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(54) Title: MRI BASED CHARACTERIZATION OF MICROVASCULAR OBSTRUCTION IN RESPONSE TO THERAPEUTIC HYPOTHERMIA FOLLOWING ACUTE MYOCARDIAL INFARCTION

(57) Abstract: The invention provides methods for reducing microvascular obstructions, reducing hemorrhagic microvascular obstructions and/or reducing ischemia-reperfusion injury in a subject in need thereof by using therapeutic hypothermia and monitoring the outcome of the intervention with a non-invasive imaging standard.



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**MRI based Characterization of Microvascular Obstruction in Response to
Therapeutic Hypothermia Following Acute Myocardial Infarction**

FIELD OF INVENTION

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The invention is directed to methods for reducing microvascular obstructions by using therapeutic hypothermia and noninvasively monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion.

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BACKGROUND

All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be
15 useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a
20 heart attack is the interruption of blood supply to a part of the heart, causing heart cells to die. Myocardial infarction is caused by ischaemic or ischemic heart disease (IHD), or myocardial ischaemia, which is characterized by reduced blood supply due to a partial or complete blockage of an artery that carries blood to the heart, usually due to coronary artery disease (atherosclerosis of the coronary arteries). The decrease in blood flow
25 reduces the heart's oxygen supply. Myocardial ischemia is an imbalance between myocardial oxygen supply and demand. Its risk increases with, for example, age, smoking, hypercholesterolaemia (high cholesterol levels), diabetes, and hypertension (high blood pressure), and is more common in men and those who have close relatives with ischaemic heart disease. Myocardial ischemia is the pathological state underlying
30 ischaemic heart disease.

In the event of a myocardial infarction, maximizing myocardial salvage from regions of pronounced ischemia in patients suffering an infarction is the most important goal of any

therapeutic strategy delivered to the patient. The therapeutic standard for countering the acute ischemic burden is the re-establishment of blood flow, while minimizing ischemia-reperfusion injury, via percutaneous transluminal coronary angioplasty (PTCA) or fibrinolysis. Of these two approaches, the most sought after therapeutic regiment is PTCA. Unfortunately reperfusion therapies do not always re-establish flow and can lead to microvascular obstructions (MVOs). It has been shown that MVOs occur at the site of severe ischemic injury and that they have been associated with poor prognosis and reduced survival rates in the months and years post reperfusion. It is also known that MVOs are associated with larger infarcts and that larger infarcts lead to poorer remodeling in the chronic stage of disease culminating in heart failure. Since heart failure is a growing epidemic in the Western World, and most heart failures have origins in ischemic heart disease it is desirable to minimize ischemia-reperfusion injury in right at the acute setting.

15 SUMMARY OF THE INVENTION

The invention is directed to a method for reducing microvascular obstructions in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish perfusion to an ischemic area in the subject using the cooled blood so as to reduce microvascular obstruction, thereby reducing microvascular obstructions in a subject in need thereof. The subject is a myocardial infarction patient whose treatment is initiated at least 6 hours after the onset of symptoms of myocardial infarction. The method further comprises monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post reperfusion.

The invention is also directed to a method for reducing hemorrhagic microvascular obstructions in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish perfusion to an ischemic area in the subject using the cooled blood, so as to reduce hemorrhagic microvascular obstruction, thereby reducing hemorrhagic microvascular obstructions in a subject in need thereof. The subject is a myocardial infarction patient whose treatment is initiated at least 6 hours after the onset of symptoms of myocardial

infarction. The method further comprises monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion.

5 The invention further provides a method for reducing ischemia-reperfusion injury in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish perfusion to an ischemic area in the subject using the cooled blood, so as to reduce ischemia-reperfusion injury, thereby reducing ischemia-reperfusion injury in a subject in need thereof. The subject is a myocardial infarction patient whose treatment is initiated at least 6 hours after
10 the onset of symptoms of myocardial infarction. The method further comprises monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion.

DETAILED DESCRIPTION OF THE INVENTION

15 All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, *Dictionary of Microbiology and Molecular Biology*
20 *3rd ed.*, J. Wiley & Sons (New York, NY 2001); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed.*, J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual 3rd ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

25 One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

30 “Beneficial results” may include, but are in no way limited to, lessening or alleviating the severity of the disease condition, preventing the disease condition from worsening, curing the disease condition, preventing the disease condition from developing, lowering the

chances of a patient developing the disease condition and prolonging a patient's life or life expectancy.

5 “Mammal” or “subject” as used herein refers to any member of the class *Mammalia*, including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are
10 intended to be included within the scope of this term.

