THE ROLE OF MICROCIRCULATION IN THE PREVENTION AND TREATMENT OF POST-STERNOTOMY MEDIASTINITIS

PhD Thesis

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Pécs

2018

CONTENTS

ABBREVIATIONS

AB	Antibiotic therapy
BITA	Bilateral internal thoracic artery
BPMFP	Bilateral pectoral muscle flap plasty
CABG	Coronary artery bypass grafting
COPD	Chronic obstructive pulmonary disease
CI	Confedential intervallum
DM	Diabetes mellitus
DSWI	Deep sternal wound infection
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
FOT	Failure of treatment
INPWT	Incisional negative pressure wound therapy
NPWT	Negative pressure wound therapy
NYHA	New York Heart Association
PMFP	Pectoral muscle flap plasty
PVD	Peripheral vascular disease
XIP	Xiphoid process

1. INTRODUCTION

Median sternotomy remains the standard surgical approach for cardiac surgery, despite the growing popularity of minimal access approaches (1-5). Median sternotomy has many advantages; it is simple, quick to perform, and provides wide access to almost all mediastinal structures. However, a major disadvantage of the median sternotomy incision is its suboptimal healing tendency. Infection of sternal wounds remains a major surgical challenge that has a significant impact on morbidity, mortality, hospital costs, long-term survival, and patient's socio-psychological state (6-9). Deep sternal wound infections are rare, with an incidence rate, depending on the definition used, of between 0.4% and 5%, and higher in-hospital mortality rate (7- 35%) (10).

1.1. The pathophysiology of sternal wound infection

Three main factors are mandatory for optimal wound healing: infection control, stable osteosynthesis, and adequate perfusion.

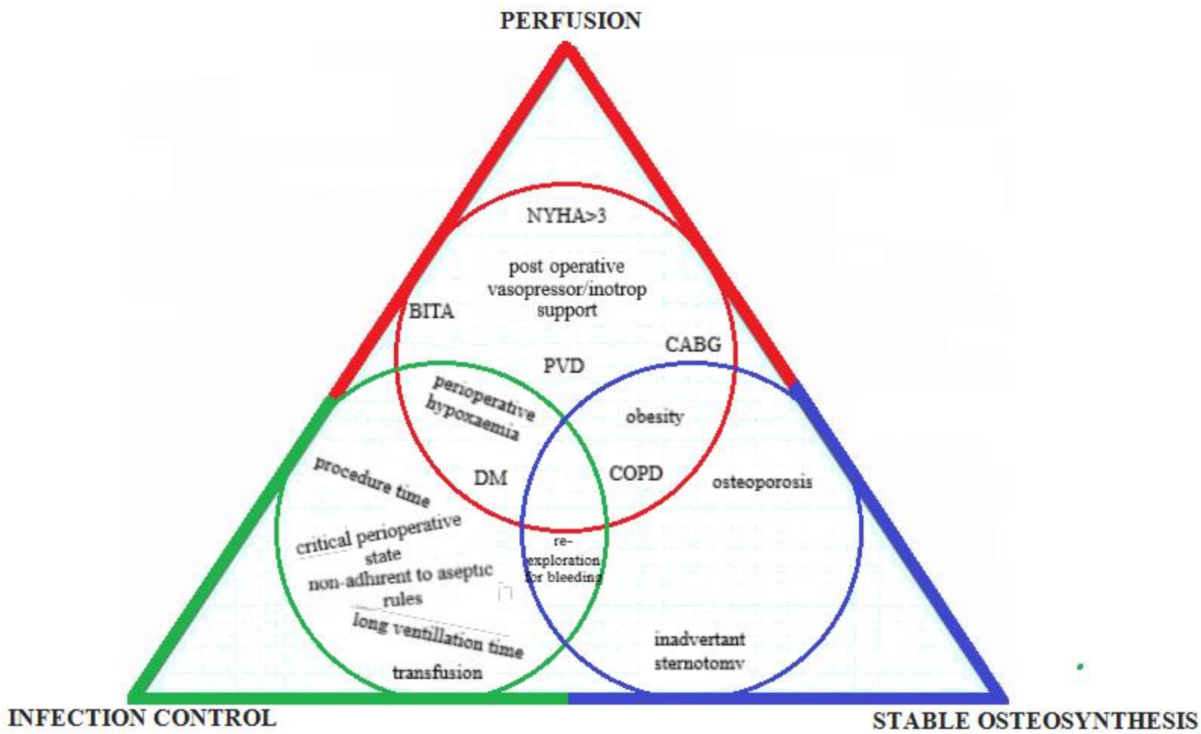

Figure 1.*The role of reported risk factors in the sternal wound healing triad.*

It is important to remember that reported risk factors predispose to sternal wound infections through breaking down one or more of the above- mentioned triad pillars (11-13).

