求項１１】
請求項１に記載の移植可能な医療装置において、
センサ部材が、基材担持部材の構造要素を更に備え、該構造要素が、形状記憶材料又は超弾性材料のうちの少なくとも１つがマルテンサイト変態したときに移植可能な基材担持部材の立体配座を変化させることのできる、移植可能な医療装置。
【請求項１２】
管腔内人工器官であって、その管腔内面又は管腔外面の少なくとも１つに一体に画成された複数のセンサ領域の少なくとも１つを有する管腔内人工器官を備える、移植可能な医療装置。
【請求項１３】
請求項１２に記載の移植可能な医療装置において、

管腔内人工器官が、ステント、ステント－移植片、移植片、弁、フィルタ及びオクルダから成る群から選ばれる、移植可能な医療装置。
【請求項１４】
請求項１２に記載の移植可能な医療装置において、
管腔内人工器官及び複数のセンサ領域の少なくとも１つが、形状記憶金属合金、超弾性金属合金、弾性的に変形可能な金属又は塑性変形可能な金属から成る群から選ばれた金属合金を更に備える、移植可能な医療装置。
【請求項１５】
請求項１４に記載の移植可能な医療装置において、
管腔内人工器官がニッケル、チタン合金を更に備える、移植可能な医療装置。
【請求項１６】
請求項１４に記載の移植可能な医療装置において、
複数のセンサ領域の少なくとも１つがニッケル－チタン合金を更に備える、移植可能な医療装置。
【請求項１７】
請求項１４に記載の移植可能な医療装置において、
複数のセンサ領域の少なくとも１つが、管腔内人工器官の遷移点と異なる１つの遷移点を更に有する、移植可能な医療装置。
【請求項１８】
請求項１４に記載の移植可能な医療装置において、
管腔内人工器官が、複数の壁要素を更に備え、該複数の壁要素の各々が、少なくとも１つの形状記憶材料又は超弾性材料を更に備え、複数の壁要素の少なくとも幾つかが、第一の遷移点$T_1$を有する第一の形状記憶材料又は超弾性材料から成り、複数の壁要素の少なくとも幾つかが、第二の遷移点$T_2$を有する第二の形状記憶材料又は超弾性材料から成り、$T_2$が$T_1$よりも大きいようにした、移植可能な医療装置。
【請求項１９】
請求項１４に記載の移植可能な医療装置において、
管腔内人工器官が、複数の壁要素を更に備え、該壁要素の各々が、少なくとも２つの形状記憶材料又は超弾性材料の積層体から成り、第一の形状記憶材料又は超弾性材料が、第一の遷移点$T_1$を有し、第二の形状記憶材料又は超弾性材料が、第二の遷移点$T_2$を有し、$T_2$が$T_1$よりも大きいようにした、移植可能な医療装置。
【請求項２０】
移植可能な医療装置において、
形状記憶材料及び超弾性材料の少なくとも１つで製造された基材要素を備え、流体圧力、流体せん断力、体温、細胞の接合、及び分子の結合から成る群から選ばれた内因性エネルギ刺激と、温度、圧力、マイクロ波、超音波、ＲＦ、紫外線、赤外線、磁気共鳴、Ｘ線、ベータ及びガンマ放射線から成る群から選ばれた外因性エネルギ刺激とによって該基材要素の少なくとも１つの遷移点を誘発させることができるようにした、移植可能な医療装置。
【発明の詳細な説明】
【発明の背景】
【０００１】
本発明は、全体として、移植可能な医療装置の分野、より具体的には、生体内の生理学的状態又は身体に関する状態に対する機械的、化学的又は電気的応答の少なくとも１つを導出し得るよう身体内に植え込むことのできるセンサに関する。本発明は、機械的、電気的、化学的、電気化学的又は電気機械的手段によって身体内の温度、圧力の変化、又は化学種又は生物化学種の存在又は不存在の少なくとも１つを検知することのできる膜の少なくとも一部分を有する材料の一体構造の単一層又は多層膜の何れかとすることのできる真空蒸着した膜を提供する。
【０００２】

具体的には、本発明は、体内通路を通る流体の流れの物理的、化学的又は電気的パラメータを監視するための移植可能なセンサの製造及び使用に関する。例えば、本発明のセンサは、体積の測定、流量の測定、圧力の測定、電気的測定、生物化学的測定、温度の測定を行い、又は、ステント或いは、その他の形式の管腔内導管のような、管腔内インプラントの管腔内での沈着の程度及び沈着物の形式を測定するため使用することができる。本発明は、感知され又は監視されたパラメータに応答して管腔内インプラントの機械的及び（又は）物理的性質を調整する手段も提供するものである。例えば、管腔内装置を通る監視した血液流の体積が生理学的基準以下であると判定され且つ（又は）血圧が生理学的基準よりも高いと判定された場合、ステントを作動させて、ステント材料の超弾性的性質による等してその直径を大きくすることができる。

【０００３】

移植後の管腔内装置の開存性を評価するためには、現在、血管造影法又は超音波によって臨床的に検査することを必要とする。これら試験の結果は、装置の開存性を定性的に評価することを可能にする。このため、管腔内装置の移植後の開存性を定期的に又は連続的に定量的に測定する手段を提供することが望まれる。管腔内装置を通る体液の体積流量、流速、生物化学的組成、流体圧力又は同様の物理的又は生物化学的性質を生体内で定量的に測定することは、医療従事者に対しより正確な診断情報を提供することになろう。

【０００４】

本明細書で使用するように、「管腔内装置」という語は、解剖学的通路内に移植され又は身体に対して移植されて、身体内の解剖学的に分離した領域の間に非解剖学的通路を形成するステント、移植片、移植片及びステント－移植片を含むことを意図するものである。本発明による管腔内装置は、血管内装置、前立腺装置、尿道装置、頸管装置、食道装置、腸内装置、胆管装置、心臓内装置、弁、肝臓装置、腎臓装置、又は身体内で同様に使用される装置を含むことができる。

【０００５】

本出願における「センサ」という語は、非限定的に、バイオセンサ、化学的センサ、電気的センサ及び機械的センサを含むことを意図するものである。生体系又は生体要素を内蔵する系を監視するため使用される多数の異なる装置を説明すべく「バイオセンサ」という語が使用されているが、国際純正応用化学連合（ＩＵＰＡＣ）は、「バイオセンサ」という語を「通常、電気的、熱的又は光学的信号を検知するため、単離酵素、免疫系、組織、細胞小器又は全細胞によって媒介される特定の生物化学的反応を使用する装置」を指すために使用すべきことを推奨している：ＩＵＰＡＣの１９９２年、化学用語概論（Ｃｏｍｐｅｎｄｉｕｍ ｏｆ Ｃｈｅｍｉｃａｌ Ｔｅｒｍｉｎｏｌｏｇｙ）の第２版６４、１４８（１９９７）。「化学的センサ」という語は、特定の試料の構成要素の濃度から全組成の解析に亙る化学的情報を解析上有用な信号に変換する装置を指すものとしてＩＵＰＡＣにより定義されている。従来のバイオセンサは、レセプタ（生体構成要素）、変換器（物理的構成要素）及び分離器（何れかの形式の薄膜又は被覆）という３つの基本的要素から成る。化学的センサのレセプタは、通常、解析物質と特に相互作用するか又は、その他のレセプタと比較したとき、多かれ少なかれ相互作用することのできる被覆した金属酸化物又は有機ポリマーから成っている。バイオセンサの場合、レセプタ又は生体構成要素は、生物化学的過程又は接合事象を測定可能な構成要素に変換する。生体構成要素は、酵素、抗原、抗体、レセプタ、組織、全細胞又は細胞器官（オルガネラ）、細菌及び核酸のような生物学的種を含む。変換器すなわち物理的構成要素は、構成要素を、通常、電気的又は光学的信号である測定可能な信号に変換する。物理的構成要素は、一例として、電気化学的装置、光学装置、音波装置、及び熱量装置を含む。境界面すなわち薄膜は、変換器を化学的又は生物学的構成要素から分離し且つ、この構成要素を変換器と連結する。これらは密着している。境界面分離器は、通常、不要な物質を遮断し、汚れを防止し且つ変換器を保護する。境界面の形式は、ポリマー薄膜、電子重合化した被覆及び自己集合モノマーを含む。

【０００６】

センサは、高選択性及び高感度を有し、ヒステリシスを伴わずに迅速な回復時間を有し、一回使用型でないならば、長寿命であり、低ドリフトで、自動式較正、自己診断性を有し、低コストであり、また、試薬の添加を必要とせず、更に、試料を作成する必要がないものでなければならない。現在、利用可能な化学的センサ及びバイオセンサはこれらの判断基準に適合しないことは明らかである（フロスト（Ｆｒｏｓｔ）、及びスリバン（Ｓｕｌｌｉｖａｎ）の世界のバイオセンサマーケット（Ｗｏｒｌｄ　Ｂｉｏｓｅｎｓｏｒ　Ｍａｒｋｅｔ）レポート、５３２６－３２、１９９７）。全国標準及び技術協会、化学的センサ用のナノ及びＭＥＭＳ技術。
（ｗｗｗ．ａｔｐ．ｎｉｓｔ．ｇｏｖ／ａｔｐ／ｆｏｃｕｓ／９８ｗｐ－ｎａｎ．ｈｔｍ）

臨床診断市場において、電子化学的センサ（電位差計ＩＳＥｓ、電流測定、伝導度測定；極小型ＩＳＥ、電界効果トランジスタ、集合トランジスタ）；光ファイバ又は表面プラズモン共鳴技術を使用する光センサ、圧電結晶及び表面音波センサのような音波装置及びサーミスタを採用する熱センサを含む色々なセンサの設計が既知である。このように、臨床用センサを形成するため、微細製造技術を採用することが既知である。現在、臨床診断市場において商業的に最も成功している微細製造されたセンサは、酵素反応の電子化学的変換を使用するメディセンス（ＭＥＤＩＳＥＮＳＥ）グルコース計である。しかし、生体内感知システムの必要性は十分に認識されている。グルコース及び乳酸エステル双方に対する生体内監視システムに関する研究は、ホスホリピド共重合体が血液適合性を向上させる効果があることを確認した。フィッシャー・ユー（Ｆｉｓｈｅｒ，Ｕ）らによる、バイオセン．（Ｂｉｏｓｅｎ．）バイオエレクトロン．（Ｂｉｏｅｌｃｔｒｏｎ．）、１０、ｘｘｉｉｉ（１９９５）。

【０００７】

移植可能なセンサは、その性質により、センサから感知された情報を身体外の人間又は機械である読み手に連絡する何らかの機構を備えなければならない。センサと外部の読み手との間の物理的接続部を植え込むことは実際的ではないから、身体外で読取り可能な信号を発生させる代替的な手段を設けなければならない。身体外で読取り可能な信号を発生させる適宜な手段は、非限定的ではあるが、放射線撮影法で視認可能な信号、磁束信号、化学的信号、化学蛍光信号及び（又は）電気信号を含む。

【０００８】

動脈硬化症の発病原因は確実に解明されていない。高コレステロール、高血圧及び糖尿病のような多数のリスク因子が動脈壁に炎症性構造を発生させ且つ白血球細胞を動脈壁内に取り込んで最終的にプラークを形成し且つ分解させ、その結果、臨床的事象が生ずるようにする働きをすることが既知である。この過程は、酸化に敏感な核調節機構により開始される。遊離基が遺伝子を制御し、この遺伝子は、内皮細胞内で発現するタンパク質を合成し、また、白血球を動脈壁内に取り込む働きをする。

【０００９】

移植した医療装置の内皮化は、化学的研究及び文献の重要な主題であった。色々な成長因子及びサイトカインが平滑筋細胞レセプタを活性化させ且つ平滑筋細胞の増殖を開始させることが周知である。線維芽細胞成長因子（ＦＧＦ）及び血管内皮成長因子（ＶＥＧＦ）のような内皮細胞成長因子は、生体内での内皮細胞成長にとって有意義であることが確認されている。ＶＥＧＦは内皮細胞に特定的であるが、ＦＧＦも平滑筋細胞の成長を刺激する。バウザーズ・シー．（Ｂａｕｔｈｅｒｓ，Ｃ．）による、虚血性心臓病の新たな治療法の可能性としての成長因子（Ｇｒｏｗｔｈ　Ｆａｃｔｏｒｓ　ａｓ　ａ　Ｐｏｔｅｎｔｉａｌ　Ｎｅｗ　Ｔｒｅａｔｍｅｎｔ　ｆｏｒ　Ｉｓｃｈｅｍｉｃ　Ｈｅａｒｔ　Ｄｉｓｅａｓｅ），Ｃｌｉｎ．Ｃａｒｄｉｏｌ．２０：ＩＩ－５２－ＩＩ－５７（１９９７）。

【００１０】

外部又は内部電源を必要とせずに、内皮細胞又は動脈硬化プラークの接合を検知することができ且つ生体外で検知可能な信号を提供することのできる生体内センサの必要性が認識されている。

【発明の概要】
【００１１】
本発明によれば、臨床的に有意義な生理学的事象を監視するのに適した移植可能な生体内センサが提供される。本発明は、血管、食道又は胃－腸管、胆管、尿管又は尿道のような腎臓系の管、膣又は子宮頸管、輸精管、気管支又は同様の解剖学的通路、臓器内の通路、心臓中隔欠損症のような解剖学的欠陥部内に植え込むことのできる一体形装置を提供する。
【００１２】
本発明の生体内センサは、全体として、移植可能な基材担持部材要素と、複数のセンサ要素の少なくとも１つとから成っている。移植可能な基材担持部材要素は、例えば、ステント、ステント－移植片、移植片、弁、フィルタ、オクルダ又はセンサ要素の基本的要素として機能するその他の移植可能な装置から成るものとすることができる。移植型基材担持部材自体が検知可能な信号を戻し得る形態とされた状態のとき、これら移植型基材担持部材要素自体がセンサ要素を構成するものとすることができる。移植型基材担持部材要素及びセンサ要素が共に接続された別個の要素である場合、これら要素は、各々が同様の又は相違する熱的、機械的、電気的及び（又は）化学的性質の何れかを有する同様の材料又は異なる材料で製造することができる。
【００１３】
基材担持部材要素及びセンサ要素の双方が、例えば、センサの領域内で流体の流れ、流体の流量又は流体の圧力を検知する熱的、電気的、機械的又は化学的センサとして使用するのに適した所定の基本的形態及び立体配座を有するような方法で担持要素及びセンサ要素の双方を形成するため、微細製造技術が採用されることが好ましい。本発明のセンサに化学的化合物又は生体化合物を追加することは、該装置を化学的センサ又はバイオセンサとしてそれぞれ使用することを可能にする。同様に、センサの表面に沈着する動脈硬化症プラークのような、センサにて生ずる電気化学的事象を検知し又はセンサが植え込まれる解剖学的環境内の電気化学的変化をセンサが検知することを可能にするため、集積回路を本発明のセンサ内に又は本発明のセンサ上にて製造すること等によって、マイクロ電子回路を本発明のセンサに追加することができる。
【００１４】
これと代替的に、本発明の移植型センサ要素及び移植型基材担持部材要素は、ステンレス鋼製ハイポチューブ、ステンレス鋼ワイヤー、形状記憶皮下管及び形状記憶ワイヤーのような鍛造材料で製造してもよい。センサ要素は、基材担持部材要素又は片持ち状部材のような構成要素の部品に取り付けるか、又はセンサ要素を多岐に亙る既知の手段によってセンサ要素に取り付けることができる。例えば、レーザ溶接、プラズマ溶接、抵抗溶接、又は電子ビーム溶接のような溶接過程を使用することができる。しかし、例えば、ステンレス鋼のようなその他の材料にニッケル－チタン合金を接合するのに溶接は一般に許容し得ない方法であり、それは、溶接領域内に脆弱な異種金属部が形成されるからである。酸化物又は窒化物が存在しない溶接部を得るため、溶接は、清浄な不活性な環境内で厳格な環境状態にて又は真空にて行い、チタンの反応性を最少にし得るようにしなければならない。場合によっては、溶接したニッケル－チタン部品は、溶接領域の応力除去のため、溶接後、熱処理が必要となることがある。熱の影響を受けた領域は、全体として、超弾性の性質を示さない。ニチノールのような形状記憶合金すなわち超弾性合金をステンレス鋼及びその他の材料に接合するため、はんだ付けを採用することができる。しかし、はんだ付け過程においては表面酸化物の形成を阻止する適正なフラックスを選ばなければならない。はんだ付けの間、表面にはんだが存在しない状態に保つための試みとして超音波はんだ付けも使用されている。形状記憶合金をそれ自体に又はその他の材料に接合するため、色々なエポキシ及びその他の接着剤を使用することができる。選ばれた接着剤は、勿論、装置の製造及び生体内の生体環境と適合しなければならない。最後に、センサ要素は、基材担持部材要素に機械的に接合するか、又はセンサ要素の構成要素部品を区輪舞加工によって接合し、締まり嵌めを提供し、或いは、センサ要素又はその構成要素部品を相互に係止す

る幾何学的形態を形成することにより共に接続することができる。

【００１５】

本発明の１つの特別な実施の形態によれば、身体通路内の管腔内インプラントを通る流体の所定の流れ状態を決定するため、解剖学的又は非解剖学的身体通路内に移植可能な管腔内インプラントが提供される。本発明の管腔内インプラントは、例えば、全体として２つの正反対の状態を有する、全体として管状形状の部材から成る、管腔内ステント、ステント移植片又は移植片を含むことができる。経管腔カテーテルの挿入を容易にするため、本発明の管腔内装置は、装置の横断面積が経皮的挿入を許容し且つ経管腔的アプローチ法を使用して装置を生体内に配置することを許容するのに十分な寸法を有する第一の状態である正反対状態を有する。第二の状態である正反対状態は、第一の正反対状態よりも大きく且つ装置が配置される解剖学的通路の直径に順応し又は非解剖学的通路に対する所望の直径である横断面積を有する。本発明の管腔内装置は、バルーン拡張可能な装置、自己拡張装置、形状記憶装置又は超弾性装置として製造することができる。当該技術分野の当業者は、「バルーン拡張可能な」という語はバルーンカテーテルにより付与されるような外部圧力を付与することにより装置をその第一の正反対状態からその第二の正反対状態まで半径方向に変形させる種類の装置を意味し、「自己拡張」という語は、装置の材料の固有の機械的性質を利用して装置をその第一の正反対状態からその第二の正反対状態まで拡張させる種類の装置を意味し、「形状記憶」という語は、特定の遷移温度にてマルテンサイト相変態を示す材料で製造される種類の装置を意味し、また、「超弾性」という語は、所定の応力－歪み状態下にて変形する材料で製造される種類の装置を意味するものであると理解される。本発明の管腔内センサは、ステンレス鋼、タンタル、チタン、金又はその他の生体適合性金属のような弾性又は塑性変形が可能な材料で製造することができる。しかし、本発明は、温度変化及び（又は）付与された応力又は歪みの変化にそれぞれ機械的に応答可能な、ニチノールとして既知のニッケル－チタン合金のような形状記憶及び（又は）超弾性材料で製造されることが好ましい。

【００１６】

全体として、本発明の管腔内センサは、ステントのような移植可能な管腔内装置と一体であり且つ機械的、電子的、電気機械的に又は化学的に応答してセンサ及び（又は）管腔内装置にて機械的、電気的、電気機械的又は化学的変化を生じさせ、この変化が放射線撮影法、超音波撮影法、磁気共鳴映像法又は高周波検知法のような非侵襲性検知方法を使用して生体内で検知可能であるステントのような移植可能な管腔内装置と一体とされた装置から成っている。

【００１７】

本発明の１つの実施の形態に従い、本発明のセンサは、異なる変態温度を有する形状記憶材料で形成された複数の片持ち梁部材として形成される移植可能な管腔内装置の少なくとも１つの一体領域を備えている。センサは、血液に接触するステントの管腔表面のような移植可能な装置の流体に接触し又は組織に接触する表面に配置するか、又は血管の新生内膜組織に接触するステントの管腔外表面に配置することができる。これと代替的に、センサは、移植可能な装置の流体に接触する面及び組織に接触する面の双方に配置してもよい。

【００１８】

本明細書で使用するように、「一体的」という語は、管腔内装置の主要材料の一部として形成された領域及び管腔内装置の主要材料と別個に形成され、該材料に結合された領域を含むことを意図するものである。

【００１９】

本発明の別の実施の形態によれば、本発明のセンサは、異なる弾性係数、可塑性又は応力－歪み特性のような異なる機械的性質を有する複数の片持ち梁部材で形成される移植可能な管腔内装置の少なくとも１つの領域を備えている。本発明に対して現在、考えられる最良の形態に従い、片持ち梁部材は超弾性材料で製造されることが好ましい。形状記憶片持ち梁部材と同様に、超弾性片持ち梁部材は、血液に接触するステントの管腔内面のような

移植可能な装置の流体接触面又は組織接触面に配置するか、又は血管の新生内膜組織に接触するステントの管腔外面に配置することができる。これと代替的に、センサは、移植可能な装置の流体接触面及び組織接触面の双方に配置してもよい。形状記憶片持ちセンサと異なり、超弾性片持ちセンサは、該センサに加えられたせん断力のような力の変化に応答可能である。

【００２０】

形状記憶片持ち梁部材センサ及び超弾性片持ち梁部材センサの双方の場合、複数の片持ち梁部材の各々は、それぞれ不作動位置又は作動位置の何れかを示す第一の位置及び第二の位置を有している。片持ち梁部材の各々の第一の位置すなわち「不作動」位置は、センサがその内部に配置される管腔内装置の表面と同一面すなわち面一である。第二の位置すなわち「作動」位置において、作動された片持ち梁部材の各々は、センサがその内部に配置される管腔内装置の面から外方に突き出す。異なる片持ち梁部材又は片持ち梁部材の群が異なる遷移温度又は異なる応力－歪み特性を有するように製造されるため、第二の位置すなわち「作動」位置にある個々の片持ち梁部材又は片持ち梁部材の群は、管腔内装置がその内部に植え込まれる身体内に存在する所定の熱又は応力－歪み状態を示す。

【００２１】

本発明の１つの特別な形態において、本発明の管腔内装置は、管腔内装置の基端領域、末端領域又は中間領域の少なくとも１つに配置され且つ管腔内装置の管腔面又は管腔外壁面の少なくとも一方に配置された複数の片持ち梁部材を有する温度センサを備えている。検知を容易にするため、片持ち梁部材の複数の群が設けられ、その群の各々は、複数の個々の片持ち梁部材で形成され、その群内の個々の片持ち梁部材の各々は同一の遷移温度を有している。複数の片持ち梁部材の群は、異なる遷移温度を有する片持ち梁部材の群の連続体を形成し得るような仕方にて管腔内装置の長手方向軸線に沿って配列されている。管腔内装置の箇所における温度変化は、放射線撮影法、超音波撮影法、核磁気共鳴映像法又は片持ち梁部材の位置及び片持ち梁部材の群の検知可能な像を提供するその他の手段によって決定される片持ち梁部材又は片持ち梁部材の群の位置によって表示される。

