Intra-cardiac infections, coronary interventions and mechanical circulatory support

Citation for published version (APA):

van den Brink, F. S. (2021). *Intra-cardiac infections, coronary interventions and mechanical circulatory support*. [Doctoral Thesis, Maastricht University]. Ridderprint. <https://doi.org/10.26481/dis.20211020fb>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20211020fb](https://doi.org/10.26481/dis.20211020fb)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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INTRA-CARDIAC INFECTIONS, CORONARY INTERVENTIONS AND MECHANICAL CIRCULATORY SUPPORT

Floris S. van den Brink

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door financiële ondersteuning van de Maatschap Cardiologie van het Medisch Centrum Leeuwarden en de Raad van Bestuur St. Antonius Ziekenhuis Nieuwegein.

Additional financial support was generously provided by Chipsoft and Terumo Nederland

ISBN: 978-94-6416-576-0
Cover design: J.M.V. van den Brink
Lay-out: Publiss | www.publiss.nl
Print: Ridderprint | www.ridderprint.nl

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INTRA-CARDIAC INFECTIONS, CORONARY INTERVENTIONS AND MECHANICAL CIRCULATORY SUPPORT

Proefschrift

ter verkrijging van de graad van doctor in de geneeskunde aan de Universiteit
Maastricht op gezag van de rector magnificus Prof. dr. Rianne M. Letschert
volgens het besluit van het College van Decanen in het openbaar te verdedigen
op woensdag 20 oktober 2021
om 13:00 uur.

Door

Floris Stefan van den Brink

Geboren 4 September 1978 te Apeldoorn

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Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged

Aan mijn vader: Ex Aequo, ouwe!

Intra-cardiac infections, coronary interventions and mechanical circulatory support

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Chapters:

1. Introduction and general outline of the thesis 9
2. Prognostic factors in infective endocarditis in general hospitals in the Netherlands. 15

FS van den Brink, J Hasenaar, V Winia, M Klomp, B van Vlies, D Nicastia, B Groenmeijer, R. Braam, W Jaarsma, A Funke Kupper

Neth Heart J. 2016 May 17 doi:10.1007/s12471-016-0846-2
(Original article)

- 3A. Increased incidence of infective endocarditis after the 2009 European Society of Cardiology guideline update: a nationwide study in the Netherlands 27

FS van den Brink, MJ Swaans, MG Hoogendijk, A Alipour, JC. Kelder, W Jaarsma, FD Eefting, B Groenmeijer, AJ Funke Kupper, JM ten Berg

Eur Heart J Qual Care Clin Outcomes august 1, 2016 doi:http://dx.doi.org/10.1093/ehjqcco/qcw039 qcw039 (Original article)

- 3B. Incidence of infective endocarditis as after antibiotic prophylaxis guidelines changed-there is a change 45

FS van den Brink. C. Zivelongi, J. ten Berg, Ann Cardiothorac Surg 2019. doi: 10.21037/acs.2019.06.05 (Editorial)

4. A combined epicardial implantation and subsequent extraction strategy in pacemaker device infection in pacemaker dependent patients 51

FS van den Brink, VF van Dijk, LVA Boersma, MCEF Wijffels, J. Gelissen, E. Daeter, U. Sonker, JC Balt

Pacing Clin Electrophysiol . 2018 May 23. doi: 10.1111/pace.13382.
(Original article)
5. Incidence and Outcome of Prosthetic Valve Endocarditis after Transcatheter Aortic Valve Replacement in the Netherlands 67

J. Brouwer, **FS van den Brink**, V.J. Nijenhuis, T.N. Vossenbergh, R. Delewi, M.S. van Mourik, P. den Heijer, W. Tanis, P.C. Kievit, W. Holvoet, R.S Hermanides and J.M. ten Berg

Neth Heart J . 2020 Apr 24. doi: 10.1007/s12471-020-01420-2.
(Original article)
- 6A. Veno Arterial Extra Corporeal Membrane Oxygenation for the treatment of Cardiac failure in Patients with infective endocarditis 81

FS van den Brink, R van Tooren, U Sonker, P Klein, F. Waanders, C. Zivelonghi, FD Eefting, E Scholten, JM ten Berg

Perfusion 2019 Apr 26:267659119842807. doi: 10.1177/0267659119842807 (Original article)
- 6B. The Successful Use of plain TTE in VV-ECMO cannula repositioning, 95

FS van den Brink, A Swadi, E Scholten

Netherlands Journal of Critical Care, volume 25 – no 5 –sep 20i7; 186-187 (Case report)

7. Veno-Arterial-Extra Corporal Membrane Oxygenation in addition 99
to primary PCI in patients presenting with ST-Elevation Myocardial
Infarction
- FS van den Brink**, AS. Magan, PG. Noordzij, C. Zivelonghi, P.
Agostoni, FD. Eefting, JM, ten Berg, MJ, Suttorp, BR, Rensing, JP van
Kuijk, P. Klein, E. Scholten, JAS. van der Heyden,

