Controlled reperfusion after ischemia may be the unifying recovery denominator

Gerald D. Buckberg, MD

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There are 2 concepts regarding the nature of recovery when arterial blood supply is interrupted to create *ischemia* and then followed by returning blood flow or *reperfusion*. First, many think that ischemia itself is the detrimental factor, and the only role of reperfusion is to inflict the ''coup de grace.'' This report suggests that ischemia creates a progressive chaos in the physiologic components responsible for retaining cellular architecture that may produce structural and metabolic cell destruction, which has been defined extensively by in-depth reviews.[E1,E2] Vulnerability to such damage after returning flow may become *accelerated by reperfusion with normal blood or modified by control of the reperfusate process*. The importance of controlled reperfusion is based on conclusions derived from data evolved during the past 35 years of our investigations of this process.

The ischemic time responsible for tissue death or necrosis is uncertain in different organs, but this interval is not fixed *only* by the time of interruption of blood supply.[1] Experimental and clinical application of modifying the reperfusion process in the heart, lung, extremity, and brain demonstrate that control of the conditions and composition of the reperfusate process exert a profound effect on ultimate necrosis and fosters recovery.[2-7, E3,E4] Moreover, further understanding of the metabolic changes during ischemia may allow tailoring of even more coordinated reperfusion approaches to address the evolving metabolic processes responsible for this injury. Advocates of control of the reperfusion state appreciate the *uncertainty* of the duration of time that becomes responsible for necrosis and understand there may be a blend of irreversibility (unavoidable damage despite reperfusion), coupled with a vulnerability to necrosis that reperfusion can either accentuate (if normal blood is delivered) or reverse if given in a controlled way.

From the Division of Cardiothoracic Surgery, David Geffen School of Medicine at the University of California at Los Angeles, Calif.

Address for reprints: Gerald D. Buckberg, MD, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, 62-258 CHS, Los Angeles, CA 90095 (E-mail: gbuckberg@mednet.ucla.edu).

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CURRENT DILEMMA

The spotlight is now on the duration of ischemia and how to minimize its consequences when blood supply is interrupted, and uses methods such as hypothermia to limit damage in organs that now extend from heart to brain.[E5,E6] For those who focus only on ischemia, their primary objective is to determine how *quickly* to reperfuse, rather than addressing the *quality* of the reperfusate. Techniques are not considered if they *delay* the central objective of very rapidly introducing reperfusion with unmodified regular blood. This ''*when, rather than how*'' concept after prolonged ischemia disregards evidence that controlled reperfusion successfully alters reflow damage in the heart, lung, extremity, and brain.[2-7,E3,E4]

An analogy that improves focus on reperfusate control is the correlation of the ischemia/reperfusion process with the concept of entropy, a process that comprises a biologic phenomenon of progressive disunity during ischemia and then *accelerates* such disorganization of normally coordinated mechanical and physiologic activities when normal blood supply is suddenly restored.

I will initially put these concepts into perspective with experimental and clinical data in the 4 organ systems (heart, brain, lung, and extremity) that have been tested. This regional approach sets the stage for introducing a biologic phenomena of global controlled perfusion that applies to the whole body and for addressing regional organ systems (eg, kidney and liver) that have not yet been evaluated. Toward that end, we have also profited from our prior work on reoxygenation after cyanosis, as occurs with congenital heart disease. *The Journal of Thoracic and Cardiovascular Surgery* recognized the importance of these issues and addressed them in supplements in 1986[8] and 1995.[9] Reoxygenation damage was markedly limited and benefit was achieved by regulating the conditions of reflow delivery and blood composition components.[E7-E9] There is commonality in that the basic issue identifies that focus should *not be on how quickly* to reperfuse, but rather to identify *how* to reperfuse in a manner that controls reflow conditions (ie, flow, temperature, pressure, mechanical behavior) and composition (ie, a cocktail that addresses different metabolic pathways) to actively salvage the cell population that did not become necrotic during the ischemic interval.