【００２２】

本発明の別の特定の形態において、センサは、管腔内装置の基端、末端又は中間領域の少なくとも１つに配置され且つ管腔内装置の管腔面又は管腔外壁面の少なくとも１つに配置された複数の片持ち梁部材を備えている。検知を容易にするため、複数の片持ち梁部材の群が設けられ、群の各々は、複数の個々の片持ち梁部材で形成され、群内の個々の片持ち梁部材の各々は同一の遷移温度を有する。複数の群の片持ち梁部材は、異なる応力－歪み遷移圧力を有する片持ち梁部材の群の連続体を形成し得るような仕方にて管腔内装置の長手方向軸線に沿って配列されている。管腔内装置の箇所における血圧又は血液流のせん断応力のような付与された応力又は歪みの変化は、片持ち梁部材又は片持ち梁部材の群に作用する応力又は歪みによって表示され、これら値は、負荷を取り除かれた片持ち梁部材の基準応力－歪みと比較したとき、反射エネルギの相応する周波数の変化を提供する。片持ち梁部材の位置及び周波数の変化は、放射線撮影法、超音波撮影法、磁気共鳴映像法又は個々の片持ち梁部材及び片持ち梁部材の群の位置を検知可能な像を提供し又は片持ち梁部材に対する異なる応力－歪みの負荷に起因する周波数の変化を測定することができるその他の手段によって決定することができる。

【００２３】

本発明の更に別の形態において、本発明のセンサは、弾性的変形、塑性変形、形状記憶変形又は超弾性変形を受けることのできる材料で微細製造されたバイオセンサであり、また、上述したように、形成された複数の片持ち梁部材を有している。複数の片持ち梁部材の各々は、内皮細胞表面タンパク質、抗原、抗体、サイトカイン、成長因子、共同因子又は内皮細胞又は内皮細胞前駆体のその他の生体標識又は生物化学的標識の群から選ばれた少なくとも１つの内皮化インジケータに対する選択可能な少なくとも１つの接合領域を有している。少なくとも１つのインジケータが複数の片持ち梁部材の少なくとも１つに接合することで片持ち梁部材に付与される歪みが変化し、これにより、関連する片持ち梁部材又

は片持ち梁部材の群は第一の位置すなわち「不作動」位置から第二の位置すなわち「作動」位置まで超弾性変態される。本発明の上述した実施の形態の場合と同様に、その後に、第二の位置すなわち「作動」位置における管腔内装置に対するセンサ片持ち梁部材の位置が検知され且つ内皮化の進行状態を表示することができる。

【００２４】

同様に、動脈硬化症プラーク形成の進化又はその進行状態は、複数の弾性的又は超弾性的片持ち梁部材を使用して感知することができる。第一の実施の形態において、複数の超弾性的片持ち梁部材は、片持ち梁部材への動脈硬化症プラークの成長に起因して片持ち梁部材に付与された歪みの結果として、マルテンサイト変態を生ずる。第二の実施の形態に従い、複数の超弾性片持ち梁部材は、動脈硬化症プラーク又はその前駆体の少なくとも１つのインジケータに対し選択可能な少なくとも１つの接合領域を有している。動脈硬化症プラーク又は動脈硬化症プラークの前駆体が片持ち梁部材の接合領域に接合することは、片持ち梁部材が第一の位置すなわち「不作動」位置から第二の位置すなわち「作動」位置まで超弾性変態するのに十分な大きさの歪みを片持ち梁部材に追加することになる。本発明の上述した実施の形態の場合と同様に、その後、管腔内装置装置に対する第二の位置すなわち「作動」位置におけるセンサの片持ち梁部材の位置を検知し且つ動脈硬化症の進行状態を表示することができる。

【００２５】

本発明の更に別の形態は、インプラントに付与される圧力の変化に応答可能な可変の正反対の幾何学的形態を有する超弾性材料で製造されたインプラントを含む。本発明のこの形態は、例えば、血管人工器官のような平滑筋の人工器官として採用され、また、血管の生来的な変化すなわち血圧の低下を感知したとき、収縮し且つより高血圧を感知したとき、拡張して生理学的に標準の血圧を維持するのと同様の仕方にて血圧の変化に応答可能である。本発明のこの実施の形態において、管状インプラントは、その全体又は一部が超弾性材料で製造されており、また、インプラント内の所定の生理学的圧力を感知したとき、インプラントの直径を拡張又は縮小させる超弾性変態を生ずる正反対に調節可能な領域を有する。

【００２６】

最後に、本発明の別の形態は、１９９７年、１１月７日付けで出願され、国際出願ＷＯ９９２３９７７Ａ１号として公開された、血管内ステント及び血管内ステントの製造方法（Ｉｎｔｒａｖａｓｃｕｌａｒ　Ｓｔｅｎｔ　Ａｎｄ　Ｍｅｔｈｏｄ　Ｆｏｒ　Ｍａｎｕｆａｃｔｕｒｉｎｇ　Ａｎ　Ｉｎｔｒａｖａｓｃｕｌａｒ　Ｓｔｅｎｔ）という名称の同時係属中の共有譲渡された米国特許出願第６０／６０４，９１６号に記載されたものと同様の管腔内インプラントから成るものである。その双方の特許出願は、その内容を参考として引用し本明細書に含めてある。これらの出願において、溝無しの管腔内インプラントに卓越する改良された内皮化を促進するその管腔内面及び（又は）管腔外面に複数の微細溝を有する管腔内インプラントが記載されている。本発明によれば、管腔内材料の弱体化した主要材料から成る部分を備える複数の推定の微細溝を有する管腔内インプラントが提供される。該管腔内インプラントは、超弾性の主要材料で製造され、また、主要材料内の弱体化領域を標準的なマイクロリソグラフィ技術を使用して形成し、推定のマイクロ部材を形成することが好ましい。複数の接合領域が管腔内インプラントの流体流動面に沿って且つ推定の微細溝の基端（血流に対して）領域に形成され、これら接合領域が内皮細胞表面のタンパク質に優先的に接合するようにすることが好ましい。内皮細胞表面のタンパク質が接合領域に接合することで超弾性主要材料に付与される歪みが変化し、これにより、超弾性主要材料が付与された歪み領域内で変形し、これにより、推定の微細溝の弱体化した領域内の原子間結合を破り且つ微細溝の一部分が形成されるようにする。一方、内皮細胞の増殖が超弾性主要材料の表面に沿って広がることは、超弾性主要材料に沿って歪みを広げ、その結果、超弾性主要材料中に微細溝が形成されることになる。

【００２７】

本発明の上記及びその他の目的、特徴並びに有利な効果は、添付図面を参照することによ

り、本発明の好ましい実施の形態に関する以下のより詳細な説明から当該技術分野の当業者に一層明らかになるであろう。

【好ましい実施の形態の詳細な説明】

【００２８】

本発明の説明を簡略化するため、別段の記載がある場合を除いて、管腔内ステントに関して最も好ましい実施の形態を説明する。しかし、非限定的であるが、ステント、移植片、ステント－移植片、弁、分路又はパッチを含む多岐に亙る移植可能な装置の実施の形態の各々が適用可能であることは当該技術分野の当業者に理解されよう。

【００２９】

本発明のセンサの変化を検知する特定の手段及び（又は）本発明のセンサの変化を励起する特定の手段は、全体として、本発明の一部であるとはみなさない。例えば、ニッケル－チタン合金にて一方向及び二方向の双方の形状記憶効果を発生させるため、超音波エネルギを採用することが可能であることは既知である。Ｖ．Ｖ．クルボビィッシュ（Ｖ．Ｖ．Ｋｌｕｂｏｖｉｃｈ）、Ｖ．Ｖ．ルバニック（Ｖ．Ｖ．Ｒｕｂａｎｉｃｋ）、Ｖ．Ｇ．ドロデイコ（Ｖ．Ｇ．Ｄｏｒｏｄｅｉｋｏ）、Ｖ．Ａ．リクハチョフ（Ｖ．Ａ．Ｌｉｋｈａｃｈｏｖ）及びＶ．Ｖ．ルバニック ジュニア（Ｖ．Ｖ．Ｒｕｂａｎｉｃｋ Ｊｒ．）（ベララス、２１００２６ビテバスク、１３ルドニコフ、音波技術協会（Ｉｎｓｔｉｔｕｔｅ ｏｆ Ｔｅｃｈ．Ａｃｏｕｓｔｉｃｓ））ＵＲＬにて見ることができる１．Ｐ１２、ＳＭＳＴ－９７会議紀要、超音波によるＴｉ－Ｎｉ合金内での形状記憶効果の発生（Ｇｅｎｅｒａｔｉｏｎ ｏｆ Ｓｈａｐｅ Ｍｅｍｏｒｙ Ｅｆｆｅｃｔ ｉｎ Ｔｉ－Ｎｉ Ａｌｌｏｙ ｂｙ ｍｅａｎｓ ｆｏｒ Ｕｌｔｒａｓｏｕｎｄ）ｈｔｔｐ：／／ｗｗｗ．ｆｗｓｙｓｔｅｍｓ．ｃｏｍ／ｐｒｏｆｅｓｓｉｏｎａｌ／ｓｍｓｔａｂｓ．ｈｔｍｌ。また、非侵襲的にステントを加熱するため超音波エネルギを使用することは、Ｂ．ラル（Ｂ．Ｌａｌ）らによってステントの非侵襲的な超音波による加熱：ステントの組成の重要性（Ｎｏｎ－Ｉｎｖａｓｉｖｅ Ｕｌｔｒａｓｏｕｎｄ Ｉｎｄｕｃｅｄ Ｈｅａｔｉｎｇ ｏｆ Ｓｔｅｎｔ：Ｉｍｐｏｒｔａｎｃｅ ｏｆ Ｓｔｅｎｔ Ｃｏｍｐｏｓｉｔｉｏｎ）という名称の要約書にて確認されており、これもＵＲＬで見ることができる。ｈｔｔｐ：／／ｗｗｗ．ｈｏｔｐｌａｑｕｅ．ｃｏｍ／ｆｒａｍｅｓ／ａｂｓｔｒａｃｔｓ／ｒａｂｓ６．ｈｔｍ及びＵＲＬ ｈｔｔｐ：／／ｅｘ２．ｅｘｃｅｒｐｔａｍｅｄｉｃａ．ｃｏｍ／００ａｃｃ／ａｂｓｔｒａｃｔｓ／ａｂｓ１０６５－１１７．ｈｔｍｌ。ラルらは、超音波（ＵＳ）を使用して穏やかな加熱を実現することができ、パルス化されたＵＳを使用して一定の温度を保つことが可能であるという仮説を立てた。同一のＵＳパワー及び周波数の下で物体を加熱する速度は、主としてその吸収率及び反射率によって決まる。彼らの仮説を実証するため、彼らは、５．０８ｃｍの厚い豚筋肉層の模型を使用し、その内部に色々な環状ステント形状材料を配置した。加熱を監視するため、多数の皮下熱電対を使用した。加熱は、パルスモード及び連続モードの双方にて治療用超音波のＦＤＡ－承認レベルを使用して励起した（強さ０．５乃至２．５Ｗ／ｃｍ$^2$、周波数１乃至３ＭＨｚ）。ナイロン、及び或る形式のＰＶＣは、その周囲の組織よりも多く（２乃至３５℃）且つ速い（１．５乃至１５倍）温度上昇を示す一方、レクサン（Ｌｅｘａｎ）、ＰＴＦＥ、ラテックス、テフロン（登録商標）、セラミック及びデルリナ（Ｄｅｌｒｉｎａ）は選択的加熱効果は示さない。また、金属製ステントによっても適度の加熱効果（１５分間に２℃の上昇）が観察された。人工器官に隣接する組織を超音波加熱することは、ステントの組成に依存し、超音波による熱アポプトシス（ａｐｏｐｔｏｓｉｓ）の誘導は重合系ステント及び移植片の再狭窄を制限する上で効果的であることが判明したということがラルらの結論であった。対処しなければならない問題点は、最適な生体適合性材料、ステントの設計及び同期させた列状ＵＳがステントを挿入した動脈及び周囲の組織に与える生体内効果を含む。迅速な加熱、非毒性材料を使用することにより、超音波加熱式ステントが開発されるであろうとラルらは考えた。

【００３０】

同様に、形状記憶合金内に形状記憶効果を発生させるため、マイクロ波放射線を使用する

ことができる。例えば、ステンレス鋼製ステント内でステントのジアテルミー療法のため、マイクロ波放射線を使用することが可能であることは既知である。Ｓ．ナジブ（Ｓ．Ｎａｇｕｉｂ）らによる収束した超音波及びマイクロ波を使用するステントのジアテルミー（Ｓｔｅｎｔ ｄｉａｔｈｅｒｍｙ ｕｓｉｎｇ ｆｏｃｕｓｅｄ ｕｌｔｒａｓｏｕｎｄ ＆ ｍｉｃｒｏｗａｖｅ）をＵＲＬで見ることができ、ｈｔｔｐ：／／ｗｗｗ．ｈｏｔｐｌａｑｕｅ．ｃｏｍ／ｆｒａｍｅｓ／ａｂｓｔｒａｃｔｓ／ｒａｂｓ３．ｈｔｍ、これは、ステント及びその周囲のプラークを非侵襲的に加熱するため超音波及びマイクロ波エネルギを使用することを図ったものである。パルマツーシャッツ（Ｐａｌｍａｚ－Ｓｃｈａｔｚ）ステント及び模型内に埋め込まれた幾つかのステント形状の生体高分子材料を使用して、ナジブらは、別個の調節値の超音波及びマイクロ波を照射したときの組織内の温度上昇を連続的にマッピングした。温度の監視は、熱電対（超音波）及び光ファイバセンサ（マイクロ波）を有する１２－チャンネル超温度計（０．０１℃）を使用して行った。１乃至３ＭＨＺの周波数及び０．５乃至２．５Ｗ／ＣＭ２の強さの治療用超音波を使用した。マイクロ波放射線の周波数は２．４５ＧＨＺの周波数及び５．３７及び１０．２２ワットのパワーを使用してアンテナによって供給した。その超音波実験において、ナジブらは、ステントの外面及びその周囲の組織の温度はその他の箇所よりも著しく高く上昇することを知った。温度上昇は生体ポリマーの形式によって変化し、シリコン製ステントはより迅速に加熱され、ポリウレタン及びポリテトラフルオロエチレン製のものの場合よりもより高温度まで加熱された。同様の結果はマイクロ波実験にて観察された。超音波及びマイクロ波放射線の双方を供給する間の温度上昇を測定するため、赤外線サーモグラフィを使用した。

【００３１】

しかし、周囲環境内には、ＲＦ、マイクロ波、超音波等のような外部から付与される力が存在することが認識される。このため、周囲の外部から付与された力を受けるとき、形状記憶変化を受けるセンサ装置を製造することは望ましくない。例えば、患者が台所の電子レンジにて食品を加熱しているとき、移植したセンサ装置がマイクロ波放射線に応答して形状記憶を変化させることは患者にとって望ましくないであろう。

【００３２】

本発明の微細製造方法は、移植可能なセンサ装置の材料組成を厳格に制御することを可能にするから、患者の周囲環境内に存在する同一形式のエネルギ信号の周波数範囲外の特定の周波数範囲に応答可能な材料組成とすることができる。このように、装置の作動エネルギの形式及び周波数並びに検知エネルギの形式及び周波数の双方が周囲環境で受けるものの範囲外になければならない。

【００３３】

金属製ステントは、放射線不透過性であり且つ蛍光透視法のような放射線撮影法の下で検知可能であることは周知である。本発明のセンサ装置の検知は、放射線撮影法、超音波撮影法（形状記憶効果を発生させる周波数を使用するか又は使用しない方法）、磁気共鳴映像法、ＲＦ映像法又は同様の方法により行うことができる。ニチノールステントの画像を得るため磁気共鳴映像法を使用することは当該技術分野にて既知である。例えば、ラーダート、Ｄ、ハキム、Ｂ（Ｒａｈｄｅｒｔ，Ｄ，Ｈａｋｉｍ，Ｂ．）のＮｉ－Ｔｉステントの磁気共鳴適合性（Ｍａｇｎｅｔｉｃ Ｒｅｓｏｎａｎｃｅ ｃｏｍｐａｔｉｂｉｌｉｔｙ ｏｆ Ｎｉ－Ｔｉ ｓｔｅｎｔｓ）アブストラクト８．Ｐ１、ＳＭＳＴ－９７会議（形状記憶及び超弾性技術に関する国際機関）、これはＵＲＬで見ることができる。ｈｔｔｐ：／／ｗｗｗ．ｆｗｓｙｓｔｅｍｓ．ｃｏｍ／ｐｒｏｆｅｓｓｉｏｎａｌ／ｓｍｓｔａｂｓ．ｈｔｍｌ。ここで、彼らは、ａ）強磁性力と、ｂ）アーチファクトとを評価するために磁気映像法を使用してＮｉ－Ｔｉ冠状血管用ステントの適合性を研究したと記載している。力を測定するため、水平方向摺動及び振り子たわみという２つの方法を使用した。強磁性力は、ステントの重量の１０％以下であることが分かった。アーティファクトは僅かであると評価された。

【００３４】

磁気共鳴映像法（ＭＲＩ）の下で血管プロフィールの画像化及びモデル化のため造影剤として常磁性磁気金属酸化鉄の微粒子を使用することは、米国、テキサス州、ヒューストンのテキサス－ヒューストン大学及び米国、テキサス州、ガルベストンのテキサス医療大学ガルベストン分校でミトラ　ラジャビ（Ｍｉｔｒａ　Ｒａｊａｂｉ）らによって実証されている。２００１年３月１８乃至２１日に予定されたアメリカ心臓化学セッションカレッジ、ＡＣＣ２００１にて発表するために出版されたアブストラクト（このアブストラクトはＵＲＬで見ることができる：ｈｔｔｐ：／／ｗｗｗ．ｈｏｔｐｌａｑｕｅ．ｃｏｍ／ＡＣＣ／ＡＣＣ２００１％２０ａｂｓｔｒａｃｔｓ．ｈｔｍ＃５）において、ラジャビらは、プラークの炎症状態を画像化する技術を記載している。超常磁性磁気酸化鉄（ＳＰＩＯ）粒子は、全体として、酸化鉄の中心コアが多糖類の層にて被覆された核磁気共鳴（ＭＲ）造影剤である。これら粒子は、緩和時間、専ら、Ｔ２緩和時間を短縮する。ラジャビらは、炎症を起こした傷付き易い動脈硬化症プラークは脈管の脈管及び裂けた細い帽から漏れる大食細胞が浸潤することでこれらのナノ粒子を優先的に取り上げるという仮説を立てた。彼らの仮説を実証するため、最初に基準ＭＲ像を得た後、６匹の栄養不足Ａｐｏ　Ｅ及び２匹のＣ５７ｂｌマウスに尾の静脈を通じて１乃至３ｍモルのＦｅ／ｋｇ超常磁性磁気酸化鉄を注射した。同一のパラメータ（ＴＲ＝２．５、ＴＥ＝０．０１２、ＦＯＸ＝６６、スライス厚さ＝２．０ｍｍ、フリップ角度（方位）＝横及びマトリックス＝２５６×２５６）にて一日に５回、後造影ＭＲ映像法を行った。基準像及び後造影の比較のため、腎臓の位置にある大動脈を選んだ。ラジャビらは、ＳＰＩＯを注射した栄養不足Ａｐｏ　ＥマウスのＳＰＩＯを注射したＣ５７ｂｌマウスの信号の強さは何ら低下しないことが分かった。

【００３５】

このように、レーザカテーテルのような熱を直接付与する方法を使用して経カテーテルアプローチ法により金属製の移植した医療装置に熱エネルギを付与することができ、又は、マイクロ波又は超音波エネルギを移植した装置に導くことにより熱エネルギを発生させることが可能であることは当該技術分野にて既知のことである。更に、形状記憶合金製の移植した医療装置は、放射線撮影法、超音波撮影法、ＭＲＩ又はＲＦ映像法又はその組合せ法を使用して生体内で検知することが可能であることが既知である。

【００３６】

本発明によれば、経カテーテル法を使用して直接的に又は誘導的方法を使用して間接的にエネルギを本発明のセンサ装置に付与する上記の方法及び生体内で本発明のセンサ装置の状態を検知する上記の方法の何れかを採用して、移植した装置の状態を変化させることが可能である。エネルギ刺激は、流体圧力、流体せん断力、体温、細胞接合又は分子接合から成る群から選ばれた内生エネルギ刺激とすることができる。これと代替的に、エネルギ刺激は、外部から付与された温度、圧力、マイクロ波、超音波、ＲＦ、紫外線、赤外線、磁気共鳴、ｘ線、ベータ又はガンマ放射線のような外生エネルギ刺激としてもよい。

【００３７】

次に、添付図面、特に、図１乃至図４を参照すると、本発明による移植可能な生体内センサの第一及び第二の実施の形態が図示されている。

温度センサ

本発明の生体内温度センサ１０は、全体として、中央管腔１４と、管腔外壁面１６と、管腔内壁面１８と、移植可能な管状部材１２の管腔外壁面１６及び管腔内壁面１８の少なくとも一方と一体的な複数の領域２０の少なくとも１つとから成っている。センサ領域２０の表面の上方の流体の流れベクトルＦが図３に示してある。複数のセンサ領域の少なくとも１つの各々は、移植可能な管状部材１２の上で１列にパターン化された複数の片持ち梁部材２２を更に備えている。移植可能な管状部材１２、センサ２０及び複数の片持ち梁部材２２は、形状記憶材料のような同様の材料で製造し、又は異なる材料で製造することができ、例えば、移植可能な管状部材１２はステンレス鋼にて製造し、センサ２０及び片持ち梁部材２２はニッケルチタン合金のような形状記憶材料で製造することができる。本発明に対して考えられる最良の形態によれば、管状部材１２、センサ２０及び片持ち梁部材

は、ニッケルーチタン合金のような形状記憶材料製とされよう。複数の片持ち梁部材２２の各々が形状記憶材料製とされる場合、単一のセンサ２０内の個々の片持ち梁部材２２又は片持ち梁部材２２の群は、異なるマルテンサイト遷移温度を有するように製造することができる。このように、例えば、センサ２０内の片持ち梁部材２２ａはＸ℃の遷移温度を有するように製造する一方、片持ち梁部材２２ｂはＸ＋１℃の遷移温度を有するように製造し、片持ち梁部材２２ｃはＸ＋２℃の遷移温度を有するように製造する等とする。これと代替的に、センサ２０内の片持ち梁部材２２の全ては、同一の遷移温度を有し、複数のセンサ２０は次のように設ける、すなわち、センサ２０ａがＸ℃の遷移温度を有する片持ち梁部材を備える一方、センサ２０ｂ内の複数の片持ち梁部材２２はＸ＋１℃の遷移温度を有するように製造し、センサ２０ｃ内の複数の片持ち梁部材２２はＸ＋２℃の遷移温度を有するように製造する等となるようにする。

【００３８】

複数の片持ち梁部材２２の各々は、弾性、塑性、形状記憶及び（又は）超弾性変形が可能な材料で製造することができる。複数の片持ち梁部材を製造するため、ステンレス鋼、チタン、ニッケル、タンタル、金、バナジウム、ニッケルーチタン又はその合金のような材料を採用することができる。材料の合金比率を変えることにより異なる電気的、熱的又は機械的性質を片持ち梁部材２２に付与することができる。材料の組成、材料の電気的、機械的及び熱的性質を厳密に制御し、更に、組織及び流体接触面並びに装置の主要材料を厳密に制御するため、管状部材１２、センサ２０及び片持ち梁部材２２の双方を真空蒸着することが好ましい。例えば、ニッケルーチタン合金の場合、ニッケルーチタンの二元標的における標的のチタン含有量は、片持ち梁部材の遷移温度を正確に変更し得るよう既知の量にて変えることができる。