1.2. New Approaches in prevention of DSWI

Recently, many new approaches have been reported to reduce the risk of DSWI. Those novel approaches reduce the risk of DSWI through one or more of the pillars involved in the sternal wound healing triad (14-22).

Infection Control	**Stable Osteosynthesis**	**Perfusion**
- Preoperative screening and decontamination of nasal carriage of *Staphylococcus aureus* - Gentamycin-collagen sponge - Vancomycin-coated paste	- Rigid sternal plating (bands or plates) - External chest support vest	- Incisional negative pressure wound therapy - Hyperbaric Oxigen therapy - Autologous platelet-rich plasma

Figure 2. *Novel approaches to reduce the risk of DSWI.*

1.3. The role of negative pressure wound therapy in prevention and treatment of sternal wound infections

In efforts to improve the microcirculation conditions in the sternal wounds, NPWT has become a standard approach in cardiac and plastic surgical practice. Two main indications can be formulated. The *traditional indication* lies in preconditioning infected sternal wounds to make them suitable for final surgical reconstruction. Under this indication negative pressure wound therapy is applied after thorough surgical debridement to improve the microcirculation conditions in the wounds, enhance the development of angiogenesis, and granulation tissue and serve as a bridge to final reconstruction (23, 24). The *novel indication* involves applying negative pressure on wounds closed by primary intention. Incisional negative pressure wound therapy (INPWT) can be applied over primary closed or surgically reconstructed wounds to improve wound healing (25-27).

2. AIMS AND OBJECTIVES

The purpose of our recent work is to cover some of the gaps in cardiac surgeon's knowledge in regards to prevention and treatment of deep sternal wound infections, emphasizing the role of the microcirculation aspects, stable biomechanics, and infection control.

2.1. Impact of INPWT on rates of failure of surgical reconstruction after DSWI

We assumed that applying INPWT on surgically reconstructed infected wounds would improve regional perfusion especially when muscle flaps were used. We attempted to verify the impact of the application of INPWT on post-reconstructional sternal wounds in regards to rates of treatment failure and hospital stay.

2.2. Predictive factors of treatment failure of DSWI

While risk factors that predispose to the development of DSWI have been well documented, factors that predispose to failure of surgical treatment are less frequently mentioned. In an effort to improve success rates, we conducted a retrospective study to explore some of the factors that might predict treatment failure.

2.3. The role of sternal rewiring in surgical reconstruction of DSWI

Sternal rewiring is thought to be mandatory to treat DSWI. Based on our experience, we attempted to prove that radical surgical debridement, even at the expense of partial or total sternectomy, and improving the microcirculation state of these wounds, through mobilization of well vascularized pectoral muscle flaps, would be more expedient. We compared our results in patients, in which sternal rewiring was performed against those for which sternal rewiring was not performed.

2.4. The role of the xiphoid process unit on the rates of DSWI

Considering the anatomical and embryological structure of the human sternum, and based on our observation that most DSWIs start with purulent discharge from the xiphoid region, we studied the role of preservation of the XIP unit in the pathophysiology of DSWI.

2.5. Microbiological results in the classification of DSWI

Finally, we examined the impact of micrbiological culture results on patients' survival rate.

3. PATIENTS AND METHODS

3.1. INPWT Study

In this study, we analyzed the data of 21 consecutive patients who developed DSWI after open heart surgery through a median sternotomy and underwent surgical reconstruction. After surgical reconstruction of the wounds, we applied INPWT together with Redon drains in ten patients (INPWT + Redon group). In 11 patients, INPWT was not applied (Redon only group).

In both groups, Redon drains were removed when daily secretion dropped below 30 ml. Incisional negative pressure over the wound was applied for 10 days.

We examined **the time between introduction and removal of Redon drains, hospital stay**, and **the rate of treatment failure**. The follow-up period was 6 months.

3.2. Predictive factors of treatment failure

In this study, data from 3177 consecutive patients who underwent median sternotomy were retrospectively analyzed and among this cohort, DSWI was diagnosed in 60 patients (1.9%).