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
CPR = cardiopulmonary resuscitation
WBC = white blood cell

INSIGHT INTO MODIFIED ELEMENTS DURING CONTROLLED REPERFUSION

Disrupted metabolic processes and structure after sudden post-ischemic reintroduction of regular blood supply was termed the ''double-edged sword'' by Braunwald and Kloner,[E10] because ''reperfusion injury'' may accentuate damage beyond that caused by ischemia. From my perspective, the disorganized cellular mechanism debris reflects ''shrapnel'' after a bomb explosion, which contains innumerable fragments that become dislodged from normality. The collective presence of this spectrum of disrupted elements keynotes the impossible task that confronts selection of any single treatment option that is earmarked to achieve the fundamental goal of rebuilding functional normality by globally remedying reperfusion damage. *There is no magic bullet* to prevent failure of any individual treatment, although several reperfusion components have been successfully used to restore near-normal function after prolonged ischemia. Simultaneously, these positive findings become balanced by recognition that they only begin to sort out the facts. The future requires blending these successful first steps with the evolving reperfusion injury management option expansion.[E1,E2]

My reperfusion injury approach started in 1975,[10] when John Kirklin at the University of Alabama told me that sudden myocardial thickness and palpable rigidity developed immediately after removing the aortic clamp after internal thoracic artery grafting. This observation initiated my questioning of the role of calcium in this injury.[10] This inquiring process continued, and the subsequently evolved components of the ''reperfusion cocktail and its delivery method'' address several factors that are disrupted by simply restoring regular blood, which will otherwise accentuate the entropy induced by ischemia. Current intervention applications include (1) lowering ionic calcium content, because unabashed calcium infiltration disrupts the capacity to use oxygen and accentuates structural changes[E11,E12]; (2) keeping the contractile apparatus (in the heart) stopped with potassium to reduce the demands for oxygen,[E13] which simulates the suggestion to rest in bed to aid recovery; (3) reducing cell swelling with drugs (mannitol) to avoid edema that in turn limits ionic and mechanical function[E14]; (4) adding ions, such as magnesium, to improve metabolism and limit calcium entry[11]; (5) supplying metabolic fuels, such as glucose and amino acids (glutamate and aspartate), to enhance metabolic recovery, because these elements are lost during ischemia and replacement is needed to speed the recovery process[12]; (6) limiting white blood cell (WBC) infiltration by filters to avoid the temporary accentuation of damage caused by these cells getting stuck to the capillaries, obstructing them, and simultaneously causing generation of toxic oxygen products after reperfusion[13]; (7) adjusting blood acid-base balance (pH) to allow the reperfused cells to metabolize in the best environment, as well as supplying a buffer for the toxic acid products that develop during ischemia and retard recovery[14,15]; (8) supplying chemical agents or drugs to combat offshoots of damage oxygen radical scavengers,[E15] calcium antagonists,[E16] and vasodilator agents[E4] that combat the tissue disruption resulting from cell swelling; (9) limiting the partial pressure of oxygen supply (from 400 mm Hg to 80–100 mm Hg) to reduce generation of destructive superoxide radicals[E17]; (10) adjusting blood pressure during reperfusion to prevent massive cell swelling that develops when new blood is supplied to areas whose blood vessel surface lining is temporarily damaged.[16] This maneuver limits subsequent fluid leakage that further disrupts architecture and function. Simultaneously, provision of an adequate perfusion pressure is essential to ensure adequate flow distribution to deep and superficial tissue within reperfused organs; (11) controlling temperature to optimize the environment for repair; a balance exists because normothermia accentuates nourishment,[E18] whereas hypothermia attenuates damage because metabolism is reduced by 50% with each 10°C lowering of temperature[17,18]; and (12) using regional pumps to control the pressure and its dynamics to afford either pulsatile or nonpulsatile delivery. Such regional delivery avoids interventions that may change body blood pressure during efforts to address single region recovery.

With increasing knowledge, the synergy of supportive agents will expand to create an even more efficacious reperfusion and composition interface, building on current knowledge to develop a fuller and more cohesive controlled reperfusion process after ischemia.