“Treatment” and “treating,” as used herein refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition, prevent the pathologic condition, pursue or
15 obtain beneficial results, or lower the chances of the individual developing the condition even if the treatment is ultimately unsuccessful. Those in need of treatment include those already with the condition as well as those prone to have the condition or those in whom the condition is to be prevented.

20 “Ischaemia” or “Ischemia” as used herein refers to reduced blood supply to a tissue and/or an organ. Ischemic heart disease refers to reduced blood supply to the heart due to a partial or complete blockage of an artery that carries blood to the heart.

“Reperfusion” as used herein the re-establishing perfusion to an ischemic area and/or
25 organ.

“Therapeutic hypothermia” or “therapeutic cooling” as used herein refers to re-establishing perfusion to an ischemic area in a subject using the cooled blood, so as to reduce microvascular obstruction. For example, the blood may be cooled to 2-7°C lower
30 than the normal systemic temperature prior to or during reperfusion. In subject not indicated for reperfusion, therapeutic hypothermia may be established via surface cooling (wherein the body is cooled by 2-5 degrees centigrade from the baseline level or via the use of a catheter inserted through the femoral artery).

“Pain to balloon time” as used herein refers to the time between the onset of symptoms of myocardial infarction up to the angioplasty.

5 As described above, it is desirable to minimize ischemia-reperfusion injury at the acute setting. In particular, methods that can minimize microvascular obstructions and enable one to track the efficacy of therapeutic strategies are in great need. One strategy for reducing ischemia-reperfusion injury may be therapeutic hypothermia (re-establish perfusion with blood cooled to, for example, 2-7°C lower than the normal systemic
10 temperature), particularly in myocardial infarction patients whose treatment is initiated, for example, at least 2 hours, 3 hours, at least 4 hours, at least 5 hours or at least 6 hours, after the onset of symptoms of myocardial infarction.

The inventor proposes the use of therapeutic cooling in candidate patients outside the
15 therapeutic window (for example, pain to balloon time of about 5 hours or more, i.e. patients whose treatment is initiated about 5 hours or more after the onset of symptoms of myocardial infarction) combined with magnetic resonance imaging to monitor the extent of microvascular obstructions. Specifically, the longer the pain to balloon time the larger and/or more severe the microvascular obstructions. The inventor also hypothesizes that it
20 is not only the MVOs that lead to poor prognosis but the more severe form of MVOs, which also lead to intramyocardial hemorrhage and that it is this intramyocardial hemorrhage that can accelerate oxidative stress in the ischemic myocardium. Therapeutic cooling may reduce MVOs and thereby reduce intramyocardial hemorrhage and improve prognosis. The extent of the MVOs and intramyocardial hemorrhage may be fully
25 evaluated on the basis of MRI.

Accordingly, the invention is directed to a method for reducing microvascular obstructions in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish
30 perfusion (“reperfusion”) to an ischemic area in the subject using the cooled blood, so as to reduce microvascular obstruction, thereby reducing microvascular obstructions in a subject in need thereof. In an embodiment, reperfusion may be established using fibrinolytic therapy. In an additional embodiment, reperfusion may be established using

both, angioplasty and fibrinolytic therapy. The method further comprises monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion (for example, during the acute (for example 1-3 days) up to sub-acute (for example 1-2 weeks) phases post reperfusion). In an embodiment, the cooled blood
5 may be reperfused for about 2 hours prior to switching to normothermic (normal temperature) perfusion (for example at the termination of the angioplasty). In some embodiments, the subject is a myocardial infarction patient whose treatment is initiated at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours or at least 6 hours after the onset of symptoms of myocardial infarction.

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Hemorrhaging is associated with microvascular obstructions. The invention is also directed to a method for reducing hemorrhagic microvascular obstructions in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish perfusion to an ischemic area in
15 the subject using the cooled blood, so as to reduce hemorrhagic microvascular obstruction, thereby reducing hemorrhagic microvascular obstructions in a subject in need thereof. In an embodiment, reperfusion may be established using fibrinolytic therapy. In an additional embodiment, reperfusion may be established using both, angioplasty and fibrinolytic therapy. The method further comprises monitoring microvascular obstructions
20 using magnetic resonance imaging during reperfusion and post-reperfusion (for example, during the acute (for example 1-3 days) up to sub-acute (for example 1-2 weeks) phases post reperfusion). In an embodiment, the cooled blood may be reperfused for about 2 hours prior to switching to normothermic perfusion (for example at the termination of the angioplasty). In some embodiments, the subject is a myocardial infarction patient whose
25 treatment is initiated at least 2 hours, at least 3, at least 4, at least 5 or at least 6 hours after the onset of symptoms of myocardial infarction.

