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(71) Applicant (for all designated States except US):
ADVANCED RESEARCH & TECHNOLOGY INSTITUTE [US/US]; 501 N. Morton Street, Suite 204, Bloomington, IN 47404 (US).

(72) Inventors; and


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(54) Title: APPARATUS AND METHOD FOR NON-INVASIVE MYOCARDIAL REVASCULARIZATION

(57) Abstract: The present invention relates to an apparatus and method for use with a particle accelerator (10) for effecting non-invasive myocardial revascularization through application of energetic heavy ions. The apparatus accepts a beam of energetic heavy ions from the accelerator and controls the timing and location of delivery of the beam to a treatment region of the myocardium. An electronic gating device (20) is provided for timing the delivery of the beam. A beam nozzle (30) is provided for directing the beam. A beam monitoring device (40) measures the energy, intensity, and position of the beam in the beam nozzle. A heart monitor (50) is provided for synchronizing the gating device to the heart beat. A range modulator (60) may be used to increase the width of the Bragg peak and a delivered-dose monitor (70) may be used for measuring the dose delivered to the target area of the heart.
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APPARATUS AND METHOD FOR NON-INVASIVE MYOCARDIAL REVASCULARIZATION

Susan B. Klein
Keith L. March

Field Of The Invention

The present invention relates generally to an apparatus and method for non-invasive myocardial revascularization, and more particularly to an apparatus and method for non-invasive myocardial revascularization using highly energetic particles.

Background Of The Invention

Coronary vessel occlusion leading to myocardial ischemia is one of the leading causes of morbidity and mortality in the Western hemisphere. Ischemia is caused by the depletion of oxygen supply to the myocardium resulting from blockage of the myocardial arteries or deterioration of the vascular structure. Several methods have been developed to achieve reversal of ischemic regions of the myocardium. These methods include mechanical approaches, such as surgical bypass and angioplasty, to circumvent or open occluded vessels; non-mechanical approaches, such as gene therapy; and, invasive laser transmyocardial revascularization (LTMR). However, many areas of the myocardium cannot be fully revascularized by the current approaches due to small or diseased vascular targets, patient health status contrary to surgery, detrimental effects of loosened plaque, repeated restinosis following angioplasty, and inherent hazards of handling radioactive isotopes.

The results from early investigations into the effectiveness of LTMR
demonstrate significant improvement in the quality of life for patients receiving LTMR. This investigation is based on patient satisfaction, number of incidents of reported angina, number visits to the hospital for angina related discomfort, and procedure survivability following LTMR. However, the procedure is complicated, high risk and available only to a small percentage of patients. A non-invasive technique capable of producing an improvement in quality of life has the potential of helping millions of people per year. Consequently a need exists for minimally invasive techniques for transmyocardial revascularization.

Summary of the Invention

The present invention relates to an apparatus and method for use with a particle accelerator for effecting non-invasive myocardial revascularization through application of energetic heavy ions. A heavy ion, as used herein, refers to any particle with one or more units of electric charge and a mass exceeding one atomic mass unit. The accelerator generates a beam of heavy ions traveling at relativistic speeds.

The apparatus of the present invention comprises an electronic gating device for timing the delivery of the beam; a beam nozzle for directing the beam; a beam monitoring device for measuring the energy, intensity, and position of the beam in the beam nozzle; and, a heart monitor for synchronizing the gating device to the heart beat. The apparatus may also include a range modulator to increase the width of the Bragg peak and a delivered-dose monitor for directly measuring the dose delivered to the target area of the heart.
Brief Description of the Drawings

Figure 1 illustrates the differences between photons, electrons, and protons for the dose deposited in tissue.

Figure 2 illustrates a block diagram of the apparatus of the present invention for use with a particle accelerator.

Figure 3 illustrates a schematic of a nozzle configuration.

Figure 4 illustrates the relative dose versus depth of a proton Bragg peak.

Figure 5 illustrates a heart monitor device and associated timing signals.