CURRENT APPLICATIONS OF CONTROLLED REPERFUSION

Heart

Cardiac surgery. Cardiac procedures (~1,000,000/year worldwide) require a quiet heart to allow surgeons to do a precise job. This requires producing ischemia by shutting off the cardiac blood supply and subsequently sets the stage for a reperfusion injury during every heart surgery procedure. Our work established the use of blood cardioplegia to limit the development of reperfusion injury to try to offset this damage,[19] and this method is now used in approximately 80% of hospitals worldwide. Of equal importance, understanding its limitations to completely prevent ischemic damage has led to our development of applying a warm-blood cardioplegic reperfusate (delivered before restoring normal blood flow) to offset this injury. This strategy

introduced the controlled reperfusion concept[12,E18,E19] and is now used in approximately 50% of centers worldwide. Its clinical background was initiated by John Kirklin's[E20] 1988 report on the ''science of cardiac surgery,'' which compared 2351 patients receiving controlled reperfusion with 3872 patients receiving normal blood reperfusion and demonstrated how it reduced mortality after 70 minutes of aortic clamping.

The cost-savings aspect of this approach was defined at the Cleveland Clinic,[E21] where application of the cardioplegic method defined by our studies saved $2100 per patient versus less-expensive crystalloid techniques, resulting in a $10,000,000/year cost salvage at that center. Moreover, the report stated that this would translate to a $680,000,000 cost savings in 1992 (400,000 procedures in the United States), and even more savings would exist if today's cost standards were applied.

That early report did not address changes in septum function as described next. The septum component of heart architecture must be considered because a) this structure occupies approximately 40% of ventricular muscle mass,[20] yet despite this observation b) septum damage has been considered an ''expected complication'' of cardiac surgery.[E22-E26]

Our integrated blood cardioplegic approach,[18,E27] which prevents the temporary and sometimes permanent loss of the ventricular septum function, has not yet been applied to this ongoing complication of conventional myocardial protection methods.[20] Other treatment approaches may be equally effective, but verification of their protective capacity value requires pre- and postoperative comparison of septum function measurements when they are used. The presence of normal function/structure relationships is essential for proper septum performance, so that development of strategies to prevent septum dysfunction is linked to understanding this fundamental interaction.[20]

Structurally, the oblique fiber orientation of septum muscle fibers results in the required twisting function needed for efficient right ventricular ejection against increased pulmonary vascular resistance; right ventricular failure results from inadequate septum contractile performance.[E28] A grading score by echocardiogram exists[E29] and is commonly used to define the extent of septum damage that ranges from mild to severe hypokinesia, to akinesia, and finally to paradoxical bulging like an aneurysm. Septum malfunction is caused by stunning, yet this complication has been considered an expected heart surgery outcome.[E22-E26] Justification of this commonly held conclusion is linked to the absence of clinical problems when pulmonary vascular resistance is low, as usually occurs in low-risk patients after coronary bypass procedures. Conversely, a recent report of approximately 3300 patients[E30] with preoperative normally contracting septum demonstrated paradoxical septum dysfunction in approximately 40% of patients, increasing to 60% after valve procedures. Septum injury was thought to be related to the duration of aortic clamping; most important, there was no report of the diminished functional that results from lesser grades of damage. Conversely, our recent studies evaluated each aspect of septum function in a cohort of 119 consecutive patients. We used the integrated blood cardioplegia method, which addresses correct delivery of myocardial protection methods, and showed septal stunning is *completely avoided* despite aortic clamping intervals extending to 157 minutes.[20]

These findings imply that maintenance of septum function should become the barometer of myocardial protection to determine adequacy of the method used, with recognition that its damage is related to an avoidable reperfusion injury. Septal damage also follows procedures without cardioplegia, such as coronary procedures without extracorporeal circulation.[E30] Cardiac manipulation during non-bypass procedures likely compromises septum nourishment when hypotension is caused by mechanically altering cardiac position. Guidelines for subsequent treatment must use this knowledge of septum injury to a) recognize and evaluate this preventable dilemma, b) maintain any current technique when septum damage is avoided, or c) change approaches if septum damage is present.

