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(54) **OPTIMAL REMOTE ISCHEMIC PRECONDITIONING (ORIP) FOR MITIGATING DNA DAMAGE**

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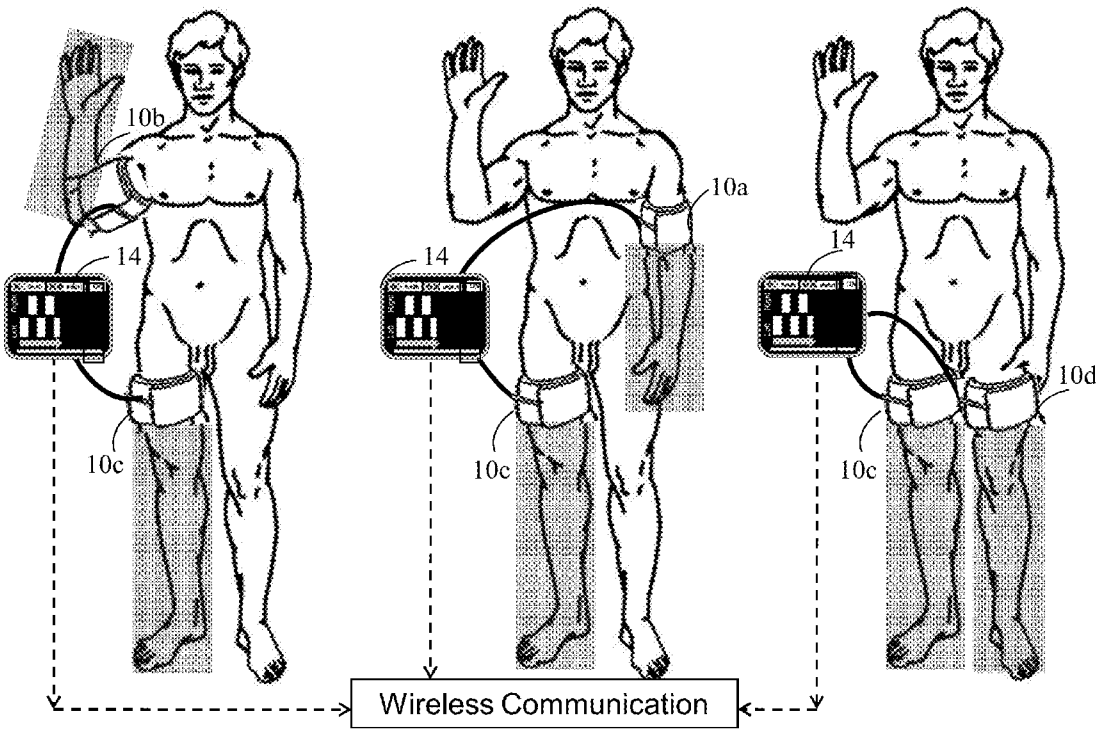
(57) **ABSTRACT**

DNA damage commonly results from exposure to diagnostic and therapeutic use of ionizing radiation, chemotoxic agents, smoking, diet and even from sedentary lifestyle. It is also a function of aging. Unrepaired DNA damage may result in accelerated aging and various forms of cancers. The invention discloses a method to harness the innate power of repetitive transient ischemia and reperfusion for protecting organs against imminent DNA damage, prevent senescence (aging) and for boosting DNA repair. This method of optimal remote ischemic preconditioning (ORIP) comprises of utilizing a pair of programmable pneumatic cuffs that inflate/deflate alternately occluding blood circulation to each of the limbs for pre-defined time intervals. ORIP can be self-administered and remotely monitored by clinician. ORIP may also be deployed as an adjunct in radiotherapy and chemotherapy for reducing the damage to normal tissue and boosting the treatment efficacy. The apparatus delivers maximal ORIP dose in shortest possible time.