【００３９】

複数の片持ち梁部材２２の各々は、片持ち梁部材２２のオーステナイト相を表示する第一の位置である「不作動」位置と、片持ち梁部材２２のマルテンサイト相を表示する第二の位置である「作動」位置とを提供する二元機能を有することが好ましい。第一の位置である「不作動」位置は、センサ２０及び（又は）管状部材に対して外方に突き出す上昇位置であるようにし、又はセンサ２０及び（又は）管状部材１２と実質的に同一面の下降位置であるような形態とすることができる。同様に、第二の位置である「作動」位置は、センサ２０及び（又は）管状部材１２と実質的に同一面である下降位置であるようにし、又は管状部材２２がセンサ２０及び管状部材１２に対して上昇位置にあるすなわち外方に突き出すような形態とすることができるが、ただし、第一の位置である「作動」位置及び第二の位置である「不作動」位置は、互いに相違することが条件である。

【００４０】

このため、移植した温度センサが異なる生体内温度に出遭うとき、異なる組みの片持ち梁部材がその遷移温度に曝され、「不作動」位置から「作動」位置まで変化することが理解されよう。何れの片持ち梁部材が「作動」位置にあるかを検知し、このため、生体内の熱状態を決定するため、温度センサは、放射線撮影法、超音波撮影法、磁気映像法によって画像を形成するか、又は外部エネルギ源に曝し、該外部エネルギ源が「作動」位置にある片持ち梁部材の数及び位置を表示する信号を戻すようにすることができる。戻された信号は、センサ２０内に画成されたソリッドステート回路内に埋め込んだ受動トランスミッタによって発生させることができ、この場合、片持ち梁部材２０は、電子機械的スイッチとして機能し、このスイッチは、例えば、インピーダンス又は容量のようなソリッドステート回路の性質を変化させ、また、次に、「作動」位置にある片持ち梁部材２２の数及び位置を表示する検知可能な信号を戻す。

【００４１】

圧力センサ

圧力センサは、上述した温度センサ１０と構造的に実質的に同一であるため、再度、図１乃至図４を参照しつつ本発明の生体内圧力センサについて説明し、その要素の説明のため、同一の参照番号を使用する。本発明の生体内圧力センサ１０は、移植可能な管状部材１

２から成っており、該移植可能な管状部材１２は、全体として、中央管腔１４と、管腔外壁面１６と、管腔内壁面１８と、移植可能な管状部材１２の管腔外壁面１６及び管腔内壁面１８の少なくとも１つと一体的な複数のセンサ領域２０の少なくとも１つとを有する。複数のセンサ領域の少なくとも１つの各々が移植可能な管状部材１２上で１列にパターン化された複数の片持ち梁部材２２を更に備えている。移植可能な管状部材１２、センサ２０及び複数の片持ち梁部材は、超弾性材料のような同様の材料で製造し又は異なる材料で製造することができ、例えば、移植可能な管状部材１２はステンレス鋼にて製造し、センサ２０及び片持ち梁部材２２はニッケルーチタン合金のような超弾性材料で製造されるものとすることができる。本発明に対して考えられる最良の形態によれば、管状部材１２、センサ２０及び片持ち梁部材は、ニッケルーチタン合金のような超弾性材料で製造される。複数の片持ち梁部材２２の各々が超弾性材料で製造される場合、単一のセンサ２０内の個々の片持ち梁部材２２又は片持ち梁部材２２の群の何れかは、異なるマルテンサイト遷移温度を有するように製造することができる。このように、例えば、センサ２０内の片持ち梁部材２２ａは、マルテンサイト応力－歪み遷移係数σを有するように製造する一方、片持ち梁部材２２ｂは、遷移係数σ＋１を有するように製造し、片持ち梁部材２２ｃは、σ＋２の遷移係数を有するように製造し、生体内で片持ち梁部材２２に付与された応力又は歪みの所定の量に基づいて異なる片持ち梁部材２２又は片持ち梁部材２２の群がその位置を変えるようにする。これと代替的に、センサ２０内の片持ち梁部材２２の全てが同一の遷移温度を有し、複数のセンサ２０は次のように設けられる、すなわち、センサ２０ａが遷移係数σを有する片持ち梁部材を備える一方、センサ２２ｂ内の複数の片持ち梁部材２２は、遷移係数σ＋１を有するように製造し、センサ２２ｃ内の複数の片持ち梁部材２２は、遷移係数σ＋２を有するように製造し、異なるセンサ２０ａ、２０ｂ、２０ｃが異なる応力－歪み状態に応答するように設けられるようにする。

【００４２】

複数の片持ち梁部材２２の各々は、形状記憶及び（又は）超弾性材料で製造することができる。材料の合金比率を変えることにより、片持ち梁部材２２に異なる電気的、熱的又は機械的性質を付与することができる。材料の組成、材料の電気的、機械的及び熱的性質を厳密に制御し且つ組織及び流体接触面並びに装置の主要材料を正確に制御し得るよう管状部材１２、センサ２０及び片持ち梁部材２２の双方を真空蒸着することが好ましい。例えば、ニッケルーチタン合金の場合、ニッケルーチタン二元標的における標的のチタン含有量は、片持ち梁部材の遷移温度を正確に変え得るように既知の量にて変化させることができる。

【００４３】

複数の片持ち梁部材２２の各々は、片持ち梁部材２２のオーステナイト相を表示する第一の位置である「不作動」位置と、片持ち梁部材２２のマルテンサイト相を表示する第二の位置である「作動」位置とを提供する二元機能を備えることができる。第一の位置である「不作動」位置は、センサ２０及び（又は）管状部材に対して外方に突き出す上昇位置となるか、又はセンサ２０及び（又は）管状部材１２と実質的に同一面である下降位置となるような形態とすることができる。同様に、第二の位置である「作動」位置は、センサ２０及び（又は）管状部材１２に対し実質的に同一面である下降位置となるか、又は片持ち梁部材２２がセンサ２０及び管状部材１２に対して上昇位置となり又は外方に突き出すような形態とすることができるが、ただし、第一の位置である「作動」位置及び第二の位置である「不作動」位置が互いに相違することが条件である。

【００４４】

これと代替的に、単に二元的機能を有することに代えて、複数の片持ち梁部材２２の各々は、材料の弾性係数及び各片持ち梁部材の慣性モーメントに依存する応答曲線となるようにしてもよい。片持ち梁部材２２の各々は、片持ち梁部材２２のＸ－Ｙ軸線に沿ってＺ軸の厚さが変わるような形態とすることができる。片持ち梁部材２２が可変のＺ軸厚さを有するような形態とすることにより、異なる片持ち梁部材２２又は片持ち梁部材の異なる群は、片持ち梁部材２２の変更した幾何学的形態に伴って異なる材料の弾性係数及び異なる

慣性モーメントによって異なる応力－歪み応答性を示す。この代替的な構造の片持ち梁部材２２の場合、片持ち梁部材２２に所定の大きさの応力－歪みが加えられたとき、片持ち梁部材２２は、撓み且つ外部エネルギ源から付与されて戻った応答周波数を変化させよう。次に、この撓み程度を片持ち梁部材２２に加わる応力及び歪み力と相関させる。勿論、この代替的な構造の片持ち梁部材２２は、依然として二元的な「作動」及び「不作動」機能を提供し、「作動」及び「不作動」位置は、単に片持ち梁部材２２の延びる位置を表示するに過ぎないことが理解されよう。

【００４５】

このため、例えば、生理学的血圧、流体のせん断応力、内皮化、動脈硬化症プラークの発生と関連した異なる応力及び歪みに出遭うとき、異なる組みの片持ち梁部材は、その遷移状態に露呈され且つ、「不作動」位置から「作動」位置に変わることが理解されよう。何れの片持ち梁部材が「作動」位置にあるかを検知し、このため、応力－歪み状態を決定するため、圧力センサは、放射線撮影法、超音波撮影法、磁気映像法により画像を得るか、又は外部エネルギ源に曝し、該外部エネルギ源が「作動」位置にある片持ち梁部材の数及び位置を表示する信号を戻す。戻される信号は、センサ２０内に画成された固体回路内に埋め込んだ受動トランスミッタによって発生させることができ、この場合、片持ち梁部材２０は、電子機械的スイッチとして機能し、この電子機械的スイッチは、例えば、インビーダンス又は容量のような固体回路の性質を変化させ、次に、「作動」位置にある片持ち梁部材２２の数及び位置を検知する検知可能な信号を戻す。

【００４６】

温度センサ及び圧力センサの双方の実施の形態の場合、片持ち梁部材２２は、移植可能な管状部材１２又はセンサ領域２０の双方から絶縁することができる。熱的又は電気的絶縁体をセンサ領域２０及び移植可能な管状部材１２の中間の位置に配置し、移植可能な管状部材１２を熱から絶縁するか、又は片持ち梁部材２２から移植可能な管状部材１２まで電気を伝導することができる。

【００４７】

血管画像化センサ

次に、図５乃至図７．Ｂを参照すると、非侵襲的血管のモデル化及び画像化が可能であるようにされた管腔内ステントの形態による本発明の生体内センサ装置３０が図示されている。本発明の生体内センサ装置３０は、センサ装置３０の壁を画成する作用を果たす複数の構造要素３２、３６を備えている。複数の構造要素３２、３６の特定の幾何学的形態は、例えば、ステント又はステント移植片のようなセンサ装置３０の所望の機能に依存して選ぶことができ且つ、本発明にとって重要な因子ではない。当該技術分野の当業者には、図面に図示した以外の構造要素３２、３６の代替的な幾何学的形態が本発明によって考えられることが理解されよう。センサ装置３０を画成する複数の構造要素３２、３６は、センサ装置３０が体温のとき、すなわちマルテンサイト遷移温度（形状記憶材料の場合）が体温よりも低いが、体温に近いとき、例えば、血管のような解剖学的通路内でセンサ装置３０が拡張することを可能にする、ステンレス鋼及び（又は）ニッケル－チタン合金のような形状記憶材料、超弾性材料、塑性変形可能な材料及び（又は）弾性的に変形可能な材料の少なくとも１つで製造される。センサの機能を提供し且つ血管の画像化及びモデル化を可能にするため、本発明のセンサ３０は、第二の形状記憶及び（又は）超弾性材料（以下「第二の材料」）を有する構造要素３２、３６の領域を備えており、該第二の形状記憶材料は、例えば、構造要素３２、３６のベース材料よりも高いマルテンサイト遷移温度（すなわちσ係数）を有する。第二の材料がより高い遷移温度又はより高σ係数を有することは、内部又は外部から力を加えたとき、装置３０の幾何学的形態又は立体配座を変えることを可能にする。例えば、熱エネルギは、身体外から装置３０に向けられた外部マイクロ波の伝送により又はレーザエネルギをセンサ装置３０に付与するために使用されるレーザカテーテルにより付与することができる。何れの場合でも、センサ装置３０を第二の材料の遷移温度よりも高い温度まで局部的に加熱する結果、構造要素３２、３６はマルテンサイト変態され、これに伴ってセンサ装置３０の幾何学的形態及び（又は）立体配座を変

化させる。マルテンサイト変態時、構造要素３２、３６の少なくとも一部は、図６に矢印３８で示すように、センサ３０の幾何学的形態に対するその位置を変え、これにより隣接する対の構造要素３２、３６の間の開口部３７の形態を変える。この変化した幾何学的形態及び（又は）立体配座のセンサ３０は、次に、従来の非侵襲的画像技術を使用して画像化し、血管のプロフィールの像を得ることができる。

【００４８】

血管のプロフィールの診断画像を検索した後、センサ装置３０の幾何学的形態又は立体配座の何れかを再モデル化することが必要であろう。例えば、装置３０は、伸延又は直径方向拡張（図７．Ａ及び図７．Ｂに図示するように）を必要とする。センサ装置３０を再モデル化するため、超弾性材料を構造要素３２、３６の一部に移植、該材料は、例えば、超音波、放射線、マイクロ波、超音波、ＲＦ、紫外線、赤外線、核磁気共鳴、Ｘ線及びガンマ放射線のような外部から付与された力に応答し、センサ装置３０に付与される応力－歪みを変化させ、構造要素３２、３６のこれら領域内でマルテンサイト変態を生じさせ、これと同時に、装置３０の立体配座を変化させる。

【００４９】

更に、センサ装置３０内の熱的変化は、外部から付与された力によって誘発させることができるため、センサ装置３０を熱的に加熱し且つ熱的に冷却させることの双方が可能である。励起信号の周波数を１８０°変化させると言ったことによる、外部エネルギ源によって誘発される分子振動を減衰させることにより生体外の冷却が実現できる。分子振動を減衰させることにより、センサ装置３０内で冷却効果を生じさせ、センサ装置３０の領域内で局部的に冷却させることができる。

【００５０】

管腔内センサ

図４乃至図７．Ｂを参照すると、センサ装置３０の壁を画成する複数の壁要素３２、３６を有する全体として管状部材を備えるセンサ装置３０が図示されている。複数の壁要素を形状記憶材料又は超弾性材料で製造し、管腔内センサ装置３０が効果的に少なくとも２つのマルテンサイト遷移点を有するようにすることが好ましい。従来の形状記憶及び超弾性材料は、単一のマルテンサイト遷移点を有する。しかし、壁要素３２、３６の全てを形状記憶材料又は超弾性材料の積層体で製造し、１つの層のみがマルテンサイト遷移点$T_1$を有し、第二の層がマルテンサイト遷移点$T_2$を有し、$T_2 > T_1$であり、第一の層がセンサ装置３０を生体内の標準の生理学的状態である状態に相応する$T_1$に遷移するようにする一方、レーザ放射線又は直接的な熱接触のような外部から付与されたマイクロ波、超音波、ＲＦエネルギ又は内部から付与されたエネルギのような追加的な量のエネルギが遷移$T_2$に適した状態を誘発させ、装置は第二の形状遷移を受ける。これと代替的に、壁要素３２、３６の部分は、遷移点$T_1$を有する第一の材料で製造することができる一方、$T_1$状態下のときセンサ装置３０に対し非構造的であるが、$T_2$状態下のときセンサ装置３０に対し構造的であることが好ましい壁要素３２、３６のその他の部分は遷移点$T_2$を有する第二の材料で製造してもよい。このように、$T_1$材料で製造されたこれらの壁要素３２、３６は、センサ装置３０の遷移点$T_1$を実現するのに適した状態のとき、最初の管腔内形状又は基本的形態に遷移する一方、$T_2$材料にて製造された壁要素３２、３６は、遷移点$T_2$に適した状態がセンサ装置３０に付与されるまで遷移しない。

【００５１】

内皮化バイオセンサ

次に、図８乃至図１０を参照すると、センサ装置の組織接触面における内皮化事象を感知するバイオセンサ４０が図示されている。上述した本発明の生体内センサ装置と同様に、本発明のバイオセンサ４０は、全体として、組織接触面４２、４６を有する移植可能な基材担持部材４２から成っている。説明の目的にのみ、バイオセンサ４０は、例えば、ステントのような全体として管状の形態とされた移植可能な基材担持部材４２を備えるものとして図示されている。複数の接合領域５０が組織接触面４２、４６の双方に画成されている。接合領域５０は、上述した実施の形態のセンサ領域と同様であるが、接合領域５０が

抗体又は配位子のような生物化学的標識が接合された移植可能な基材担持部材４２の領域を備えており、これら生物化学的標識は、血管内皮成長因子又はその他の成長因子のような、内皮及び（又は）平滑筋細胞表面タンパク質又は内皮細胞及び平滑筋細胞増殖の前駆体に特有のものである。移植可能な基材担持部材４２の材料は、形状記憶材料又は超弾性材料で出来たものであることが好ましく、形状記憶材料又は超弾性材料は、接合領域５０内で生物学的材料が生物化学的標識に接合したとき、生物化学的標識への接合のみにより又は接合合成物に付与されたエネルギと組み合わさって、相変態する。移植可能な基材担持部材４２の材料が相変態すると、付与されたエネルギ源から戻った信号の周波数が変化し、接合領域５０の接合状態を表示することになる。

【００５２】

１９９７年１１月７日付けで出願され、国際出願ＷＯ９９２３９７７Ａ１号として公開された、血管内ステント及び血管内ステントの製造方法（Ｉｎｔｒａｖａｓｃｕｌａｒ Ｓｔｅｎｔ Ａｎｄ Ｍｅｔｈｏｄ Ｆｏｒ Ｍａｎｕｆａｃｔｕｒｉｎｇ Ａｎ Ｉｎｔｒａｖａｓｃｕｌａｒ Ｓｔｅｎｔ）という名称の出願係属中の共有譲渡された米国特許出願第６０／０６４，９１６号（その双方を参考として引用し本明細書に含めてある）を特に参照すると、接合領域５０は、基材担持部材４２の材料の結晶構造体内にパターン化した脆い原子結合を有する移植可能な基材担持部材４２の領域である推定の微細溝５０を形成することもできる。内皮細胞が接合したとき、基材担持部材４２に対する材料である、平滑筋細胞又は接合領域に対するその前駆体は、外部エネルギによって直接、相変態を受け、又は相変態が誘発され、この相変態により基材担持部材４２の材料の結晶構造体の脆い原子格子が破断し且つ接合領域５０と隣接する複数の微細溝５２を開放する。微細溝５２は、接合領域５０にて生体材料が標識に更に接合することにより広がることができる。このようにして、移植した基材担持部材の内皮化を促進する自己拡大性の微細溝が存在する。

【００５３】

その好ましい実施の形態に関して本発明を説明したが、当該技術分野の当業者は、特許請求の範囲内で多数の改変例を為すことが可能であることが理解されよう。従って、本発明の範囲は、何ら上記の説明によって限定されず、特許請求の範囲を参照することによってのみ完全に判断されることを意図するものである。

【図面の簡単な説明】

【００５４】

【図１】本発明による管腔内インプラントの斜視図である。

【図２】図１の線２－２に沿った断面図である。

【図３】複数の片持ち梁部材にて形成された一体型センサを示す、本発明の第一の実施の形態の概略平面図である。

【図４】図３の線４－４に沿った断面図である。

【図５】本発明の第二の実施の形態による管腔内インプラントの斜視図である。

【図６】本発明の第二の実施の形態の正反対に調節可能な領域の部分平面図である。

【図７．Ａ】７．Ａは、その正反対に縮小した状態にある本発明の管腔内インプラントの第二の実施の形態を示す斜視図である。

【図７．Ｂ】７．Ｂは、その正反対に拡張した状態にある本発明の管腔内インプラントの第二の実施の形態を示す斜視図である。

【図８】主要材料中の弱体化領域を仮想線で示した、本発明の管腔内インプラントの第三の実施の形態を示す斜視図である。

【図９】図８の丸で囲った領域９の部分拡大平面図である。

【図１０】本発明の第三の実施の形態の主要材料中の弱体化領域にて内皮細胞を接合領域に接合したときの微細溝の伝播状態を示す部分平面図である。

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(71) Applicant *(for all designated States except US)*: **ADVANCED BIO PROSTHETIC SURFACES, LTD.** [US/US]; 4778 Research Drive, San Antonio, TX 78240 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAILEY, Steven, R.** [US/US]; 3 Village Knoll, San Antonio, TX 78232 (US). **BOYLE, Christopher, T.** [US/US]; 7667 Callaghan, #604, San Antonio, TX 78229 (US). **MARTON, Denes** [US/US]; 11015 Whisper Hollow, San Antonio, TX 78230 (US). **BANAS, Christopher, E.** [US/US]; 102 Rock Squirrel, San Antonio, TX 78231 (US).

(74) Agent: **ROSENBAUM, David, G.**; Rosenbaum & Associates, P.C., Suite #3653, 875 North Michigan Avenue, Chicago, IL 60611 (US).

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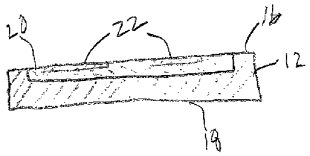
(54) Title: IN VIVO SENSOR AND METHOD OF MAKING SAME




(57) Abstract: Implantable *in vivo* sensors used to monitor physical, chemical or electrical parameters within a body. The *in vivo* sensors are integral with an implantable medical device and are responsive to externally or internally applied energy. Upon application of energy, the sensors undergo a phase change in at least part of the material of the device which is then detected external to the body by conventional techniques such as radiography, ultrasound imaging, magnetic resonance imaging, radio frequency imaging or the like. The *in vivo* sensors of the present invention may be employed to provide volumetric measurements, flow rate measurements, pressure measurements, electrical measurements, biochemical measurements, temperature, measurements, or measure the degree and type of deposits within the lumen of an endoluminal implant, such as a stent or other type of endoluminal conduit. The *in vivo* sensors may also be used therapeutically to modulate mechanical and/or physical properties of the endoluminal implant in response to the sensed or monitored parameter.

WO 02/064019 A2

# *IN VIVO* SENSOR AND METHOD OF MAKING SAME

## Background of the Invention

The present invention relates generally to the field of implantable medical devices, and more particularly pertains to sensors that may be implanted into a body to elicit at least one of a mechanical, chemical or electrical response to an *in vivo* physiological condition or state with the body. The present invention provides a vacuum deposited film which may be either a monolithic monolayer of material or a multilayered film having at least portions of the film capable of sensing at least one of changes in temperature, pressure, or the presence or absence of chemical or biochemical species in the body by mechanical, electrical, chemical, electrochemical or electromechanical means.

Specifically, the present invention relates to the manufacture and use of implantable sensors to monitor physical, chemical or electrical parameters of a fluid flow through a body passageway. For example, the sensors of the present invention may be employed to provide volumetric measurements, flow rate measurements, pressure measurements, electrical measurements, biochemical measurements, temperature, measurements, or measure the degree and type of deposits within the lumen of an endoluminal implant, such as a stent or other type of endoluminal conduit. The present invention also provides a means to modulate mechanical and/or physical properties of the endoluminal implant in response to the sensed or monitored parameter. For example, where the monitored blood flow volume through an endoluminal device is determined to be below physiological norms and/or the blood pressure is determined to be above physiological norms, the stent may be actuated to increase its diameter, such as by superelastic properties of the stent materials.

Post-implantation evaluation of the patency of an endoluminal device presently requires clinical examination by angiography or ultrasound. The results of these tests provide a qualitative evaluation of device patency. It is, therefore, desirable to provide a means for quantitatively measuring the post-implantation patency of an endoluminal device on either a periodic or continuous basis. Quantitative *in vivo* measurements of volumetric flow rate, flow velocity, biochemical constitution, fluid pressure or similar physical or biochemical property of the body fluid through an endoluminal device would provide more accurate diagnostic information to the medical practitioner.

As used herein, the term "endoluminal device" is intended to include stents, grafts and stent-grafts which are implanted within an anatomical passageway or are implanted with a body to create a non-anatomical passageway between anatomically separated regions within the body. Endoluminal devices in accordance with the present invention may include endovascular devices, prostatic devices, urethral devices, cervical devices, esophageal devices, intestinal devices, biliary devices, intra-cardiac devices, valves, hepatic devices, renal devices or devices with similar application within the body.