ACUTE MYOCARDIAL INFARCTION

Aside from improving the results in open surgery, as reported by the Cleveland Clinic several years ago, these reperfusion solutions have been shown to allow survival of heart muscle involved in heart attacks (1,500,000 events in the United States per year) by applying the only valid guideline of gauging their capacity to return function of ischemic muscle that has suffered up to 6 or more hours of no blood supply.[2,E3] Verification of this functional end point is critical because it addresses the currently misguided conclusion that viability without function is a satisfactory result. Unfortunately, treatment that provides only an open vessel that now supplies an akinetic muscle reflects the wrong results; this nonfunctional segment leads to subsequent heart failure if its size exceeds 20% of left ventricular muscle mass.[E31,E32] Development of this noncontractile or akinetic muscle after reflow with normal blood is evident from experimental reports of myocardial cell death after replacement of regular blood after 2 hours of ischemia.[4] The clinical model for this end point exists in the population with acute myocardial infarction, because current methods of urgent emergency angioplasty *only* restore normal blood reperfusion, without consistently demonstrating regional muscle recovery. In many instances, angioplasty successfully opens the coronary lumen to provide blood supply, but such reflow is delivered to damaged myocardium that cannot resume function if more than 50% of its mass is necrotic.[E33] Stated more simply, ''the heart is a pump, not a highway map.''

The infrastructure for controlled reperfusion was established by our experimental studies that delivered controlled

reperfusion to a decompressed heart in the operating room. *The Journal of Thoracic and Cardiovascular Surgery* supplement published in 1986 addressed this issue.[4,8,E3,E13] These experimentally developed outcomes were then transposed toward early clinical application, and the results confirmed these findings by demonstrating remarkable functional recovery of muscle in patients with more than 6 hours of myocardial infarction.[2] Subsequent clinical application of controlled reperfusion by an international cohort in 156 patients undergoing approximately 6 hours of ischemia (ranging from 2–24 hours)[4] were evaluated by echocardiogram or left ventriculogram studies before discharge, demonstrating recovery of substantial regional function in 87% of patients with previously ischemic muscle.

Controlled reperfusion is the keynote management issue, rather than focusing on who (surgeon or cardiologist) delivers this treatment. These baseline clinical observations led to our 1986 suggestion of future development of methods to introduce controlled reperfusion in the catheterization laboratory rather than in the operating room.[21] The offshoot is the potential to initiate less-invasive warm reperfusion methods in selective patients, an endeavor that may markedly broaden delivery of warm controlled reperfusion to the vast population of patients with myocardial infarction.

The importance of restoring contractile function after acute myocardial infarction has enormous implications. Current cardiology and surgical management only restores normal blood flow by using the concept of ''how quickly to open new blood supply,'' rather than ''how to properly employ controlled reperfusion.'' Consequently, muscle loss occurs, as the revascularized bulging ischemic segment simply becomes akinetic.[E32] This architectural event is caused by salvaging the epicardium segment rather than rescuing transmural muscle.[E34] This current cardiology end point reduces mortality and slows remodeling,[E35] but retains an akinetic segment (that exists when > 50% of muscle is irreversibly damaged)[E33] and sets the stage for subsequent progressive cardiac dilation in the 20% of patients whose end-systolic volume index exceeds 40 mL/m^2.[E36,E37] Unfortunately, normal blood reperfusion creates the structural surrogate for subsequent development of congestive heart failure…our greatest health risk. Conversely, controlled reperfusion offsets this hazard and may have a major health care impact. In its simplest form, inadequate treatment of acute myocardial infarction *reflects the primary therapy failure*, because later ventricular dilation leading to congestive heart failure becomes *a potentially avoidable secondary complication* that stems from the conventionally used regular blood reperfusion approaches to treat acute myocardial infarction.

THE LAZARUS SYNDROME—SUDDEN DEATH MANAGEMENT

A fascinating recent application of this controlled reperfusion technology was described by our report of using these solutions to treat sudden death after witnessed arrest, where conventional in- and out-of-hospital survival is approximately 10%[E38-E41] and approximately 33% of survivors have permanent brain damage.[E42] The nidus was our experimental studies (in a model of left anterior descending artery occlusion and circumflex artery stenosis) that showed near complete cardiac recovery after 2 hours of intractable ventricular fibrillation. This cardiac end point was achieved by using a management protocol whereby (1) cardiopulmonary resuscitation (CPR) was performed for 2 hours with effective compressions aimed at achieving high systemic perfusion pressure to ensure brain blood flow; (2) cardiopulmonary bypass (CPB) was introduced via the femoral vessels with the intent to (a) support the systemic circulation that became distributed to the brain and other regions, while (b) simultaneously allowing cardiac catheterization studies to diagnose the responsible cardiac lesion causing intractable ventricular fibrillation; and (3) performing controlled reperfusion of the underlying cardiac lesion in the same fashion described for treating acute myocardial infarction.

