Sympathetic and sensory nerve activation during negative pressure therapy of sternotomy wounds

Christian Torbrand, Angelica Wackenfors, Sandra Lindstedt, Rolf Ekman, Richard Ingemansson, Malin Malmsjö

Department of Medicine, Lund University Hospital, Lund, Sweden
Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden
Department of Cardiothoracic Surgery, Lund University Hospital, Lund, Sweden

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Abstract

Negative pressure wound therapy (NPWT) has been adopted as the first-line treatment for poststernotomy mediastinitis as a result of the excellent clinical outcome. The knowledge concerning the effects of NPWT on the cardiovascular system and homeostasis is still limited. The aim of the present study was to investigate whether the plasma levels of neurohormones change during NPWT. Six pigs underwent median sternotomy followed by NPWT at –125 mmHg. The plasma levels of noradrenaline, adrenaline, neuropeptide Y, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP) were determined before (0 min) and 5, 20, 60 and 180 min after the application of NPWT. The results show a transient increase in the plasma levels of noradrenaline and adrenaline when NPWT was applied. The plasma level of the adrenergic co-transmitter neuropeptide Y was higher in NPWT than in sham-treated pigs, after 180 min of negative pressure. After 180 min of NPWT there was an increase in the plasma levels of the sensory nerve transmitter substance P, while no such effect was observed for CGRP or VIP. In conclusion, the results suggest sympathetic nerve activation during NPWT. This may be the result of an increase in workload on the heart during the initial phase of NPWT.

Keywords: Experimental surgery; Mediastinal infection; Wound healing; Noradrenaline; Adrenaline

1. Introduction

Negative pressure wound therapy (NPWT) has remarkable effects on the healing of chronic and difficult wounds and has drastically reduced the mortality in poststernotomy mediastinitis following cardiac surgery. The technique entails application of negative pressure to a sealed, airtight wound. The suction force created by the subatmospheric pressure enables the drainage of excessive fluid and debris, which leads to the removal of wound edema, reduction in bacterial count and enhanced granulation tissue formation [1, 2]. Knowledge of the effects of NPWT in a sternotomy wound is limited [1]. The organs in the mediastinum are hemodynamically crucial and both vulnerable bypass grafts and reduced cardiac function should be taken into consideration during NPWT of sternotomy wounds.

Recent publications have reported right ventricular rupture during NPWT in cardiac surgery [3]. Also, reduced cardiac output during NPWT has been reported [4]. No study has yet been performed to examine the effect of NPWT on neurohormones, many of which are considered to be released upon increased cardiac load. In the present study, we analyzed the plasma levels of noradrenaline, adrenaline, neuropeptide Y, substance P, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP).

Noradrenaline is a transmitter that is released by the sympathetic nerve terminals. The sympathetic nervous system also acts on the adrenal medulla to release catecholamines including adrenaline and, to a lesser extent, noradrenaline. Neuropeptide Y is co-localized with norepinephrine in sympathetic nerve terminals and is released when the rate of nerve firing is high [5]. Neuropeptide Y enhances the effects of noradrenaline and accounts for the long-lasting effects of sympathetic nerve transmission [5]. Sympathetic nerve activation results in increased cardiac pumping, sodium retention via the kidneys and constriction and hypertrophic effects on the peripheral vasculature.

VIP is a co-transmitter in parasympathetic nerves [6]. It is involved in the autonomic regulation of the cardiovascular system, where it exerts positive inotropic and chron-
otropic effects, and causes coronary vasodilatation. Substance P and CGRP are released from primary afferent neurons and act in the periphery to stimulate vasodilatation and promote inflammation [7]. This mechanism, known as ‘neurogenic inflammation’, amplifies and sustains an inflammatory reaction.

In the present study, the effects of NPWT on the plasma levels of neurohormones were examined in a pig sternotomy wound model. Noradrenaline, adrenaline, neuropeptide Y, VIP, substance P and CGRP were analysed before (0 min) and after 5, 20, 60 and 180 min of NPWT at −125 mmHg.