Ischemic Zones In Different Embodiments Of ORIP

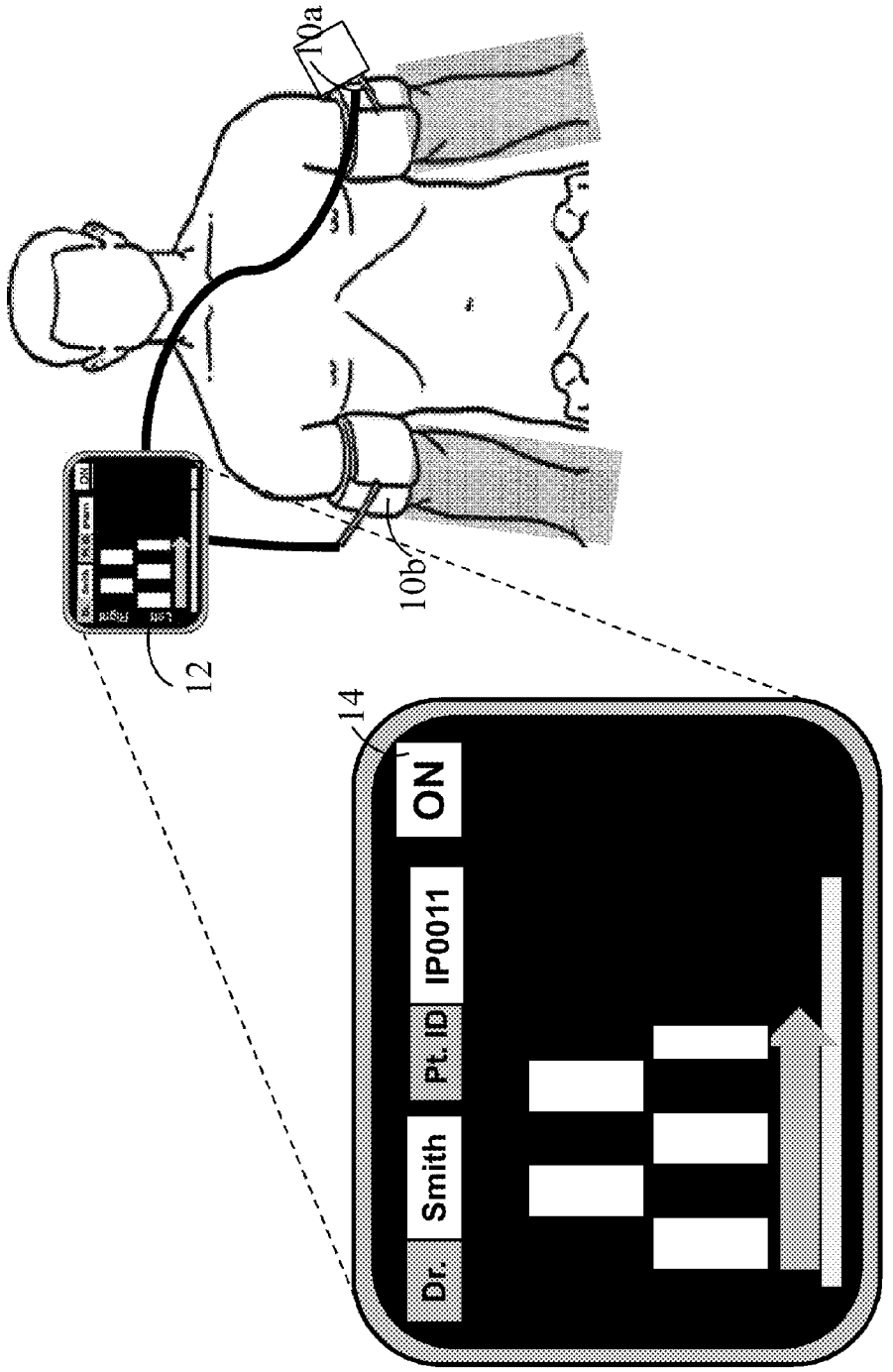


FIG. 1. ORIP Treatment Session In Progress

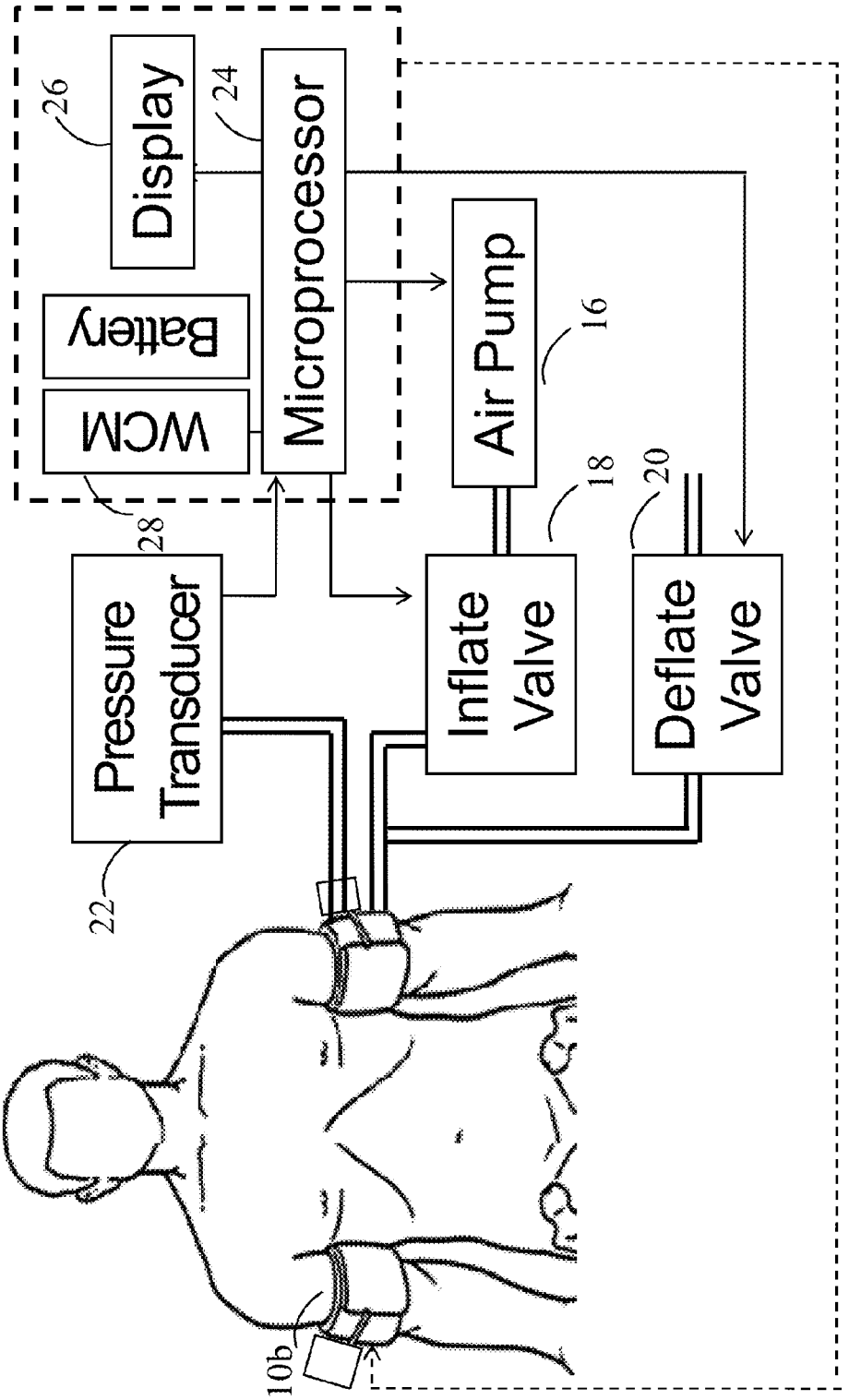


FIG. 2. Block Diagram - Elements of ORIP & Each Pneumatic Cuff

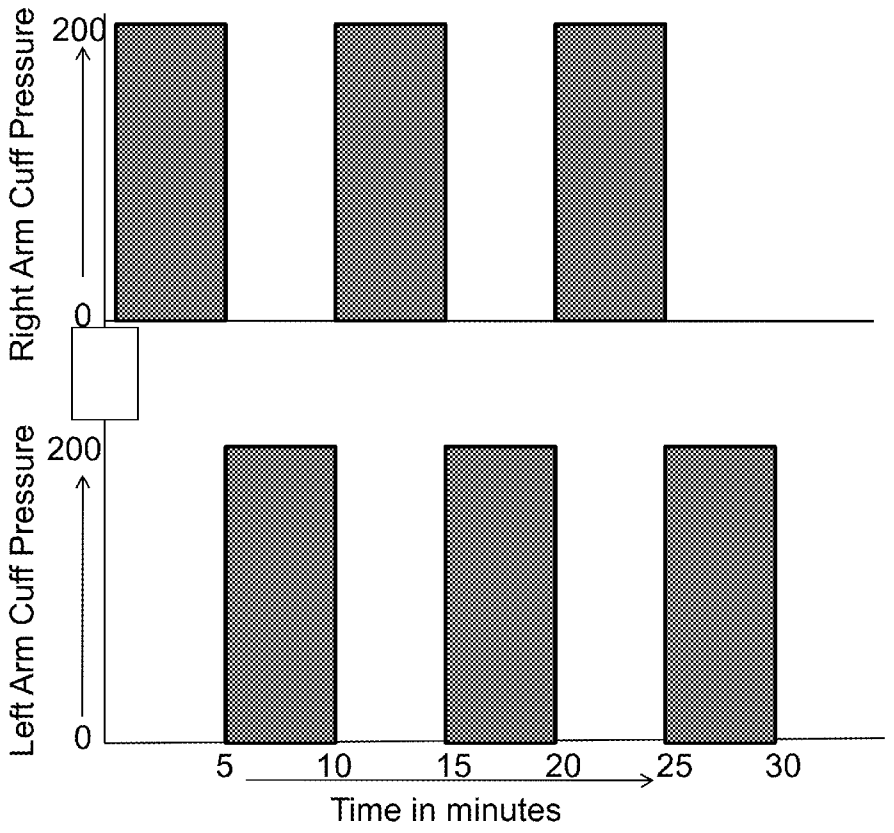


FIG. 3. Sequence of Equal & Alternating Inflation/Deflation Cycles In Limbs

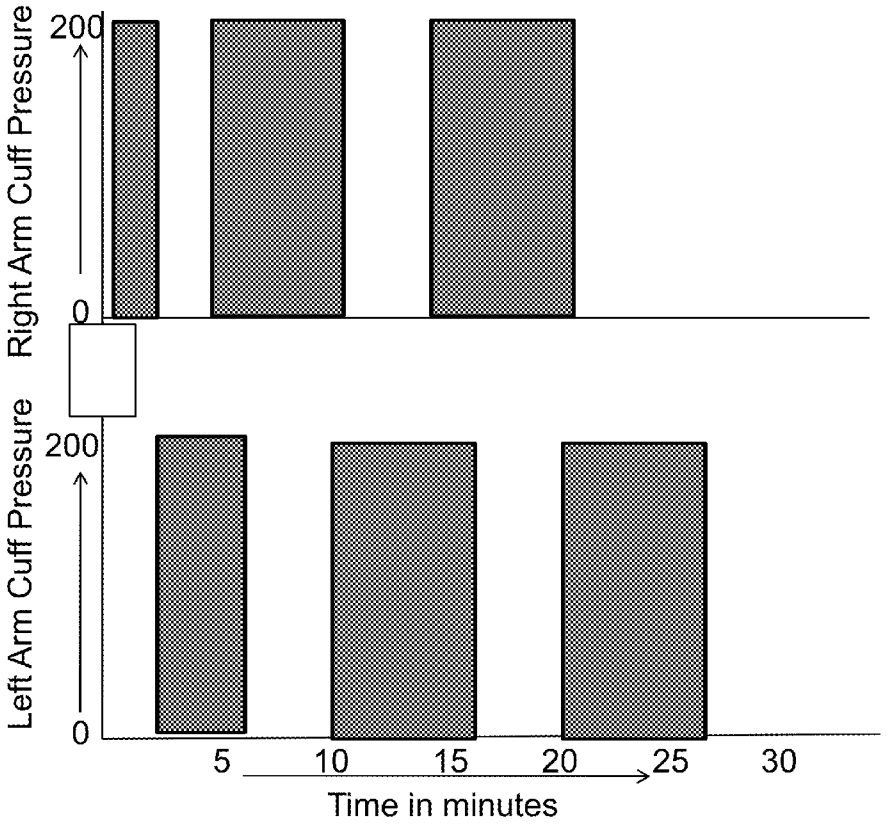


FIG. 4. Sequence of Escalating Timing of Inflation/Deflation Cycles In Limbs

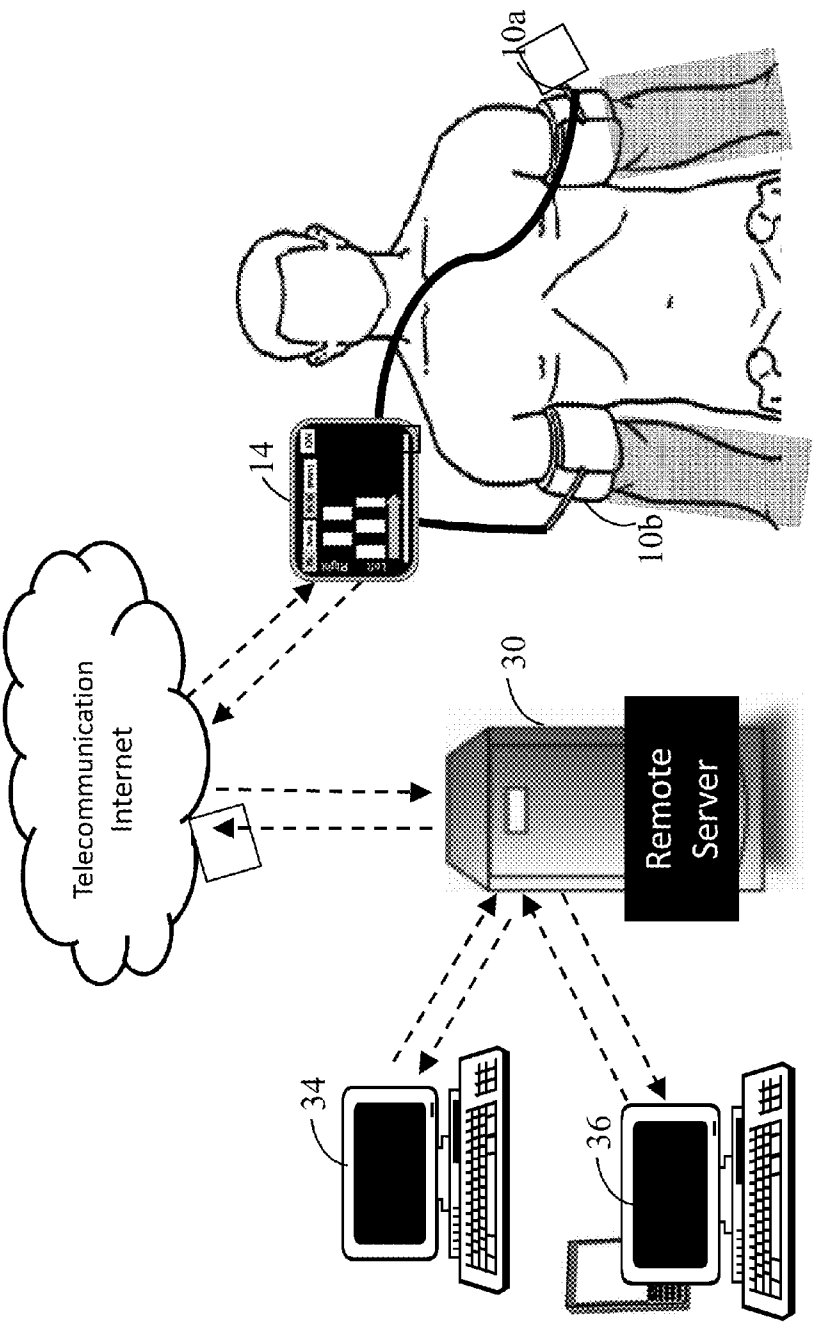


FIG. 5. ORIP EMS / P3 / CC Web Architecture In An Acute Treatment Scenario

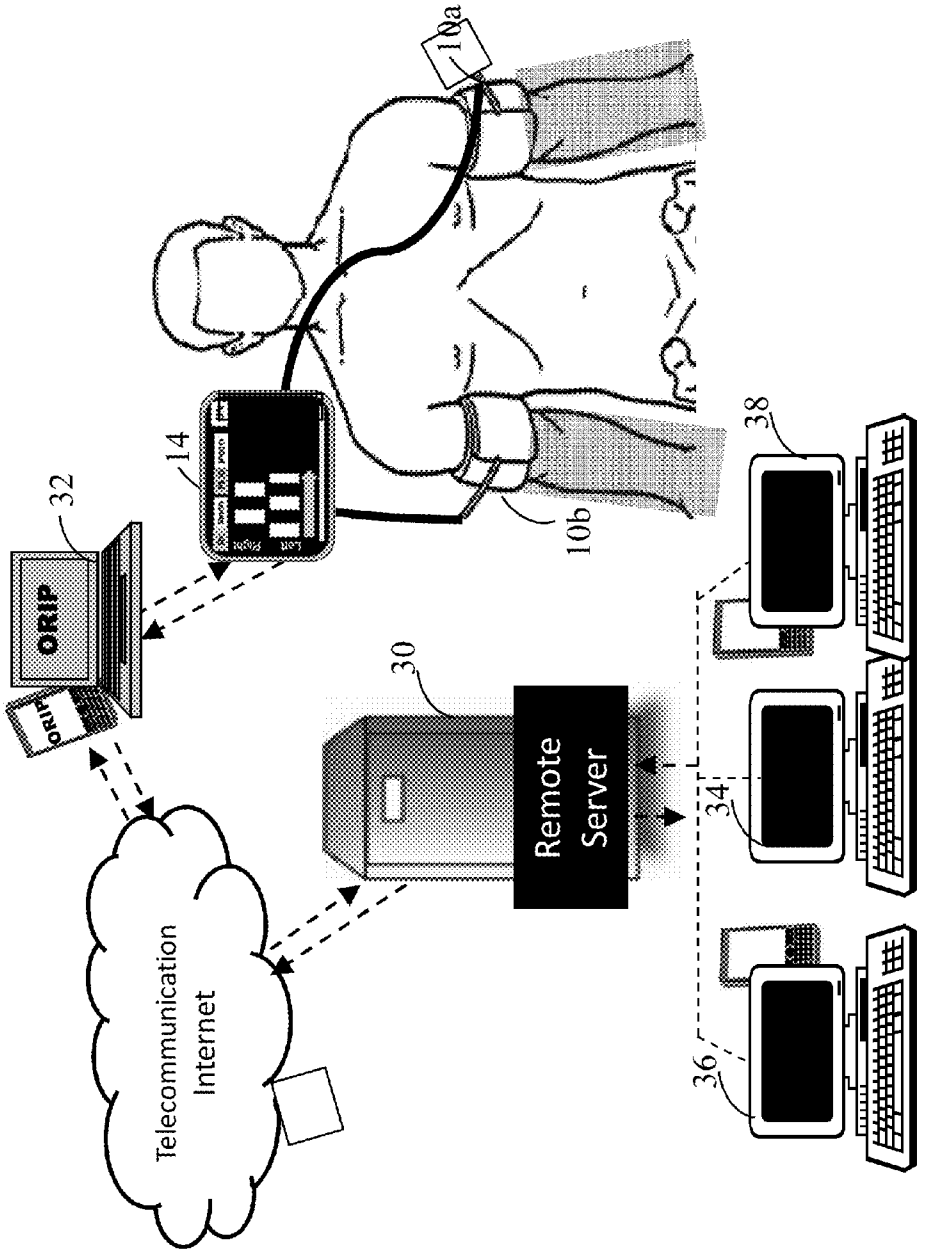


FIG. 6. ORIP Apparatus With RF Module

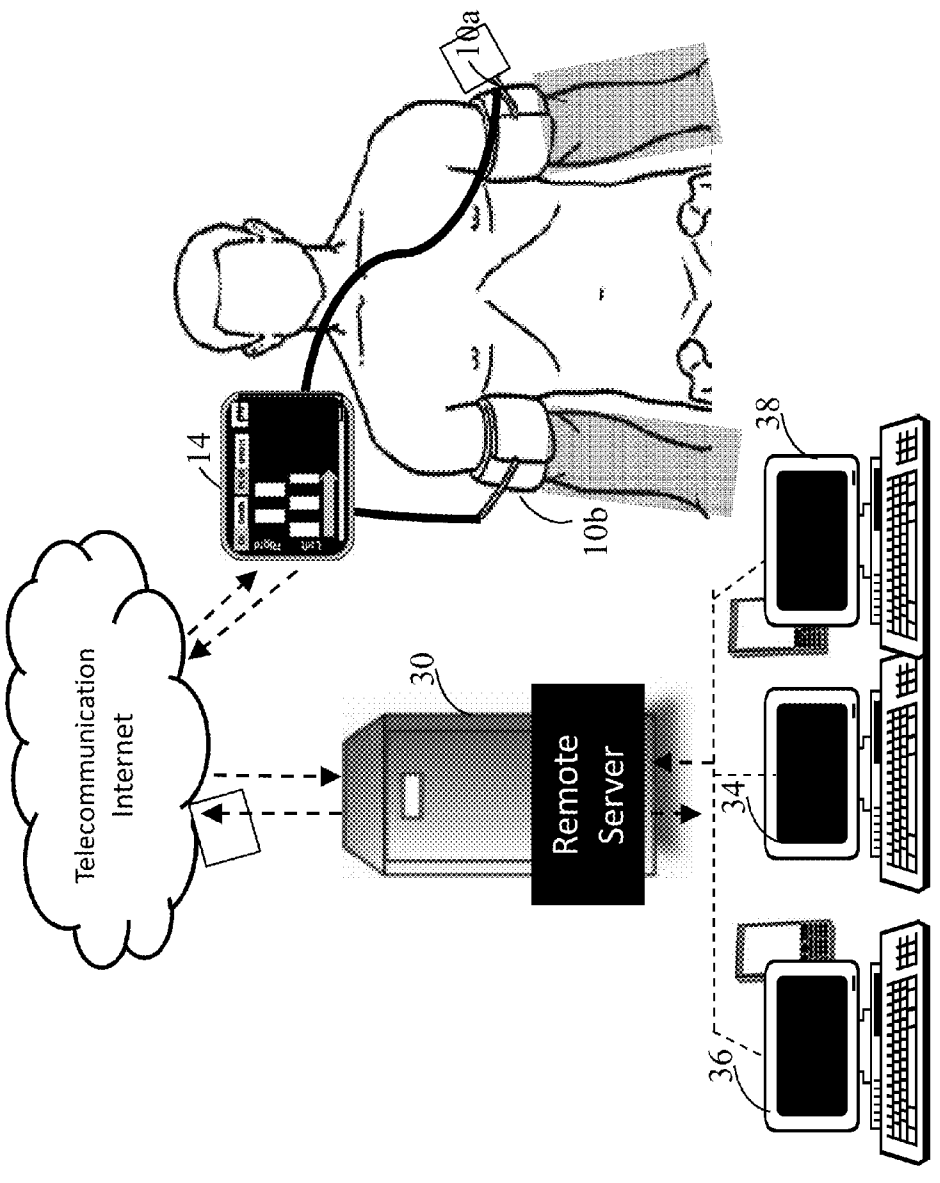


FIG. 7. ORIP Web Architecture In Chronic/Sub-acute Treatment Scenario

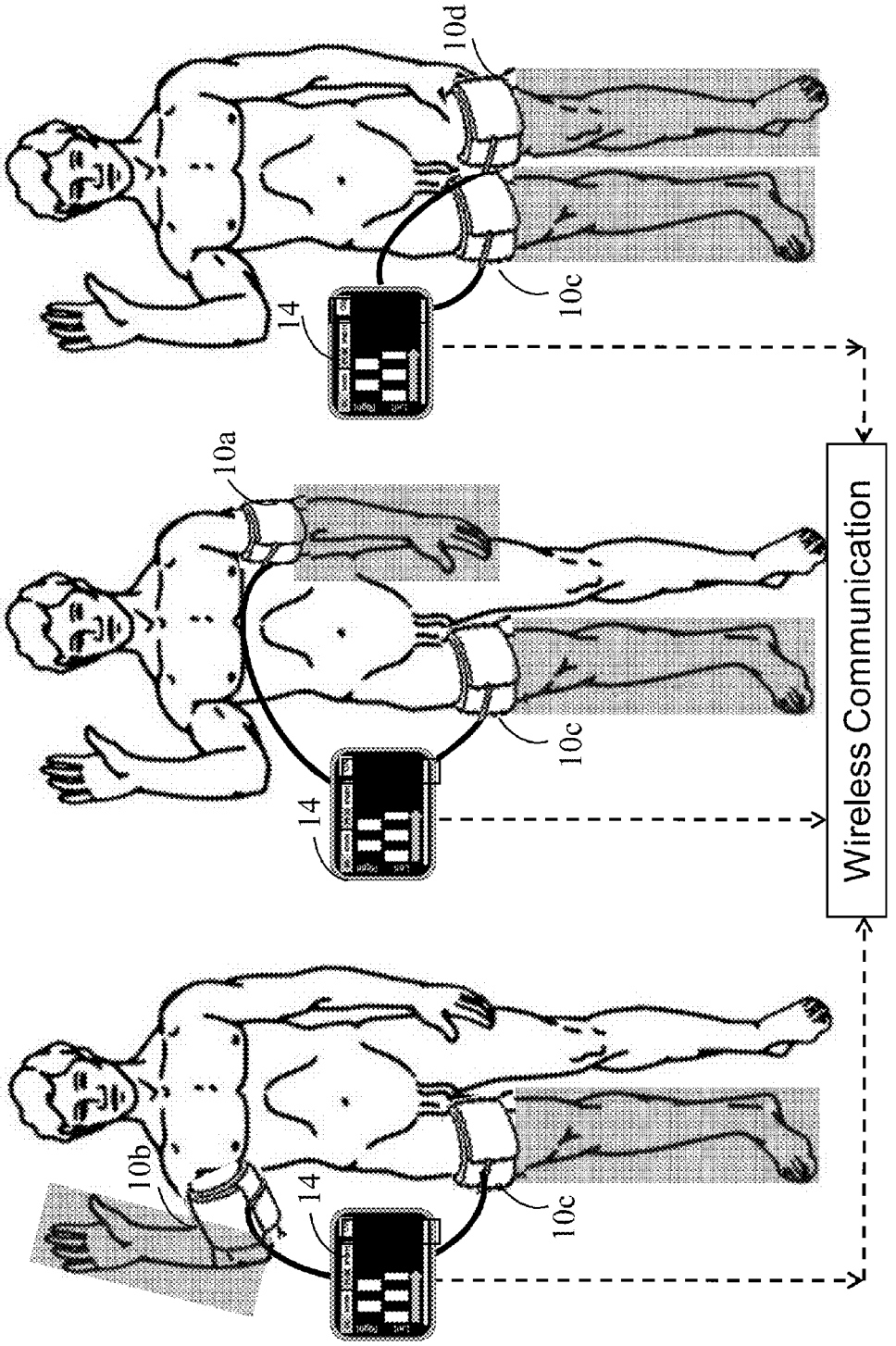


FIG. 8. Ischemic Zones In Different Embodiments Of ORIP

OPTIMAL REMOTE ISCHEMIC PRECONDITIONING (ORIP) FOR MITIGATING DNA DAMAGE

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation-in-part (CIP) of U.S. patent application Ser. No. 12/898,259 filed Oct. 5, 2010, which claimed the benefit of U.S. Provisional Application No. 61/317,294 filed Mar. 25, 2010. These above referenced applications are herein incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] Not Applicable

REFERENCE TO A MICROFICHE APPENDIX

[0003] Not Applicable

FIELD OF THE INVENTION

[0004] The present invention relates generally to transiently and repeatedly auto inflating pneumatic cuffs for inducing limb ischemia distal to its site of occlusion and preconditioning the entire human body to subsequent ischemic and other physiological and pathological insults. More particularly it is a method of remote ischemic preconditioning by occluding limb circulation utilizing a pair of pneumatic cuffs that inflate and deflate alternately for a prespecified time to induce optimal limb ischemia sufficient for inducing system-wide ischemic preconditioning for protecting the organs from DNA damage resulting from physiological, pathological, radiological, chemical insults or merely as result of aging.

BACKGROUND OF THE INVENTION

[0005] There are numerous references mentioned in the parent application incorporated by reference herein which provide background information of the invention, and which themselves are incorporated by reference herein.

[0006] Background information about the embodiments of the invention claimed herein is found in particular in the Ser. No. 12/898,259 application. Definitions of terms used in the instant application are also set forth in the '259 application.

[0007] Preferred embodiments of the present invention are described below and unless specifically noted, it is the applicant's intention that the words and phrases in the specification and claims be given the ordinary and accustomed meaning to those of ordinary skill in the applicable art(s). Likewise, it is applicant's intention to cover and include any and all structure, materials or acts that perform the claimed function, along with any and all known or later developed equivalent structures, materials or acts for performing the claimed function.