Netherlands Heart Journal DOI : 10.1007/s12471-017-1068-y
NEHJ-D-17-00146.3 (*Original Article*)
8. Prophylactic Veno-Arterial Extra Corporal Membrane Oxygenation 115
in Patients undergoing High Risk Percutaneous Coronary
Intervention
- FS van den Brink**, T. Meijers, S. Hofma, A. van Boven, A. Nap, A.
Vonk, P. Symersky, K. Sjauw, P Knaapen

Neth Heart J . 2020 Mar;28(3):139-144. doi: 10.1007/s12471-019-
01350-8. (*Original article*)
9. Intra aortic balloon pump and Veno Arterial-Extra Corporeal 129
Membrane Oxygenation is associated with better outcome than
VA-ECMO alone in the treatment of cardiogenic shock in ST-
Elevation Myocardial Infarction
- FS van den Brink**, C Zivelonghi, T Vossenbergh, G Bleeker, VL
Winia, KD Sjauw, JM ten Berg J

Invasive Cardiol. 2021 May;33(5):E387-E392. Epub 2021 Apr 20
(*Original article*)

10.	<i>Future perspectives en Nederlandse samenvatting van het Proefschrift</i>	145
11.	<i>Impact Paragraph</i>	151
12.	<i>List op publications</i>	157
13.	<i>Dankwoord</i>	163
14.	<i>Curriculum Vitae</i>	169

CHAPTER 1

INTRODUCTION AND GENERAL OUTLINE OF THE THESIS

Infective endocarditis is a relatively rare disease which makes it difficult to study. Randomized controlled trials are extremely rare and only a handful were ever conducted. Most research in the field is being performed in tertiary or referral centers. In the second chapter of this thesis we present a study on infective endocarditis performed in general hospitals. Studies like these present a representation of an all-comers population and illustrate that mortality and morbidity might be higher than first anticipated due to underrepresentation in studies performed in centers with surgical intervention as an option.

In the third chapter of this thesis we seek to answer a very controversial question: Is chemoprophylaxis for endocarditis effective in preventing this devastating disease. In 2009 the European Society of Cardiology guidelines for endocarditis saw a dramatic change; indication for prophylaxis was limited to a select population. Since that same time there has been a rise in endocarditis incidence and a simultaneous increase in enterococci mediated endocarditis. In this chapter we demonstrate this on the basis of Dutch endocarditis incidence and we advocate a return to the previous broader indications for chemoprophylaxis (chapter 3B).

The fourth chapter illustrates how to handle patients who have an infected pacemaker and who are dependent on that pacemaker at the same time. We describe a novel implantation strategy in which the infected device is extracted while an epicardial device is implanted via mini-thoracotomy in the same procedure, thus ensuring permanent pacing in pacemaker dependent patients.

The fifth chapter of this thesis tackles the incidence and outcome of infective endocarditis after trans-catheter aortic valve implantation (TAVI) in a multi-centre study. It illustrates that infective endocarditis after TAVI has a relatively low incidence, yet outcome is poor when contracted, albeit better than surgically implanted prosthetic valve endocarditis.

The sixth chapter describes the outcome of cardiac failure after surgery for infective endocarditis. Patients who develop cardiac failure can be supported with veno-arterial extra corporeal membrane oxygenation (VA-EMCO). This is a form of mechanical circulatory support using a centrifugal pump to generate flow across a membrane to oxygenate the blood and supply circulatory support.

Imaging skills are pivotal in managing these patients. This is illustrated by the case-report in chapter 6B.

VA-ECMO can also be used in patients suffering from cardiogenic shock due to ST-elevation myocardial infarction. This subject is addressed in chapter seven. Using various predictive scores we illustrate that outcome in this group of patients is much better than predicted and that VA-ECMO might be a solution in treating patients with severe cardiogenic shock due to ST-elevation myocardial infarction.

In the eight chapter of this thesis we describe the use of prophylactic VA-ECMO to support elective patients undergoing high risk PCI in whom cardiac failure is to be expected. It can be used safely and successfully in aiding high risk percutaneous coronary interventions.

One of the drawbacks of VA-ECMO is that it increases afterload. This may influence outcome as it stresses the left ventricle which is a predictor for outcome in cardiogenic shock. In the ninth and final chapter we present the outcome of patients undergoing VA-ECMO treatment combined with the intra-aortic balloon pump (IABP) when compared to VA-ECMO alone and illustrate that combining the two techniques seems to lead to a better outcome through the combined actions of circulatory support of the VA-ECMO and the afterload reduction of the IABP.