Detailed Description of the Preferred Embodiments

Irradiation of the myocardium with high energy heavy ions is useful to effect myocardial revascularization. Heavy ion radiation is fundamentally different from other ionizing radiations, such as x-rays or γ-rays, in that heavy ions traveling at relativistic speeds interact weakly with the outer shell electrons of the material through which they pass. The strong interactions at the end of the heavy ion’s range result in the deposition of all of the remaining energy deep within the target. As the heavy ions traverse the material, successive weak interactions slow the heavy ions. The slower, less energetic heavy ions interact more strongly with the material through which they pass. In contrast, electron and photon beams deposit most of their energy near the surface. Figure 1 illustrates the differences between photons, electrons, and protons for the dose deposited in tissue. In addition, a proton beam exhibits a sharper, better defined penumbra and distal cut off than is possible with maximally collimated photon beams. For these reasons, it is desirable to use protons or other heavy ions for non-invasive myocardial revascularization. For describing the apparatus of the
invention, the proton is chosen as an exemplary heavy ion.

The apparatus of the present invention comprises an electronic gating
device (20) for use with a particle accelerator (10), such as a cyclotron or
synchrotron as shown in Fig. 2. The gating device (20) includes a laminated,
fast switching magnet located in the beam line, a variable delay circuit, a strain
gauge, and associated electronics and software controls. The gating device (20)
diverts the proton beam from a shunt line of the accelerator (10) to a patient
treatment line at a prescribed time. The diversion of the proton beam into the
patient treatment line defines the exposure time of the proton dose delivered to
the patient. Electronic gating avoids the problem of the dose rate ramping up
and down as the dose is initialized and terminated, which occurs in mechanical
gates as the lead gates move into and out of the proton beam. Additional
electronic gates can be added, so that the ECG trigger is only allowed during
exhalation, as discussed below. This minimizes the tissue thickness effects and
dispersion of the beam within the patient’s tissue.

The apparatus of the invention further comprises a beam nozzle (30) for
receiving and modifying the beam of protons in the patient treatment line. In a
first configuration, the nozzle (30) includes focusing magnets which are adjusted
so the focal point of the beam coincides with the target location of the
myocardial wall at a selected phase of the cardiac cycle. This nozzle
configuration produces a very small, 2 – 8 mm diameter, 100% isodose area,
with a fairly small penumbra of 2 – 8 mm. The penumbra is defined as the
distance between 80% point and 20% point of the energy peak across the beam
diameter. The advantage of this nozzle configuration is that no beam intensity is
lost, which can occur when other beam modification devices are present in the
nozzle.

In a second nozzle configuration, as shown in Fig. 3, the nozzle (32) comprises a scattering foil (33) to receive the beam from the gating device (20) and flatten the beam profile by expanding the central portion of the beam. The scattering foil (33) may be formed of metal, such as aluminum, lead, or copper, or plastic, or a combination of plastic and metal. The second nozzle (32) includes a collimator array having one or more collimators (34) arranged in series to substantially decrease the number of scattered protons and produce a substantially collimated beam. The collimators (34) are arranged in series so that the output from one collimator provides the input to the subsequent collimator. The first collimator (34) in the collimator array intercepts the beam emitted by the scattering foil (33). The collimated beam profile produces a larger 100% isodose area (5 – 9 mm) and a smaller penumbra (2 – 5 mm) than the focused beam of the first nozzle configuration. The maximum diameter of the irradiation spot may be equivalent in both first and second nozzle configurations, but the second nozzle configuration (32) substantially reduces the available beam current, and therefore requires higher initial beam intensity. The beam emitted by the nozzle (30) or (32) is delivered to the myocardial wall of the heart (90) at a selected phase of the cardiac cycle.

A range modulator (60) may also be incorporated in the apparatus to accept the beam in the patient line and emit a beam that has a spread-out Bragg peak width. The width of the Bragg peak is generally measured at the point halfway between the maximum dose and the proximal plateau, called the “full width half max” (FWHM). The range modulator (60) may comprise a plastic propeller. As the propeller spins, varying thicknesses of plastic pass through the
beam, rapidly shifting the Bragg peak back and forth. Alternately, spreading of
the Bragg peak may be accomplished by sliding wedges through the beam or
expanding volumes of liquid within the beam. Spreading out the Bragg peak
may be desirable to compensate for heart motion or, if necessary, to increase the
Bragg peak width so that it encompasses the entire thickness of the heart wall as
best seen in Fig. 4.

