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Topical Negative Pressure, Applied onto the Myocardium, a Potential Alternative Treatment for Patients with Coronary Artery Disease in the Future

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1. Introduction

The majority of patients who require intervention for coronary artery disease are adequately treated by percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG). However, a major reason for failure of these treatments is their dependency on luminal size and coronary outflow. Methods stimulating myocardial angiogenesis and new vessel formation that are not dependent on vessel caliber therefore provide an important alternative means of treatment. Topical negative pressure (TNP) has been used in the treatment of chronic and problematic wounds since the beginning of the 1990´s, and has been shown to increase blood flow and stimulate angiogenesis in the underlying tissue. Because of TNP´s stimulating effect on blood flow and angiogenesis TNP has been tried to be applied directly onto the myocardium, referred to as myocardial topical negative pressure (MTNP) to increase myocardial blood flow and reduce myocardial ischemia, and reduce myocardial infarction (Lindstedt et al. 2008a, Lindstedt et al. 2008b, Lindstedt et al. 2007c, Lindstedt et al. 2007a, Lindstedt et al. 2007b, Lindstedt et al. 2008c, Lindstedt et al. 2008d).

2. Development of the topical negative pressure technique

Topical negative pressure (TNP) therapy (also called vacuum-assisted closure (VAC) therapy, vacuum sealing or vacuum therapy) has developed from the standard surgical procedure of vacuum-assisted drainage to remove blood or serous fluid from a wound or surgical site. In essence, the TNP technique is very simple. A piece of foam, with an open structure, is inserted into the wound cavity and a wound drain with lateral perforations is placed on top of it. The entire area is then covered with a transparent adhesive membrane, which is firmly secured to the healthy skin around the wound margin. When the exposed

end of the drain tube is connected to a vacuum source, fluid is drawn from the wound through the foam into a reservoir for subsequent disposal. The plastic membrane prevents the ingress of air and allows a partial vacuum to form within the wound, reducing its volume and facilitating the removal of fluid.

The practice of exposing a wound to sub-atmospheric pressure for an extended period of time to promote healing was first described by Fleischmann et al. in 1993, following the successful use of this technique in 15 patients with open fractures. They reported that the treatment resulted in, "efficient cleaning and conditioning of the wound, with marked proliferation of granulation tissue". No bone infections occurred in any of the patients, although one developed a soft tissue infection, which subsequently resolved with further treatment. In two further papers, Fleischmann and his colleagues described the treatment of 25 patients with compartment syndromes of the lower limb and 313 patients with various types of acute and chronic infections. Further success with topical negative pressure treatment in Germany was reported by Muller following the treatment of 300 patients with infected wounds.

In these early studies, negative pressure was achieved by the use of conventional methods such as wall suction equipment or surgical vacuum bottles. Both these systems are associated with practical problems in terms of the delivery, control and maintenance of the required levels of negative pressure, as discussed by Banwell et al. . In 1995, a commercial system for vacuum-assisted closure was introduced in the United States. This equipment, called the VAC®, was designed to overcome some of the problems described by Banwell. The heart of the system is a microprocessor-controlled vacuum unit that is capable of providing controlled levels of continuous or intermittent sub-atmospheric pressure ranging from -25 to -200 mmHg.

In early studies no attempts were made to investigate the physiological mechanisms behind the observed clinical effects, or to determine the optimum level of pressure. A seminal study by Morykwas et al. addressed both these issues using a series of animal studies. Deep circular defects, 2.5 cm in diameter, produced on the backs of pigs were dressed with open-cell polyurethane-ether foam with a pore size ranging from 400-600 μm. In the first series of experiments, a laser Doppler technique was used to measure blood flow in the subcutaneous tissue and muscles surrounding the wounds as these were exposed to increasing levels of negative pressure, applied both continuously and intermittently. Their results indicated that while an increase in blood flow equivalent to four times the baseline value occurred with a negative pressure of -125 mmHg, blood flow was inhibited by the application of negative pressures of -400 mmHg and above. A negative pressure of -125 mmHg was therefore used in subsequent studies. The rate of granulation tissue production under negative pressure was determined using the same model by measuring the reduction in wound volume over time. Compared with control wounds dressed with saline-soaked gauze, significantly increased rates of granulation tissue formation were observed with the application of both continuous (63.3 ± 26.1%) and intermittent (103% ±35.3%) negative pressure.