[0008] Optimal Remote Ischemic Preconditioning (ORIP) is a non-invasive medical device that induces systemic production of ischemia triggered cellular modulators (ITCMs) by means of causing repetitive and intermittent ischemia and reperfusion in a remote organ such as upper or lower limbs. A large body of peer-reviewed literature establishes that such ITCMs, prominent among them being NF-Kappa B inhibitors, are released in circulation and reach the target organs to protect them against impending stress or injuries including DNA damage. These cellular modulators increase the threshold of the tissue to tolerate biological insults anywhere in the body. ORIP therefore is a very broad platform technology that has applications in a wide range of health conditions.

[0009] In the parent application '259, applicant disclosed following six broad categories of ORIP treatment regimens for preventing organs from eminent pathophysiological insults:

1. EMS (Emergency Medical Services): [0081]

2. P3 (Pre-Procedure Preconditioning): [0082]

3. CC (Critical Care): [0083]

4. CMS (Chronic Medical Service. [0085]

5. Coronary Revascularization Adjunct: [0086]

6. Heart Repair Adjunct [0088]

[0010] A very important category of biological insult that results from our modern lifestyle is the damage caused to our DNA as a result of exposure to ionizing radiations, chemicals, smoking, diet, lack of exercise, and even as a result of normal aging process. DNA damaged cells if left unrepaired may either age faster or become cancerous.

[0011] As disclosed in '259 ORIP can be deployed as a "pre-procedure preparation (P3) device prior to an elective intervention such as, coronary bypass surgery, coronary angioplasty, vascular surgery, organ transplant so on and so forth." In medical practice, particularly in practice of oncology and radiology, a substantial number of elective interventions result in unwanted DNA damage as a result of such diagnostic or therapeutic procedures. Increased DNA damage also results from unhealthy lifestyle that includes but not limited to environmental and medical exposure to ionizing radiation, oxidative stress due to chemotoxic agents, smoking, diet, lack of exercise and even normal aging process. Very recently a research group reported DNA damage resulting from third hand smoke and potential cancer (Bo Hang. American Chemical Society, Mar. 14, 2014). Increased DNA damage not only cause cancers, but also accelerates the aging process.

Ionizing Radiation Related DNA Damage

[0012] Diagnostic x-rays are the largest man-made source of radiation exposure, and interventional radiologic procedures differ from other x-ray-exposing procedures in terms of a variety of parameters. As compared with plain-film radiography, CT involves much higher doses of radiation, resulting in a marked increase in radiation exposure in the population. CT accounts for 15% of all procedures in radiology but contributes 50% of the population dose resulting from the diagnostic use of ionising radiation. The widespread use of CT represents probably the single most important advance in diagnostic radiology.

[0013] Preceding decades have seen a continuous increase in the frequency of diagnostic and interventional cardiac procedures. It is paramount that radiation protection in such procedures must be a matter of primary concern. In addition to this the patients are becoming increasingly aware and concerned about radiation hazards acquired during interventional procedures. As we know that the effects of radiation exposure are not apparent immediately but long-term conse-