A heart monitor (50) is provided to monitor the motion of the heart
and/or cardiac phase as shown in Fig. 5. Suitable methods for monitoring heart
position and/or cardiac phase include ultrasonography, fluoroscopy, CT, MRI,
ECG and similar techniques. For example, in one configuration of the apparatus
an ECG communicates with the gating device (20) to coordinate the proton
delivery with the heart motion, so that protons may be delivered to the target
area of the heart despite target area movement.

The apparatus of the current invention may also include one or more
beam monitoring devices (40) for measuring the energy, intensity, and position
of the proton beam in the nozzle (30) and (32), before delivery to the patient.
Standard radiotherapy devices, such as split ion chambers and secondary
electron emission monitors (SEM) may be used. The beam monitoring device
samples the charged current passing through the nozzle (30) and (32) and
estimates the dosage that will be delivered to the target area of the heart. The
beam monitoring device (40) is calibrated to account for the expected decrease
in dosage due to the presence of intervening tissue between the beam and the
target area of the heart. From the calibration, the beam current at the beam
monitoring device is converted to the expected dose delivered at the target.

The apparatus of the current invention may also include a delivered-dose
monitor (70) for directly measuring the dose actually delivered to the target area of the heart. The delivered-dose monitor (70) measures radioactive emissions, such as positron emissions, caused by the nuclear absorption of proton energy within the tissue. Proton energy absorbed by blood within the lumen of the heart may also create radioactive emissions, but proton-exposed blood, as it is pumped from the heart, does not reveal persistent radioactive emissions within the treatment region. Thus, radioactive emissions detected by the monitor (70) are indicative of the delivery of protons within tissue.

The delivered-dose monitor (70) may be a positron emission tomography (PET) system. Occasionally, protons interact not with the electrons of the target atoms, but with the nuclei. When this happens, a positively charged electron, a positron, is emitted as a result of the reaction. The emitted positron is extremely short lived and combines almost instantly with a negatively charged electron. The collision produces two gamma rays, 180 degrees opposed, of a specific energy (115 keV). The PET system includes two gamma ray detectors disposed on opposing sides of the sample object, i.e. the heart in this application. The PET system identifies the location of the positron emission by calculating the difference in arrival time of the two gamma rays at the gamma ray detectors.

The method of use of the apparatus encompasses the delivery of both the proximal plateau or the Bragg peak to the target area of the heart. The dose delivered to the myocardial wall is determined by the energy, intensity, and temporal characteristics of the proton beam. Two different delivery schemes for proton delivery are possible using the method and apparatus of the invention. The first scheme delivers the proximal plateau, and the second scheme delivers the Bragg peak. The differences between these two delivery schemes is
understood in terms of the mechanics of interaction of the protons with the matter through which they travel.

Protons traveling at relativistic speeds lose energy via small interactions with outer shell electrons of the target material. Because each interaction is small, small amounts of energy are transferred to secondary electrons. These secondary electrons do not travel far and do not cause significant damage. As the protons slow, the ionization potential rises rapidly. The increased interactions between target electrons and the beam of protons cause a further energy loss (slowing) and an increased ionization potential. This characteristic produces a sudden loss of energy at the end of the proton’s range. When the dose delivered versus distance is plotted, loss of energy at the end of the proton’s range is depicted by the Bragg peak phenomenon as shown Fig. 1. No dose is delivered beyond the distal edge of the Bragg peak. Although protons are not considered high linear energy transfer (LET) particles, the microscopic LET increases from approximately 0.4 keV/\( \mu \)m, approaching the Bragg peak, to 100 keV/\( \mu \)m, at the Bragg peak.

The operator selects the nozzle configuration depending on the type of proton delivery desired for a particular treatment. The method and apparatus using the first nozzle configuration (30) delivers the proximal plateau of the depth/dose curve to the myocardial target. This method minimizes the beam diameter at the target location while maximizing the beam current and reducing the positioning uncertainty. The method using the second nozzle configuration (32) delivers the Bragg peak to the myocardial wall. The distal edge of the Bragg peak can be located at the inner myocardial wall, within the blood chamber of the heart, or within the myocardial wall, Fig. 4.
The operator positions the patient relative to the nozzle (30) so that the trajectory of protons emitted from the nozzle (30) is directed towards the target treatment area of the heart. The heart monitor (50) and delivered-dose monitor (70) are also positioned relative to the patient.