The observation that intermittent or cycled treatment appeared to be more effective than continuous therapy is interesting, although the reasons for this are not fully understood. Two possible explanations were advanced by Philbeck et al.. They suggested that

intermittent pressure application results in rhythmic perfusion of the tissue, which is maintained because the process of capillary autoregulation is not activated. They also suggested that as cells that are undergoing mitosis must go through a cycle of rest, cellular component production and division, constant stimulation may cause the cells to 'ignore' the stimulus. Intermittent stimulation allows the cells time to rest and prepare for the next cycle. For this reason, it has been suggested that cyclical negative pressure should be used clinically, although some authors suggest that this should follow a 48-hour period of continuous vacuum to bring about a rapid initial cleansing effect. Following these investigations, Morykwas and colleagues postulated that multiple mechanisms might be responsible for the effects observed. In particular, they suggested that the removal of interstitial fluid decreased localized oedema and increased blood flow, which in turn decreased bacterial levels in tissue. It has since been proposed that the application of sub-atmospheric pressure produces mechanical deformation or stress within the tissue resulting in protein and matrix molecule synthesis and enhanced angiogenesis. Using the rabbit ear as a model, Fabian et al. provided further evidence of the stimulatory effects of sub-atmospheric pressure on the production of granulation tissue, and also demonstrated a trend towards enhanced epithelialisation. In experimental partial-thickness burns in pigs, sub-atmospheric pressure was shown to prevent progressive tissue damage in the zone of stasis that surrounds the area of the initial injury. This effect was demonstrable within 12 hours of injury, with treatment times as short as six hours being sufficient to exert a measurable effect. The authors proposed that the removal of oedema fluid, containing suspended cellular debris, osmotically active molecules and biochemical mediators released following the initial injury, may lessen the obstruction of blood flow.

Numerous other papers have described the use of TNP in the treatment of a variety of wound types, including extensive degloving injuries, infected sternotomy wounds and various soft tissue injuries prior to surgical closure, and in burn wound management.

3. Physiological basis of TNP

Numerous theories have been advanced to explain the physiological basis of the marked improvement in clinical outcomes achieved with TNP. Two basic, broad mechanisms have been proposed to account for the increased rate of granulation tissue formation and accelerated healing rate: a fluid-based mechanism and a mechanical mechanism. Application of a controlled vacuum to the wound interface facilitates the removal of excess interstitial fluid due to the higher pressure gradient. This physically results in a decrease in interstitial pressure. When the interstitial pressure falls below the capillary pressure, the capillaries reopen and flow to the periwound tissue is restored. This same mechanism is responsible for the success of the vacuum technique for decompression of both muscle compartment and abdominal compartment syndrome. All non-bound soluble factors will also be removed with the fluid, including inhibiting factors and promoting factors. Numerous descriptions have been presented of the change in concentration of various factors over time. Factors measured range from growth factors to metalloproteinases to C-reactive protein. The interactions between the soluble factors related to wound healing, and also those factors and interactions that inhibit or delay healing, are extremely complex. The same factor can both promote and inhibit wound healing, depending on the concentration and timing during the healing process. Moreover, the negative pressure and increase in

blood flow to the wound bed have been shown to accelerate the formation of granulation tissue. Interestingly, intermittent application of sub-atmospheric pressure has produced superior results, possibly due to mitigation of the cellular desensitization that occurs with exposure to continuous sub-atmospheric pressure. Although it is likely that each of these factors plays a role in the action of TNP, the application of mechanical forces to the wound site is probably the most significant mechanism of action.