quences can be serious, Ionizing radiation is a hazard that cannot be detected by the human senses.

[0014] Non-invasive imaging technologies continue to revolutionize every subspecialty of medicine. Multi-slice CT delivers increased levels of focused radiation compared with single slice CT. Clinical use of multi-slice CT is increasing and the 64-slice cardiac CT heralds the new age of non-invasive cardiac imaging. Nevertheless, despite the promise of 64-slice CT in non-invasive cardiac diagnostics, there are serious concerns in their widespread use because of very high levels of radiation exposure. Median estimated radiation dose for cardiac computed tomography angiography is equivalent to 12 mSv, which is comparable with 1.2 times the dose of an abdominal CT, more than twice that of invasive coronary angiography or 600 chest radiographs. Such high radiation exposure does enhance the risk of cancer substantially.

[0015] A study estimating diagnostic X-Ray related risk of cancer in developed countries found that the attributable risk ranged from 0.6% to 1.8% except in Japan, which was more than 3% (Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet. 2004 Jan. 31; 363(9406):345-51). In US it was estimated that 29,000 new cancers resulted from 72 million CT scans in 2007 (Berrington de Gonzalez, A et al. Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007. Arch Intern Med. 2009; 169(22):2071-2077). It is estimated that 1 in 270 women who underwent CT coronary angiography at age 40 years will develop cancer from that CT scan, as against **1** in 600 men. Despite these caveats, the technology is a major advance and continues to be refined. Prototypes for 128-slice and even 256-slice scanners are aggressively developed. However, the small risk of cancer from radiation exposure to multi-slice CT scanners is limiting the utility of this highly effective innovation in imaging. If this risk is eliminated the risk-benefit analysis will favor the use of this revolutionary technology in screening the general population that is at risk of coronary artery disease.

[0016] Approximately 150 million scans can be attributed to US, Europe and Japan annually. Thus a substantial majority of population at risk of cardiovascular and life style diseases would immensely benefit if an approach was available to make these high resolution CT imaging procedures safer with reduced damage to DNA and reduced life-term risk for cancers.

[0017] Apart from diagnostic radiation exposure, therapeutic use of radiotherapy, chemotherapy and a combination thereof is also a major cause of collateral DNA damage to the normal healthy cells. If such collateral DNA damage to healthy cells is checked, the practice of oncology will greatly improve in terms of cancer treatment.

[0018] Nuclear factor Kappa B (NF-KappaB) is activated as part of the DNA damage response induced by ionizing radiation. NF-Kappa B triggers inflammatory and cell survival pathways that promote mutations, senescence and eventual carcinogenic transformation of the DNA-damaged cells. It down-regulates apoptosis, thereby promoting survival of cells with damaged DNA that serve as precursors of cancer. NF-Kappa B activity also down-regulates the DNA repair Ku protein and p53 expression resulting in more DNA damage.