The term "sensor," as used in this application, is intended to include, without limitation, biosensors, chemical sensors, electrical sensors and mechanical sensors. While the term "biosensor" has been used to variously describe a number of different devices which are used to monitor living systems or incorporating biological elements, the International Union for Pure and Applied Chemistry (IUPAC) has recommended that the term "biosensor" be used to describe "a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" 1992, 64, 148 IUPAC Compendium of Chemical Terminology 2nd Edition (1997). The term "chemical sensor" is defined by the IUPAC as a device that transforms chemical information, ranging from concentration of a specific sample component to total composition analysis, into an analytically useful signal. Conventional biosensors are a type of chemical sensor that consists of three basic elements: a receptor (biocomponent), transducer (physical component) and a separator (membrane or coating of some type). The receptor of a chemical sensor usually consists of a doped metal oxide or organic polymer capable of specifically interacting with the analyte or interacting to a greater or lesser extent when compared to other receptors. In the case of a biosensor the receptor or biocomponent converts the biochemical process or binding event into a measurable component. Biocomponents include biological species such as: enzymes, antigens, antibodies, receptors, tissues, whole cells, cell organelles, bacteria and nucleic acids. The transducer or physical component converts the component into a measurable signal, usually an electrical or optical signal. Physical components include: electrochemical devices, optical devices, acoustical devices, and calorimetric devices as examples. The interface or membrane separates the transducer from the chemical or biocomponent and links this component with the transducer. **They are in intimate contact**. The interface separator usually screens out unwanted materials, prevents fouling and protects the transducer. Types

of interfaces include: polymer membranes, electropolymerized coatings and self-assembling monomers.

Sensors should have high selectivity and sensitivity, have rapid recovery times with no hysteresis, long lifetimes if not single use, low drift, automated calibration, self-diagnostic, low cost, no reagent additions required and no sample preparation. It is obvious that presently available chemical sensors and biosensors do not meet these criteria (World Biosensor Market, Frost and Sullivan, Report 5326-32, 1997). National Institute of Standards and Technology, *Nano-and MEMS Technologies for Chemical Biosensors*, (www.atp.nist.gov/atp/focus/98wp-nan.htm).

In the clinical diagnostic market, various sensor designs are known including electrochemical sensors (potentiometric ISEs; amperometric; conductometric; miniaturized ISEs; field effect transistors; interdigitated transistors); optical sensors using fiber-optic or surface plasmon resonance technologies; acoustic sensors such as piezo-crystal and surface acoustic wave sensors; and thermal sensors which employ thermistors. Thus, it is known to employ microfabrication techniques to make clinical sensors. Currently, the most commercially successful microfabricated sensor in the clinical diagnostic market is the MEDISENSE glucose meter that uses an electrochemical transduction of an enzymatic reaction. However, the need for *in vivo* sensing systems is well recognized. Work on *in vivo* sensing systems for both glucose and lactate has confirmed the effectiveness of phospholipid copolymers in improving hemocompatibility. Fisher, U., et al. *Biosen. Bioelectron.*, 10, xxiii (1995).

By their nature, implantable sensors must have some mechanism for communicating sensed information from the sensor to a reader, which may be human or machine, outside the body. Since it is impractical to implant a physical connection between the sensor and the external reader, alternative means for generating a readable signal external the body must be provided. Suitable means for generating a readable signal external the body include, without limitation, radiographically visible signals, magnetic flux signals, chemical signals, chemifluorescent signals, and/or electrical signals.

The pathogenesis of arteriosclerosis has not been positively identified. A number of risk factors, such as high cholesterol, hypertension, and diabetes are known to serve to turn on inflammatory mechanisms at the arterial wall and recruit white cells into the arterial wall to ultimately cause the formation and breakdown of plaque, which, in turn, lead to clinical

events. The process starts out with oxidation-sensitive nuclear regulatory mechanisms. Free radicals control the genes that cause the synthesis of proteins that are expressed in the endothelial cells and serve to attract white cells into the arterial wall.

Endothelialization of an implanted medical device has been the subject of considerable scientific study and literature. It is know known that various growth factors and cytokines are responsible for activating smooth muscle cell receptors and initiating smooth muscle cell proliferation. Endothelial cell growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) have been identified as significant for endothelial cell growth in vitro. While VEGF is specific for endothelial cells, FGFs also stimulate smooth muscle cell growth. Bauthers, C., Growth Factors as a Potential New Treatment for Ischemic Heart Disease, *Clin. Cardiol.* 20:II-52-II-57 (1997).

It has been recognized that there is a need for an *in vivo* sensor capable of sensing binding of endothelial cells or arterioschlerotic plaque, and providing an *ex vivo* detectable signal, without requiring external or internal power sources.

**Summary Of The Invention**

In accordance with the present invention there is provided an implantable *in vivo* sensor suitable for monitoring clinically significant physiological events. The present invention provides an integrated device which is implantable within an anatomical passageway, such as a blood vessel, in the esophageal or gastro-intestinal tract, bile duct, hepatic duct, within the renal system, such as within a ureter or urethra, vagina or cervix, vas deferens, bronchi or similar anatomical passageways; within an organ, or within an anatomical defect, such as a cardiac septal defect.

The inventive *in vivo* sensor consists generally of an implantable substrate carrier element and at least one of a plurality of sensor elements. The implantable substrate carrier element may consist of, for example, a stent, stent-graft, graft, valve, filter, occluder or other implantable medical device, which serves as a foundational element for the sensor elements. Under conditions where the implantable substrate carrier, itself, is configured to return a detectable signal, the implantable carrier element, itself, may constitute the sensor element. Where the implantable substrate carrier element and the sensor element are discrete, conjoined elements, they may be fabricated of like materials or of dissimilar materials, each having either similar or dissimilar thermal, mechanical, electrical and/or chemical properties.

Microfabrication techniques are preferably employed to create both the carrier element and the sensor element in such a manner that both the substrate carrier element and the sensor element have a defined geometry and conformation that is suitable for use as a thermal, electrical, mechanical or chemical sensor, for sensing, for example, fluid flow, fluid flow rate, or fluid pressure in the region of the sensor. The addition of chemical or biological compounds to inventive sensor permits the device to be used as either a chemical or a biosensor, respectively. Similarly, microelectronic circuits may be added to the inventive sensor, such as by fabricating integrated circuits into or onto the inventive sensor, to enable the sensor to detect electrochemical events occurring at the sensor, such as **arteriosclerotic** plaque being deposited onto the surface of the sensor, or to detect electrochemical changes in the anatomical environment into which the sensor is implanted.

Alternatively, the inventive implantable sensor element and the implantable substrate carrier element may be fabricated of wrought materials, such as stainless steely hypotubes, stainless steel wire, shape memory hypotubes and shape memory wires. The sensor element may be attached to the substrate carrier element, or component parts, such as cantilever members, of the sensor element may be attached to the sensor element by a variety of known means. For example, welding processes may be used, such as laser welding, plasma welding, resistance welding, or e-beam welding. Welding, however, is generally not an acceptable method for joining nickel-titanium alloys to other materials, *e.g.*, stainless steel, because brittle intermetallics may be formed in the weld zone. In order to obtain a weld that is free of oxides or nitrides, welding should be performed under stringent environmental conditions in a clean, inert atmosphere or in vacuum in order to minimize reactivity of the titanium. In some cases, welded nickel-titanium parts may require heat-treating after welding to stress relieve the weld zone. The heat-affected zone will generally not exhibit superelastic properties. Soldering may be employed to join shape memory or superelastic alloys, such as nitinol, to stainless steel and other materials. However, a proper flux must be selected which inhibits the formation of surface oxides during the soldering process. Ultrasonic soldering has also been used to try to keep the surface free of oxides during soldering. Various epoxies and other adhesives may be used to join shape memory alloys either to themselves or to other materials. The chosen adhesives must, of course, be compatible with both the manufacturing and *in vivo* biological environments of the device. Finally, the sensor element may be mechanically joined to the substrate carrier element, or component parts of the sensor

element maybe joined together by crimping, providing an interference fit or by creating interlocking geometries of the sensor element or its component parts.

In accordance with a particular embodiment of the present invention, an endoluminal implant is provided which is implantable within an anatomical or non-anatomical body passageway to determine a given condition of a fluid flow through the endoluminal implant within the body passage. The inventive endoluminal implant may include, for example, an endoluminal stent, stent graft, or graft that consists of a generally tubular shaped member having two diametric states. In order to facilitate transluminal catheter introduction, the inventive endoluminal device has a first diametric state in which the transverse cross-sectional area of the device is of sufficient size to permit percutaneous introduction and *in vivo* placement of the device using transluminal approaches. A second diametric state has a transverse cross-sectional area which is larger than the first diametric state and conforms to the diameter of the anatomical passageway into which the device is placed, or is of a desired diameter for non-anatomical passageways. The inventive endoluminal device may be fabricated as a balloon expandable device, a self-expanding device, a shape-memory device or a superelastic device. It will be understood by those of skill in the art that the term "balloon expandable" refers to a class of devices which rely upon application of an external pressure, such as that applied by a balloon catheter, to radially deform the device from its first diametric state to its second diametric state; that the term "self-expanding" refers to a class of devices which rely upon the inherent mechanical properties of the device material to expand the device from its first diametric state to its second diametric state; that the term "shape-memory" refers to a class of devices which are fabricated of materials which exhibit martensitic phase transformation at certain transition temperatures; and the term "superelastic" refers to a class of devices which are fabricated of materials which deform under given stress-strain conditions. The inventive endoluminal sensor may be fabricated of materials capable of undergoing elastic or plastic deformation, such as stainless steel, tantalum, titanium, gold, or other biocompatible metals. However, the present invention is preferably fabricated of a shape-memory and/or superelastic material, such as nickel-titanium alloys known as Nitinol, which are mechanically responsive to temperature changes and/or changes in applied stress or strain, respectively.

Generally, the inventive endoluminal sensor consists of a sensor which is integral with an implantable endoluminal device, such as stent, and which is configured to respond either mechanically, electronically, electromechanically, or chemically, to cause a

mechanical, electrical, electromechanical or chemical change at the sensor and/or the endoluminal device which is detectable *ex vivo* using non-invasive detection methodologies such as radiography, ultrasonography, magnetic resonance imaging, or radio frequency detection.

In accordance with one embodiment of the invention, the inventive sensor comprises at least one integral region of the implantable endoluminal device that is formed as a plurality of cantilever members fabricated of shape-memory materials having different transformation temperatures. The sensor may be positioned on either a fluid contacting or tissue-contacting surface of the implantable device, such as the luminal surface of a stent which contacts blood, or on the abluminal surface of a stent which contacts neointimal tissue of the blood vessel. Alternatively, the sensors may be positioned on both the fluid contacting and the tissue-contacting surface of the implantable device.

As used herein, the term "integral" is intended to include regions that are formed as a part of the bulk material of the endoluminal device and regions which are formed separately from the bulk material of the endoluminal device, but which are coupled thereto.

In accordance with another embodiment of the invention, the inventive sensor comprises at least one region of the implantable endoluminal device that is formed of a plurality of cantilever members having different mechanical properties, such as different modulus of elasticity, plasticity or stress-strain behaviors. In accordance with the best mode presently contemplated for the invention, the cantilever members are preferably fabricated of a superelastic material. As with the shape-memory cantilever members, the superelastic cantilever members may be positioned on either a fluid contacting or tissue contacting surface of the implantable device, such as the luminal surface of a stent which contacts blood, or on the abluminal surface of a stent which contacts neointimal tissue of the blood vessel. Alternatively, the sensors may be positioned on both the fluid contacting and the tissue-contacting surface of the implantable device. Unlike the shape-memory cantilever sensors, the superelastic cantilever sensors are responsive to changes in force, such as shear forces, applied to the sensors.

With both the shape-memory cantilever members sensor and the superelastic cantilever members sensor, each of the plurality of cantilever members have first and second positions that are indicative of either an off or on position, respectively. The first or "off" position of each cantilever members is coplanar or flush with the surface of the endoluminal

device into which the sensor is positioned. In the second or "on" position, each activated cantilever members projects outwardly from the surface of the endoluminal device into which the sensor is positioned. Because different cantilever members or groups of cantilever members are fabricated to have either different transition temperatures or different stress-strain properties, individual cantilever members or groups of cantilever members which are in the second or "on" position, are indicative of a given thermal or stress-strain condition existing within the body into which the endoluminal device is implanted.

In one particular form of the invention, the inventive endoluminal device comprises a temperature sensor having a plurality of cantilever members positioned on at least one of the proximal, distal or intermediate regions of the endoluminal device and positioned on at least one of the luminal or abluminal wall surfaces of the endoluminal device. To facilitate ease of detection, a plurality of groups of cantilever members are provided, each group is formed of a plurality of individual cantilever members, with each individual cantilever members in the group having identical transition temperatures. The plurality of groups of cantilever members are arrayed along the longitudinal axis of the endoluminal device in such a manner as to create a continuum of groups of cantilever members having different transition temperatures. Changes in temperature at the site of the endoluminal device are indicated by the position of the cantilever members or groups of cantilever members as determined by radiography, ultrasonography, magnetic resonance imaging or other means that provides a detectable image of the position of the cantilever members and groups of cantilever members.

In another particular form the invention, the sensor comprises a plurality of cantilever members positioned on at least one of the proximal, distal or intermediate regions of the endoluminal device and positioned on at least one of the luminal or abluminal wall surfaces of the endoluminal device. To facilitate ease of detection, a plurality of groups of cantilever members are provided, each group is formed of a plurality of individual cantilever members, with each individual cantilever members in the group having identical transition temperatures. The plurality of groups of cantilever members are arrayed along the longitudinal axis of the endoluminal device in such a manner as to create a continuum of groups of cantilever members having different stress-strain transition pressures. Changes in applied stress or strain, such as blood pressure or blood flow shear stress, at the site of the endoluminal device are indicated by the stress and strain acting on the cantilever members or groups of cantilever members which provides a corresponding frequency shift in energy

reflected, when compared to a baseline stress-strain for unloaded cantilever members. The position and frequency shift of the cantilever members may be determined by radiography, ultrasonography, magnetic resonance imaging or other means which provides a detectable image of the position of the individual cantilever members and groups of cantilever members or is capable of measuring frequency shifts due to differential stress-strain loading onto the cantilever members.

In yet another form of the invention, the inventive sensor is a biosensor that is microfabricated from a material capable of undergoing elastic, plastic, shape-memory or superelastic deformation, and has a plurality of cantilever members formed therein, as described above. Each of the plurality of cantilever members has at least one binding domain selective for at least one indicator of endothelialization selected from the group of endothelial cell surface proteins, antigens, antibodies, cytokines, growth factors, co-factors, or other biological or biochemical marker of endothelial cells or endothelial cell precursors. Binding of the at least one indicator to at least one of the plurality of cantilever members causes a change in strain applied to the cantilever members, thereby causing the relevant cantilever members or groups of cantilever members to undergo superelastic transformation from the first or "off" position to the second or "on" position. As with the above-described embodiments of the invention, the position of the sensor cantilever members in the second or "on" position relative to the endoluminal device is then detected and is indicative of the progress of endothelialization.

Similarly, the fact of or the progress of arterioschlerotic plaque formation may be sensed using a plurality of elastic or superelastic cantilever members. In accordance with a first embodiment, the plurality of superelastic cantilever members undergo martensitic transformation as a result of the strain applied to the cantilever members resulting from growth of arterioschlerotic plaque onto the cantilever members. In accordance with a second embodiment, the plurality of superelastic cantilever members has at least one binding domain selective for at least one indicator of arterioschlerotic plaque or its precursors. Binding of the arterioschlerotic plaque or precursors of arterioschlerotic plaque to the binding domain on the cantilever members, adds a quantum of strain to the cantilever members sufficient to cause the cantilever members to undergo superelastic transformation from the first or "off" position to the second or "on" position. As with the above-described embodiments of the invention, the position of the sensor cantilever members in the second or "on" position relative to the endoluminal device is then detected and is indicative of the progress of arteriosclerosis.

Yet another form of the invention entails an implant fabricated of a superelastic material that has a variable diametric geometry responsive to changes in pressure applied to the implant. This form of the invention is preferably employed as a smooth muscle prosthesis, for example, as a vascular prosthesis, and is responsive to blood pressure changes in a manner similar to those changes native to blood vessels, *i.e.*, contracting upon sensing lowered blood pressures and expanding upon sensing higher blood pressures, in order to maintain physiologically normal blood pressure. In this embodiment of the invention, a tubular implant is fabricated, in whole or in part, of a superelastic material and has diametrically adjustable regions that undergo superelastic transformation to increase or decrease the diameter of the implant upon sensing given physiological pressures within the implant.

Finally, another form of the invention consists of an endoluminal implant similar to that described in co-pending, commonly assigned U.S. Patent Application Serial No. 60/064,916, filed November 7, 1997 which was published as PCT International Application WO9923977A1 entitled *Intravascular Stent And Method For Manufacturing An Intravascular Stent*, both of which are hereby incorporated by reference. In those applications there is described an endoluminal implant having a plurality of microgrooves on the luminal and/or abluminal surfaces thereof which facilitate improved endothelialization over a non-grooved endoluminal implant. In accordance with the present invention there is provided an endoluminal implant having a plurality of putative microgrooves comprising sections of weakened bulk material of the endoluminal implant. The endoluminal implant is preferably fabricated of a superelastic bulk material and weakened regions in the bulk material are formed using standard microlithographic techniques to form the putative microgrooves. A plurality of binding domains are created along the fluid flow surface of the endoluminal implant and at proximal (relative to the blood flow) regions of the putative microgrooves that preferentially bind to endothelial cell surface proteins. Binding of the endothelial cell surface proteins to the binding domains causes a shift in the applied strain to the superelastic bulk material, which causes the superelastic bulk material to deform in the region of the applied strain, thereby breaking the interatomic bonds in the weakened regions of the putative microgrooves and causing formation of a portion of a microgroove. Propagation of the endothelial cell proliferation along the surface of the superelastic bulk material causes, in turn, a propagation of strain along the superelastic bulk material that causes the formation of the microgrooves in the superelastic bulk material.

These and other objects, features and advantages of the present invention will become more apparent to those of ordinary skill in the art from the following more detailed description of the preferred embodiments of the present invention taken with reference to the accompanying figures.

**Brief Description of the Figures**

Figure 1 is a perspective view of an endoluminal implant in accordance with the present invention.

Figure 2 is a cross-sectional view taken along line 2-2 of Figure 1.

Figure 3 is a fragmentary plan view of a first embodiment of the present invention illustrating an integral sensor formed of a plurality of cantilever members.

Figure 4 is a cross-sectional view taken along line 4-4 of Figure 3.

Figure 5 is a perspective view of an endoluminal implant in accordance with a second embodiment of the present invention.

Figure 6 is a fragmentary plan view of a diametrically adjustable region of the second embodiment of the present invention.

Figure 7A is a perspective view of the second embodiment of the inventive endoluminal implant of the present invention in its diametrically reduced state.

Figure 7B is a perspective view of the second embodiment of the inventive endoluminal implant of the present invention in its diametrically expanded state.

Figure 8 is a perspective view of a third embodiment of the inventive endoluminal implant of the present invention depicting weakened regions in the bulk material in phantom.

Figure 9 is a fragmentary enlarged plan view of circled region 9 in Figure 8.

Figure 10 is a fragmentary plan view illustrating propagation of a microgroove upon binding of an endothelial cell to a binding domain at the weakened region in the bulk material of the third embodiment of the present invention.

**Detailed Description of the Preferred Embodiments**

To simplify description of the present invention, most of the preferred embodiments will be described with reference to an endoluminal stent, except where otherwise stated. However, those of ordinary skill in the art will understand that each embodiment has application to a variety of implantable devices including, without limitation, stents, grafts, stent-grafts, valves, shunts or patches.

The particular means for detecting a change in the inventive sensor and/or the particular means for activating a change in the inventive sensor is generally not considered part of the present invention. For example, it is known that ultrasound energy may be employed to generate both one-way and two-way shape memory effects in nickel-titanium alloys. **V.V. Klubovich, V.V. Rubanick, V.G. Dorodeiko, V.A. Likhachov, and V.V. Rubanick Jr.** (Institute of Tech. Acoustics, 13 Ludnikova, 210026 Vitebsk, Belarus,) *Generation of Shape Memory Effect in Ti-Ni Alloy by means for Ultrasound,* Abstract 1.P12, SMST-97 conference found at URL http://www.fwsystems.com/professional/smstabs.html. Using ultrasound energy to non-invasively induce stent heating has also been confirmed by B. Lal, et al. in their abstract entitled *Non-Invasive Ultrasound Induced Heating of Stents: Importance of Stent Composition,* which may be found at URL http://www.hotplaque.com/frames/abstracts/rabs6.htm and URL http://ex2.excerptamedica.com/00acc/abstracts/abs1065-117.html. Lal, et al. hypothesized that gentle heating can be accomplished using ultrasound (US) and a constant temperature can be maintained using pulsed US. The heating rate of an object under the same US power and frequency is determined primarily by its absorption and reflection rates. To test their hypothesis, they used a phantom of 5.08 cm thick layer of pork muscle, in which various annular stent shape materials were placed. To monitor the heating multiple hypodermic thermocouples were used. The heating was induced using FDA-approved levels of therapeutic ultrasound (intensity 0.5-2.5 W/cm$^2$, frequency 1-3 MHz) in both pulse and continuous modes. It was found that nylon, and some types of PVC, exhibit temperature increases that are larger (2-35° C) and faster (1.5-15 times) than the surrounding tissue, while Lexan, PTFE, Latex, Teflon, Ceramic and Delrina do not display selective heating. A modest heating effect (2° C increase in 15 minutes) was also found in a metal stent. Lal, et al. concluded that ultrasound heating of tissue adjacent to a prosthesis depends on stent composition, induction of thermal apoptosis by ultrasound may prove to be effective in

limiting restenosis in polymeric stents and grafts. Issues that need to be addressed include the optimal biocompatible material and design of stents and the *in vivo* effects of phased-array US on the stented artery and its surrounding tissues. Lal, et al. believed that by using fast-heating, non-toxic materials, ultrasound-heated stents could be devised.

Similarly, microwave radiation may be used to generate shape memory effects in shape memory alloys. It is known, for example, that microwave radiation may be used for stent diathermy in stainless steel stents. S. Naguib, *et al.* in *Stent diathermy using focused ultrasound & microwave* found at URL http://www.hotplaque.com/frames/abstracts/rabs3.htm sought to use ultrasound and microwave energy to non-invasively heat the stent and its surrounding plaque. Using Palmaz-Schatz stents as well as several stent-shape biopolymer materials embedded inside the phantom, Naguib, *et al.* continuously mapped rise in temperatures in the system upon ultrasound and microwave irradiations in separate settings. Temperature monitoring was done using a 12-channel ultra-thermometer (0.01°C) with thermocouples (ultrasound) and fiber optic sensors (microwave). Therapeutic ultrasound at the frequency of 1-3 MHZ and intensity of 0.5-2.5W/CM2 was used. Microwave radiofrequency was delivered by an antenna using a frequency of 2.45 GHZ and a power of 5.37 & 10.22 watts. In their ultrasound experiment Naguib, *et al.* found that the temperature of outer surface of stent and its surrounding tissue increased significantly higher than other sites. The rise in temperature varies by the type of biopolymer where silicon stent heated faster and more than polyurethane and polytetrafluoroethylene. Similar results were observed in the microwave experiments. Infrared thermography was used to measure the increased temperatures during delivery of both ultrasound and microwave radiation.

It is recognized, however, that externally applied forces, such as RF, microwave, ultrasound, etc. exist in the ambient environment. It is, therefore, undesirable to fabricate sensor device which will undergo a shape memory change upon encountering an ambient externally applied force. For example, it would be undesirable for a patient with an implanted sensor device responsive to microwave irradiation to have the implanted sensor device undergo a shape memory transition when the patient is warming food in a kitchen microwave appliance.