The operator selects the dose delivery time to avoid smearing of the delivered dose. It may be preferable that the total dose be delivered in a single pulse of short enough duration to be unaffected by the heart motion. For example, if the dose is delivered when the heart is resting between diastole and systole, heart motion is suspended for approximately 0.4 seconds. This position correlates with the plateau region of the ECG following the "T" wave, preceding the "P" wave, as shown in Fig. 5. It is possible to deliver a 0.2 second proton pulse of highly accurate dose by triggering the proton delivery off of the electronic ECG signal. The large "R" signal is used to trigger the delivery. A variable delay is programmed into the system. The delay is set for the duration of the "Q" wave, the plateau, and the "T" wave in the ECG of the individual patient. The trigger signal is then sent to a switch that alters the field of the laminated magnet within the electronic gating device (20), which switches the proton beam from the shunt line to the patient treatment line for 0.2 seconds. The switching process takes less than 0.000002 seconds. Electronic switching is many orders of magnitude faster than mechanical gating. A single pulse of 50 Gy delivered in 0.2 seconds requires approximately 100 nA of beam current at the target site.

Prior to delivery of the pulse, the operator further adjusts the characteristics of the Bragg peak to provide the desired type of proton delivery.

The characteristics of the Bragg peak are determined by the initial energy of the
protons at the extraction site from the accelerator. The higher the energy, the
further the protons will penetrate the patient. For example, assuming an average
distance through tissue to the myocardium to be about 16 cm, a 110 MeV proton
deposits maximum energy in the myocardial wall. The operator may adjust the
energy to a desired amount by degrading the initial output energy from the
accelerator or, if the accelerator is a synchrotron, by adjusting the selected
output of the synchrotron. The operator may adjust the width of the Bragg peak
through use of the range modulator (60). The slope of the distal edge of the
Bragg peak is approximately 2 mm for an initial energy of 210 MeV (degraded
or not). Lower initial energy will produce a steeper distal slope; lower energy
also affects the width of the Bragg peak. The width of the Bragg peak is also
affected by the diagnostic and dosimetry devices which intersect the beam. If
the placement of the Bragg peak can be very precisely controlled, it is not
necessary to alter the width of the Bragg peak.

Prior to dose delivery, the operator may also adjust the width of the
Bragg peak to be delivered through use of the range modulator (60).
Manipulation of the beam energy, which results in the translocation of the Bragg
peak, will scatter the beam to some degree, depending upon the change in
energy. Significant degradation of beam energy will scatter the protons and may
require a collimated method of delivery.

The operator uses the PET system to locate the tissue through which the
protons pass. The PET system does not image the tissue per se. Specifically,
the PET system locates the position in three-dimensional space where the
proximal plateau and/or Bragg peak are delivered. The position located by the
PET system is superimposed on an image of the patient created via a traditional
imaging device, such as an MRI, CT, fluoroscopy, or x-ray device, to create an image of the heart showing the region of the delivered protons. For example, the region of the delivered protons may be superimposed on a digitized fluoroscopy image grabbed at the exact 0.2 seconds of irradiation, which also can be triggered by the gating device. The operator may collect the PET signal anywhere from seconds to hours after irradiation. It is also possible, by knowing the cross section and concentration of the nucleus with which the proton interacted to calculate the dose delivered based on the positron emission.

These and other advantages of the present invention will be apparent to those skilled in the art from the foregoing specification. Accordingly, it will be recognized by those skilled in the art that changes or modifications may be made to the above-described embodiments without departing from the broad inventive concepts of the invention. For example, while the above illustrations have been made with respect to treatment of the heart, the apparatus and method of this invention may also be applied to treatment of the lungs. It should therefore be understood that this invention is not limited to the particular embodiments described herein, but is intended to include all changes and modifications that are within the scope and spirit of the invention as set forth in the claims.
We claim:

1. A non-invasive myocardial revascularization apparatus for use with a beam of energetic heavy ions produced by an accelerator comprising:
   a electronic gating device for controlling the exposure time of a myocardium to the beam;
   a beam nozzle for directing the beam to a target area of the myocardium;
   a beam monitor for measuring a selected property of the heavy ion beam in the beam nozzle to control beam dosage to the myocardium; and
   a heart monitor for detecting the heart beat and for synchronizing the gating device to the heart beat.