Mechanical force is known to be responsible for the induction of cell proliferation and division. Plastic surgeons use tissue expansion to obtain soft-tissue envelopes in reconstructive surgery, while orthopaedic surgeons and maxillofacial surgeons use distraction osteogenesis to lengthen bones. Ingber et al. have shown that for cells to respond to soluble mitogenic factors and proliferate, they must be extended, leading to isometric tension, either by adherence to a stiff substrate or by external application of mechanical forces. Only stretched cells can divide and proliferate in response to soluble growth factors, whereas cells that are not stretched and assume a more spherical shape are cell-cycle arrested and tend to undergo apoptosis. It has also been shown in vitro that directional growth of capillary sprouts is promoted by the application of tension in three-dimensional angiogenesis models. The applied forces deform the extracellular matrix and, as cells are anchorage-dependent, the cells in the stretched tissue are deformed. Cell deformation has been shown to cause a wide variety of molecular responses, including changes in ion concentration and permeability of membrane ion channels, release of secondary messengers, stimulation of molecular pathways, and alterations in gene expression. Moreover, it is known that vascular endothelial cells express a different array of genes depending on whether they have been exposed to static, laminar or turbulent flow. It is apparent that cells are able to sense mechanical forces and respond through the regulation of specific genes and the induction of cellular programs. The exact mechanisms behind these effects are not fully understood, but are probably related to conformational changes in the cytoskeleton in response to mechanical forces. This behavior provides a natural mechanism for tissue homeostasis, where tissue mass expands, cells are stretched and are thus stimulated to divide.

The application of negative pressure may promote wound angiogenesis by directly stimulating endothelial cells. For example, the application of TNP may cause local wound hypoxia, which is a potent stimulator of vascular endothelial growth factor (VEGF) production, the major endothelial cell mitogen. Alternatively, TNP may activate signal transduction pathways leading to endothelial cell division and growth factor production since endothelial tension causes capillary sprouting, gene expression, and changes in matrix metalloproteinase (MMP) activity. While TNP may directly stimulate endothelial proliferation by local hypoxia or cell deformation, increased wound angiogenesis may be an indirect effect of the TNP-mediated reduction in MMP activity. Although low levels of MMPs have been shown to favour angiogenesis, elevated MMP activity inhibits neovascularization and is associated with chronic wounds. Specifically, the levels of the gelatinases MMP-9 and MMP-2 are significantly higher in nonhealing wounds, but return to normal as wound healing progresses towards closure. In addition, chronic wound exudates that inhibit endothelial activity will instead stimulate angiogenesis after treatment with an MMP inhibitor. A reduction in MMP activity may promote endothelial proliferation by lowering MMP-mediated angiostatin and endostatin production. Alternatively, the

inhibition of a MMP-propagated inflammatory cascade may provide an environment more favorable to capillary growth.

Mechanical properties seem to have a greater influence on clinical efficacy than fluid-based properties, according to a recently published article, in which the authors showed that the application of mechanical shear stresses was able to activate the VEGF pathway without any VEGF being present in the culture fluid

4. Application of TNP directly onto the myocardium

It was first described by Lindstedt et al that application of a negative pressure directly onto the myocardium resulted in an increase in blood flow in the underlying myocardium. In this first study microvascular blood flow in the myocardium was measured by laser Doppler flowmetry (LDF). The LDF probes were located 5-6 mm lateral to the middle part of the left anterior descending (LAD) , 5-6 mm down into the myocardial wall, and measurements were made before and after application of a MTNP of -50 mmHg. A significant increase was seen in all the animals when the myocardium was exposed to MTNP of -50 mmHg. The increase in blood flow was seen both in non-ischaemic myocardium (normal myocardium), in ischemic myocardium (after 20 minutes of LAD occlusion), and also in reperfused myocardium (formerly ischaemic myocardium after 20 minutes of reperfusion). In all the settings the increase in microvascular blood flow appeared immediately when MTNP was applied. In another study myocardial blood flow was measured using ultrasonic flow meter probes at the proximal part of the left anterior descending artery (LAD), the circumflex coronary artery (CCX) and the right coronary artery (RCA), before and after application of MTNP of -50 mmHg. Measurements were performed during normal conditions (non ischemic) and after occlusion of the LAD, i.e. ischemic conditions. The results implying that MTNP increases the total amount of coronary blood flow to the myocardium. Interestingly, an increase in myocardial perfusion measured by LDF, when the MTNP was applied, correlated to an increase in coronary blood flow in every animal. A non-uniform or a decrease in the total coronary blood flow might hypothetically cause ischemia in parts of the myocardium not exposed to MTNP. Since the present results shows a significant increase in the total amount of coronary blood flow, the authors believe that ischemic areas are not likely to occur. However, local effects in the myocardium could not be deduced from the study.