Because the microfabrication methods of the present invention allow for stringent control over the material composition of the implantable sensor device, the material

composition may be made responsive to a particular frequency range that is outside the frequency range of the same type of energy signals existing in the ambient environment of the patient. Thus, both the device activation energy type and frequency and the detection energy type and frequency must fall outside that encountered in the ambient environment.

It is well known that metal stents are radioopaque and are detectable under radiographic imaging, such as fluoroscopy. Detection of the inventive sensor device may be accomplished by radiographic imaging, ultrasound imaging (either using frequencies which also generate a shape memory effect or not), magnetic resonance imaging, RF imaging or similar methods. The use of magnetic resonance imaging to image nitinol stents is known in the art. See, *e.g.*, Rahdert, D, Hakim, B., *Magnetic Resonance compatibility of Ni-Ti Stents,* Abstract 8.P1, SMST-97 conference (International Organization on Shape Memory and Superelastic Technologies) found at URL http://www.fwsystems.com/professional/smstabs.html, in which they describe they studied the compatibility of Ni-Ti coronary stents using magnetic imaging to assess a) ferromagnetic forces; and b) artifacts. Two methods were used to measure force: horizontal sliding and pendulum deflection. Ferromagnetic forces were found to be less than 10% of stent weight. Artifacts were assessed to be small.

The use of particulate paramagnetic metal iron oxide as a contrast medium to image and model vascular profiles under magnetic resonance imaging (MRI) has been demonstrated by Mitra Rajabi, *et al.* at the University of Texas-Houston, Houston, Texas, United States and the University of Texas-Medical Branch at Galveston, Galveston, Texas, United States. In an abstract published for presentation at the ACC 2001, the American College of Cardiology Scientific Session scheduled for March 18-21, 2001, the abstract may be found at URL: http://www.hotplaque.com/ACC/ACC2001%20abstracts.htm#5), Rajabi, *et al.* describe a technique for imaging plaque inflammation. Super paramagnetic iron oxide (SPIO) particles are magnetic resonance (MR) imaging contrast media that have a central core of iron oxide generally coated by a polysaccharide layer. They shorten the relaxation time, predominantly the T2 relaxation time. Rajabi, *et al.* hypothesized that inflamed vulnerable arteriosclerotic plaques would preferentially take up these nano-particles by virtue of macrophage infiltration, leaking vasa vasorum and fissured thin caps. To test their hypothesis, they injected 1- 3 mmol Fe/kg super paramagnetic iron oxide to six Apo E deficient and two C57bl mice through the tail vein, after first obtaining baseline MR imaging. Post-contrast MR imaging were performed in day 5 with the same parameters (TR=2.5, TE=0.012, FOX=6

6, slice thickness=2.0mm, flip angle (orient)=trans, and matrices=256 x 256). The aorta at the level of kidney was selected for comparison of the baseline and post-contrast images. Rajabi, *et al.* found decreased signal intensity in SPIO injected Apo E deficient mice and no decrease in signal intensity in SPIO injected C57bl mice.

Thus, it is known in the art that thermal energy may be imparted to implanted medical devices fabricated of metal either by transcatheter approaches using direct application of heat, such as by a laser catheter, or may be induced by directing microwave or ultrasound energy toward the implanted device. Moreover, it is known implanted medical devices fabricated of shape memory alloys may be detected *in vivo* using radiography, ultrasonography, MRI, or RF imaging or combinations thereof.

In accordance with the present invention, any of the foregoing methods of applying energy to the inventive sensor device, either directly through transcatheter application or indirectly through inductive methods, as well as any of the foregoing methods for detecting the state of the inventive sensor device *in vivo* may be employed to effectuate change in the state of the implanted device. The energy stimulus may be an endogenous energy stimulus selected from the group consisting of fluid pressure, fluid shear forces, body temperature, cellular binding or molecular binding. Alternatively, the energy stimulus may be an exogenous energy stimulus such as externally applied temperature, pressure, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays, beta or gamma irradiation.

Turning now the accompanying Figures, and in particular Figures 1-4 there is illustrated first and second embodiments of implantable *in vivo* sensor in accordance with the present invention.

***Temperature Sensor***

The inventive *in vivo* temperature sensor 10 consists generally of an implantable tubular member 12 having a central lumen 14, an abluminal wall surface 16, a luminal wall surface 18 and at least one of a plurality of sensor regions 20 integral with at least one of the abluminal wall surface 16 and the luminal wall surface 18 of the implantable tubular member 12. The flow vector F of a fluid over the surface of the sensor region 20 is illustrated in Figure 3. Each of the at least one of a plurality of sensor regions further comprise a plurality of cantilever members 22 patterned in an array on the implantable tubular member 12. The

implantable tubular member 12, the sensor 20 and the plurality of cantilever members may be fabricated of like materials, such as shape memory materials, or may be fabricated of different materials, *e.g.*, the implantable tubular member 12 being fabricated of stainless steel and the sensor 20 and cantilever members 22 being fabricated of a shape memory material, such as nickel-titanium alloys. In accordance with the best mode contemplated for the present invention, the tubular member 12, the sensor 20 and the cantilever members will be fabricated of shape memory materials, such as nickel-titanium alloys. Where each of the plurality of cantilever members 22 are fabricated of a shape memory material, either individual cantilever members 22 or groups of cantilever members 22 within a single sensor 20 may be fabricated to have different martensite transition temperatures. Thus, for example, cantilever members 22a within sensor 20 may be fabricated to have a transition temperature of X degrees Centigrade, while cantilever members 22b are fabricated to have a transition temperature of X + 1 degrees Centigrade, cantilever members 22c are fabricated to have a transition temperature of X +2 degrees Centigrade, etc. Alternatively all of the cantilever members 22 in a sensor 20 may have the same transition temperature, and a plurality of sensors 20 are provided such that sensor 20a has cantilever members having a transition temperature of X degrees Centigrade, while the plurality of cantilever members 22 in sensor 20b are fabricated to have a transition temperature of X + 1 degrees Centigrade, and the plurality of cantilever members 22 in sensor 20c are fabricated to have a transition temperature of X +2 degrees Centigrade, etc.

Each of the plurality of cantilever members 22 may be fabricated of a material capable of undergoing elastic, plastic, shape memory and/or a superelastic deformation. Materials such as stainless steel, titanium, nickel, tantalum, gold, vanadium, nickel-titanium, or alloys thereof may be employed to fabricate the plurality of cantilever members. Different electrical, thermal or mechanical properties may be imparted to the cantilever members 22 by altering the alloy ratios of the material. It is preferable to vacuum deposit both the tubular member 12, the sensors 20 and the cantilever members 22 to permit tight control over the material composition, electrical, mechanical and thermal properties of the material, as well as provide for tight control over the tissue and fluid contacting surfaces and the bulk material of the device. For example with nickel-titanium alloys, the titanium content of the target, in a nickel-titanium binary target, may be changed a known amount to precisely alter the transition temperature of a cantilever members.

Each of the plurality of cantilever members 22 preferably have binary functionality to provide a first "off" position indicative of an austenite phase of the cantilever members 22 and a second "on" position indicative of a martensite phase of the cantilever members 22. The first "off" position may be configured such that it is in a raised position which projects outwardly relative to the sensor 20 and/or the tubular member or in the lowered position that is substantially co-planar with the sensor 20 and/or the tubular member 12. Similarly, the second "on" position may be configured such that it is in a lowered position that is substantially coplanar with the sensor 20 and/or the tubular member 12 or the cantilever members 22 may be in the raised position or projecting outwardly relative to the sensor 20 and the tubular member 12, provided, however, that the first "on" position and the second "off" positions are different from one and other.

It will be understood, therefore, that as the implanted temperature sensor encounters different *in vivo* temperatures, different sets of cantilever members will be exposed to their transition temperature and change from the "off" position to the "on" position. In order to detect which cantilever members are in the "on" position and, therefore, determine the *in vivo* thermal conditions, the temperature sensor may be imaged radiographically, ultrasonically, magnetically or may be exposed to an external energy source which returns a signal representative of the number and position of the cantilever members that are in the "on" position. The returned signal may be generated by a passive transmitter embedded in solid state circuitry defined within the sensor 20, wherein the cantilever members 20 serve as electromechanical switches which alter a property of the solid state circuitry, for example, impedance or capacitance, and which then returns a detectable signal representative of the number and position of cantilever members 22 in the "on" position.

***Pressure Sensor***

Because it is structurally virtually identical to the temperature sensor 10, described above, the inventive *in vivo* pressure sensor will also be described with reference to Figures 1-4 and use identical reference numerals to describe the elements thereof. The inventive *in vivo* pressure sensor 10 consists generally of an implantable tubular member 12 having a central lumen 14, an abluminal wall surface 16, a luminal wall surface 18 and at least one of a plurality of sensor regions 20 integral with at least one of the abluminal wall surface 16 and the luminal wall surface 18 of the implantable tubular member 12. Each of the at least one of

a plurality of sensor regions further comprise a plurality of cantilever members 22 patterned in an array on the implantable tubular member 12. The implantable tubular member 12, the sensor 20 and the plurality of cantilever members may be fabricated of like materials, such as superelastic materials, or may be fabricated of different materials, *e.g.*, the implantable tubular member 12 being fabricated of stainless steel and the sensor 20 and cantilever members 22 being fabricated of a superelastic material, such as nickel-titanium alloys. In accordance with the best mode contemplated for the present invention, the tubular member 12, the sensor 20 and the cantilever members will be fabricated of superelastic materials, such as nickel-titanium alloys. Where each of the plurality of cantilever members 22 are fabricated of a superelastic material, either individual cantilever members 22 or groups of cantilever members 22 within a single sensor 20 may be fabricated to have different martensite transition temperatures. Thus, for example, cantilever members 22a within sensor 20 may be fabricated to have a martensitic stress/strain transition coefficient $\sigma$, while cantilever members 22b are fabricated to have a transition coefficient $\sigma$ +1, cantilever members 22c are fabricated to have a transition coefficient of $\sigma$ +2, etc. such that different cantilever members 22 or groups of cantilever members 22 change their position based upon a given quantum of stress or strain applied to the cantilever members 22 *in vivo*. Alternatively all of the cantilever members 22 in a sensor 20 may have the same transition temperature, and a plurality of sensors 20 are provided such that sensor 20a has cantilever members having a transition coefficient $\sigma$, while the plurality of cantilever members 22 in sensor 20b are fabricated to have a transition coefficient of $\sigma$ + 1, and the plurality of cantilever members 22 in sensor 20c are fabricated to have a transition coefficient of $\sigma$ +2, etc. such that different sensors 20a, 20b, 20c respond to different stress-strain conditions.

Each of the plurality of cantilever members 22 may be fabricated of a shape memory and/or a superelastic material. Different electrical, thermal or mechanical properties may be imparted to the cantilever members 22 by altering the alloy ratios of the material. It is preferable to vacuum deposit both the tubular member 12, the sensors 20 and the cantilever members 22 to permit tight control over the material composition, electrical, mechanical and thermal properties of the material, as well as provide for tight control over the tissue and fluid contacting surfaces and the bulk material of the device. For example with nickel-titanium alloys, the titanium content of the target, in a nickel-titanium binary target, may be changed a known amount to precisely alter the transition temperature of a cantilever members.

Each of the plurality of cantilever members 22 may have binary functionality to provide a first "off" position indicative of an austenite phase of the cantilever members 22 and a second "on" position indicative of a martensite phase of the cantilever members 22. The first "off" position may be configured such that it is in a raised position which projects outwardly relative to the sensor 20 and/or the tubular member or in the lowered position that is substantially co-planar with the sensor 20 and/or the tubular member 12. Similarly, the second "on" position may be configured such that it is in a lowered position that is substantially coplanar with the sensor 20 and/or the tubular member 12 or the cantilever members 22 may be in the raised position or projecting outwardly relative to the sensor 20 and the tubular member 12, provided, however, that the first "on" position and the second "off" positions are different from one and other.

Alternatively rather than having merely binary functionality, each of the plurality of cantilever members 22 may have a response curve which is dependent upon the modulus of the material and the moment of inertia of each cantilever member. Each of the cantilever members 22 may be configured to have a variation in Z-axis thickness along an X-Y axis of the cantilever member 22. By configuring the cantilever members 22 with variable Z-axis thicknesses, different cantilever members 22 or different groupings of cantilever members will exhibit different stress-strain responses due to the different material modulus and different moment of inertia attendant to the altered geometry of the cantilever member 22. With this alternate construct of the cantilever members 22, for a given quantum of stress-strain applied to the cantilever members 22, the cantilever members 22 will deflect and shift a returned resonance frequency applied from an external energy source. The degree of deflection will then correlate to the stress and strain forces acting upon the cantilever members 22. It will be understood, of course, that this alternate construct of the cantilever members 22 still provides binary "on" and "off" functionality with the "on" and "off" positions merely being indicative of the outlying positions of the cantilever member 22.

It will be understood, therefore, that as the implanted pressure sensor encounters different stress and strain associated with, for example, changes in physiological blood pressure, fluid shear stress, endothelialization, arterioschlerotic plaque development, different sets of cantilever members will be exposed to their transition conditions and change from the "off" position to the "on" position. In order to detect which cantilever members are in the "on" position and, therefore, determine the stress-strain conditions, the pressure sensor may

be imaged radiographically, ultrasonically, magnetically or may be exposed to an external energy source which returns a signal representative of the number and position of the cantilever members that are in the "on" position. The returned signal may be generated by a passive transmitter embedded in solid state circuitry defined within the sensor 20, wherein the cantilever members 20 serve as electromechanical switches which alter a property of the solid state circuitry, for example, impedance or capacitance, and which then returns a detectable signal representative of the number and position of cantilever members 22 in the "on" position.

With both the temperature sensor and pressure sensor embodiments, the cantilever members 22 may also be insulated from either the implantable tubular member 12 or from the sensor region 20. Thermal or electrical insulators may be positioned intermediate the sensor region 20 and the implantable tubular member 12 to insulate the implantable tubular member 12 from heat or electrical transfer from the cantilever members 22 to the implantable tubular member 12.

***Vascular Imaging Sensor***

We turn now to Figures 5-7B, in which there is illustrated the inventive *in vivo* sensor device 30 in the form of an endoluminal stent adapted for non-invasive vascular modeling and imaging. The inventive *in vivo* sensor device 30 comprises a plurality of structural elements 32, 36 that serve to define walls of the sensor device 30. The particular geometry of the plurality of structural elements 32, 36 may be selected based upon the intended function of the sensor device 30, *e.g.*, a stent or stent-graft, and is not a significant factor in the present invention. It will be appreciated by those of ordinary skill in the art that alternative geometries of the structural elements 32, 36 other than those depicted in the Figures are contemplated by the present invention. The plurality of structural elements 32, 36 which define the sensor device 30 are fabricated of at least one of a shape memory materials, superelastic materials, plastically deformable materials and/or elastically deformable materials, such as stainless steel and/or nickel-titanium alloys, that permit the sensor device 30 to expand within an anatomical passageway, for example a blood vessel, at body temperature, *i.e.*, the martensite transition temperature (in the case of a shape memory material) is below, but in proximity to, body temperature. In order to provide sensor functionality and permit vascular imaging and modeling, the inventive sensor 30 further

comprises regions of the structural elements 32, 36 which have a second shape memory and/or superelastic material therewith (hereinafter the "second material"), which has, for example, a martensite transition temperature (or σ coefficient) which is higher than that of the base material for the structural elements 32, 36. Having a second material with either a higher transition temperature or a higher σ coefficient, allows for changing device 30 geometry or conformation upon application of internally or externally applied forces. For example, heat energy may be applied by either external microwave transmissions directed from outside the body to the device 30 or by a laser catheter that is used to apply laser energy to the sensor device 30. In either case, localized heating of the sensor device 30 to above the transition temperature of the second material causes the structural elements 32, 36 to undergo martensitic transformation with a concomitant change to the geometry and/or conformation of the sensor device 30. Upon martensitic transformation, at least some of the structural elements 32, 36 will change their positioning relative to the geometry of the sensor 30, as represented by arrows 38 in Figure 6, thereby changing the configuration of openings 37 between adjacent pairs of structural elements 32, 36. The sensor 30 in its changed geometry and/or conformation may then be imaged using conventional non-invasive imaging techniques to provide an image of the vascular profile.

After retrieving a diagnostic image of the vascular profile, it may be necessary to remodel either the geometry or conformation of the sensor device 30. For example, the device 30 may require elongation or diametric enlargement (as depicted in Figures 7A and 7B). In order to remodel the sensor device 30, a superelastic material may be included in some of the structural elements 32, 36 which is responsive to externally applied forces, *e.g.*, ultrasound, irradiation, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays and gamma irradiation, which will alter the stress-strain applied to the sensor device 30, causing a martensitic transformation in those portions of the structural elements 32, 36 and a concomitant change in the conformation of device 30.

Additionally, because thermal changes in the sensor device 30 may be induced by externally applied force, it is possible to both thermally heat, and thermally cool the sensor device 30. *Ex vivo* cooling may be accomplished by dampening the molecular vibrations induced by an external energy source, such as by shifting the frequency of the excitatory signal by 180 degrees. By dampening the molecular vibrations, a cooling effect may be

generated in the sensor device 30 in order to induce localized cooling in the region of the sensor device 30.

***Endoluminal Sensor***

Also with reference to Figures 4-7B there is illustrated a sensor device 30 which comprises a generally tubular member having a plurality of wall elements 32, 36 that define walls of the sensor device 30. The plurality of wall elements are preferably fabricated of shape memory or superelastic materials such that the endoluminal sensor device 30 effectively has at least two martensite transition points. Conventional shape memory and superelastic materials have a single martensite transition point. However, by fabricating all of the wall elements 32, 36 of laminates of shape memory or superelastic materials such that one ply has a martensite transition point of $T_1$ and a second ply has a martensite transition point of $T_2$ wherein $T_2 > T_1$, the first ply will cause the sensor device 30 to transition at $T_1$ which corresponds to the condition for normal *in vivo* physiological conditions, while the an additional quantum of energy, such as externally applied microwave, ultrasound, RF energy or internally applied energy, such as laser irradiation or direct thermal contact, will induce the condition suitable for transition at $T_2$ and the device will undergo a second shape transition. Alternatively, portions of the wall elements 32, 36 may be fabricated of a first material having a transition point $T_1$, while other portions of the wall elements 32, 36, which are preferably non-structural for the sensor device 30 under the $T_1$ conditions, but are structural for the sensor device 30 under $T_2$ conditions, are fabricated of a second material having a transition point $T_2$. Thus, those wall elements 32, 36 fabricate of the $T_1$ material will cause the sensor device 30 to transition into an initial endoluminal shape or geometry under the conditions appropriate to achieve transition point $T_1$, while those wall elements 32, 36 fabricated of the $T_2$ material will not transition until the appropriate conditions for transition point $T_2$ are applied to the sensor device 30.

***Endothelialization BioSensor***

Turning now to Figures 8-10 there is illustrated a biosensor 40 for sensing endothelialization events at the tissue-contacting surface of the sensor device. Like the inventive *in vivo* sensor devices described above, the inventive biosensor 40 consists

generally of an implantable substrate carrier 42 having tissue contacting surfaces 42, 46 thereupon. For purposes of illustration only, biosensor 40 is depicted with the implantable substrate carrier 42 being of a generally tubular configuration, such as for example, as stent. A plurality of binding regions 50 are defined on either of the tissue contacting surfaces 42, 46. The binding regions 50 are similar to the sensor regions of the above-described embodiments, except the binding regions 50 comprise regions of the implantable substrate carrier 42 which have biochemical markers, such as antibodies or ligands, bound thereto which are specific for endothelial and/or smooth muscle cell surface proteins or precursors of endothelial cell and smooth muscle cell proliferation, such as vascular endothelial growth factor or other growth factors. The material of the implantable substrate carrier 42 is preferably fabricated of a shape memory or superelastic material, which, upon binding of biological material to the biochemical markers in the binding regions 50, undergoes phase transformation due either the binding to the biochemical markers alone or in combination with an applied energy to the bound complex. The phase transformation of the material of the implantable substrate carrier 42 will cause a frequency shift in a returned signal from the applied energy source and will be indicative of the bound state of the binding domains 50.

With particular reference to co-pending, commonly assigned U.S. Patent Application Serial No. 60/064,916, filed November 7, 1997 which was published as PCT International Application WO9923977A1 entitled *Intravascular Stent And Method For Manufacturing An Intravascular Stent*, both of which are hereby incorporated by reference, the binding regions 50 may also form putative microgrooves 50 which are regions of the implantable substrate carrier 42 having patterned weakened atomic bonds in the crystalline structure of the substrate carrier 42 material. Upon binding of an endothelial cell, smooth muscle cell or a precursor thereof to the binding domain, the material of the substrate carrier 42 may either directly undergo or be induced by an external energy source to undergo a phase transformation which will cause the weakened atomic lattice of the crystalline structure of the substrate carrier 42 material to fracture and open a plurality of microgrooves 52 contiguous with the at the binding regions 50. The microgrooves 52 may be propagated by the additional binding of biological material to the markers at the binding regions 50. In this manner, there are self-propagating microgrooves which facilitate endothelialization of the implanted substrate carrier.

Although the present invention has been described in connection with the preferred form of practicing it, those of ordinary skill in the art will understand that many

modifications can be made thereto within the scope of the claims that follow. Accordingly, it is not intended that the scope of the invention in any way be limited by the above description, but instead be determined entirely by reference to the claims that follow.

**WHAT IS CLAIMED IS:**

1. An implantable medical device, comprising:

   a. an implantable substrate carrier; and

   b. a sensor member fabricated of at least one of a shape memory or a superelastic material coupled to the implantable substrate carrier.

2. The implantable medical device according to Claim 1, wherein the implantable substrate carrier is fabricated of a biocompatible material selected from the group of stainless steel, tantalum, gold, platinum, titanium, nickel, vanadium metal alloys thereof, nickel-titanium, elgiloy and combinations thereof.

3. The implantable medical device according to Claim 1, wherein the implantable substrate carrier consists essentially of a metal alloy.

4. The implantable medical device according to Claim 1, wherein the implantable substrate carrier consists essentially of a nickel-titanium alloy.

5. The implantable medical device according to Claim 2, wherein the sensor member consists essentially of a metal alloy.

6. The implantable medical device according to Claim 4, wherein the sensor member consists essentially of a nickel-titanium alloy.

7. The implantable medical device according to Claim 1, wherein the sensor member further comprises a plurality of cantilever members.

8. The implantable medical device according to Claim 7, wherein the plurality of cantilever members are fabricated of at least one of a shape memory material, a superelastic material, an elastically deformable material or a plastically deformable material.

9. The implantable medical device according to Claim 8, wherein the plurality of cantilever members have binary functionality having a first "off" position and a second "on" position.

10. The implantable medical device according to Claim 7, wherein the plurality of cantilever members are configured to have electromechanical response curves which shift upon a quantum of applied energy thereto.

11. The implantable medical device according to Claim 1, wherein the sensor member further comprises structural elements of the substrate carrier that are capable of altering a conformation of the implantable substrate carrier upon martensitic transformation of the at least one of a shape memory or a superelastic material.

12. An implantable medical device comprising and endoluminal prosthesis having at least one of a plurality of sensor regions integrally defined on at least one of a luminal or abluminal surface of the endoluminal prosthesis.