2. The apparatus of claim 1 wherein the electronic gating device comprises a laminated, fast switching magnet.

3. The apparatus of claim 1 wherein the electronic gating device comprises a variable delay circuit.

4. The apparatus of claim 1 wherein the electronic gating device comprises a strain gauge.

5. The apparatus of claim 1 wherein the nozzle comprises a focusing magnet for focusing the beam of heavy ions.

6. The apparatus of claim 1 wherein the nozzle comprises a scattering foil for flattening the beam profile.
7. The apparatus of claim 6 wherein the nozzle comprises a collimator for collimating the flattened the beam profile produced by the scattering foil.

8. The apparatus of claim 1 wherein the heart monitor comprises one of an ultrasound device, fluoroscope, CT, MRI, or ECG.

9. The apparatus of claim 1 comprising a range modulator for increasing the Bragg peak width of the heavy ions.

10. The apparatus of claim 1 comprising a delivered-dose monitor for measuring the dosage delivered to the target area of the heart.

11. The apparatus of claim 10 wherein the delivered-dose monitor comprises PET system.

12. The apparatus of claim 1 wherein the beam monitor comprises a beam energy detector.

13. The apparatus of claim 1 wherein the beam monitor comprises a beam intensity detector.

14. The apparatus of claim 1 wherein the beam monitor comprises a beam position detector.

15. The apparatus of claim 1 wherein the heart monitor comprises a heart
position detector.

16. The apparatus of claim 1 wherein the heart monitor comprises a heart beat detector.

17. The apparatus of claim 1 wherein the heart monitor comprises a cardiac phase detector.

18. The apparatus of claim 1 wherein the beam nozzle is disposed downstream from the gating device.

19. The apparatus of claim 1 wherein the selected property is the beam energy.

20. The apparatus of claim 1 wherein the selected property is the beam intensity.

21. The apparatus of claim 1 wherein the selected property is the beam location relative to the beam nozzle.

22. A method for non-invasive myocardial revascularization using a beam of energetic heavy ions produced by an accelerator comprising:

   detecting the cardiac phase with a heart monitor;

   opening an electronic gating device in response to the detected cardiac phase to pass a beam of heavy ions from the accelerator to a beam nozzle;
measuring a selected property of the heavy ion beam with a beam
monitor to control beam dosage;
directing the beam with the beam nozzle to a target area of a
myocardium; and
5 closing the electronic gating device in response to the detected cardiac
phase.

23. The method of claim 22 wherein the selected property is the beam
energy.

24. The method of claim 22 wherein the selected property is the beam
intensity.

25. The method of claim 22 wherein the selected property is the beam
location relative to the beam nozzle.

26. The method of claim 22 comprising the step of increasing the Bragg
peak width of the heavy ions with a range modulator.

15 27. The method of claim 22 comprising the step of measuring the dosage
delivered to the target area of the heart with a delivered-dose monitor.

28. The method of claim 27 wherein the step of measuring the delivered
dosage comprises the step of measuring positron emissions.
29. The method of claim 22 wherein the step of detecting a heart beat includes detecting the heart location.
Fig 1.
Fig 4.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(7) : A61B 18/04
   US CL : 606/34
   According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
   Minimum documentation searched (classification system followed by classification symbols)
   U.S. : 606/34, 32, 7, 11, 12, 13, 14, 15, 17
   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
   Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>US 5,957,916 A (JEEVANANDAM et al) 28 September 1999, See entire document.</td>
<td>1 and 14-17</td>
</tr>
<tr>
<td>A</td>
<td>US 5,807,384 A (MUELLER) 15 September 1998, See entire document.</td>
<td>1-29</td>
</tr>
<tr>
<td>X</td>
<td>US 5,951,543 A (BRAUER) 14 September 1999, See figures 5-8b.</td>
<td>1, 3, and 8-14</td>
</tr>
<tr>
<td>X</td>
<td>US 5,931,834 A (MURPHY-CHUTORIAN et al) 03 August 1999. See entire document.</td>
<td>1, 18, 21, 22</td>
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☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230
Authorized officer DAVID RUDY
Telephone No. (703) 308-1148

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