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Intramyocardial hemorrhaging may occur in non-reperfused infarction as well as in reperfused infarctions. Therefore, therapeutic hypothermia may be used to prevent and/or
reduce myocardial hemorrhage. Accordingly, invention provides methods for reducing hemorrhagic microvascular obstructions in a subject in need thereof wherein the subject has not and/or will no undergo reperfusion therapy. For example, the subject may be a patient for whom reperfusion therapy is not indicated based on the American Heart

Association (AHA) guidelines. The method comprises establishing therapeutic hypothermia so as to cool the blood in a subject and monitoring microvascular obstructions and/or decreased burden of hemorrhaging using imaging method including magnetic resonance imaging, for at least 1-2 days, at least 2-3 days, at least 3-4 days, at least 4-5 days, at least 5-6 days, at least 6-7 days, at least 7-8 days, at least 8-9 days and/or at least 9-10 days post therapy. In one embodiment, therapeutic hypothermia is established using surface cooling wherein the patient is cooled for at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 7 hours or at least 8 hours. In another embodiment, therapeutic hypothermia is established using a catheter inserted through the femoral artery to cool the circulating blood.

The invention further provides a method for reducing ischemia-reperfusion injury in a subject in need thereof comprising establishing therapeutic hypothermia by cooling blood prior to reperfusion and performing an angioplasty to re-establish perfusion to an ischemic area in the subject using the cooled blood, so as to reduce ischemia-reperfusion injury, thereby reducing ischemia-reperfusion injury in a subject in need thereof. In an embodiment, reperfusion may be established using fibrinolytic therapy. In an additional embodiment, reperfusion may be established using both, angioplasty and fibrinolytic therapy. The method further comprises monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion (for example, during the acute (for example 1-3 days) up to sub-acute (for example 1-2 weeks) phases post reperfusion). In an embodiment, the cooled blood may be reperfused for about 2 hours prior to switching to normothermic perfusion (for example at the termination of the angioplasty). In some embodiments, the subject is a myocardial infarction patient whose treatment is initiated at least 2 hours, at least 3, at least 4, at least 5 or at least 6 hours after the onset of symptoms of myocardial infarction

In an embodiment of the claimed methods, blood is cooled to 2-7°C lower than the normal systemic temperature. The blood may be cooled with endovascular or surface cooling approaches using Thermogard XP Temperature Management System (Zoll Medical, Chelmsford, MA, USA) or the RTx Endovascular System, STx Surface Pad System, combined with Accutrol Catheter by Philips (Andover, MA, USA), and other similar devices.

In one embodiment, the claimed methods further comprise monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion (for example, during the acute (for example 1-3 days) up to sub-acute (for example 1-2 weeks) phases post reperfusion). As described above, in one embodiment, the claimed methods are directed to performing therapeutic hypothermia in patients whose treatment is initiated outside the therapeutic window, specifically, in patients whose treatment is initiated at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours or at least 6 hours after the onset of the symptoms of myocardial infarction. In preferred embodiments, therapeutic hypothermia is performed in patients whose treatment is initiated at least 4 hours or at least 5 hours after the onset of symptoms of myocardial infarction. In the most preferred embodiment, the therapeutic hypothermia is performed in patients whose treatment is initiated at least 6 hours after the onset of symptoms of myocardial infarction.

In a further embodiment, symptoms of myocardial infarction include but are not limited to any one or more of chest pain, elevated ST segment in an electrocardiogram (ECG) and/or elevated troponin levels in the blood. Chest pains may be accompanied by shortness of breath, dizziness or lightheadedness, jaw pain, nausea/vomiting, unusual fatigue, cold sweat and/or pain in the arm, back, neck, abdomen, and or shoulder blades.