13. The implantable medical device according to Claim 12, wherein the endoluminal prosthesis is selected from the group consisting of stents, stent-grafts, grafts, valves, filters and occluders.

14. The implantable medical device according to Claim 12, wherein the endoluminal prosthesis and the at least one of a plurality of sensor regions further comprise a metal alloy selected from the group consisting of shape memory metal alloys, superelastic metal alloys, elastically deformable metals or plastically deformable metals.

15. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises of a nickel-titanium alloy.

16. The implantable medical device according to Claim 14, wherein the at least one of a plurality of sensor regions further comprises a nickel-titanium alloy.

17. The implantable medical device according to Claim 14, wherein the at least one of a plurality of sensor regions further have a transition point different than a transition point of the endoluminal prosthesis.

18. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises a plurality of wall elements, each of the plurality of wall elements further comprised of at least one shape memory or superelastic material, at least some of the plurality of wall elements being comprised of a first shape memory or superelastic material having a first transition point $T_1$ and at least some of the plurality of wall elements being comprised of a second shape memory or superelastic material having a second transition point $T_2$, wherein $T_2$ is greater than $T_1$.

19. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises a plurality of wall elements; each of the wall elements being comprised of a laminate of at least two shape memory or superelastic materials, a first shape memory or superelastic material having a first transition point $T_1$ and a second shape memory or superelastic material having a second transition point $T_2$, wherein $T_2$ is greater than $T_1$.

20. An implantable medical device comprising a substrate element fabricated of at least one of a shape memory and superelastic material, at least one transition point of the substrate element being capable of being induced by at least one of an endogenous energy stimulus selected from the group consisting of fluid pressure, fluid shear forces, body temperature, cellular binding and molecular binding, and exogenous energy stimulus selected from the group consisting of temperature, pressure, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays, beta and gamma irradiation.

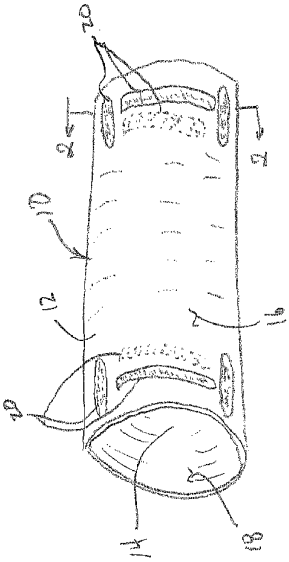


FIG. 1

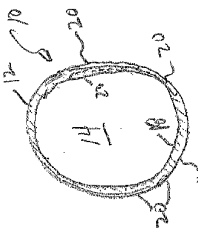


FIG 2

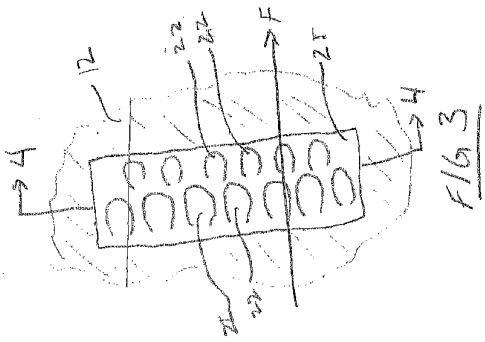


FIG 3

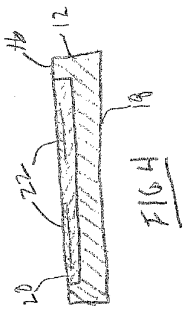


FIG 4

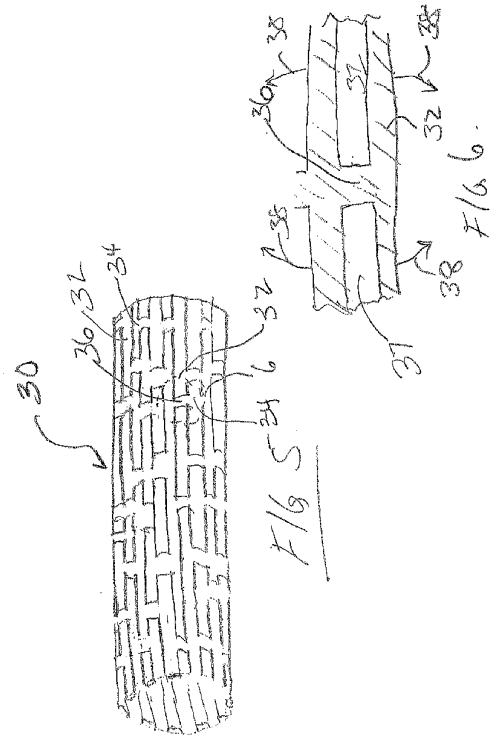



FIG 5

FIG 6

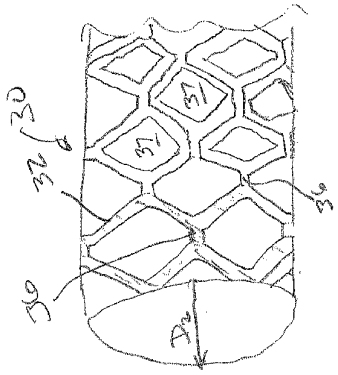



FIG 7B

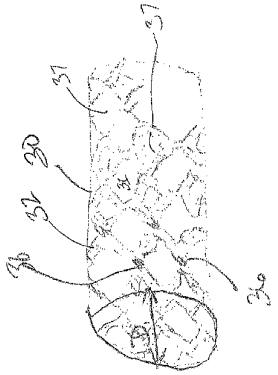



FIG 7A

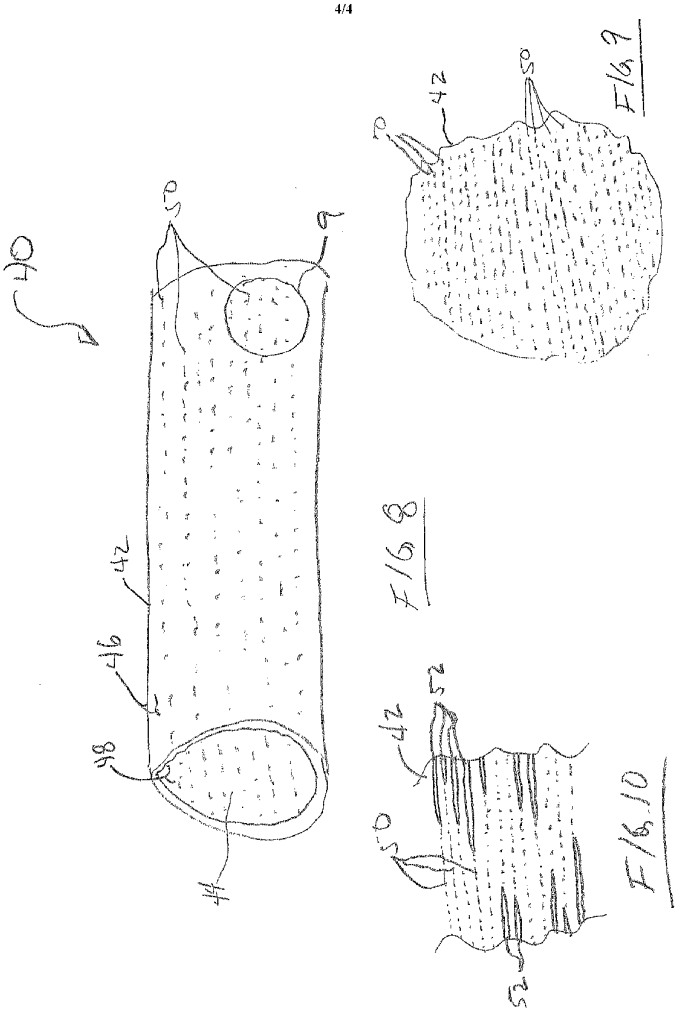



FIG 8

FIG 9

FIG 10

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(71) Applicant *(for all designated States except US)*: **ADVANCED BIO PROSTHETIC SURFACES, LTD.** [US/US]; 4778 Research Drive, San Antonio, TX 78240 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAILEY, Steven, R.** [US/US]; 3 Village Knoll, San Antonio, TX 78232 (US). **BOYLE, Christopher, T.** [US/US]; 7667 Callaghan, #604, San Antonio, TX 78229 (US). **MARTON, Denes** [US/US]; 11015 Whisper Hollow, San Antonio, TX 78230 (US). **BANAS, Christopher, E.** [US/US]; 102 Rock Squirrel, San Antonio, TX 78231 (US).

(74) Agent: **ROSENBAUM, David, G.**; Rosenbaum & Associates, P.C., Suite #3600, 875 North Michigan Avenue, Chicago, IL 60611 (US).

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(54) Title: IN VIVO SENSOR AND METHOD OF MAKING SAME

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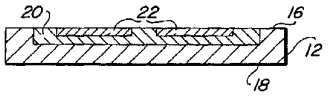


(57) Abstract: Implantable *in vivo* sensors used to monitor physical, chemical or electrical parameters within a body. The *in vivo* sensors are integral with an implantable medical device and are responsive to externally or internally applied energy. Upon application of energy, the sensors undergo a phase change in at least part of the material of the device which is then detected external to the body by conventional techniques such as radiography, ultrasound imaging, magnetic resonance imaging, radio frequency imaging or the like. The *in vivo* sensors of the present invention may be employed to provide volumetric measurements, flow rate measurements, pressure measurements, electrical measurements, biochemical measurements, temperature, measurements, or measure the degree and type of deposits within the lumen of an endoluminal implant, such as a stent or other type of endoluminal conduit. The *in vivo* sensors may also be used therapeutically to modulate mechanical and/or physical properties of the endoluminal implant in response to the sensed or monitored parameter.

# *IN VIVO* SENSOR AND METHOD OF MAKING SAME

## Background of the Invention

The present invention relates generally to the field of implantable medical devices, and more particularly pertains to sensors that may be implanted into a body to elicit at least one of a mechanical, chemical or electrical response to an *in vivo* physiological condition or state with the body. The present invention provides a vacuum deposited film which may be either a monolithic monolayer of material or a multilayered film having at least portions of the film capable of sensing at least one of changes in temperature, pressure, or the presence or absence of chemical or biochemical species in the body by mechanical, electrical, chemical, electrochemical or electromechanical means.

Specifically, the present invention relates to the manufacture and use of implantable sensors to monitor physical, chemical or electrical parameters of a fluid flow through a body passageway. For example, the sensors of the present invention may be employed to provide volumetric measurements, flow rate measurements, pressure measurements, electrical measurements, biochemical measurements, temperature, measurements, or measure the degree and type of deposits within the lumen of an endoluminal implant, such as a stent or other type of endoluminal conduit. The present invention also provides a means to modulate mechanical and/or physical properties of the endoluminal implant in response to the sensed or monitored parameter. For example, where the monitored blood flow volume through an endoluminal device is determined to be below physiological norms and/or the blood pressure is determined to be above physiological norms, the stent may be actuated to increase its diameter, such as by superelastic properties of the stent materials.

Post-implantation evaluation of the patency of an endoluminal device presently requires clinical examination by angiography or ultrasound. The results of these tests provide a qualitative evaluation of device patency. It is, therefore, desirable to provide a means for quantitatively measuring the post-implantation patency of an endoluminal device on either a periodic or continuous basis. Quantitative *in vivo* measurements of volumetric flow rate, flow velocity, biochemical constitution, fluid pressure or similar physical or biochemical property of the body fluid through an endoluminal device would provide more accurate diagnostic information to the medical practitioner.

As used herein, the term "endoluminal device" is intended to include stents, grafts and stent-grafts which are implanted within an anatomical passageway or are implanted with a body to create a non-anatomical passageway between anatomically separated regions within the body. Endoluminal devices in accordance with the present invention may include endovascular devices, prostatic devices, urethral devices, cervical devices, esophageal devices, intestinal devices, biliary devices, intra-cardiac devices, valves, hepatic devices, renal devices or devices with similar application within the body.

The term "sensor," as used in this application, is intended to include, without limitation, biosensors, chemical sensors, electrical sensors and mechanical sensors. While the term "biosensor" has been used to variously describe a number of different devices which are used to monitor living systems or incorporating biological elements, the International Union for Pure and Applied Chemistry (IUPAC) has recommended that the term "biosensor" be used to describe "a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" 1992, 64, 148 IUPAC Compendium of Chemical Terminology 2nd Edition (1997). The term "chemical sensor" is defined by the IUPAC as a device that transforms chemical information, ranging from concentration of a specific sample component to total composition analysis, into an analytically useful signal. Conventional biosensors are a type of chemical sensor that consists of three basic elements: a receptor (biocomponent), transducer (physical component) and a separator (membrane or coating of some type). The receptor of a chemical sensor usually consists of a doped metal oxide or organic polymer capable of specifically interacting with the analyte or interacting to a greater or lesser extent when compared to other receptors. In the case of a biosensor the receptor or biocomponent converts the biochemical process or binding event into a measurable component. Biocomponents include biological species such as: enzymes, antigens, antibodies, receptors, tissues, whole cells, cell organelles, bacteria and nucleic acids. The transducer or physical component converts the component into a measurable signal, usually an electrical or optical signal. Physical components include: electrochemical devices, optical devices, acoustical devices, and calorimetric devices as examples. The interface or membrane separates the transducer from the chemical or biocomponent and links this component with the transducer. **They are *in intimate contact***. The interface separator usually screens out unwanted materials, prevents fouling and protects the transducer. Types

of interfaces include: polymer membranes, electropolymerized coatings and self-assembling monomers.

Sensors should have high selectivity and sensitivity, have rapid recovery times with no hysteresis, long lifetimes if not single use, low drift, automated calibration, self-diagnostic, low cost, no reagent additions required and no sample preparation. It is obvious that presently available chemical sensors and biosensors do not meet these criteria (World Biosensor Market, Frost and Sullivan, Report 5326-32, 1997). National Institute of Standards and Technology, *Nano-and MEMS Technologies for Chemical Biosensors*, (www.atp.nist.gov/atp/focus/98wp-nan.htm).

In the clinical diagnostic market, various sensor designs are known including electrochemical sensors (potentiometric ISEs; amperometric; conductometric; miniaturized ISEs; field effect transistors; interdigitated transistors); optical sensors using fiber-optic or surface plasmon resonance technologies; acoustic sensors such as piezo-crystal and surface acoustic wave sensors; and thermal sensors which employ thermistors. Thus, it is known to employ microfabrication techniques to make clinical sensors. Currently, the most commercially successful microfabricated sensor in the clinical diagnostic market is the MEDISENSE glucose meter that uses an electrochemical transduction of an enzymatic reaction. However, the need for *in vivo* sensing systems is well recognized. Work on *in vivo* sensing systems for both glucose and lactate has confirmed the effectiveness of phospholipid copolymers in improving hemocompatibility. Fisher, U., et al. *Biosen. Bioelectron.*, 10, xxiii (1995).

By their nature, implantable sensors must have some mechanism for communicating sensed information from the sensor to a reader, which may be human or machine, outside the body. Since it is impractical to implant a physical connection between the sensor and the external reader, alternative means for generating a readable signal external the body must be provided. Suitable means for generating a readable signal external the body include, without limitation, radiographically visible signals, magnetic flux signals, chemical signals, chemifluorescent signals, and/or electrical signals.

The pathogenesis of arteriosclerosis has not been positively identified. A number of risk factors, such as high cholesterol, hypertension, and diabetes are known to serve to turn on inflammatory mechanisms at the arterial wall and recruit white cells into the arterial wall to ultimately cause the formation and breakdown of plaque, which, in turn, lead to clinical

events. The process starts out with oxidation-sensitive nuclear regulatory mechanisms. Free radicals control the genes that cause the synthesis of proteins that are expressed in the endothelial cells and serve to attract white cells into the arterial wall.

Endothelialization of an implanted medical device has been the subject of considerable scientific study and literature. It is know known that various growth factors and cytokines are responsible for activating smooth muscle cell receptors and initiating smooth muscle cell proliferation. Endothelial cell growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) have been identified as significant for endothelial cell growth in vitro. While VEGF is specific for endothelial cells, FGFs also stimulate smooth muscle cell growth. Bauthers, C., Growth Factors as a Potential New Treatment for Ischemic Heart Disease, *Clin. Cardiol.* 20:II-52-II-57 (1997).

It has been recognized that there is a need for an *in vivo* sensor capable of sensing binding of endothelial cells or arterioschlerotic plaque, and providing an *ex vivo* detectable signal, without requiring external or internal power sources.

**Summary Of The Invention**

In accordance with the present invention there is provided an implantable *in vivo* sensor suitable for monitoring clinically significant physiological events. The present invention provides an integrated device which is implantable within an anatomical passageway, such as a blood vessel, in the esophageal or gastro-intestinal tract, bile duct, hepatic duct, within the renal system, such as within a ureter or urethra, vagina or cervix, vas deferens, bronchi or similar anatomical passageways; within an organ, or within an anatomical defect, such as a cardiac septal defect.

The inventive *in vivo* sensor consists generally of an implantable substrate carrier element and at least one of a plurality of sensor elements. The implantable substrate carrier element may consist of, for example, a stent, stent-graft, graft, valve, filter, occluder or other implantable medical device, which serves as a foundational element for the sensor elements. Under conditions where the implantable substrate carrier, itself, is configured to return a detectable signal, the implantable carrier element, itself, may constitute the sensor element. Where the implantable substrate carrier element and the sensor element are discrete, conjoined elements, they may be fabricated of like materials or of dissimilar materials, each having either similar or dissimilar thermal, mechanical, electrical and/or chemical properties.

Microfabrication techniques are preferably employed to create both the carrier element and the sensor element in such a manner that both the substrate carrier element and the sensor element have a defined geometry and conformation that is suitable for use as a thermal, electrical, mechanical or chemical sensor, for sensing, for example, fluid flow, fluid flow rate, or fluid pressure in the region of the sensor. The addition of chemical or biological compounds to inventive sensor permits the device to be used as either a chemical or a biosensor, respectively. Similarly, microelectronic circuits may be added to the inventive sensor, such as by fabricating integrated circuits into or onto the inventive sensor, to enable the sensor to detect electrochemical events occurring at the sensor, such as **arteriosclerotic** plaque being deposited onto the surface of the sensor, or to detect electrochemical changes in the anatomical environment into which the sensor is implanted.

Alternatively, the inventive implantable sensor element and the implantable substrate carrier element may be fabricated of wrought materials, such as stainless steely hypotubes, stainless steel wire, shape memory hypotubes and shape memory wires. The sensor element may be attached to the substrate carrier element, or component parts, such as cantilever members, of the sensor element may be attached to the sensor element by a variety of known means. For example, welding processes may be used, such as laser welding, plasma welding, resistance welding, or e-beam welding. Welding, however, is generally not an acceptable method for joining nickel-titanium alloys to other materials, *e.g.*, stainless steel, because brittle intermetallics may be formed in the weld zone. In order to obtain a weld that is free of oxides or nitrides, welding should be performed under stringent environmental conditions in a clean, inert atmosphere or in vacuum in order to minimize reactivity of the titanium. In some cases, welded nickel-titanium parts may require heat-treating after welding to stress relieve the weld zone. The heat-affected zone will generally not exhibit superelastic properties. Soldering may be employed to join shape memory or superelastic alloys, such as nitinol, to stainless steel and other materials. However, a proper flux must be selected which inhibits the formation of surface oxides during the soldering process. Ultrasonic soldering has also been used to try to keep the surface free of oxides during soldering. Various epoxies and other adhesives may be used to join shape memory alloys either to themselves or to other materials. The chosen adhesives must, of course, be compatible with both the manufacturing and *in vivo* biological environments of the device. Finally, the sensor element may be mechanically joined to the substrate carrier element, or component parts of the sensor

element maybe joined together by crimping, providing an interference fit or by creating interlocking geometries of the sensor element or its component parts.

In accordance with a particular embodiment of the present invention, an endoluminal implant is provided which is implantable within an anatomical or non-anatomical body passageway to determine a given condition of a fluid flow through the endoluminal implant within the body passage. The inventive endoluminal implant may include, for example, an endoluminal stent, stent graft, or graft that consists of a generally tubular shaped member having two diametric states. In order to facilitate transluminal catheter introduction, the inventive endoluminal device has a first diametric state in which the transverse cross-sectional area of the device is of sufficient size to permit percutaneous introduction and *in vivo* placement of the device using transluminal approaches. A second diametric state has a transverse cross-sectional area which is larger than the first diametric state and conforms to the diameter of the anatomical passageway into which the device is placed, or is of a desired diameter for non-anatomical passageways. The inventive endoluminal device may be fabricated as a balloon expandable device, a self-expanding device, a shape-memory device or a superelastic device. It will be understood by those of skill in the art that the term "balloon expandable" refers to a class of devices which rely upon application of an external pressure, such as that applied by a balloon catheter, to radially deform the device from its first diametric state to its second diametric state; that the term "self-expanding" refers to a class of devices which rely upon the inherent mechanical properties of the device material to expand the device from its first diametric state to its second diametric state; that the term "shape-memory" refers to a class of devices which are fabricated of materials which exhibit martensitic phase transformation at certain transition temperatures; and the term "superelastic" refers to a class of devices which are fabricated of materials which deform under given stress-strain conditions. The inventive endoluminal sensor may be fabricated of materials capable of undergoing elastic or plastic deformation, such as stainless steel, tantalum, titanium, gold, or other biocompatible metals. However, the present invention is preferably fabricated of a shape-memory and/or superelastic material, such as nickel-titanium alloys known as Nitinol, which are mechanically responsive to temperature changes and/or changes in applied stress or strain, respectively.

Generally, the inventive endoluminal sensor consists of a sensor which is integral with an implantable endoluminal device, such as stent, and which is configured to respond either mechanically, electronically, electromechanically, or chemically, to cause a

mechanical, electrical, electromechanical or chemical change at the sensor and/or the endoluminal device which is detectable *ex vivo* using non-invasive detection methodologies such as radiography, ultrasonography, magnetic resonance imaging, or radio frequency detection.

In accordance with one embodiment of the invention, the inventive sensor comprises at least one integral region of the implantable endoluminal device that is formed as a plurality of cantilever members fabricated of shape-memory materials having different transformation temperatures. The sensor may be positioned on either a fluid contacting or tissue-contacting surface of the implantable device, such as the luminal surface of a stent which contacts blood, or on the abluminal surface of a stent which contacts neointimal tissue of the blood vessel. Alternatively, the sensors may be positioned on both the fluid contacting and the tissue-contacting surface of the implantable device.

As used herein, the term "integral" is intended to include regions that are formed as a part of the bulk material of the endoluminal device and regions which are formed separately from the bulk material of the endoluminal device, but which are coupled thereto.

In accordance with another embodiment of the invention, the inventive sensor comprises at least one region of the implantable endoluminal device that is formed of a plurality of cantilever members having different mechanical properties, such as different modulus of elasticity, plasticity or stress-strain behaviors. In accordance with the best mode presently contemplated for the invention, the cantilever members are preferably fabricated of a superelastic material. As with the shape-memory cantilever members, the superelastic cantilever members may be positioned on either a fluid contacting or tissue contacting surface of the implantable device, such as the luminal surface of a stent which contacts blood, or on the abluminal surface of a stent which contacts neointimal tissue of the blood vessel. Alternatively, the sensors may be positioned on both the fluid contacting and the tissue-contacting surface of the implantable device. Unlike the shape-memory cantilever sensors, the superelastic cantilever sensors are responsive to changes in force, such as shear forces, applied to the sensors.