First, those patients who developed DSWI were divided into three groups: *Group I (n=18)* , infections presented between the day of operation and the sixth postoperative day (day 0-6); *Group II (n=32)*, infections presented between the seventh and 30th day postoperatively (day

7-30); and *Group III (n=10)* : infections presented after the 30th postoperative day (after day 30).

Other factors that might contribute to the development of FOT, including risk factors (sex, age, body mass index, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, type and urgency of cardiac operation, use of internal mammary artery, and transfusion), nature of surgical intervention, and microbiological culture were all identified and statistically analyzed.

The first surgical reconstruction was performed by conventional surgical procedures in all patients (debridement and application of negative pressure wound therapy, mediastinal irrigation, sternal rewiring and closure over Redon drainage). Patients in whom the first surgical reconstruction failed underwent a second reconstruction attempt (n =29). We divided these patients into two subgroups depending on the radical nature of the second surgical intervention. The more radical surgical intervention included hemi- or total sternectomy, resection of the cartilaginous part of the ribs, and closure with unilateral or bilateral pectoral muscle, advancement or turnover, flaps, (R group n =11). Eighteen patients underwent another conventional reintervention (C group n = 18).

3.3. Role of sternal rewiring in surgical reconstruction of DSWI

After exlusion of four patients from the 3.2 study, who died before final surgical reconstruction, data from the remaining 56 patients, who developed DSWI and underwent final surgical reconstruction were analyzed. Based on the surgeon's decision, patients were divided into two groups: patients where sternal rewiring was performed (sternal rewiring group), and patients where other interventions, but no sternal rewiring (no sternal rewiring group), were performed.

We examined: the need for **readmission** or **death within 90 days**, and **length of hospital stay**. The follow- up period was 12 months.

3.4. Role of XIP unit in reducing rates of DSWI

We conducted a cohort study to estimate the impact of the preservation of XIP unit integrity on the development of DSWI; data from 948 patients, who underwent coronary bypass grafting with the left internal thoracic artery, in the period between January 2012 and May 2017 were prospectively collected and retrospectively analyzed. Patients were divided into two groups: Group I *(XIP group*, n =250), and Group II *(non-XIP group*, n =698).

We examined: the impact of preservation of the XIP unit on the **rates of DSWI**.

3.5. Microbiological classification of DSWI

We performed a retrospective analysis of data from 92 consecutive patients who developed DSWI based on clinical, biomarker, and intraoperative view, independently of the results of the microbiological culture. Based on the intraoperative view, sternal involvement was documented in all cases and surgical reconstruction was performed in all patients. Based on results of microbiological cultures, patients in this study were divided into two groups: those with positive- culture wounds including patients with clinically infected sternal wounds and positive microbiological culture; and those with negative-culture wounds including patients with clinically infected sternal wounds but negative microbiological culture. We examined the **90-days**, **1-year**, and **2-years survival rates** in both groups.

4. STATISTICAL ANALYSIS

Statistical analysis used IBM SPSS software (Version 20, IBM Corp., released 2011. IBM) For the comparison of data, Chi-squared and Student's *t*-tests were applied. P values less than 0.05 were considered to indicate statistically significant differences. Categorical variables were presented as frequencies and percentages and compared between groups using Chi-squared or Fisher's exact tests. In **Section 3.4.** the differences in the baseline and operative characteristics of patients included in the two groups were compared using the independent sample t-test for continuous variables and the Chi-square test for categorical variables. To reduce the impact of treatment selection bias and potential confounding, we balanced the distribution of covariates between the XIP-sparing and non-XIP subgroups with the inverse probability of treatment weighting. Using XIP unit sparing as a dependent variable, related outcomes and confounding (related to treatment) covariates [diabetes mellitus, chronic obstructive pulmonary disease, European System for Cardiac Operative Risk Evaluation (EuroSCORE II), operative time, red blood cells, and freshly frozen plasma transfusion] were included in the binary logistic regression analysis to compute the propensity score. The model was well calibrated according to the Hosmer-Lemeshow test ($p = 0.371$). To estimate the treatment effect of XIP sparing on the development of DSWI, a binary logistic model was used.

In **Section 3.5.** Kaplan-Meier estimates were used to calculate survival curves. Any differences between curves in 90-days, 1-year, and 2-years survival rates were explored using log-rank chi-square (Mantel-Cox) tests.

5. RESULTS

5.1. INPWT Study

There were no significant differences between the baseline characteristics of patients (age, sex, risk factors, and type of operation) in both groups.