2. Material and methods

2.1. Animals

An uninfected porcine sternotomy wound model was used in the present study. Twelve domestic Landrace pigs of both genders, with a mean body weight of 70 kg, were fasted overnight with free access to water. The study was approved by the Ethics Committee for Animal Research, Lund University, Sweden. All animals received humane care in compliance with the European Convention on Animal Care.

2.2. Anesthesia

The pigs were premedicated with an intramuscular injection of ketamine (Ketaminol Vet™ 100 mg/ml, 15 mg/kg body weight, Farmaceutici Gellini SpA, Aprilia, Italy) in combination with xylazine (Rompun Vet™, 2 mg/kg body weight; Bayer AG; Leverkusen, Germany). Anesthesia was maintained by continuous intravenous infusion of propofol (Diprivan™; 0.1–0.2 mg/kg body weight/min, Astra Zene ca; Sweden) in combination with fentanyl (Leptanal™; 0.02 μg/kg body weight, Lilly, France) and atracurium besylate (Tracrium™; 0.2–0.5 mg/kg body weight, Glaxo, Täby, Sweden). The pigs were mechanically ventilated with a Siemens-Elema 900B ventilator in the volume-controlled mode.

2.3. Surgical procedure

A midline sternotomy was performed and the pericardium was opened. The sternotomy wound was prepared for NPWT. A polyurethane foam dressing was placed between the sternum bone edges and the soft tissue, and the wound filler will thereby be in direct contact with the soft tissue, and the wound will be opened. The sternotomy wound was prepared for NPWT. In the cases when the whole sternotomy wound is reopened, the plasma levels of neuropeptide Y were significantly higher in the NPWT-treated than in the sham-treated pigs (Fig. 1).

2.4. Biochemical analysis of neurohormones

The plasma levels of CGRP, neuropeptide Y, substance P, VIP, adrenaline and noradrenaline were analyzed, as described previously [8–10].

2.5. Calculations and statistics

Results were obtained from six sham-treated and six NPWT-treated pigs. Statistical analysis was performed using Students’ t-test. Significance was defined as P<0.05. The results are presented as mean values ± the standard error on the mean (S.E.M.).

3. Results

The levels of noradrenaline and adrenaline were found to be higher in NPWT-treated than in sham-treated pigs after 20 min of negative pressure therapy at −125 mmHg. This elevation was transient and after 60 and 180 min, respectively, the levels of noradrenaline and adrenaline were similar in NPWT- and sham-treated pigs (Fig. 1).

The plasma levels of neuropeptide Y were similar in NPWT- and sham-treated pigs at the beginning of NPWT. The levels then declined in both sham-treated and NPWT-treated pigs, but the decline was considerably slower in the NPWT-treated pigs, and after 180 min of negative pressure therapy, the plasma levels of neuropeptide Y were significantly higher in the NPWT-treated than in the sham-treated pigs (Fig. 1).

After 180 min of NPWT there was an increase in the plasma levels of substance P (Fig. 2). No such difference was observed for CGRP of VIP.

4. Discussion

4.1. Effects of NPWT on neurohormones

The experiment in the present study was performed in an experimental model of sternotomy wound. In the clinic, there are different approaches to treat mediastinitis; either the sternotomy is reopened and the NPWT is applied between the sternum bone edges and the soft tissue, and the wound filler will thereby be in direct contact with the heart, or only the soft tissue parts of the wound is reopened for NPWT. In the cases when the whole sternotomy wound is opened, negative pressure therapy is in direct communication with the heart. This is the setup used for the current experiments.

Following the application of NPWT, the plasma levels of noradrenaline and adrenaline were elevated. These are sympathetic nervous system transmitters and are known to be released upon increased cardiac workload [11]. Recent reports show that NPWT decreases cardiac pumping efficiency [4], while MRI measurements have revealed that the heart is drawn up towards the anterior thoracic wall and is mechanically deformed when NPWT is applied [12]. Taken together, these findings suggest that NPWT results in increased cardiac workload. The strain placed on the heart by NPWT may thus result in compensatory increases in sympathetic nerve activity. Indeed, numerous studies report elevated noradrenaline and adrenaline plasma levels in patients with heart failure, and these have been proposed as suitable biomarkers [13].