With both the shape-memory cantilever members sensor and the superelastic cantilever members sensor, each of the plurality of cantilever members have first and second positions that are indicative of either an off or on position, respectively. The first or "off" position of each cantilever members is coplanar or flush with the surface of the endoluminal

device into which the sensor is positioned. In the second or "on" position, each activated cantilever members projects outwardly from the surface of the endoluminal device into which the sensor is positioned. Because different cantilever members or groups of cantilever members are fabricated to have either different transition temperatures or different stress-strain properties, individual cantilever members or groups of cantilever members which are in the second or "on" position, are indicative of a given thermal or stress-strain condition existing within the body into which the endoluminal device is implanted.

In one particular form of the invention, the inventive endoluminal device comprises a temperature sensor having a plurality of cantilever members positioned on at least one of the proximal, distal or intermediate regions of the endoluminal device and positioned on at least one of the luminal or abluminal wall surfaces of the endoluminal device. To facilitate ease of detection, a plurality of groups of cantilever members are provided, each group is formed of a plurality of individual cantilever members, with each individual cantilever members in the group having identical transition temperatures. The plurality of groups of cantilever members are arrayed along the longitudinal axis of the endoluminal device in such a manner as to create a continuum of groups of cantilever members having different transition temperatures. Changes in temperature at the site of the endoluminal device are indicated by the position of the cantilever members or groups of cantilever members as determined by radiography, ultrasonography, magnetic resonance imaging or other means that provides a detectable image of the position of the cantilever members and groups of cantilever members.

In another particular form the invention, the sensor comprises a plurality of cantilever members positioned on at least one of the proximal, distal or intermediate regions of the endoluminal device and positioned on at least one of the luminal or abluminal wall surfaces of the endoluminal device. To facilitate ease of detection, a plurality of groups of cantilever members are provided, each group is formed of a plurality of individual cantilever members, with each individual cantilever members in the group having identical transition temperatures. The plurality of groups of cantilever members are arrayed along the longitudinal axis of the endoluminal device in such a manner as to create a continuum of groups of cantilever members having different stress-strain transition pressures. Changes in applied stress or strain, such as blood pressure or blood flow shear stress, at the site of the endoluminal device are indicated by the stress and strain acting on the cantilever members or groups of cantilever members which provides a corresponding frequency shift in energy

reflected, when compared to a baseline stress-strain for unloaded cantilever members. The position and frequency shift of the cantilever members may be determined by radiography, ultrasonography, magnetic resonance imaging or other means which provides a detectable image of the position of the individual cantilever members and groups of cantilever members or is capable of measuring frequency shifts due to differential stress-strain loading onto the cantilever members.

In yet another form of the invention, the inventive sensor is a biosensor that is microfabricated from a material capable of undergoing elastic, plastic, shape-memory or superelastic deformation, and has a plurality of cantilever members formed therein, as described above. Each of the plurality of cantilever members has at least one binding domain selective for at least one indicator of endothelialization selected from the group of endothelial cell surface proteins, antigens, antibodies, cytokines, growth factors, co-factors, or other biological or biochemical marker of endothelial cells or endothelial cell precursors. Binding of the at least one indicator to at least one of the plurality of cantilever members causes a change in strain applied to the cantilever members, thereby causing the relevant cantilever members or groups of cantilever members to undergo superelastic transformation from the first or "off" position to the second or "on" position. As with the above-described embodiments of the invention, the position of the sensor cantilever members in the second or "on" position relative to the endoluminal device is then detected and is indicative of the progress of endothelialization.

Similarly, the fact of or the progress of arterioschlerotic plaque formation may be sensed using a plurality of elastic or superelastic cantilever members. In accordance with a first embodiment, the plurality of superelastic cantilever members undergo martensitic transformation as a result of the strain applied to the cantilever members resulting from growth of arterioschlerotic plaque onto the cantilever members. In accordance with a second embodiment, the plurality of superelastic cantilever members has at least one binding domain selective for at least one indicator of arterioschlerotic plaque or its precursors. Binding of the arterioschlerotic plaque or precursors of arterioschlerotic plaque to the binding domain on the cantilever members, adds a quantum of strain to the cantilever members sufficient to cause the cantilever members to undergo superelastic transformation from the first or "off" position to the second or "on" position. As with the above-described embodiments of the invention, the position of the sensor cantilever members in the second or "on" position relative to the endoluminal device is then detected and is indicative of the progress of arteriosclerosis.

Yet another form of the invention entails an implant fabricated of a superelastic material that has a variable diametric geometry responsive to changes in pressure applied to the implant. This form of the invention is preferably employed as a smooth muscle prosthesis, for example, as a vascular prosthesis, and is responsive to blood pressure changes in a manner similar to those changes native to blood vessels, *i.e.*, contracting upon sensing lowered blood pressures and expanding upon sensing higher blood pressures, in order to maintain physiologically normal blood pressure. In this embodiment of the invention, a tubular implant is fabricated, in whole or in part, of a superelastic material and has diametrically adjustable regions that undergo superelastic transformation to increase or decrease the diameter of the implant upon sensing given physiological pressures within the implant.

Finally, another form of the invention consists of an endoluminal implant similar to that described in co-pending, commonly assigned U.S. Patent Application Serial No. 60/064,916, filed November 7, 1997 which was published as PCT International Application WO9923977A1 entitled *Intravascular Stent And Method For Manufacturing An Intravascular Stent*, both of which are hereby incorporated by reference. In those applications there is described an endoluminal implant having a plurality of microgrooves on the luminal and/or abluminal surfaces thereof which facilitate improved endothelialization over a non-grooved endoluminal implant. In accordance with the present invention there is provided an endoluminal implant having a plurality of putative microgrooves comprising sections of weakened bulk material of the endoluminal implant. The endoluminal implant is preferably fabricated of a superelastic bulk material and weakened regions in the bulk material are formed using standard microlithographic techniques to form the putative microgrooves. A plurality of binding domains are created along the fluid flow surface of the endoluminal implant and at proximal (relative to the blood flow) regions of the putative microgrooves that preferentially bind to endothelial cell surface proteins. Binding of the endothelial cell surface proteins to the binding domains causes a shift in the applied strain to the superelastic bulk material, which causes the superelastic bulk material to deform in the region of the applied strain, thereby breaking the interatomic bonds in the weakened regions of the putative microgrooves and causing formation of a portion of a microgroove. Propagation of the endothelial cell proliferation along the surface of the superelastic bulk material causes, in turn, a propagation of strain along the superelastic bulk material that causes the formation of the microgrooves in the superelastic bulk material.

These and other objects, features and advantages of the present invention will become more apparent to those of ordinary skill in the art from the following more detailed description of the preferred embodiments of the present invention taken with reference to the accompanying figures.

**Brief Description of the Figures**

Figure 1 is a perspective view of an endoluminal implant in accordance with the present invention.

Figure 2 is a cross-sectional view taken along line 2-2 of Figure 1.

Figure 3 is a fragmentary plan view of a first embodiment of the present invention illustrating an integral sensor formed of a plurality of cantilever members.

Figure 4 is a cross-sectional view taken along line 4-4 of Figure 3.

Figure 5 is a perspective view of an endoluminal implant in accordance with a second embodiment of the present invention.

Figure 6 is a fragmentary plan view of a diametrically adjustable region of the second embodiment of the present invention.

Figure 7A is a perspective view of the second embodiment of the inventive endoluminal implant of the present invention in its diametrically reduced state.

Figure 7B is a perspective view of the second embodiment of the inventive endoluminal implant of the present invention in its diametrically expanded state.

Figure 8 is a perspective view of a third embodiment of the inventive endoluminal implant of the present invention depicting weakened regions in the bulk material in phantom.

Figure 9 is a fragmentary enlarged plan view of circled region 9 in Figure 8.

Figure 10 is a fragmentary plan view illustrating propagation of a microgroove upon binding of an endothelial cell to a binding domain at the weakened region in the bulk material of the third embodiment of the present invention.

**Detailed Description of the Preferred Embodiments**

To simplify description of the present invention, most of the preferred embodiments will be described with reference to an endoluminal stent, except where otherwise stated. However, those of ordinary skill in the art will understand that each embodiment has application to a variety of implantable devices including, without limitation, stents, grafts, stent-grafts, valves, shunts or patches.

The particular means for detecting a change in the inventive sensor and/or the particular means for activating a change in the inventive sensor is generally not considered part of the present invention. For example, it is known that ultrasound energy may be employed to generate both one-way and two-way shape memory effects in nickel-titanium alloys. **V.V. Klubovich, V.V. Rubanick, V.G. Dorodeiko, V.A. Likhachov, and V.V. Rubanick Jr.** (Institute of Tech. Acoustics, 13 Ludnikova, 210026 Vitebsk, Belarus,) *Generation of Shape Memory Effect in Ti-Ni Alloy by means for Ultrasound,* Abstract 1.P12, SMST-97 conference found at URL http://www.fwsystems.com/professional/smstabs.html. Using ultrasound energy to non-invasively induce stent heating has also been confirmed by B. Lal, et al. in their abstract entitled *Non-Invasive Ultrasound Induced Heating of Stents: Importance of Stent Composition,* which may be found at URL http://www.hotplaque.com/frames/abstracts/rabs6.htm and URL http://ex2.excerptamedica.com/00acc/abstracts/abs1065-117.html. Lal, et al. hypothesized that gentle heating can be accomplished using ultrasound (US) and a constant temperature can be maintained using pulsed US. The heating rate of an object under the same US power and frequency is determined primarily by its absorption and reflection rates. To test their hypothesis, they used a phantom of 5.08 cm thick layer of pork muscle, in which various annular stent shape materials were placed. To monitor the heating multiple hypodermic thermocouples were used. The heating was induced using FDA-approved levels of therapeutic ultrasound (intensity 0.5-2.5 W/cm$^2$, frequency 1-3 MHz) in both pulse and continuous modes. It was found that nylon, and some types of PVC, exhibit temperature increases that are larger (2-35° C) and faster (1.5-15 times) than the surrounding tissue, while Lexan, PTFE, Latex, Teflon, Ceramic and Delrina do not display selective heating. A modest heating effect (2° C increase in 15 minutes) was also found in a metal stent. Lal, et al. concluded that ultrasound heating of tissue adjacent to a prosthesis depends on stent composition, induction of thermal apoptosis by ultrasound may prove to be effective in

limiting restenosis in polymeric stents and grafts. Issues that need to be addressed include the optimal biocompatible material and design of stents and the *in vivo* effects of phased-array US on the stented artery and its surrounding tissues. Lal, et al. believed that by using fast-heating, non-toxic materials, ultrasound-heated stents could be devised.

Similarly, microwave radiation may be used to generate shape memory effects in shape memory alloys. It is known, for example, that microwave radiation may be used for stent diathermy in stainless steel stents. S. Naguib, *et al.* in *Stent diathermy using focused ultrasound & microwave* found at URL http://www.hotplaque.com/frames/abstracts/rabs3.htm sought to use ultrasound and microwave energy to non-invasively heat the stent and its surrounding plaque. Using Palmaz-Schatz stents as well as several stent-shape biopolymer materials embedded inside the phantom, Naguib, *et al.* continuously mapped rise in temperatures in the system upon ultrasound and microwave irradiations in separate settings. Temperature monitoring was done using a 12-channel ultra-thermometer (0.01°C) with thermocouples (ultrasound) and fiber optic sensors (microwave). Therapeutic ultrasound at the frequency of 1-3 MHZ and intensity of 0.5-2.5W/CM2 was used. Microwave radiofrequency was delivered by an antenna using a frequency of 2.45 GHZ and a power of 5.37 & 10.22 watts. In their ultrasound experiment Naguib, *et al.* found that the temperature of outer surface of stent and its surrounding tissue increased significantly higher than other sites. The rise in temperature varies by the type of biopolymer where silicon stent heated faster and more than polyurethane and polytetrafluoroethylene. Similar results were observed in the microwave experiments. Infrared thermography was used to measure the increased temperatures during delivery of both ultrasound and microwave radiation.

It is recognized, however, that externally applied forces, such as RF, microwave, ultrasound, etc. exist in the ambient environment. It is, therefore, undesirable to fabricate sensor device which will undergo a shape memory change upon encountering an ambient externally applied force. For example, it would be undesirable for a patient with an implanted sensor device responsive to microwave irradiation to have the implanted sensor device undergo a shape memory transition when the patient is warming food in a kitchen microwave appliance.

Because the microfabrication methods of the present invention allow for stringent control over the material composition of the implantable sensor device, the material

composition may be made responsive to a particular frequency range that is outside the frequency range of the same type of energy signals existing in the ambient environment of the patient. Thus, both the device activation energy type and frequency and the detection energy type and frequency must fall outside that encountered in the ambient environment.

It is well known that metal stents are radioopaque and are detectable under radiographic imaging, such as fluoroscopy. Detection of the inventive sensor device may be accomplished by radiographic imaging, ultrasound imaging (either using frequencies which also generate a shape memory effect or not), magnetic resonance imaging, RF imaging or similar methods. The use of magnetic resonance imaging to image nitinol stents is known in the art. See, *e.g.*, Rahdert, D, Hakim, B., *Magnetic Resonance compatibility of Ni-Ti Stents,* Abstract 8.P1, SMST-97 conference (International Organization on Shape Memory and Superelastic Technologies) found at URL http://www.fwsystems.com/professional/smstabs.html, in which they describe they studied the compatibility of Ni-Ti coronary stents using magnetic imaging to assess a) ferromagnetic forces; and b) artifacts. Two methods were used to measure force: horizontal sliding and pendulum deflection. Ferromagnetic forces were found to be less than 10% of stent weight. Artifacts were assessed to be small.

The use of particulate paramagnetic metal iron oxide as a contrast medium to image and model vascular profiles under magnetic resonance imaging (MRI) has been demonstrated by Mitra Rajabi, *et al.* at the University of Texas-Houston, Houston, Texas, United States and the University of Texas-Medical Branch at Galveston, Galveston, Texas, United States. In an abstract published for presentation at the ACC 2001, the American College of Cardiology Scientific Session scheduled for March 18-21, 2001, the abstract may be found at URL: http://www.hotplaque.com/ACC/ACC2001%20abstracts.htm#5), Rajabi, *et al.* describe a technique for imaging plaque inflammation. Super paramagnetic iron oxide (SPIO) particles are magnetic resonance (MR) imaging contrast media that have a central core of iron oxide generally coated by a polysaccharide layer. They shorten the relaxation time, predominantly the T2 relaxation time. Rajabi, *et al.* hypothesized that inflamed vulnerable arteriosclerotic plaques would preferentially take up these nano-particles by virtue of macrophage infiltration, leaking vasa vasorum and fissured thin caps. To test their hypothesis, they injected 1- 3 mmol Fe/kg super paramagnetic iron oxide to six Apo E deficient and two C57bl mice through the tail vein, after first obtaining baseline MR imaging. Post-contrast MR imaging were performed in day 5 with the same parameters (TR=2.5, TE=0.012, FOX=6

6, slice thickness=2.0mm, flip angle (orient)=trans, and matrices=256 x 256). The aorta at the level of kidney was selected for comparison of the baseline and post-contrast images. Rajabi, *et al.* found decreased signal intensity in SPIO injected Apo E deficient mice and no decrease in signal intensity in SPIO injected C57bl mice.

Thus, it is known in the art that thermal energy may be imparted to implanted medical devices fabricated of metal either by transcatheter approaches using direct application of heat, such as by a laser catheter, or may be induced by directing microwave or ultrasound energy toward the implanted device. Moreover, it is known implanted medical devices fabricated of shape memory alloys may be detected *in vivo* using radiography, ultrasonography, MRI, or RF imaging or combinations thereof.

In accordance with the present invention, any of the foregoing methods of applying energy to the inventive sensor device, either directly through transcatheter application or indirectly through inductive methods, as well as any of the foregoing methods for detecting the state of the inventive sensor device *in vivo* may be employed to effectuate change in the state of the implanted device. The energy stimulus may be an endogenous energy stimulus selected from the group consisting of fluid pressure, fluid shear forces, body temperature, cellular binding or molecular binding. Alternatively, the energy stimulus may be an exogenous energy stimulus such as externally applied temperature, pressure, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays, beta or gamma irradiation.

Turning now the accompanying Figures, and in particular Figures 1-4 there is illustrated first and second embodiments of implantable *in vivo* sensor in accordance with the present invention.

***Temperature Sensor***

The inventive *in vivo* temperature sensor 10 consists generally of an implantable tubular member 12 having a central lumen 14, an abluminal wall surface 16, a luminal wall surface 18 and at least one of a plurality of sensor regions 20 integral with at least one of the abluminal wall surface 16 and the luminal wall surface 18 of the implantable tubular member 12. The flow vector F of a fluid over the surface of the sensor region 20 is illustrated in Figure 3. Each of the at least one of a plurality of sensor regions further comprise a plurality of cantilever members 22 patterned in an array on the implantable tubular member 12. The

implantable tubular member 12, the sensor 20 and the plurality of cantilever members may be fabricated of like materials, such as shape memory materials, or may be fabricated of different materials, *e.g.*, the implantable tubular member 12 being fabricated of stainless steel and the sensor 20 and cantilever members 22 being fabricated of a shape memory material, such as nickel-titanium alloys. In accordance with the best mode contemplated for the present invention, the tubular member 12, the sensor 20 and the cantilever members will be fabricated of shape memory materials, such as nickel-titanium alloys. Where each of the plurality of cantilever members 22 are fabricated of a shape memory material, either individual cantilever members 22 or groups of cantilever members 22 within a single sensor 20 may be fabricated to have different martensite transition temperatures. Thus, for example, cantilever members 22a within sensor 20 may be fabricated to have a transition temperature of X degrees Centigrade, while cantilever members 22b are fabricated to have a transition temperature of X + 1 degrees Centigrade, cantilever members 22c are fabricated to have a transition temperature of X +2 degrees Centigrade, etc. Alternatively all of the cantilever members 22 in a sensor 20 may have the same transition temperature, and a plurality of sensors 20 are provided such that sensor 20a has cantilever members having a transition temperature of X degrees Centigrade, while the plurality of cantilever members 22 in sensor 20b are fabricated to have a transition temperature of X + 1 degrees Centigrade, and the plurality of cantilever members 22 in sensor 20c are fabricated to have a transition temperature of X +2 degrees Centigrade, etc.

Each of the plurality of cantilever members 22 may be fabricated of a material capable of undergoing elastic, plastic, shape memory and/or a superelastic deformation. Materials such as stainless steel, titanium, nickel, tantalum, gold, vanadium, nickel-titanium, or alloys thereof may be employed to fabricate the plurality of cantilever members. Different electrical, thermal or mechanical properties may be imparted to the cantilever members 22 by altering the alloy ratios of the material. It is preferable to vacuum deposit both the tubular member 12, the sensors 20 and the cantilever members 22 to permit tight control over the material composition, electrical, mechanical and thermal properties of the material, as well as provide for tight control over the tissue and fluid contacting surfaces and the bulk material of the device. For example with nickel-titanium alloys, the titanium content of the target, in a nickel-titanium binary target, may be changed a known amount to precisely alter the transition temperature of a cantilever members.

Each of the plurality of cantilever members 22 preferably have binary functionality to provide a first "off" position indicative of an austenite phase of the cantilever members 22 and a second "on" position indicative of a martensite phase of the cantilever members 22. The first "off" position may be configured such that it is in a raised position which projects outwardly relative to the sensor 20 and/or the tubular member or in the lowered position that is substantially co-planar with the sensor 20 and/or the tubular member 12. Similarly, the second "on" position may be configured such that it is in a lowered position that is substantially coplanar with the sensor 20 and/or the tubular member 12 or the cantilever members 22 may be in the raised position or projecting outwardly relative to the sensor 20 and the tubular member 12, provided, however, that the first "on" position and the second "off" positions are different from one and other.

It will be understood, therefore, that as the implanted temperature sensor encounters different *in vivo* temperatures, different sets of cantilever members will be exposed to their transition temperature and change from the "off" position to the "on" position. In order to detect which cantilever members are in the "on" position and, therefore, determine the *in vivo* thermal conditions, the temperature sensor may be imaged radiographically, ultrasonically, magnetically or may be exposed to an external energy source which returns a signal representative of the number and position of the cantilever members that are in the "on" position. The returned signal may be generated by a passive transmitter embedded in solid state circuitry defined within the sensor 20, wherein the cantilever members 20 serve as electromechanical switches which alter a property of the solid state circuitry, for example, impedance or capacitance, and which then returns a detectable signal representative of the number and position of cantilever members 22 in the "on" position.

***Pressure Sensor***

Because it is structurally virtually identical to the temperature sensor 10, described above, the inventive *in vivo* pressure sensor will also be described with reference to Figures 1-4 and use identical reference numerals to describe the elements thereof. The inventive *in vivo* pressure sensor 10 consists generally of an implantable tubular member 12 having a central lumen 14, an abluminal wall surface 16, a luminal wall surface 18 and at least one of a plurality of sensor regions 20 integral with at least one of the abluminal wall surface 16 and the luminal wall surface 18 of the implantable tubular member 12. Each of the at least one of

a plurality of sensor regions further comprise a plurality of cantilever members 22 patterned in an array on the implantable tubular member 12. The implantable tubular member 12, the sensor 20 and the plurality of cantilever members may be fabricated of like materials, such as superelastic materials, or may be fabricated of different materials, *e.g.*, the implantable tubular member 12 being fabricated of stainless steel and the sensor 20 and cantilever members 22 being fabricated of a superelastic material, such as nickel-titanium alloys. In accordance with the best mode contemplated for the present invention, the tubular member 12, the sensor 20 and the cantilever members will be fabricated of superelastic materials, such as nickel-titanium alloys. Where each of the plurality of cantilever members 22 are fabricated of a superelastic material, either individual cantilever members 22 or groups of cantilever members 22 within a single sensor 20 may be fabricated to have different martensite transition temperatures. Thus, for example, cantilever members 22a within sensor 20 may be fabricated to have a martensitic stress/strain transition coefficient $\sigma$, while cantilever members 22b are fabricated to have a transition coefficient $\sigma$ +1, cantilever members 22c are fabricated to have a transition coefficient of $\sigma$ +2, etc. such that different cantilever members 22 or groups of cantilever members 22 change their position based upon a given quantum of stress or strain applied to the cantilever members 22 *in vivo*. Alternatively all of the cantilever members 22 in a sensor 20 may have the same transition temperature, and a plurality of sensors 20 are provided such that sensor 20a has cantilever members having a transition coefficient $\sigma$, while the plurality of cantilever members 22 in sensor 20b are fabricated to have a transition coefficient of $\sigma$ + 1, and the plurality of cantilever members 22 in sensor 20c are fabricated to have a transition coefficient of $\sigma$ +2, etc. such that different sensors 20a, 20b, 20c respond to different stress-strain conditions.

Each of the plurality of cantilever members 22 may be fabricated of a shape memory and/or a superelastic material. Different electrical, thermal or mechanical properties may be imparted to the cantilever members 22 by altering the alloy ratios of the material. It is preferable to vacuum deposit both the tubular member 12, the sensors 20 and the cantilever members 22 to permit tight control over the material composition, electrical, mechanical and thermal properties of the material, as well as provide for tight control over the tissue and fluid contacting surfaces and the bulk material of the device. For example with nickel-titanium alloys, the titanium content of the target, in a nickel-titanium binary target, may be changed a known amount to precisely alter the transition temperature of a cantilever members.