Although there was no statistically significant difference between the duration of Redon drainage and the rate of treatment failure, these two parameters were lower in the INPWT+Redon group than in the Redon only group (6.9 ± 5.2, vs. 13 ± 11.6, p= 0.122; and 10% vs. 45.5%, p= 0.072, respectively). Hospitalization time was significantly shorter in the INPWT+Redon group than in the Redon only group (22.5 vs. 95.7 days, p= 0.001). Only one patient needed surgical reintervention in the INPWT+Redon group compared to five patients in the Redon only group. Two patients died during their hospital stay in the Redon only group. In the follow-up period, survival was 100% in the INPWT+Redon group, and computed tomography scans revealed no signs of inflammation of the mediastinal structures.

5.2. Predictive factors of FOT

Out of 60 patients, the FOT criteria were reached in 29 (48.3%). FOT occured in 27.8% of Group I, 53.1% of Group II, and 70% of Group III, (P= 0.005).

Treatment failure was more frequent if wound cultures were positive at the time of reconstruction than when cultures were negative (69.0% vs. 22.6%, p <0.001).

Peripheral vascular disease was the only risk factor, among those included in the study, that significantly contributed to FOT, p= 0.002.

Success rates in the radical surgery group were significantly higher than in the conventional group (88.1 vs. 11.1%, p <0.001), (Figure 9). In this retrospective study, five patients died

(12%). Mortality was higher in the conventional group (5/18 [27.6%] vs. 0/11 [0%], p = 0.002).

5.3. The role of sternal rewiring in the development of FOT

The rate of readmission was higher in the sternal rewiring group than in the no sternal rewiring group (63.6% vs. 14.7%, respectively; P <0.001). The overall 90-day mortality rate was 8.9% (5/56; sternal rewiring, 21.7% [5/23] vs. no sternal rewiring, 0%, [0/33]; p = 0.030). No additional deaths occurred during the 12-month follow-up period. Further, the median length of hospitalization was significantly longer in the sternal rewiring group than in the no sternal rewiring group (51 vs. 30 days; p = 0.006).

5.4. The role of preservation of the XIP unit in reducing the risk of DSWI

The DSWI rates in the XIP-sparing and non-XIP sparing groups were 0.8% and 6.1%, respectively, (p = 0.001). No statistically significant differences were observed between baseline and operative characteristics and clinical outcome data of the patients in the XIP-sparing and non-XIP subgroups groups.

Based on the binary logistic model using inverse propensity score-weighted samples, the XIP-sparing approach had a significant therapeutic impact on DSWI rates after coronary artery surgery compared to conventional sternotomy. The adjusted odds ratio of DSWI in the XIP sparing-group was 0.087 (95% CI: 0.020–0.381, p = 0.001).

5.5. Impact of results of microbiological cultures on survival rates after DSWI

Consistent with our findings in Section 3.2, in this study, FOT was more frequent when wound cultures were positive, p= 0.001. Nevertheless, the FOT rate in the negative-culture wounds group was 20%, which might be due to incomplete surgical debridement. Survival rates were significantly better at 90 days, 1 year, and 2 years in the negative-culture wounds group than in the positive-culture wounds group, (Log rank tests; 90 days: $p < 0.001$, 1 year $p = 0,005$, 2 years $p = 0,003$).

6. DISCUSSION

6.1. Our retrospective observational study was the first study that attempted to assess the effect of INPWT on the wound-healing process after reconstructive surgery of DSWI. We observed a shorter Redon drainage time in the INPWT+Redons group. We assume that a decreasing amount of drainage is related, among many other factors, to the state of dead spaces in the area of reconstruction. The shorter hospital stay in the INPWT+ Redon group, compared to Redons only goup, indicated fewer complications regarding wound dehiscence and the development of seroma, which might be the result of the vacuum effect in reducing edema and improving the microcirculation conditions.

6.2. In our study, we observed higher rates of treatment failure if infection appeared later during the wound healing process. We found that positive wound cultures contributed significantly to treatment failure. We identified a significant contribution from peripheral vascular disease—poor microvasculature and low tissue hypoperfusion might underlie this observation. Other risk factors had no impact on surgical reconstruction failure.

Radical surgical debridement, even at the expense of sternectomy, and applying plastic surgical principles to wound treatment is more expedient than conventional surgical methods. A combination of radical surgical reconstruction with the applying of incisional negative pressure therapy has led to better surgical results, and shorter hospital stay in our patients.

6.3. We compared the treatment outcomes after conventional sternal rewiring and reconstruction without sternal rewiring in patients with DSWIs and detected higher readmission and early mortality rates in the sternal rewiring group.