To date the inventor has characterized large ischemia-reperfusion injuries in canine models (n=13) and has demonstrated that microvascular obstructions, in particular hemorrhage is extensive when reperfusion is late (for example, long pain-to-balloon time). This data may serve as controls in our studies. In addition the inventor will collect other control data where reperfusion is done rapidly (~30 minutes) from the time of induction of severe ischemia. The inventor will also study similar number of animals subjected to later reperfusion injury and therapeutic hypothermia during reperfusion to demonstrate that hemorrhagic MVOs can be significantly reduced. In some embodiments, an RTx endovascular system by Philips may be used. The extent of MVOs and the appearance or absence of MVOs and/hemorrhage will be demonstrated with a combined T1-weighted, T2*-weighted cardiac MRI scans. In final phase of the study, the inventor will aim to show that groups receiving therapeutic hypothermia had significantly

improved myocardial remodeling and functional indices. T1-weighted scans, often utilized in conjunction with the infusion of an exogenous contrast media (gadolinium chelates), is the standard for identifying infarcted territories within the heart muscle. The first-passage of the contrast media can be used to identify perfusion deficit territories (such as those from microvascular obstruction) as regions of hypointensities within the myocardium. Short delay following the administration of the contrast media (~1-3 min) can also be used to gather information on microvascular obstruction should the first passage of the contrast agent not provide adequate coverage of the left ventricular mass. In these images, as in first pass-perfusion images, regions of MVOs also appear as hypointense regions. Finally, late-enhancement images (typically acquired 10-15 minutes after the administration of the contrast agent) can be used to identify persistent MVOs. Persistent MVOs are understood to be myocardial territories that are significantly impaired by MVOs. In addition to these scans, either pre- or post-contrast administration, it is possible to identify territories of myocardial hemorrhage with T2*-weighted cardiac MR scans. T2* images are specific for identifying the degradation products of red blood cells hence the T1-weighted and T2* images can be evaluated together to quantify the regional extent of necrosis, MVOs, and hemorrhagic. In a preferred embodiment, T2* images may be used to identify hemorrhage in acute reperfused myocardial infarction with MRI.

Candidate subjects are identified to undergo reperfusion therapy (percutaneous coronary intervention (PCI) or fibrinolytic therapy) by establishing therapeutic hypothermia by cooling blood prior to reperfusion. In subjects receiving PCI (for example, those going to catheterization labs), blood is cooled with the help of surface cooling or endovascular cooling systems to 2-7 degrees Celsius below core body temperature first and then reperfusion is started. The cooled blood can be reperfused by a standard procedure by opening up the collapsed vessel and leaving it open with the aid of a stent or modulating the rate delivery of the cooled blood by slowly vascularizing the obstructed artery to full patency or by more advanced approaches where the reperfusion is punctuated by periods of no or reduced flow (for instance via post-conditioning approaches). This intervention can be done in a cardiac catheterization laboratory under X-ray fluorescence or under XMR systems, where X-ray and MR acquisition are used in an interleaved fashion to assess the effectiveness of reperfusion at the time of intervention. If the procedure is

performed only under X-ray guidance (most common), the subject may be brought back to MR imaging in the acute or sub-acute period following reperfusion and cardiac MR acquisitions are performed to assess myocardial function (wall motion via myocardial tagging), volumetric indices (ejection fraction, end-diastolic volume, end-systolic volume etc via cine imaging), tissue characterization (edema (via T1, T2, magnetization transfer, or SSFP imaging), MVO (first pass imaging, early enhancement imaging, late gadolinium enhancement imaging), hemorrhage (T1, T2, or T2* imaging), fibrosis (T1 imaging), perfusion (first pass imaging), necrosis (late gadolinium enhancement imaging), and coronary angiography (with or without contrast media). In cases where, MR is not available ultrasound can be used as well to assess cardiac function, volumetric indices, or tissue characterization. This may help determine the effectiveness of therapeutic cooling. Subjects may also be followed up at later time point (chronic phases of infarction, months or years after infarction) for infarct/cardiac remodeling with MRI, ultrasound, or computed tomography (CT).

In cases where only fibrinolytic therapy is available, surface and/or endovascular cooling may be used. If the procedure is performed only under X-ray guidance (most common), the subject may be brought back to MR imaging in the acute or sub-acute period following reperfusion and cardiac MR acquisitions are performed to assess myocardial function (wall motion via myocardial tagging), volumetric indices (ejection fraction, end-diastolic volume, end-systolic volume etc via cine imaging), tissue characterization (edema (via T1, T2, magnetization transfer, or SSFP imaging), MVO (first pass imaging, early enhancement imaging, late gadolinium enhancement imaging), hemorrhage (T1, T2, or T2* imaging), fibrosis (T1 imaging), perfusion (first pass imaging), necrosis (late gadolinium enhancement imaging), and coronary angiography (with or without contrast media). In cases where, MR is not available ultrasound can be used as well to assess cardiac function, volumetric indices, or tissue characterization. This may help determine the effectiveness of therapeutic cooling. Subjects may also be followed up at later time point (chronic phases of infarction, months or years after infarction) for infarct/cardiac remodeling with MRI, ultrasound, or computed tomography (CT).