[0019] NF-Kappa B regulates over 300 genes involved in cellular injury/stress, inflammation and repair cycle. Xuan et al were amongst the first to report that NF-Kappa B is involved in remote ischemic preconditioning (Xuan Y T, Tang X L, Banerjee S, et al: Nuclear factor-kB plays an essential role in the late phase of ischemic preconditioning in conscious rabbits. Circ Res 1999; 84:1095-1109). Remote ischemic preconditioning is known to reduce the expression of NF-kappa B, TNF-alpha, IL-1beta, and ICAM-1. Activation of NF-Kappa B is a key event in brain injury and tolerance can be induced by remote ischemic preconditioning (Steiger H J, Hanggi D. Ischaemic preconditioning of the brain, mechanisms and applications. Acta Neurochir (Wien). 2007 January; 149(1):1-10. Epub 2006 Dec. 14.).

[0020] Remote ischemic preconditioning modifies gene expression by regulating protective genes via the NF-Kappa B activity modulation (Saxena P et al. Remote Ischemic Conditioning: Evolution of the Concept, Mechanisms, and Clinical Application. J Card Surg 2010; 25; 127-134). Changes in gene expression occur in both early and delayed phases of remote preconditioning. Remote ischemic preconditioning can regulate NF-KB via multiple pathways including innate immunity pathways and a ubiquitous phosphoinositide-3 kinase (PI3K) pathway. The ability of remote ischemic preconditioning to modulate NF-Kappa B pathway has been hailed as Holy Grail and a road to an amazing discovery (Konstantinov E and Redington, A N. Linking gene expression, nuclear factor kappa B, remote ischemic preconditioning, and transplantation: A quest for an elusive Holy Grail or a road to an amazing discovery? J. Thorac. Cardiovasc. Surg., 2006; 131(2): 507-509.)

[0021] Currently there is no product that satisfies this substantial and urgent unmet need to mitigate the effects of ionizing radiation exposure or countering the rigors of oxidative stress. ORIP technology provides an approach to minimize the radiation or oxidative stress induced DNA damage and consequently eliminates or minimizes the risk for consequential cancers and cell senescence. ORIP treatment regimen of instant invention can be administered to a patient in one or more sessions prior to exposure to a high radiation diagnostic or therapeutic procedure and as required thereafter to minimize DNA damage, radio-toxicity and resultant cancer risk.

Oxidative DNA Damage

[0022] Free radicals and other reactive species are constantly generated in vivo and cause oxidative damage to DNA at a rate that is probably a significant contributor to the age-related development of cancer. Oxidative DNA damage is an inevitable consequence of cellular metabolism, with a propensity for increased levels following toxic insult. (Cooke et al. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 2003 July; 17(10):1195-214). Research suggests that oxidative DNA damage is induced in lung DNA by cigarette smoking. Even third-hand smoke has be implicated in DNA damage and potential cancer (Bo Hang. American Chemical Society, Mar. 14, 2014). Oxidative stress and DNA damage has also been shown to result from high fat and high calorie diets. Mutations caused by oxidative DNA damage contribute to many human diseases. Therefore oxidative DNA damage is a "biomarker" for identifying persons at risk (for lifestyle or genetic reasons, or both) of developing cancer and for suggesting how the lifestyles of these persons could be modified to decrease that risk. Measures that decrease oxidative DNA damage should thus decrease the risk of cancer development. As discussed earlier Optimal Remote Ischemic Preconditioning inhibits the NF-Kappa b activation

and therefore plays a crucial role in preventing or mitigating the impact of DNA damage resulting from all kinds of oxidative stress.

DNA Repair

[0023] DNA damage usually results in repair within hours of the DNA damaging insult. If repair fails, either apoptosis (programmed cell death) ensues, or unregulated cell division eventually results in malignancy. In high-risk individuals or in those with DNA repair disorders these biological insults may result in cumulative DNA damage that cannot be repaired by their overburdened DNA repair mechanisms. Several reports establish that ischemic preconditioning directly triggers several DNA repair pathways and modulators, thereby enhancing the repair of endogenous oxidative DNA damage, which would result in lowering the cumulative burden of damaged DNA in individuals who are already overwhelmed because of the defective DNA repair system.

[0024] Cellular response to DNA damage is complex and relies on the simultaneous activation of different networks. It involves DNA damage recognition, repair, and induction of signaling cascades leading to cell cycle determining responses. If the rate of DNA damage exceeds the capacity of the cell to repair it, the accumulation of errors can overwhelm the cell and result in early senescence, apoptosis or cancer. The fate of damaged cells depends on the balance between pro- and anti-apoptotic signals. In this decisive life or death choice, the transcription factor NF-kappa B has emerged as a pro-survival actor in most cell types, consequently associated with tumorigenic process as it protects cancerous cells from programed death. NF-Kappa B activity down-regulates the DNA repair Ku protein and p53 expression.

[0025] Besides down-regulating NF-Kappa B, remote ischemic preconditioning triggers a cascade of ischemia cellular modulators (ITCMs), some of which may supplement the impaired DNA repair pathways. Such ITCSMs include sirtuin (SIRT1)—the longevity protein, now known to perform additional function of DNA repair. Similarly p53, primarily a cancer suppressor gene inversely modulated by NF-Kappa B activity, is also known to perform DNA repair functions.

[0026] Considering countless number of sources of DNA damage that humanity faces on daily basis, there's no known intervention that can prevent or minimize DNA damage, accelerate DNA repair, stop mutations in damaged DNA, facilitate apoptosis of irreparable DNA, and prevent early senescence of the healthy cells. Therefore there is urgent need to solve these problems and accomplish the entire procedure of prescribing, administering, monitoring and measuring and optimizing the ischemic preconditioning regimen with a single touch user-friendly device requiring very little of the physician time or with his remote supervision of the treatment protocol.

SUMMARY OF THE INVENTION

[0027] The present invention addresses the foregoing need for a method and apparatus for prescribing, administering and monitoring optimal remote ischemic preconditioning for the purpose of preventing DNA damage to organs as a result of routine biological or physiological insults. Accordingly, there is a need for a versatile invention as summarized herein in some detail. Consequently, it is an advantage of the invention that it objectively administers the prescribed remote ischemic preconditioning dose optimally with a single touch and in half the time of any manual or automatic procedure known to the prior art, without significant pain or discomfort to the patient. It is further advantage of the method that it creates at least two ischemic-reperfusion zones in two different remote organs of the patient in a single dosing session thereby creating a much larger ischemic preconditioning space resulting in a much stronger protective response to ongoing or impending DNA damage.

[0028] It is therefore an object of the present invention to provide an entirely new method of prescribing a non-pharmacological prophylactic and therapeutic ORIP treatment regimen for preventing DNA damage resulting from modern lifestyle, by means of a user friendly portable device that administers, monitors, measures and ensures compliance of the ORIP treatment regimen with the eventual goal of minimizing the consequences of DNA damage.

[0029] It is also an object of the present invention to deliver the maximal dose of ischemia in shortest possible time without patient discomfort for inducing optimal system wide ischemic preconditioning for increasing the threshold of organs to withstand oxidative stress and DNA damage.

[0030] It is also an object of the present invention to place ORIP dosing protocol under the direct control of the clinician who can prescribe and monitor the DNA damage prevention regimen remotely in real time. It is also another object of the invention to allow the home-based self-administration of the ORIP treatment by a chronically ill ambulatory patient at risk of oxidative stress and DNA damage. It is yet another object to make the method and apparatus user friendly and painless for the patient, the clinician and any clinical personnel engaged in administering the ORIP treatment.

[0031] It is yet another object of the invention to make ORIP treatment easily deployable across the board in any pre-intervention settings that involve damage to the DNA. It is yet further object of the invention to treat, prevent or mitigate oxidative stress and DNA damage resulting from exposure to chemotoxic substances, high fat high calorie diets, smoking and other lifestyle related causes. It is also an object of the invention to provide an anti-aging device that decelerates the process of aging by means of mitigating DNA damage, cell senescence and accelerating repair of DNA damage.

[0032] Present invention meets these objectives by providing a means for preventing, treating or mitigating the impact of DNA damage to a healthy human tissue comprising of releasing ischemia triggered cellular modulators (ITCMs) by means of non-invasively inducing transient, repetitive and alternate cycles of ischemia and reperfusion, each lasting not less than 1 minute and not more than 10 minutes, in one or more remote organs, in one or more sessions, thereby increasing the tissue injury threshold for DNA breaks, promoting apoptosis of damaged cell, preventing senescence of damaged cell, and accelerating the process of DNA repair.

[0033] In one preferred embodiment, optimal remote ischemic preconditioning system is implemented as disclosed in the parent '259 application, that uses paired cuffs at two different anatomical locations (both upper limbs or both lower limbs or one upper and one lower limb etc.), which alternately inflate and deflate rendering ischemic stimuli to a march larger volume of the body in half the time and least patient discomfort.

[0034] Accordingly, the present invention is directed to devices, systems, methods, programs, computer products, computer readable media, software algorithms and other

hardware components such as pneumatic cuffs, air pumps, valves, transducers and modules for controlling one or more operating parameters and components of the ORIP apparatus by either an attending clinician or remotely by a clinician not in attendance by sending and receiving programming from a remote server or system, such as the Web interface.

[0035] These advantages in addition to other objects and advantages of the invention will be set forth in the description which follows, and may be learned by the practice of the invention. The objects and advantages of the invention may be realized and obtained by means of the software, algorithms, devices, remote servers and combinations thereof particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] FIG. **1**. An illustration of an ORIP treatment session in progress.