Where tissue perfusion is inadequate and in cases of poor microcirculation, (e.g. bilateral internal thoracic artery harvesting, obesity, diabetes mellitus, and peripheral vasculopathy), a stable osteosynthesis may not be sufficient for effective wound healing.

6.4. In our surgical experience, discharge from the sternal wounds appears, in most cases, at the lower part of these wounds. This observation led us to suspect the possible role of XIP in the development of these wounds. The healing process of cartilage tissue usually differs from that of bone. This is mainly because cartilage is avascular and the repair process after the damage to this tissue type is slow.

6.5. Many classifications of deep sternal wound infections (DSWI) were reported based on the time and localization of infection, risk factors, or intraoperative view. No available classification consider results of microbiological cultures an important concern. Negative-culture sternal wound infections are a common issue for the cardiac and plastic surgeon dealing with these wounds. Due to their impact on survival rates, classifying of clinical deep sternal wound infections on the base of microbiological culture would likely be useful.

7. NEW OBSERVATIONS

Our investigations on the role of microcirculation in the treatment and prevention of deep sternal wound infections resulted in new technical and clinical insights into the surgical management of primary and infected sternal wounds.

7.1. Although incisional negative pressure wound has been previously reported to be an effective procedure to reduce the risk of the deep sternal wound in high- risk patients, our work was the first to emphasize the impact of INPWT on infected sternal wounds reconstructed surgically.

7.2. Our work shows that, among those tested, peripheral vascular disease is the only risk factor that contributes to the development of sternal wound infections that might lead to failure of surgical treatment of these wounds. This finding demonstrates the significant impact of the microvasculature and tissue perfusion in preventing failure of surgical treatment.

7.3. Although sternal refixation might lead to a biomechanically stable thorax, our work shows that sternal rewiring is not mandatory in surgical reconstruction of these wounds, and that eliminating the infected sternum, even at the expense of hemi- or total sternectomy, and preservation of tissue perfusion by wound coverage by well- vascularized muscle flaps with a combination of INPWT, might also lead to stable thorax with complete freedom of symptoms.

7.4. Our work shows that the concept of the „XIP unit" is likely to be useful when dealing with deep sternal wounds. Xip- sparing midline sternotomy significanty reduced the risk of DSWI after open heart surgery.

7.5. Our work has revealed that deep sternal wound infections are still a devastating complication after median sternotomy, even if standard microbiological cultures are negative. However, in cases of successful surgical reconstruction, survival rates are better when wound cultures were negative. This might call for the significance of classifying sternal wound on the base of microbiological cultures, and reflect the fact that radical surgical debridement is mandatory, even if wound cultures are negative.

Considering the findings of our studies together, we sought to formulate an applicable treatment algorithm that would take into account all pillars of the sternal wound healing triad. The following algorithm is shown in Figure 3.