In subjects who are not indicated for reperfusion (by AHA or equivalent standards), surface and/or endovascular cooling may be used. If the procedure is performed only

under X-ray guidance (most common), the subject may be brought back to MR imaging in the acute or sub-acute period following reperfusion and cardiac MR acquisitions are performed to assess myocardial function (wall motion via myocardial tagging), volumetric indices (ejection fraction, end-diastolic volume, end-systolic volume etc via
5 cine imaging), tissue characterization (edema (via T1, T2, magnetization transfer, or SSFP imaging), MVO (first pass imaging, early enhancement imaging, late gadolinium enhancement imaging), hemorrhage (T1, T2, or T2* imaging), fibrosis (T1 imaging), perfusion (first pass imaging), necrosis (late gadolinium enhancement imaging), and coronary angiography (with or without contrast media). In cases where, MR is not
10 available ultrasound can be used as well to assess cardiac function, volumetric indices, or tissue characterization. This may help determine the effectiveness of therapeutic cooling. Subjects may also be followed up at later time point (chronic phases of infarction, months or years after infarction) for infarct/cardiac remodeling with MRI, ultrasound, or computed tomography (CT).

15 The invention also provides method for monitoring the course of microvascular obstruction in a subject comprising providing a subject in need of reduction and/or inhibition of microvascular obstruction, establishing therapeutic hypothermia by cooling blood prior to reperfusion, re-establishing reperfusion to an ischemic area and monitoring
20 microvascular obstructions using magnetic resonance imaging during reperfusion. Contrast-enhanced MRI delineating slow filling territories identified on early-enhancement, late-enhancement and non-contrast enhanced T2 and T2* weighted imaging may be used for MVOs and severe MVOs associated with myocardial hemorrhage.

25 Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall
30 within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be
5 exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is
10 intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes
15 and modifications may be made without departing from this invention and its broader aspects. It will be understood by those within the art that, in general, terms used herein are generally intended as “open” terms (*e.g.*, the term “including” should be interpreted as “including but not limited to,” the term “having” should be interpreted as “having at least,” the term “includes” should be interpreted as “includes but is not limited to,” etc.).

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CLAIMS

What is claimed is:

1. A method for reducing microvascular obstructions in a subject in need thereof comprising:
 - (i) establishing therapeutic hypothermia by cooling blood prior to reperfusion, and
 - (ii) re-establishing perfusion to an ischemic area in the subject using the cooled blood, so as to reduce microvascular obstruction,wherein the subject is a myocardial infarction patient whose treatment is initiated at least 6 hours after the onset of symptoms of myocardial infarction, thereby reducing microvascular obstructions in a subject in need thereof.
2. A method for reducing hemorrhagic microvascular obstructions in a subject in need thereof comprising:
 - (i) establishing therapeutic hypothermia by cooling blood prior to reperfusion, and
 - (ii) establishing reperfusion to an ischemic area in the subject using the cooled blood, so as to reduce hemorrhagic microvascular obstruction,wherein the subject is a myocardial infarction patient whose treatment is initiated at least 6 hours after the onset of symptoms of myocardial infarction, thereby reducing hemorrhagic microvascular obstructions in a subject in need thereof.
3. A method for reducing hemorrhagic vascular obstruction in a subject in need thereof comprising:
 - (i) establishing therapeutic hypothermia, and
 - (ii) monitoring the hemorrhagic , wherein decreased burden of hemorrhage is indicative of decreased microvascular obstruction.
4. The method of claim 3, wherein the subject is not indicated for reperfusion therapy.

5. The method of claim 3, wherein therapeutic hypothermia is established via surface cooling or via the use of a catheter through the femoral artery.
6. A method for reducing ischemia-reperfusion injury in a subject in need thereof by the method of claims 1 or 2.
7. The method of claims 1 or 2, further comprising monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post-reperfusion.
8. The method of any one of claims 1 or 2, wherein the symptoms of onset of myocardial infarction are any one or more of chest pain, elevated ST segment in an electrocardiogram (ECG) and/or elevated troponin levels in the blood
9. The method of claims 1 or 2, wherein the blood is cooled to 2-7°C lower than the normal systemic temperature.
10. A method for monitoring the course of microvascular obstruction in a subject comprising:
 - (i) providing the subject of claim 1, and
 - (ii) monitoring microvascular obstructions using magnetic resonance imaging during reperfusion and post reperfusion.
11. The method of claim 1, wherein perfusion is re-established using fibrinolytic therapy or via an angioplasty.