These concepts were then clinically performed by application in centers in the United States and Europe, where 36 patients underwent CPR for approximately 72 minutes (range, 20–150 minutes).[E43] Each patient had similar treatment that included a) CPR to support the brain blood flow with a monitored CPR systolic blood pressure of 60 mm Hg; b) determination of the cardiac cause of the sudden death in the catheterization laboratory, sometimes with percutaneous body support with a heart–lung machine to support the body, and c) remedy of the cause of sudden death by providing controlled reperfusion during coronary bypass grafting.

This treatment strategy led to 80% survival and only 6% neurologic damage, findings that dramatically differ from those of conventional approaches. Moreover, normal heart function was restored because ejection fraction at discharge exceeded preoperative values in 13 of 14 patients who had undergone pre-sudden death cardiac catheterization to document underlying coronary anatomy and functional performance.[22] Immediate postoperative cardiac functional recovery among these 36 patients was similar to that achieved routinely after conventional cardiac procedures. Furthermore, investigators in Japan,[E44] Taiwan,[E45] and Korea[E46] recently studied sudden death and used *only* the CPB and regular blood (or uncontrolled) reperfusion components; cardiac survival improved to 30% after their initiating percutaneous bypass after sudden death, followed by standard angioplasty. However, their overall approaches and results differ from our method, because they did not use controlled reperfusion or ensure ventricular venting. Myocardial infarction-related myocardial necrosis was not avoided, and their outcomes included stunning of remote muscle to further diminish post-reperfusion cardiac performance. The consequent low output state limited brain reperfusion and

accentuated the neurologic damage that existed in approximately 50% of survivors. Their end points were ''*saved the heart, but lost the brain,*'' and several collaborative centers in Japan are now planning to test our approach to determine if their findings are in agreement with our prior report.[E43] If confirmed, controlled reperfusion may become the benchmark for new sudden death treatment strategies that can avoid the current grim prognosis.

BRAIN ISCHEMIA: GLOBAL AND REGIONAL APPLICATION

The biologic importance of introducing controlled reperfusion to ''save the brain and heart'' after prolonged total brain ischemia has multiple settings, including (a) deep hypothermic circulatory arrest during cardiac surgery of infants and adults; (b) sudden death without cardiac cause, as in drowning of children; and (c) unwitnessed arrest after sudden death. The extremely adverse effects of unwitnessed arrest are well defined clinically, because recovery is approximately 1% and severe brain injury is nearly universal. Such delays also exist during cold circulatory arrest during cardiac surgery, because ischemic times are usually restricted to less than 45 minutes to limit reperfusion brain damage.[23]

In contrast, successful application of controlled whole-body reperfusion was experimentally documented after 90 minutes of deep hypothermic circulatory arrest,[23] a management strategy used in infants with congenital heart disease, as well as in adults undergoing great vessel procedures. The prime of the heart–lung machine was adjusted with additives so that it became a controlled reperfusate delivered immediately after 90 minutes of deep cooling. This approach offset the reperfusion damage resulting from regular blood reperfusion and markedly improved cardiac, hepatic, pulmonary, and brain recovery.[23] Recent studies[24] also showed that substituting a controlled reperfusate prime for the regular blood reflow after 15 minutes of unwitnessed normothermic arrest for 15 minutes (ventricular fibrillation without ventilation) allowed complete neurologic recovery in 6 of 7 pigs to supplement evidence of the validity of the global concept of controlled reperfusion (Video 1). In contrast, severe brain damage followed regular blood reperfusion on bypass, despite salvage of cardiovascular function.