Each of the plurality of cantilever members 22 may have binary functionality to provide a first "off" position indicative of an austenite phase of the cantilever members 22 and a second "on" position indicative of a martensite phase of the cantilever members 22. The first "off" position may be configured such that it is in a raised position which projects outwardly relative to the sensor 20 and/or the tubular member or in the lowered position that is substantially co-planar with the sensor 20 and/or the tubular member 12. Similarly, the second "on" position may be configured such that it is in a lowered position that is substantially coplanar with the sensor 20 and/or the tubular member 12 or the cantilever members 22 may be in the raised position or projecting outwardly relative to the sensor 20 and the tubular member 12, provided, however, that the first "on" position and the second "off" positions are different from one and other.

Alternatively rather than having merely binary functionality, each of the plurality of cantilever members 22 may have a response curve which is dependent upon the modulus of the material and the moment of inertia of each cantilever member. Each of the cantilever members 22 may be configured to have a variation in Z-axis thickness along an X-Y axis of the cantilever member 22. By configuring the cantilever members 22 with variable Z-axis thicknesses, different cantilever members 22 or different groupings of cantilever members will exhibit different stress-strain responses due to the different material modulus and different moment of inertia attendant to the altered geometry of the cantilever member 22. With this alternate construct of the cantilever members 22, for a given quantum of stress-strain applied to the cantilever members 22, the cantilever members 22 will deflect and shift a returned resonance frequency applied from an external energy source. The degree of deflection will then correlate to the stress and strain forces acting upon the cantilever members 22. It will be understood, of course, that this alternate construct of the cantilever members 22 still provides binary "on" and "off" functionality with the "on" and "off" positions merely being indicative of the outlying positions of the cantilever member 22.

It will be understood, therefore, that as the implanted pressure sensor encounters different stress and strain associated with, for example, changes in physiological blood pressure, fluid shear stress, endothelialization, arterioschlerotic plaque development, different sets of cantilever members will be exposed to their transition conditions and change from the "off" position to the "on" position. In order to detect which cantilever members are in the "on" position and, therefore, determine the stress-strain conditions, the pressure sensor may

be imaged radiographically, ultrasonically, magnetically or may be exposed to an external energy source which returns a signal representative of the number and position of the cantilever members that are in the "on" position. The returned signal may be generated by a passive transmitter embedded in solid state circuitry defined within the sensor 20, wherein the cantilever members 20 serve as electromechanical switches which alter a property of the solid state circuitry, for example, impedance or capacitance, and which then returns a detectable signal representative of the number and position of cantilever members 22 in the "on" position.

With both the temperature sensor and pressure sensor embodiments, the cantilever members 22 may also be insulated from either the implantable tubular member 12 or from the sensor region 20. Thermal or electrical insulators may be positioned intermediate the sensor region 20 and the implantable tubular member 12 to insulate the implantable tubular member 12 from heat or electrical transfer from the cantilever members 22 to the implantable tubular member 12.

***Vascular Imaging Sensor***

We turn now to Figures 5-7B, in which there is illustrated the inventive *in vivo* sensor device 30 in the form of an endoluminal stent adapted for non-invasive vascular modeling and imaging. The inventive *in vivo* sensor device 30 comprises a plurality of structural elements 32, 36 that serve to define walls of the sensor device 30. The particular geometry of the plurality of structural elements 32, 36 may be selected based upon the intended function of the sensor device 30, *e.g.*, a stent or stent-graft, and is not a significant factor in the present invention. It will be appreciated by those of ordinary skill in the art that alternative geometries of the structural elements 32, 36 other than those depicted in the Figures are contemplated by the present invention. The plurality of structural elements 32, 36 which define the sensor device 30 are fabricated of at least one of a shape memory materials, superelastic materials, plastically deformable materials and/or elastically deformable materials, such as stainless steel and/or nickel-titanium alloys, that permit the sensor device 30 to expand within an anatomical passageway, for example a blood vessel, at body temperature, *i.e.*, the martensite transition temperature (in the case of a shape memory material) is below, but in proximity to, body temperature. In order to provide sensor functionality and permit vascular imaging and modeling, the inventive sensor 30 further

comprises regions of the structural elements 32, 36 which have a second shape memory and/or superelastic material therewith (hereinafter the "second material"), which has, for example, a martensite transition temperature (or σ coefficient) which is higher than that of the base material for the structural elements 32, 36. Having a second material with either a higher transition temperature or a higher σ coefficient, allows for changing device 30 geometry or conformation upon application of internally or externally applied forces. For example, heat energy may be applied by either external microwave transmissions directed from outside the body to the device 30 or by a laser catheter that is used to apply laser energy to the sensor device 30. In either case, localized heating of the sensor device 30 to above the transition temperature of the second material causes the structural elements 32, 36 to undergo martensitic transformation with a concomitant change to the geometry and/or conformation of the sensor device 30. Upon martensitic transformation, at least some of the structural elements 32, 36 will change their positioning relative to the geometry of the sensor 30, as represented by arrows 38 in Figure 6, thereby changing the configuration of openings 37 between adjacent pairs of structural elements 32, 36. The sensor 30 in its changed geometry and/or conformation may then be imaged using conventional non-invasive imaging techniques to provide an image of the vascular profile.

After retrieving a diagnostic image of the vascular profile, it may be necessary to remodel either the geometry or conformation of the sensor device 30. For example, the device 30 may require elongation or diametric enlargement (as depicted in Figures 7A and 7B). In order to remodel the sensor device 30, a superelastic material may be included in some of the structural elements 32, 36 which is responsive to externally applied forces, *e.g.*, ultrasound, irradiation, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays and gamma irradiation, which will alter the stress-strain applied to the sensor device 30, causing a martensitic transformation in those portions of the structural elements 32, 36 and a concomitant change in the conformation of device 30.

Additionally, because thermal changes in the sensor device 30 may be induced by externally applied force, it is possible to both thermally heat, and thermally cool the sensor device 30. *Ex vivo* cooling may be accomplished by dampening the molecular vibrations induced by an external energy source, such as by shifting the frequency of the excitatory signal by 180 degrees. By dampening the molecular vibrations, a cooling effect may be

generated in the sensor device 30 in order to induce localized cooling in the region of the sensor device 30.

***Endoluminal Sensor***

Also with reference to Figures 4-7B there is illustrated a sensor device 30 which comprises a generally tubular member having a plurality of wall elements 32, 36 that define walls of the sensor device 30. The plurality of wall elements are preferably fabricated of shape memory or superelastic materials such that the endoluminal sensor device 30 effectively has at least two martensite transition points. Conventional shape memory and superelastic materials have a single martensite transition point. However, by fabricating all of the wall elements 32, 36 of laminates of shape memory or superelastic materials such that one ply has a martensite transition point of $T_1$ and a second ply has a martensite transition point of $T_2$ wherein $T_2 > T_1$, the first ply will cause the sensor device 30 to transition at $T_1$ which corresponds to the condition for normal *in vivo* physiological conditions, while the an additional quantum of energy, such as externally applied microwave, ultrasound, RF energy or internally applied energy, such as laser irradiation or direct thermal contact, will induce the condition suitable for transition at $T_2$ and the device will undergo a second shape transition. Alternatively, portions of the wall elements 32, 36 may be fabricated of a first material having a transition point $T_1$, while other portions of the wall elements 32, 36, which are preferably non-structural for the sensor device 30 under the $T_1$ conditions, but are structural for the sensor device 30 under $T_2$ conditions, are fabricated of a second material having a transition point $T_2$. Thus, those wall elements 32, 36 fabricate of the $T_1$ material will cause the sensor device 30 to transition into an initial endoluminal shape or geometry under the conditions appropriate to achieve transition point $T_1$, while those wall elements 32, 36 fabricated of the $T_2$ material will not transition until the appropriate conditions for transition point $T_2$ are applied to the sensor device 30.

***Endothelialization BioSensor***

Turning now to Figures 8-10 there is illustrated a biosensor 40 for sensing endothelialization events at the tissue-contacting surface of the sensor device. Like the inventive *in vivo* sensor devices described above, the inventive biosensor 40 consists

generally of an implantable substrate carrier 42 having tissue contacting surfaces 42, 46 thereupon. For purposes of illustration only, biosensor 40 is depicted with the implantable substrate carrier 42 being of a generally tubular configuration, such as for example, as stent. A plurality of binding regions 50 are defined on either of the tissue contacting surfaces 42, 46. The binding regions 50 are similar to the sensor regions of the above-described embodiments, except the binding regions 50 comprise regions of the implantable substrate carrier 42 which have biochemical markers, such as antibodies or ligands, bound thereto which are specific for endothelial and/or smooth muscle cell surface proteins or precursors of endothelial cell and smooth muscle cell proliferation, such as vascular endothelial growth factor or other growth factors. The material of the implantable substrate carrier 42 is preferably fabricated of a shape memory or superelastic material, which, upon binding of biological material to the biochemical markers in the binding regions 50, undergoes phase transformation due either the binding to the biochemical markers alone or in combination with an applied energy to the bound complex. The phase transformation of the material of the implantable substrate carrier 42 will cause a frequency shift in a returned signal from the applied energy source and will be indicative of the bound state of the binding domains 50.

With particular reference to co-pending, commonly assigned U.S. Patent Application Serial No. 60/064,916, filed November 7, 1997 which was published as PCT International Application WO9923977A1 entitled *Intravascular Stent And Method For Manufacturing An Intravascular Stent*, both of which are hereby incorporated by reference, the binding regions 50 may also form putative microgrooves 50 which are regions of the implantable substrate carrier 42 having patterned weakened atomic bonds in the crystalline structure of the substrate carrier 42 material. Upon binding of an endothelial cell, smooth muscle cell or a precursor thereof to the binding domain, the material of the substrate carrier 42 may either directly undergo or be induced by an external energy source to undergo a phase transformation which will cause the weakened atomic lattice of the crystalline structure of the substrate carrier 42 material to fracture and open a plurality of microgrooves 52 contiguous with the at the binding regions 50. The microgrooves 52 may be propagated by the additional binding of biological material to the markers at the binding regions 50. In this manner, there are self-propagating microgrooves which facilitate endothelialization of the implanted substrate carrier.

Although the present invention has been described in connection with the preferred form of practicing it, those of ordinary skill in the art will understand that many

modifications can be made thereto within the scope of the claims that follow. Accordingly, it is not intended that the scope of the invention in any way be limited by the above description, but instead be determined entirely by reference to the claims that follow.

**WHAT IS CLAIMED IS:**

1. An implantable medical device, comprising:

   a. an implantable substrate carrier; and

   b. a sensor member fabricated of at least one of a shape memory or a superelastic material coupled to the implantable substrate carrier.

2. The implantable medical device according to Claim 1, wherein the implantable substrate carrier is fabricated of a biocompatible material selected from the group of stainless steel, tantalum, gold, platinum, titanium, nickel, vanadium metal alloys thereof, nickel-titanium, elgiloy and combinations thereof.

3. The implantable medical device according to Claim 1, wherein the implantable substrate carrier consists essentially of a metal alloy.

4. The implantable medical device according to Claim 1, wherein the implantable substrate carrier consists essentially of a nickel-titanium alloy.

5. The implantable medical device according to Claim 2, wherein the sensor member consists essentially of a metal alloy.

6. The implantable medical device according to Claim 4, wherein the sensor member consists essentially of a nickel-titanium alloy.

7. The implantable medical device according to Claim 1, wherein the sensor member further comprises a plurality of cantilever members.

8. The implantable medical device according to Claim 7, wherein the plurality of cantilever members are fabricated of at least one of a shape memory material, a superelastic material, an elastically deformable material or a plastically deformable material.

9. The implantable medical device according to Claim 8, wherein the plurality of cantilever members have binary functionality having a first "off" position and a second "on" position.

10. The implantable medical device according to Claim 7, wherein the plurality of cantilever members are configured to have electromechanical response curves which shift upon a quantum of applied energy thereto.

11. The implantable medical device according to Claim 1, wherein the sensor member further comprises structural elements of the substrate carrier that are capable of altering a conformation of the implantable substrate carrier upon martensitic transformation of the at least one of a shape memory or a superelastic material.

12. An implantable medical device comprising and endoluminal prosthesis having at least one of a plurality of sensor regions integrally defined on at least one of a luminal or abluminal surface of the endoluminal prosthesis.

13. The implantable medical device according to Claim 12, wherein the endoluminal prosthesis is selected from the group consisting of stents, stent-grafts, grafts, valves, filters and occluders.

14. The implantable medical device according to Claim 12, wherein the endoluminal prosthesis and the at least one of a plurality of sensor regions further comprise a metal alloy selected from the group consisting of shape memory metal alloys, superelastic metal alloys, elastically deformable metals or plastically deformable metals.

15. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises of a nickel-titanium alloy.

16. The implantable medical device according to Claim 14, wherein the at least one of a plurality of sensor regions further comprises a nickel-titanium alloy.

17. The implantable medical device according to Claim 14, wherein the at least one of a plurality of sensor regions further have a transition point different than a transition point of the endoluminal prosthesis.

18. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises a plurality of wall elements, each of the plurality of wall elements further comprised of at least one shape memory or superelastic material, at least some of the plurality of wall elements being comprised of a first shape memory or superelastic material having a first transition point $T_1$ and at least some of the plurality of wall elements being comprised of a second shape memory or superelastic material having a second transition point $T_2$, wherein $T_2$ is greater than $T_1$.

19. The implantable medical device according to Claim 14, wherein the endoluminal prosthesis further comprises a plurality of wall elements; each of the wall elements being comprised of a laminate of at least two shape memory or superelastic materials, a first shape memory or superelastic material having a first transition point $T_1$ and a second shape memory or superelastic material having a second transition point $T_2$, wherein $T_2$ is greater than $T_1$.

20. An implantable medical device comprising a substrate element fabricated of at least one of a shape memory and superelastic material, at least one transition point of the substrate element being capable of being induced by at least one of an endogenous energy stimulus selected from the group consisting of fluid pressure, fluid shear forces, body temperature, cellular binding and molecular binding, and exogenous energy stimulus selected from the group consisting of temperature, pressure, microwave, ultrasound, RF, ultraviolet, infrared, magnetic resonance, x-rays, beta and gamma irradiation.

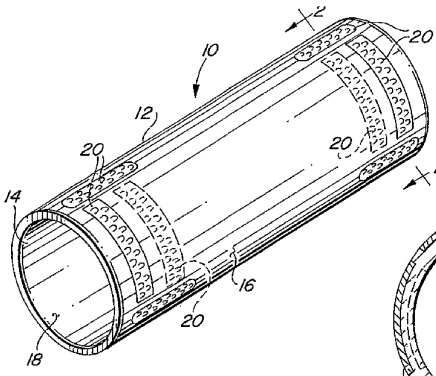


Fig. 1

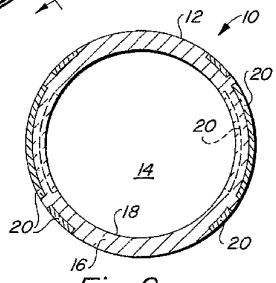


Fig. 2

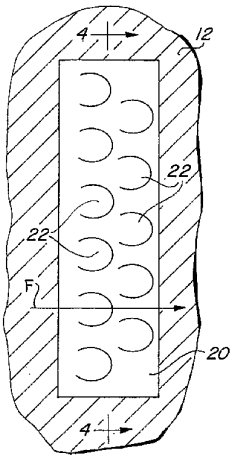


Fig. 3

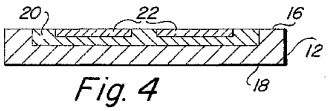


Fig. 4

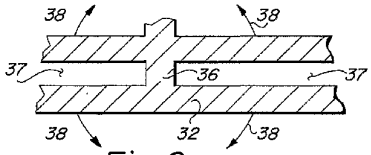


Fig. 6

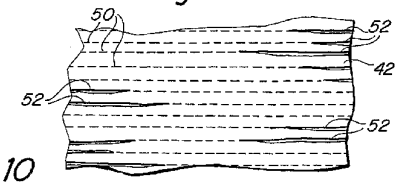


Fig. 10

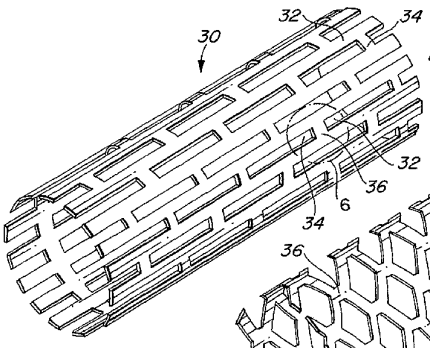


Fig. 5

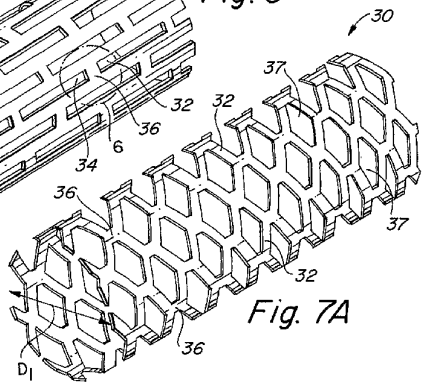


Fig. 7A

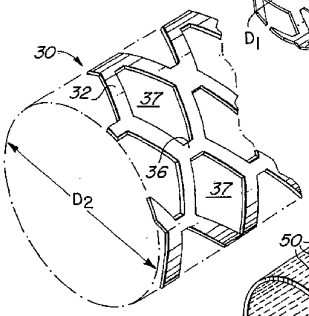


Fig. 7B

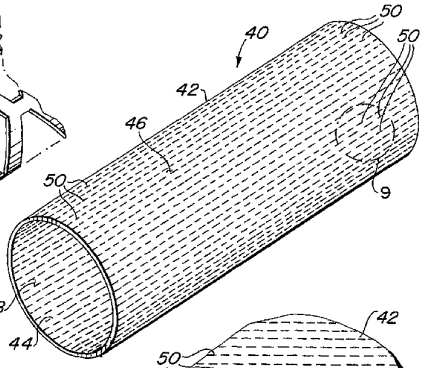


Fig. 8

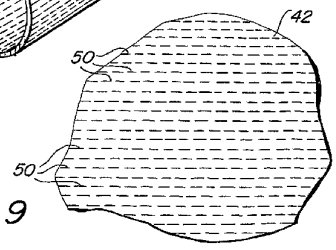


Fig. 9

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(71) Applicant *(for all designated States except US)*: **ADVANCED BIO PROSTHETIC SURFACES, LTD.** [US/US]; 4778 Research Drive, San Antonio, TX 78240 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BAILEY, Steven, R.** [US/US]; 3 Village Knoll, San Antonio, TX 78232 (US). **BOYLE, Christopher, T.** [US/US]; 7667 Callaghan, #604, San Antonio, TX 78229 (US). **MARTON, Denes** [US/US]; 11015 Whisper Hollow, San Antonio, TX 78230 (US). **BANAS, Christopher, E.** [US/US]; 102 Rock Squirrel, San Antonio, TX 78231 (US).

(74) Agent: **ROSENBAUM, David, G.**; Rosenbaum & Associates, P.C., Suite #3600, 875 North Michigan Avenue, Chicago, IL 60611 (US).

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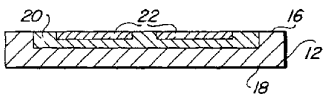
*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: IN VIVO SENSOR AND METHOD OF MAKING SAME




(57) Abstract: Implantable *in vivo* sensors used to monitor physical, chemical or electrical parameters within a body. The *in vivo* sensors are integral with an implantable medical device and are responsive to externally or internally applied energy. Upon application of energy, the sensors undergo a phase change in at least part of the material of the device which is then detected external to the body by conventional techniques such as radiography, ultrasound imaging, magnetic resonance imaging, radio frequency imaging or the like. The *in vivo* sensors of the present invention may be employed to provide volumetric measurements, flow rate measurements, pressure measurements, electrical measurements, biochemical measurements, temperature, measurements, or measure the degree and type of deposits within the lumen of an endoluminal implant, such as a stent or other type of endoluminal conduit. The *in vivo* sensors may also be used therapeutically to modulate mechanical and/or physical properties of the endoluminal implant in response to the sensed or monitored parameter.

WO 02/064019 A3

【国際調査報告】

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International application No.
PCT/US02/04219

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US CL :623/1.18
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. : 623/1.18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST: sensor, shape memory, niti, stent, pressure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 6,053,873 A (Govari et al) 04 April 2000, see entire document, specifically column 6, lines 29-35. | 12-16, 17-20NO |
| X | US 6,007,298 A (Tu et al) 06 June 2000, Tu teaches a shape memory stent having a temperature sensor. | 12-15, 17-20 |
| A | US 5,865,801 A (Houser) 02 February 1999, see column 8, lines 28-50. | 1-20 |

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

* Special categories of cited documents:
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(74)代理人 100096013
弁理士 富田 博行
(72)発明者 バイリー，スティーブン・アール
アメリカ合衆国テキサス州７８２３２，サン・アントニオ，ビレッジ・クノール ３
(72)発明者 ボイル，クリストファー・ティー
アメリカ合衆国テキサス州７８２２９，サン・アントニオ，ナンバー６０４，カラハン ７６６７
(72)発明者 マートン，デネス
アメリカ合衆国テキサス州７８２３０，サン・アントニオ，ウィスパー・ホロー １１０１５
(72)発明者 バナス，クリストファー・イー
アメリカ合衆国テキサス州７８２３１，サン・アントニオ，ロック・スクウィレル １０２

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| [标]发明人 | バイリースティーブンアール<br>ボイルクリストファーティー<br>マートンデネス<br>バナスクリストファーイー | | |
| 发明人 | バイリー,スティーブン·アール<br>ボイル,クリストファー·ティー<br>マートン,デネス<br>バナス,クリストファー·イー | | |
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| 代理人(译) | 小林 泰<br>千叶昭夫 | | |
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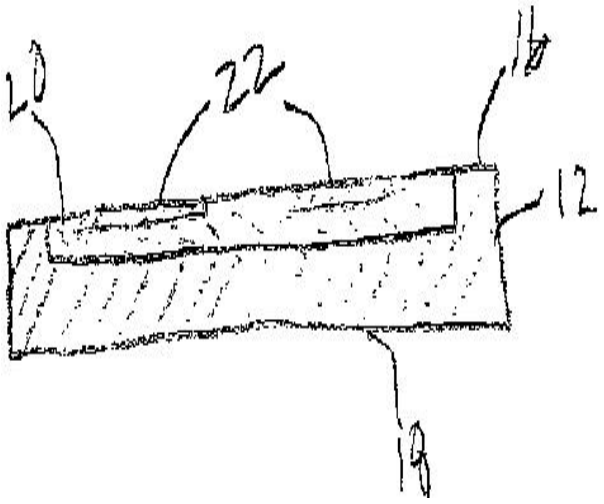
摘要(译)

是一种植入式体内传感器，用于监测身体内的物理，化学或电气参数。体内传感器与可植入医疗设备集成在一起，并且对外部或内部施加的能量作出响应。当施加能量时，传感器与器件的至少一部分材料发生相变，然后现有技术如射线照相，超声波成像，核磁共振成像，在身体外部检测相变。沉积物在管腔注入内腔，如支架或测量的其他形式的管腔内导管，或体积，流量测量，压力测量，电测量，生化测定的程度和类型本发明的体内传感器可以用于温度测量。体内传感器还可用于治疗目的，以响应于感测或监测的参数调节腔内植入物的机械和/或物理性质。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