Neuropeptide Y is a co-transmitter of sympathetic nerves and is released at high rates of nerve firing [5]. In the present study, the plasma levels of neuropeptide Y were initially similar, but with increasing duration of NPWT, the
Fig. 1. The plasma levels of noradrenaline, adrenaline and neuropeptide Y in pigs subjected to negative pressure wound therapy at –125 mmHg (NPWT) and sham-treated pigs (Sham). The results are presented as mean values ± S.E.M. from six experiments. Statistical analysis was performed using Students’ t-test. Significance was defined as P < 0.05 (*). Note that the levels of noradrenaline and adrenaline are initially increased and then decline, and then followed by a slight increase in the levels of neuropeptide Y.

Fig. 2. The plasma levels of VIP, substance P and CGRP in pigs treated with negative pressure wound therapy at –125 mmHg (NPWT) and sham-treated pigs. The results are presented as mean values ± S.E.M. from six experiments. Statistical analysis was performed using Students’ t-test. Significance was defined as P < 0.05 (*).

Levels were higher in the NPWT-treated than in the sham-treated pigs. This is in accordance with the general belief that neuropeptide Y is responsible for the long-lasting effects of sympathetic nerve activity [5]. The maintained high plasma levels of neuropeptide Y in the NPWT-treated pigs may be a consequence of the stress placed on the heart by the application of negative pressure [4, 14]. Indeed, plasma levels of neuropeptide Y are known to be high during sympathetic activation in stress-related cardiac conditions [15]. There was a steady decline in neuropeptide Y levels in the sham-treated pigs. Neuropeptide Y levels are presumably high during surgery, as a result of the trauma, and when surgery is completed, the neuropeptide Y levels decline.
4.2. Transient increases in noradrenaline and adrenaline levels

The increase in noradrenaline and adrenaline plasma levels upon the application of NPWT was transient and after 60 and 180 min, respectively, the levels were similar to baseline values. The increase in noradrenaline and adrenaline may be the result of decreased cardiac output, which is known to occur immediately after the application of NPWT [4]. No study has yet been performed to analyze the long-term effects of NPWT on cardiac pumping. The changes in noradrenaline and adrenaline plasma levels may be transient because the decrease in cardiac output is transient, or may be the result of the body acclimatizing to slightly reduced cardiac output levels.

4.3. Sensory nerve activation

Substance P is released from primary afferent sensory nerves upon stimulation [7]. The plasma levels of substance P were increased after 180 min of NPWT. This may be due to the sensory nerve stimulation by the negative pressure on the wound edge. It is well known that NPWT causes a mechanical deformation of the tissue in the wound edge and shearing forces at the foam–wound interface [2]. This is presumably the reason for why some patients experience pain during NPWT.

4.4. Other levels of negative pressure

In the present study, we used a negative pressure level of −125 mmHg, since this is commonly used in clinical practice. The effects of other negative pressure levels on the release of neurohormones cannot be deduced from the results of the present study. However, we have previously shown that −75, −125, and −175 have similar effects on cardiac pumping [4], and we therefore believe that these levels of negative pressure may have similar effects on the release of neurohormones.

5. Conclusions

The results of the present study show elevated plasma levels of noradrenaline and adrenaline upon NPWT application, followed by an increase in neuropeptide Y. This enhanced sympathetic nerve activity may be the result of the increased cardiac workload on the heart during the initial phase of NPWT. However, the increase in catecholamine levels is only transient, suggesting that the body acclimatizes to negative pressure therapy. The results also show increased sensory nerve activation during NPWT. This may be a result of the mechanical deformation of the wound edge tissue and shearing forces at the foam–wound interface during NPWT.

References