When applying different negative pressures to periwound tissues (skeletal muscle and subcutaneous tissue) may causes different changes in blood flow. When the negative pressure exceeds a specific level it seems to constringe the vessels in periwound tissue and a decrease in local blood flow is seen. Morykwas et al has previously reported that the microvascular blood flow to a wound increased to four times the baseline value when a negative pressure of 125 mm Hg was applied, whereas it was inhibited at negative pressures of 400 mm Hg and above. The changes in blood flow is thought to be related to local effects, since the blood flow at a distance of 4.5 cm from the wound edge was not affected by the negative pressure between -50 and -200 mmHg. A zone of relative hypoperfusion has been observed close to the wound edge. Hypoperfusion induced by TNP is thought to depend on tissue density, distance from the negative pressure source, and the amount negative pressure applied. In the myocardium, however, MTNP between -25 and -50 mmHg have been shown to induce a significant increase in blood flow, whereas MTNP between -75 and -150 mmHg have not been shown to induce any significant blood flow changes in the

underlying myocardium. The differences in blood flow pattern between periwound tissue and myocardium might be due to the differences in tissue histology, where the myocardium has a higher density than periwound tissue. The absence of increase in blood flow when the myocardium is exposed to pressures between -75 and -150 mmHg might, in part be due to, counteract forces. Hypothetic pressures above -150 mmHg might have led to constringe of the vessels, thus reducing the microvascular blood flow to the exposed myocardium. In a study, comparing the two negative pressures -25 and -50 mmHg, both pressures resulted in a significant increase in myocardial blood flow, and no significant difference could be observed between the two pressures. However, the increase in blood flow was greater in normal myocardium when the pressure of -25 mmHg was used. Furthermore, in ischemic myocardium the increase was greater when using -50 mmHg. The study, however, only contained six animals, and the difference might have been significant in a larger study. The authors believe that the optimal MTNP in clinical perspective might be -50 mmHg, since ischemic conditions would be of greater interest than normal.

As earlier mentioned, a zone of relative hypoperfusion has been observed in studies when TNP is applied on wounds. The zone of hypoperfusion is believed to appear close to the negative pressure source. When MTNP, a large zone of hypoperfusion, would theoretically cause ischemia in the epicardium that would theoretically cause ischemia. In wound healing the effect of hypoperfusion or ischemia close to the negative pressure source might be beneficial to wound healing, since hypoxia has been shown to be a strong factor for stimulating VEGF and new vessel formation. In MTNP however, a zone of hypoperfusion would probably not be desirable. Interestingly, three different studies on animals have shown a significant increase in epicardial blood flow when exposed to MTNP of -50mmHg. MTNP between -75 and -150mmHg did not; in any of the studies induce a significant change in myocardial blood flow. Probably because the amount of negative pressure applied is to large, resulting in an obstruction of the vessels. Consequently, no hypoperfusion could be observed during MTNP in either normal, ischemic, or reperfused myocardium during both normo- and hypo-thermia. The absence of hypoperfusion could possibly be explained by the higher density of myocardium than wound tissue. It could however also possibly be explained by the release of vasodilators close to the negative pressure source. Another possible explanation is that the increase in blood flow is due to a redistribution of the microvascular blood flow to the epicardium caused by natural physiological microvascular mechanisms in the myocardial wall, as seen during for example systolic blood pressure below 50 mmHg. Another possible explanation is that the negative force is greater closer to the vacuum source and subsequently decreases with distance.