Remarkable implications follow this observation, because CPR after unwitnessed arrest may cause marked reperfusion damage that may be avoided by controlled reperfusion. Consequently, further studies are required to introduce the appropriately delayed time intervals needed for peripheral CPB cannula placement after encountering patients with unwitnessed arrest. The required time interval suggested by recent reports show extracorporeal circulation implemented within 15 minutes in patients with sudden death undergoing witnessed arrest will improve results by achieving 30% survival.[E44,E46] To address this need, a new model of brain death was developed to study 30 minutes of totally absent brain flow without CPB. This novel approach accounted for the 15-minute delay for canula insertion and also excluded the secondary CPB complications (release of mediators from other organs and inflammation alterations) to allow better understanding of brain ischemia. The severe brain damage that follows normal blood reperfusion after 30 minutes *was avoided*; 3 of 6 animals recovered normal neurologic function (Video 2), and the other 3 subjects demonstrated minimal injury at 48 hours.[E47] This complete neurologic recovery after 30 minutes of total brain vascular occlusion *totally contradicts traditional conclusions* that imply irreversible brain damage follows only 5 minutes of no brain blood flow.

More important, these findings of complete brain recovery after 30 minutes of no brain flow were achieved by applying peripheral perfusion methods that may be applied to stroke victims. Regional reperfusion methods via cannulation of peripheral vessels exist, so that a combined blood-based reperfusate condition and composition approach may be developed in a manner that uses a patient's own blood. Consequently, such percutaneous observations may open the door to subsequent study of regional ischemia during stroke, a major worldwide health care hazard.

PULMONARY ISCHEMIA AND TRANSPLANTATION

Lung ischemia/reperfusion injury was studied by developing an in vivo model to simulate the clinical transplant setting used by Halldorsson and colleagues[6,E4] and Allen,[E48] which was derived from our earlier collaborative analysis of controlled heart reperfusion.[4,E3] Results after 2 hours of warm left lung ischemia were compared after (a) uncontrolled reperfusion with normal blood, (b) uncontrolled reperfusion with WBC filtration, (c) controlled reperfusion with a modified solution, and (d) modified solution and WBC filtration. The severe lung injury characterized by a marked increase in pulmonary vascular resistance decreased, altered compliance, increased lung water, and minimized alveolar capillary damage by using either a modified solution or WBC filtration alone. In contrast, both use of a modified solution and WBC filter to prevent reperfusion injury essentially avoided these adverse alterations, as there was no change in pulmonary compliance, lung water, or alveolar capillary function, and pulmonary vascular resistance was only slightly increased. [6,E4]

Of equal importance, the contralateral right lung also sustained the secondary effect of an unanticipated injury after uncontrolled reperfusion of the ischemic left lung; this damage was prevented by controlled WBC free reperfusion of the ischemic lung. This finding documents that reperfusion injury metabolic by-products play a significant role in contralateral lung damage and that controlled reperfusion prevents this secondary injury.

Translation of these short-term studies into the area of clinical lung transplantation was then accomplished by

analyzing results after 24 hours of storage of a single lung under hypothermic conditions, and results were almost identical to the findings after 2 hours of warm ischemia.[6,E4] The severe pulmonary reperfusion injury after uncontrolled (normal blood) reperfusion after 24 hours of cold lung ischemia was almost completely avoided by the controlled (WBC and modified) reperfusion solution, because near complete pulmonary function recovery occurred.[E4] These experimental findings became the infrastructure for clinical studies by Lick and associates[E49] (who validated their importance) and Schnickel and associates,[E50] who used these methods at the University of California at Los Angeles in more than 100 lung transplants. Translation of experimental findings in clinical lung ischemia/reperfusion studies closely mirrors the previous cardiac and brain observations that document controlled reperfusion effectiveness.

Similar lung reflow problems also confront pediatric and adult patients who undergo open surgery because the process of lung ischemia/reperfusion routinely occurs during and after extracorporeal circulation. Development of respiratory distress syndrome may follow a successful cardiac operation, because noncardiac lung congestion may occur and initiate pulmonary problems, which prolongs intensive care area hospitalization and may become fatal. Potential expansion of this approach by applying a specialized pulmonary delivery method, together with a solution that resembles our cardiac solution without added potassium (because the lung does not beat), may open new research arenas. Certainly, the large number of high-risk adults who might have lung reperfusion injury during CPB exist, as they account for approximately 40% of the 1,000,000 worldwide cardiac operations.