[0037] FIG. **2**. Block diagram of the elements ORIP apparatus and each of the pneumatic cuffs.

[0038] FIG. **3**. Sequence of equal & alternating inflation/deflation cycles in left and right limbs.

[0039] FIG. **4**. Sequence of escalating timing of inflation/deflation cycles in left and right limbs.

[0040] FIG. **5**. ORIP EMS/P3/CC web architecture in an acute treatment scenario.

[0041] FIG. **6**. Schematic representation of ORIP apparatus with RF Module.

[0042] FIG. **7**. ORIP web architecture in an acute/sub-acute treatment scenario.

[0043] FIG. **8**. Illustration of ischemic zones in different embodiments of ORIP.

DETAILED DESCRIPTION OF THE INVENTION

[0044] Detailed description about the ORIP apparatus, its operation and its variants claimed in the instant invention is found in particular in the Ser. No. 12/898,259 application. Definitions of terms are also set forth in the '259 application. Numerous embodiments of treatment regimens were mentioned in the parent application that remain relevant to enabling the method of the present invention, and hence incorporated by reference herein. Nevertheless, pertinent features of parent invention are reproduced herein for placing the teachings of the present invention in proper perspective.

[0045] The novel features of the non-pharmacological ORIP treatment of the instant invention can be deployed in many different DNA damage and oxidative stress scenarios for preventing, treating or mitigating the impact of DNA damage to a healthy human tissue by means of releasing ischemia triggered cellular modulators (ITCMs). Such DNA damage may be caused as a result of an exposure to ionizing radiation during a therapeutic or diagnostic medical procedure. Such DNA damage may also result from exposure to chemotoxic agents, or may be cause as a result of oxidative stress resulting from lifestyle related causes or aging. In such DNA injury situations, ORIP treatment acts by increasing the tissue injury threshold for DNA breaks by down-regulating NF Kappa B, accelerating the process of DNA repair through various cell repair pathways, promoting apoptosis of irreparable cells, preventing senescence of affected cells, so on and so forth.

[0046] In the following detailed description numerous specific details are set forth in order to provide a thorough understanding of the present invention for preventing, treating or mitigating the impact of DNA damage to a healthy human tissue. Such method comprises of releasing ischemia triggered cellular modulators (ITCMs) by means of non-invasively inducing transient, repetitive and alternate cycles of ischemia and reperfusion, each lasting not less than 1 minute and not more than 10 minutes, in one or more remote organs, in one or more sessions, thereby increasing the tissue injury threshold for DNA breaks, promoting apoptosis of damaged cell, preventing senescence of damaged cell, and accelerating the process of DNA repair. However, so as not to obscure the present invention, every minor detail may not be covered. Nevertheless, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. Accordingly, optimal remote ischemic preconditioning (ORIP) is a technology platform that can be adapted and implemented in a long list of clinical and lifestyle conditions requiring protection from DNA damage and accelerated aging.

[0047] Based on the design features, networkability of the ORIP apparatus and the physiological mechanism that triggers the cascade of ischemia triggered cellular modulators (ITCMs), the clinical utility of ORIP treatment can be classified as acute deployment, sub-acute deployment or chronic deployment. Acute deployment of the ORIP device treatment may be as brief as a single session, and may be in an elective procedure pre-conditioning setting. While sub-acute treatment regimen includes scenarios requiring a limited time repeated ORIP dosing sessions ranging from a few weeks to a few months. However, chronic treatment will be long term permanent or semi-permanent use of the device.

[0048] These embodiments are herein described and illustrated through self-explanatory drawings in FIGS. **1** through **8**. In a preferred embodiment the apparatus comprises of using a pair of pneumatic cuffs wrapped around each of the limbs, for example left upper limb **10***a* and right upper limb **10***b*. Alternatively the cuffs can be used on the wrist. These pneumatic cuffs are very similar to those used with self-inflating oscillometric sphygmomanometers. These easy to apply cuffs, which can be used on any of the upper and lower limb combinations, can either be used by a clinician or the patient himself/herself without any assistance by simply wrapping the cuffs around the patient's selected pair of limbs. Separate air tubing connect both the pneumatic cuffs to an ORIP Console **12** housing the mechanical as well electronic components that operate both the cuffs automatically inflating and deflating in accordance to a pre-defined algorithm protocol upon pressing the Start or ON Button **14** on the ORIP Console. A series of protocols may be permanently programmed in the ORIP Console providing as options for the user to choose a particular ORIP regimen, or can be delivered to the Console from a remote location as a prescription from a remote clinician. For such remote wireless connectivity the ORIP Console may incorporate a Communication Module which may be wired or wireless **28** (WCM).

[0049] It should be noted at this point that in the various wireless embodiments described herein, all client-server data transfer between the wired or wireless nodes is implemented either through the telecommunication network or the Internet, using protocols such as but not limited to WAP (Wireless Application Protocol) or HTTP or TCP/IP communication or SMPP (short message peer-to-peer protocol) to and from the ORIP Console's wireless communication module preferentially according to the availability of the 802.11 and cellular data channels.

[0050] When the Internet connectivity hardware is either not incorporated within the ORIP Device Console or when the Internet is not accessible, a peer to peer communication can also be established with another wireless communication device in the vicinity via radiofrequency (RF) transmission between the RF Modules embedded within the Console and the wireless communication device (FIG. **6**). Such wireless communication device can be a mobile phone, a laptop computer or even a stationary communication terminal placed within the radiofrequency range of the ORIP Console. These wireless communication devices may in turn transfer the data received from the ORIP Console to the ORIP network via the Internet. If the ORIP device or such other wireless communication devices in the vicinity support multiple communication modes, communication is attempted first using a TCP/IP connection over open 802.11 channels, second using GPRS-enabled bulk or stream transfer, and finally SMS/MMS can be used as a fallback.

[0051] Each ORIP cycle comprises of simultaneous alternating phases in each limb such as:

[0052] a) an ischemic phase wherein first of the two auto-inflatable pneumatic cuffs inflate to a cuff pressure that significantly exceeds beyond the systolic blood pressure to completely occlude blood flow to the patient's first remote organ **10***a* (left limb) for a pre-defined period that is not less than 1 minute and not more than 10 minutes, and,

[0053] b) a reperfusion phase wherein second of the auto-inflatable pneumatic cuffs deflates to allow free flow of blood to second remote organ such as the right limb **10***b* for a pre-defined period, which may not be less than 1 minute and not more than 5 minutes.

[0054] A single ORIP session may comprise of not less than 2 and not more than 5 of either escalating/deescalating/unequally/equally timed phases of alternating cycles per limb, accomplishing twice the ischemic body area for optimal release of the therapeutic ITCMs in half the time required by a single cuff procedure thereby resulting in more potent effect in a much shorter time without significant pain or discomfort to the patient. Nevertheless, a single cuff remote ischemic procedure may also be implemented to combat DNA damage.

[0055] As illustrated schematically in FIG. **2** each cuff may have its own corresponding air pump, which comprise of an air pump **16** with an inflate valve **18** to allow and sustain inflation during the ischemic phase at a cuff pressure that is significantly above the systolic blood pressure, and a deflate valve **20** to deflate the cuff during the reperfusion phase such that when the first limb **10***a* is in ischemic phase the second limb **10***b* is in reperfusion phase. Each pump of the air-pumping module is connected to its corresponding cuff through tube. A pressure transducer **22** for each cuff senses pressure oscillations in the artery by changes in the counter-pressure off the cuff thus measuring the cuff pressure during an ORIP session. The pressure transducer may use either an oscillometric, or a photoplethysmographic, or an ultrasonic, or a thermal or an infrared transduction method to measure the minimal blood flow occlusion pressure (systolic blood pressure) to set up the maximal occlusion pressure (10-30% higher than systolic pressure) in the ischemic phase for each of the cuffs.

[0056] In addition to these hardware components for each cuff, there is a Microprocessor **24** that controls and operates both the cuffs **10***a* and **10***b*, and a Display **26** that provides user interface to start, monitor and review the ORIP data, display in a real time graphic user interface the ORIP treatment protocol, the status, interact with the clinician, receive treatment reminders, review the prognosis of the treatment and provide the user means controls and switch to start or stop device. The microprocessor is either pre-programmed or programmable to automatically inflate and deflate the pneumatic cuffs alternatively in predefined repetitive cycles in predefined order of each of the two remote organs (limbs). The console display and controls provide graphic user interface for real time user interaction with the microprocessor and other components that are stored in the microprocessor's memory bay which may include but are not limited to the selection and initiation of a particular ORIP session, calling for a readout of some previously stored data or the like, or setting into the microprocessor patient related data, as well as times and dates relating to specific ORIP sessions and regimen.

[0057] In FIG. **1**, the upper arms **10***a* and **10***b* of a human subject are shown wearing automatic flexible inflatable and deflatable cuff for occluding the brachial artery when inflated beyond the subject's systolic blood pressure. Systolic pressure is the maximum arterial pressure that is produced during contraction of the left ventricle of the heart. A typical ORIP session begins when the user uses the ORIP Console Start/On button **14** to first select the specific ORIP regimen and then begins the process of inflating the pneumatic cuff. The Console Microprocessor **24** either utilizes a predefined target of inflation pressure or actually measures the systolic blood pressure to estimate the target inflation pressure in each cuff. Such target inflation pressure when predefined is not less than 200 mm Hg, and when it is estimated, it is not less than 10% and not more than 30% above systolic pressure in upper arm or wrist; and not less than 210 mm Hg, or not less than 10% and not more than 30% above systolic pressure in thigh. The Microprocessor retrieves the user selected ORIP regimen from its memory and initiates the ORIP session by inflating the first pneumatic cuff to a pressure that is 10-30% greater than the highest expected systolic reading using the oscillometric method. When the oscillations cease the maximum systolic pressure is reached. An ischemic zone is created distal to the inflated cuff. These ischemic zones are illustrated in each of the FIGS. **1**, **5**, **6**, **7** and **8** by shaded areas. The preferred remote organs for administering the ORIP treatment regimen are but not limited to the extremities, more preferably the upper arm of the upper limbs and thigh of the lower limbs. For an ORIP session either both cuffs can be applied to upper arms of upper limbs, or to wrists, or to thighs of lower limbs or a combination of upper and lower limbs. As illustrated in FIG. **8**, a right upper arm cuff **10***b* can be paired with a right thigh **10***c*, or left upper arm cuff **10***a* can be paired with right thigh **10***c*, or the cuffs can be applied to each of the right **10***c* and left thighs **10***d*. As can be inferred from FIG. **8** larger ischemic zones can be created with thigh cuffs as compared to upper arm cuffs as a much larger tissue mass is exposed to the ischemic effect in legs than in arms. As represented by the shaded areas FIG. **8** the ischemic zones created in lower limbs are larger than those created in upper limbs. Accordingly, the cycles of ischemic and reperfusion phases in an ORIP session can be further varied depending upon the remote organs selected for dosing.