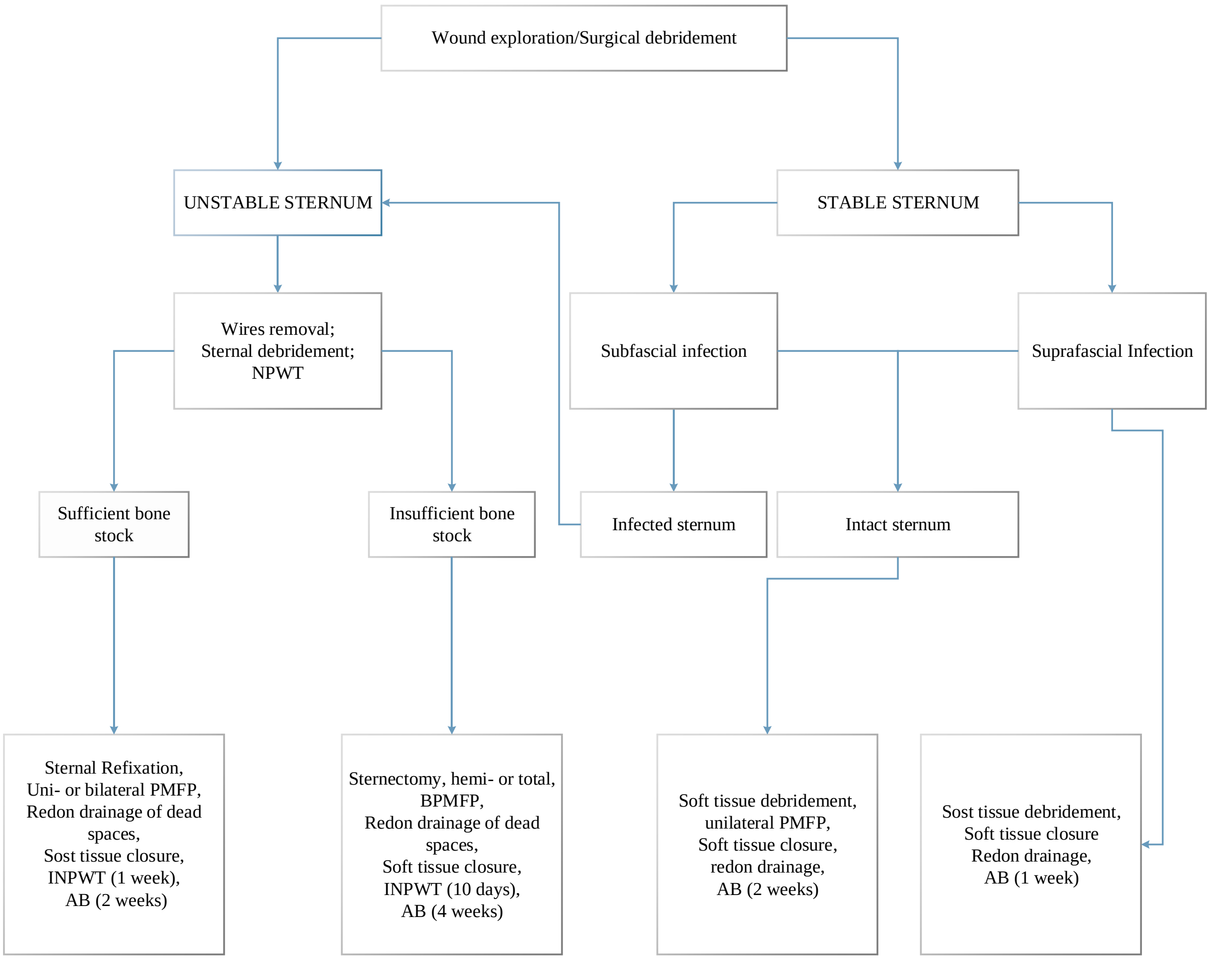

Figure 3. *Algorithm for the treatment of DSWIs.*

8. TOPIC-RELATED PUBLICATIONS

Aref Rashed, Magdolna Frenyó, Károly Gombocz, Sándor Szabados, Nasri Alotti. (2017) Incisional negative pressure wound therapy in reconstructive surgery of poststernotomy mediastinitis. *IWJ*, 14 (1). pp. 180-183. ISSN 1742-4801. *IF: 2.848.*

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Rashed Aref, Gombocz Károly, Frenyó Magdolna, Verzár Zsófia, Alotti Nasri. Sternotomiát követően létrejött sebfertőzések nyított és zárt kezelésével szerzett tapasztalaink pozitív sebváladék tenyésztési eredmények esetében. Magyar sebész Társaság, Kisérletes sebészeti szekció XXVI.kongresszusa, Herczeghalom, 2017. Szeptember 28-30.

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Rashed Aref (2017): Az incisionális NPWT alkalmazása a szívsebészetben: In Elméleti Ismeretek és Gyakorlati Alkalmazás Negatív- Nyomás-Terápia. Budapest, pp.142-4. ISBN: 978-615-00-1000-7.

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Rashed Aref, Frenyó Magdolna, Fónagy Gergely, Mazur Mónika, Alotti Nasri. Incizionális negatív nyomás terápia a poszt-szternotómiás mediastinitis reconstructiós kezelésében, Szeged, MSZT XXII. Kongresszusa, 2015.

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10. ACKNOWLEDGMENTS

I would first like to express my gratitude to my wife, *Piroska*, who gave me the opportunity and support throughout my professional career. Without her and the inspiration of our three sons, *Alex, Adam, Marcell,* this work would not have been done. I would like to express my thanks to my friend, Karoly Gombocz, who spared no effort in assisting me from the beginning to the end of this work. I would like to express my thanks to my project leader, *Dr. Zsófia Verzár*, for her practical assistance and guidance throughout the synthesis of this work. I should express my thanks to my boss, *Dr. Nasri Alotti,* for his help, and to all my colleagues who assisted directly or indirectly in the synthesis of this work. Finally, I would like to express thanks and respect to all the patients included in this work.