LOWER EXTREMITY

Reperfusion after acute loss of peripheral leg circulation (from either thrombosis or embolism) may lead to a massive reperfusion injury that is life threatening when toxic products that accumulate during ischemia are released after reflow. Furthermore, the leg with new blood flow may become congested and develop post-reperfusion severe edema and contracture, which normally result in leg amputation.

Application of the concept of controlled reperfusion of ischemic limbs was carried out in initial experimental studies in Germany by Schlensak and colleagues[E51] and Beyersdorf and colleagues[E52] and then applied clinically. The infrastructure of this understanding began in the 1980s during our collaborative cardiac studies.[25,E53] Minor modifications of the cardiac warm-extremity reperfusate were made (eg, no potassium was added to simulate the lung study approach), and results after 6 hours of lower-extremity ischemia were compared with those after normal blood reperfusion. Controlled reperfusion resulted in complete leg salvage, together with recovery of normal vascular resistance, minimal creatine phosphokinase release, negligible efflux systemic potassium build-up, normal recovery of glucose and oxygen consumption, and limited edema formation.[E52,E54]

These baseline experimental observations became the keynote to initial clinical studies in 12 patients with clinical contracture after prolonged ischemia.[5] Contracture was reversed when the regional warm reperfusate was delivered by mixing the designed chemical solution with the recipient's own blood; all legs were salvaged with recovery of normal function in most. These findings were compared with the adverse outcomes in 1213 cumulative patients evaluated from literature review.[E54,E55]

Moreover, these reproducible early observations led to the current ongoing European clinical study to determine how to treat patients with acute extremity ischemia after they seek medical advice. In addition, this preventable complication of extremity reperfusion injury may be avoided by clinically implementing this controlled reperfusion strategy after a) prolonged femoral cannula insertion during extended CPB procedures or extracorporeal perfusion for cardiac support, and b) longer intervals with intraaortic balloon counterpulsation support. If successful, controlled reperfusion would replace amputation for this patient cohort.

Ramifications of reperfusion damage may also assume importance after vascular surgery for obstructive femoral popliteal disease. Subsequent testing of controlled reperfusion (using a patient's own blood mixed with the solution) may be compared with normal blood reperfusion; results will determine whether early leg swelling and prolonged hospitalization after lower-extremity revascularization are minimized. If so, then controlled reperfusate delivery may broaden management options for this currently unrecognized vascular surgery reperfusion injury complication.

OTHER APPLICATIONS

The aforementioned experimental and clinical applications to the heart, brain, lung, and extremity reflect the *opening act* to a novel concept linked to appreciation that controlled reperfusion reflects a biologic phenomena that mandates revision of current concepts based on conventional ischemia time frames thought to cause ultimate organ death, a concept that is not currently related to varying the mechanisms of reperfusion. The yardstick of studied organs may expand to address renal, hepatic, and gastrointestinal organs that either undergo transplantation or are subject to ischemic intervals during operative procedures needed for their repair. Moreover, multiorgan failure evolves in patients in shock when normal blood reperfusion causes a low output syndrome. Gearing a reflow approach that takes advantage of principles emerging from both regional and global studies may innovate novel strategies that offset current reperfusion damage when only regular blood is used. Although clinical teams exist to deal with such regional and global ischemia events, they currently do not recognize (a) the potential

role of reperfusion control or (b) their subsequent charge to develop creative ways to implement this treatment.

CONCLUSIONS

Reperfusion injury is a biologic event, and the complications of simply returning regular blood can be offset in the heart, brain, lung, and extremity by administering a controlled reperfusate that alters reperfusion conditions (ie, pressure, flow, temperature) and composition (ie, ionic content, nutrients, acid-base balance). Such a reperfusion strategy returns function to organs that would otherwise develop necrosis if only regular blood was restored.

Future application of controlled reperfusion may include the brain, kidney, liver, and whole body. The biologic nature of reperfusion injury, together with experimental and clinical effectiveness in the heart, lung, extremity, and brain, implies that controlled reperfusion after ischemia may become a unifying recovery denominator that will lead to new improved results in a large number of patients who may recover from periods of ischemia durations that are now thought to be irreversible.

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