[0058] The ORIP Console housing may also incorporate a Wireless Communication Module **28** to receive and send feeds from and to the clinician regarding the compliance to the clinician-prescribed ORIP treatment regimen, or to alter the ORIP treatment regimen, or to prescribe a new ORIP

treatment regimen. The wireless communication module may use WIFI, GPRS, TCP/IP or a telecommunication protocol to transmit data to the Internet either directly (FIGS. **5** & **7**) or use peer to peer RF transmission through an RF-enabled handheld communication device in the vicinity of the ORIP Console as illustrated in FIG. **6**.

[0059] A graphic representation of the pressure in each of the two cuffs during ischemia and reperfusion cycles of a typical ORIP session is presented in FIGS. **3** and **4**. In a preferred embodiment in FIG. **3** the ischemia and reperfusion phases are equal and alternating, meaning that when one cuff is inflated the other one is deflated. There is no overlap of the inflation and deflation cycles in this embodiment. However, in another preferred embodiment in FIG. **4** the ischemia/reperfusion cycles alternate at initiation of the first cycle but the inflation time escalates with subsequent inflation and there may be some overlapping of ischemic phase in respective limbs as the ORIP session continues because the deflation time remains constant in each limb. In gradually increasing the duration of the ischemic phase, the pre-conditioning effect may be more attuned to the natural physiological response to the ischemic episodes.

[0060] FIG. **5** illustrates an embodiment in which the ORIP apparatus is deployed in an acute or P3 (pre-procedure preconditioning) setting such as in which ORIP regimen comprise of a single ORIP session of not less than 2 and not more than 5 ischemia/reperfusion cycles. Repeat sessions may be warranted depending on the condition of the patient. FIG. **6** also illustrates the networkability of the ORIP apparatus, although it will be understood by those skilled in the relevant art that the ORIP treatment can be administered even if the ORIP apparatus is not networkable. As described previously the ORIP Console **14** may incorporate within its housing a wireless communication module **28** to connect to a remote server **30**, which enables Internet connectivity using any of the Internet connectivity protocols known to the prior art, such as WIFI, GPRS, TCP/IP or a telecommunication protocol to transmit data to the Internet either directly or using peer to peer RF transmission through an RF-enabled communication device **32** in the vicinity of the ORIP Console as illustrated in FIG. **6**. Such RF-enabled communication device may be a mobile phone, a laptop or any computer connected to the Internet. The ORIP data, whether stored or real time, can be accessed through Web interfaces designed for the Administrator **34**, the Clinician **36** and the patient **38** mostly in sub-acute or chronic treatment settings, wherein, because of its networkability, the apparatus can also be implemented with a single cuff. In fact this method of mitigating DNA damage and delaying senescence and aging of cells can be implemented with adequate efficiency using a single automated cuff operated by a device that is not networked.

[0061] Following are examples of how the preferred embodiments of ORIP can be deployed in mitigating the effects of DNA damage. These examples are only broadly illustrative of the scope of the novelty of the invention disclosed, and do not limit the utility of the ORIP procedure in any oxidative stress condition where the organs and the vasculature is at risk of injury or compromised function on account of sub-optimal regulation of cellular mediators of protection against DNA damage, DNA repair, cell apoptosis, cell senescence, cell mutation, cell mutagenicity, etc. The scope of the novelty of the invention is also not limited to simultaneous deployment of all the modules of the apparatus. For example absence of communication module, paired cuff module, web interface module or missing network architecture may still enable the invention achieving its objective of mitigating DNA damage

[0062] P3 (Pre-Procedure Preconditioning):

[0063] Certain high DNA injury procedures in diagnostic and therapeutic radiology and chemotherapy in medical practice are performed on an elective basis. These procedures such high radiation CT scans, such as coronary angiography, abdominal CT, radiation and chemotherapy in practice of oncology, are schedule ahead of time. ORIP treatment can be applied with the convenience of short treatment administration time, maximal ischemic dosing, patient comfort, and single touch command without clinician supervision. The ORIP method of the instant invention accomplishes the remote ischemic preconditioning in just 20-25 minutes automatically with one push on the start button and without continuously engaging a clinician in process that may take up to an hour without the ORIP device. ORIP pre-procedure preconditioning treatment can be completed in a single session comprising of not less than 1 minute and not more than 10 minutes each of the ischemia and reperfusion phases. At least 2 and not more than 5 of equally timed phases of such ischemia and reperfusion cycles per limb are administered in a single session. Alternatively the session may comprise of at least 2 and not more than 5 increasingly timed phases of ischemia cycles may be administered per limb. In either way the entire ORIP treatment can be accomplished during the time patient is prepared for the CT scan, radiotherapy, chemotherapy session or any such exposure to ionizing radiation or oxidative stress condition.

[0064] Chronic DNA Damage Prevention & Wellness Promotion:

[0065] ORIP can also be deployed in long term mitigation of DNA damage, countering oxidative stress, or delaying aging as a wellness device. As discussed earlier, modern lifestyle has introduced many ways in which DNA damage can be intensified or DNA repair can be impaired, resulting in surplus unrepaired DNA which may cause point mutations, cell senescence, eventually causing malignancies and accelerating aging. Clinicians can prescribe ORIP therapy particularly in high-risk conditions. ORIP treatment can not only afford protection against DNA damage, but can boost DNA repair, reduce oxidative stress and thus mitigate the long term risk of developing cancers and decelerate the process of aging.

[0066] ORIP treatment regimen in chronic treatment scenario comprise of not less than 2 sessions per week and not more than 14 sessions per week, and each session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemic and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of ischemia and reperfusion respectively. As DNA damage and repair is an ongoing activity in human body and aging and lifetime cancer risk is an inevitable reality of life, ORIP treatment can continue lifelong if necessary.

[0067] Radiotherapy & Chemotherapy Adjunct:

[0068] Apart from diagnostic radiation exposure, therapeutic use of radiotherapy, chemotherapy and a combination thereof is also a major cause of collateral DNA damage to the normal healthy cells. Prognosis in radiotherapy and chemotherapy relies on the maximum tolerable dose of cancer killing radiotherapy/chemotherapy interventions. Because these interventions cause plenty of collateral damage to the healthy

cell population cancer treatment is limited by the magnitude of deployable therapeutic doses. If such collateral DNA damage to healthy cells is checked, the practice of oncology will greatly improve in terms of cancer treatment. Because ORIP treatment promotes DNA damage preventing activities such as reducing inflammation, down-regulating NF Kappa B, interrupting life cycle of damaged cells by inducing apoptosis, down-regulating cell senescence, and at the same time promotes DNA repair, it can have profound effect on the short and long term prognosis of cancer patients who are treated with radiation and chemotherapeutic agents. ORIP can thus enhance the overall efficacy of cancer treatment and reduce the impact of the associated side effects,

[0069] ORIP treatment regimen in such cancer patients undergoing radiation or chemotherapy or a combination thereof, can be prescribed by the clinician as adjunct to cancer therapy, and comprise of two phases:

[0070] a) An acute phase ORIP treatment consisting of a single session minutes or hours prior to the radiotherapy/chemotherapy session, such session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemic and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of ischemia and reperfusion respectively.

[0071] b) A sub-acute phase ORIP treatment regimen initiated not earlier than the third day subsequent to the procedure whether radiation or chemotherapy or combination thereof, and continuing until 6 months post-procedure, such regimen comprising of not less than 2 sessions per week and not more than 14 sessions per week, and each session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemic and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of ischemia and reperfusion respectively.

[0072] The description of the present invention has been presented for purposes of illustration and description, and is not intended to be exhaustive or limited only to the novelty in the form disclosed. Many modifications and variations as suited to any specific use contemplated will be apparent to those of ordinary skill in the art.

What I claim as my invention is:

1. A method of preventing, treating or mitigating the impact of DNA damage to a healthy human tissue comprising of releasing ischemia triggered cellular modulators (ITCMs) by means of non-invasively inducing transient, repetitive and alternate cycles of ischemia and reperfusion, each lasting not less than 1 minute and not more than 10 minutes, in one or more remote organs, in one or more sessions, thereby increasing the tissue injury threshold for DNA breaks, promoting apoptosis of damaged cell, preventing senescence of damaged cell, and accelerating the process of DNA repair.

2. A method of claim **1**, wherein the DNA damage is caused as a result of an exposure to ionizing radiation during a therapeutic or diagnostic medical procedure.

3. A method of claim **1**, wherein the DNA damage is caused as a result of exposure to chemotoxic agents.

4. A method of claim **1**, wherein the DNA damage is caused as a result of oxidative stress resulting from lifestyle related causes or aging.

5. A method of claim **1**, wherein DNA damage to the healthy human tissue is as a consequence of either radiotherapy or chemotherapy or combination thereof in practice of oncology.