Argenta et al. investigated in 2010 if MTNP applied onto the myocardium followed acute myocardial infarction could decrease the size of myocardial infarction in an animal model. They induce ischemia by 75 minutes of left main coronary artery occlusion and thereafter three hours of reperfusion. Animals were assigned to one of three groups: (A) untreated control; treatment of involved myocardium for 180 minutes of MTNP with (B) -50 mmHg, or (C) -125 mmHg. Treatment of the ischemic area with MTNP for 180 minutes significantly reduced infarct size (area of necrosis/area at risk) in both treatment groups compared to control. Total area of cell death was reduced by 65% with -50 mmHg treatment and 55% in the -125 mmHg group. They concluded that treatment of ischemic myocardium with MTR, for a controlled period of time during reperfusion, successfully reduced the extent of myocardial death after acute myocardial infarction.

5. Ischemic heart disease; clinical application of TNP

The majority of patients who require intervention for coronary artery disease are adequately treated by PCI or CABG. However, a major reason for failure of these treatments is their dependency on luminal size and coronary outflow. Methods of stimulating new vessel formation in the myocardium that are not dependent on vessel caliber therefore provide an important alternative treatment. A large group of patients suffer from refractory angina pectoris. Conventional treatment such as PCI and CABG has not been successful in these patients. Various other therapies have been tried, such as percutaneous myocardial laser revascularization, and enhanced external counter-pulsation, with varying success. Even spinal cord stimulation has been used in an attempt to ease their ischaemic pain. However, a satisfactory means of treating these patients has yet to be found. A new form of treatment resulting in new collateral vessel formation would thus be of interest for these patients. Numerous studies have evaluated the efficacy of gene therapy in the treatment of ischemic heart disease for the restoration of myocardial function by stimulation of angiogenesis and collateral vessel formation. VEGF has been found to be one of the most interesting growth factors in therapeutic angiogenesis. Interestingly, the mechanical forces exerted by TNP stimulate the endogenous production of VEGF.

In patients with acute coronary syndrome and coronary vessel occlusion, it is of great importance to improve or, if possible, restore the blood flow to the ischemic myocardium to protect it from ischemic stress and, in some cases, acute coronary infarction. Most patients are successfully treated with conventional methods such as PCI or CABG. However, these procedures do not result in satisfactory results in all patients due to extensive coronary disease or small vessel caliber. Furthermore, the procedure is not suitable for some patients due to their advanced age, renal failure, or other complicating factors. In some cases of acute ST elevation myocardial infarction there is no reflow during PCI. No-reflow situations may also arise during saphenous vein graft intervention, and rotational atherectomy. During no-reflow, epicardial flow is reduced due to obstructions at the microvasculature level. This no-reflow condition is usually transient, but patients with refractory no-reflow are associated with a markedly increased risk of 30-day mortality, compared with patients in whom no-reflow is transient. MTNP of -50 mmHg significantly increased the microvascular blood flow in both the epicardium and the myocardium. Interestingly, MTNP increases both the velocity and volume of blood flow by opening up the capillary beds. Furthermore, the method is not dependent on vessel caliber.

6. Conclusion

In conclusion, MTNP increases blood flow to the heart during normal, ischemic and reperfused conditions during both normo- and hypo-thermia. Interestingly, MTNP increases blood flow both in the endocardium and in the epicardium of the myocardial wall. The authors believe that MTNP may in the future represent an alternative treatment for patients with coronary artery disease and in particular patients with refractory angina pectoris.

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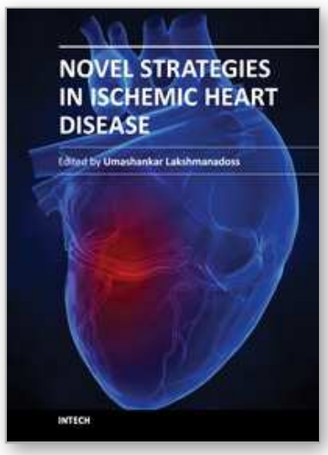

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The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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