6. A method of claim **1**, wherein the treatment is administered as an adjunct to radiotherapy or chemotherapy, or combination thereof to enhance the overall efficacy of treatment and reduce the impact of side effects, the treatment comprising the steps of:

a) providing an acute phase consisting of one or more sessions minutes or hours prior to the administration of chemotherapy or radiotherapy regimen, wherein the session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemia and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of ischemia and reperfusion respectively; and

b) providing a sub-acute phase ORIP treatment regimen initiated not earlier than the third day subsequent to the administration of a chemotherapy or radiotherapy regimen, and continuing until at least 8-12 weeks post-procedure, such regimen comprising of not less than 2 sessions per week and not more than 14 sessions per week, and each session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemic and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of alternating ischemia and reperfusion cycles respectively.

7. The method of claim **1**, wherein:

a) at least one of the remote organs comprises an upper arm or a wrist, wherein the highest occlusion pressure is set to not less than 10% and not more than 30% higher than the highest systolic blood pressure measured in the corresponding upper limb, or not more than 200 mm Hg when the systolic upper limb pressure is not measured by the device; or

a) at least one of the remote organs comprises a lower limb like a thigh in which case the highest occlusion pressure is set to not less than 10% and not more than 30% higher than the highest systolic blood pressure measured in the corresponding thigh, or not more than 210 mm Hg when the systolic thigh pressure is not measured by the device; or

b) the remote organs comprise a combination of the upper and the lower limbs thereof at their corresponding occlusion pressures respectively.

8. A method of claim **1**, wherein a treatment regimen involves at least a pair of remote organs that includes a first limb and a second contralateral limb attached to an optimal remote ischemic preconditioning (ORIP) apparatus comprising the steps of:

a) providing a pair of auto-inflatable pneumatic cuffs, attaching a first cuff to the first limb and a second cuff to the second limb, wherein one of the cuffs inflates significantly beyond systolic blood pressure to completely occlude the blood flow in ischemic phase, and deflate one of the contralateral paired cuffs to allow free flow of blood in the contralateral limb in reperfusion phase, wherein inflation and deflation in the paired cuffs is done in cycles that alternate with similar but opposite ischemia-reperfusion cycles of the paired cuff attached

to the patient's remote organ resulting in systemic release of optimal levels of therapeutic ITCMs,

b) providing an air pumping module with a single or paired air pump, an inflate and a deflate valve for each of the paired cuffs, which pump air to each cuff through a tube and holds air in the ischemic phase at a cuff pressure significantly beyond the systolic blood pressure for occluding the blood flow to the patient's first remote organ for a predefined time, and releases the air in the reperfusion phase allowing the blood to flow freely, thereby when the first organ is in ischemic phase the second organ is in reperfusion phase, resulting accomplishing twice the ischemic body area for the release of the therapeutic ITCMs in half the time required by a single cuff ischemic preconditioning procedure and thus providing a more potent protection against DNA breaks and boost DNA repair without causing significant patient discomfort,

c) providing a pressure transducer module for measuring the minimal blood flow occlusion pressure to set up the maximal occlusion pressure in the ischemic phase for each of the paired cuffs, wherein the transducer is selected from the group consisting of: an oscillometric transducer, a photoplethysmographic transducer, an ultrasonic transducer, a thermal transducer, or an infrared transducer,

d) providing a controller console housing which has mechanical and electronic components that automatically operate both the paired cuffs, the air pumping module, the transducers, a user interface and a microprocessor that is programmable to automatically inflate and deflate the pneumatic cuffs alternatively to predefined cuff pressure levels, in predefined repetitive cycles, and in predefined order of each of the two remote organs, wherein the controller console displays the ORIP treatment protocol and the status in a real time graphic user interface for user interaction with the microprocessor and other electronic components that are stored in the microprocessor selected from a group consisting of: selection and initiation of a particular ORIP session in compliance with clinician's prescription, calling for a readout of some previously stored data, or setting into the microprocessor patient related data, times and dates relating to specific ORIP sessions and regimen, and also providing user with means to switch the device on or off, and

e) providing a wired or wireless communication module to receive and send feeds from and to a clinician regarding the compliance to a clinician-prescribed ORIP treatment regimen, to alter the ORIP treatment regimen, or to prescribe a new ORIP treatment regimen, wherein the wireless communication module is selected from a group consisting of WIFI, GPRS, TCP/IP or peer to peer RF transmission through an RF-enabled handheld communication device in the vicinity of the ORIP console.

9. A method of preventing, treating or mitigating the impact of DNA damage to a healthy human tissue comprising of releasing ischemia triggered cellular modulators (ITCMs) by means of non-invasively inducing transient, repetitive and alternate cycles of ischemia and reperfusion in a pair of remote organs including a first limb and a second contralateral limb attached to an optimal remote ischemic preconditioning (ORIP) apparatus comprising the steps of:

a) providing a pair of auto-inflatable pneumatic cuffs, attaching a first cuff to the first limb and a second cuff to the second limb, wherein one of the cuffs inflates significantly beyond systolic blood pressure to completely occlude the blood flow in ischemic phase, and deflate one of the contralateral paired cuffs to allow free flow of blood in the contralateral limb in reperfusion phase, wherein inflation and deflation in the paired cuffs is done in cycles that alternate with similar but opposite ischemia-reperfusion cycles of the paired cuff attached to the patient's remote organ resulting in systemic release of optimal levels of therapeutic ITCMs,

b) providing an air pumping module with a single or paired air pump, an inflate and a deflate valve for each of the paired cuffs, which pump air to each cuff through a tube and holds air in the ischemic phase at a cuff pressure significantly beyond the systolic blood pressure for occluding the blood flow to the patient's first remote organ for a predefined time, and releases the air in the reperfusion phase allowing the blood to flow freely, thereby when the first organ is in ischemic phase the second organ is in reperfusion phase, resulting accomplishing twice the ischemic body area for the release of the therapeutic ITCMs in half the time required by a single cuff ischemic preconditioning procedure and thus providing a more potent protection against DNA breaks and boost DNA repair without causing significant patient discomfort,

c) providing a pressure transducer module for measuring the minimal blood flow occlusion pressure to set up the maximal occlusion pressure in the ischemic phase for each of the paired cuffs, wherein the transducer is selected from the group consisting of: an oscillometric transducer, a photoplethysmographic transducer, an ultrasonic transducer, a thermal transducer, or an infrared transducer,

d) providing a controller console housing which has mechanical and electronic components that automatically operate both the paired cuffs, the air pumping module, the transducers, a user interface and a microprocessor that is programmable to automatically inflate and deflate the pneumatic cuffs alternatively to predefined cuff pressure levels, in predefined repetitive cycles, and in predefined order of each of the two remote organs, wherein the controller console displays the ORIP treatment protocol and the status in a real time graphic user interface for user interaction with the microprocessor and other electronic components that are stored in the microprocessor selected from a group consisting of: selection and initiation of a particular ORIP session in compliance with clinician's prescription, calling for a readout of some previously stored data, or setting into the microprocessor patient related data, times and dates relating to specific ORIP sessions and regimen, and also providing user with means to switch the device on or off, and

e) providing a wired or wireless communication module to receive and send feeds from and to a clinician regarding the compliance to a clinician-prescribed ORIP treatment regimen, to alter the ORIP treatment regimen, or to prescribe a new ORIP treatment regimen, wherein the wireless communication module is selected from a group consisting of WIFI, GPRS, TCP/IP or peer to peer

RF transmission through an RF-enabled handheld communication device in the vicinity of the ORIP console.

10. A method of claim **9**, wherein the DNA damage is caused as a result of an exposure to ionizing radiation during a therapeutic or diagnostic medical procedure.

11. A method of claim **9**, wherein the DNA damage is caused as a result of exposure to chemotoxic agents.

12. A method of claim **9**, wherein the DNA damage is caused as a result of oxidative stress resulting from lifestyle related causes or aging.

13. A method of claim **9**, wherein DNA damage to the healthy human tissue is as a consequence of either diagnostic radiation exposure, radiotherapy or chemotherapy or combination thereof in practice of oncology.

14. A method of claim **9**, wherein the treatment is administered as an adjunct to radiotherapy or chemotherapy, or combination thereof to enhance the overall efficacy of treatment and reduce the impact of side effects, the treatment comprising the steps of:

a) providing an acute phase ORIP treatment consisting of one or more sessions minutes or hours prior to the administration of chemotherapy or radiotherapy regimen, wherein the session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemia and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of ischemia and reperfusion respectively; and

b) providing a sub-acute phase ORIP treatment regimen initiated not earlier than the third day subsequent to the administration of a chemotherapy or radiotherapy regimen, and continuing until at least 8-12 weeks post-procedure, such regimen comprising of not less than 2 sessions per week and not more than 14 sessions per week, and each session comprising of not less than 2 and not more than 5 ischemic phases per limb, and not less than 2 and not more than 5 reperfusion phases per limb, each of the ischemic and reperfusion phases comprising of not less than 1 minute and not more than 10 minutes of alternating ischemia and reperfusion cycles respectively.

15. The method of claim **9**, wherein:

a) at least one of the remote organs comprises an upper arm or a wrist, wherein the highest occlusion pressure is set to not less than 10% and not more than 30% higher than the highest systolic blood pressure measured in the corresponding upper limb, or not more than 200 mm Hg when the systolic upper limb pressure is not measured by the device; or

b) at least one of the remote organs comprises a lower limb like a thigh in which case the highest occlusion pressure is set to not less than 10% and not more than 30% higher than the highest systolic blood pressure measured in the corresponding thigh, or not more than 210 mm Hg when the systolic thigh pressure is not measured by the device; or

c) the remote organs comprise a combination of the upper and the lower limbs thereof at their corresponding occlusion pressures respectively.

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