CHAPTER 2

PROGNOSTIC FACTORS IN INFECTIVE ENDOCARDITIS IN GENERAL HOSPITALS IN THE NETHERLANDS

FS van den Brink, J Hasenaar, V Winia, M Klomp, B van Vlies, D Nicastia,
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Neth Heart J. 2016 May 17 doi:10.1007/s12471-016-0846-2 (Original article)

ABSTRACT

Introduction

Despite advances in treatment, infective endocarditis (IE) still ranks amongst the most lethal infectious diseases. We sought to determine prognostic factors in general hospitals in the Netherlands as research in this setting is scarce.

RESULTS

Between 2004 and 2011, we identified 216 cases of IE, 30.1% of which were prosthetic valve IE. This leads to an annual incidence of IE of 5.7 new cases per 100,000 persons per year.

Women were less likely to undergo surgical intervention (OR=1.96, 95% CI 1.06-3.61, $p=0.031$). Also, ageing was an independent prognostic factor for not receiving surgery in a multivariate analysis (annual OR=1.04, 95% CI 1.02-1.06, $p<0.001$). Female sex was a prognostic factor for mortality (OR=2.35, 95% CI 1.29-4.28, $p=0.005$). Age was also an independent prognostic factor for mortality (OR=0.95, 95% CI 0.93-0.97, $p<0.001$). Conservative treatment was a prognostic factor for mortality (OR=3.39, 95% CI 1.80-6.38, $p<0.001$) whereas surgical intervention was an independent prognostic factor for adverse events (OR=0.33, 95% CI 0.18-0.61, $p<0.001$). *Staphylococcus aureus* was an independent prognostic factor for adverse events (OR=2.05, 95% CI 1.10-3.84, $p=0.024$) but not for mortality.

CONCLUSION

This study shows that endocarditis in general hospitals has a high rate of morbidity and mortality. Even when treated, it ranks as one of the most lethal infectious diseases in the Netherlands, especially in women and the elderly.

KEYWORDS

Endocarditis; Survival analysis; Hospitals, general; Mortality; Morbidity; *Staphylococcus aureus*

INTRODUCTION

Since William Osler first described ‘malignant endocarditis’ in 1885, there has been an evolution in the pathophysiology and treatment of this rare but often lethal disease [1,2,3,4].

A decreased incidence of rheumatic heart valve disease but increased incidence of degenerative heart valve disease has changed the demographics of patients affected with infective endocarditis (IE) in the Western world [5,6,7,8]. Interestingly, in the Netherlands, due to lower numbers of intravenous drug users, the frequency of right-sided endocarditis has notably dropped [9]. At the same time, the worldwide rise in methicillin-resistant staphylococcus aureus (MRSA) has augmented MRSA-related IE [10,11,12,13,14,]. Furthermore, there has been a substantial increase in the use of prosthetic heart valves, both mechanical and biological [15]. Also, the increased use of devices such as pacemakers and implantable cardiac defibrillators is posing new challenges [10].

Previous studies in the Netherlands that assess the treatment of IE enrolled patients who were treated in a tertiary hospital [16,17,18,19]. One can hypothesise that patient demographics and outcome between a general and a tertiary hospital differ due to patient selection and available treatment modalities. Our experience is that an IE population in a tertiary centre will largely consist of patients eligible for surgical intervention or those who have undergone an operation. There will be very few patients who receive conservative treatment. A general hospital’s population, on the other hand, will mainly consist of patients who receive conservative treatment and a few patients recovering from an earlier operation. However, studies focussing on IE in general hospitals are scarce [20]. The primary aim of our study is to describe the demographics and identify the prognostic factors of IE in general hospitals in the Netherlands.

Furthermore, a changing insight into the demography and prophylaxis of IE [16,17] has led to the development of the 2009 European Society of Cardiology (ESC) guideline on prevention, diagnosis and treatment of IE [21]. The result of this guideline has been a less strict use of prophylaxis. The secondary aim of this study is to evaluate implementation of the revised guideline on the prevention of IE in our patient population [21].

MATERIAL AND METHODS

A multicentre retrospective cohort study was performed in three general hospitals in the Netherlands (Spaarne (former Kennemer) Gasthuis Haarlem, Gelre Hospital Apeldoorn, Gelre Hospital Zutphen). Data collection was performed between 2012 and 2013. Patients treated for IE were identified using the Dutch national in-hospital insurance registry (Diagnose Behandel Combinatie). All patients treated for definite or possible IE between 2004 and 2011 were included. All patient charts, echocardiogram reports and microbiology reports were reviewed. Median follow-up was 4.2 years (0.3-8.0). The modified Duke criteria were applied to identify patients with definite IE [21]. Patients with possible IE, according to the modified Duke criteria, but treated as definite IE were also included. Patients with native and/or prosthetic valve IE were enrolled as well as pacemaker device and/or lead infection. The treating cardiologist evaluated the transthoracic and transoesophageal echocardiograms and identified the valve or lead vegetation. MRSA was defined as such after consultation with a microbiologist or when another antibiotic was used than the first-line therapy according to the local guidelines.

Mortality was defined as all-cause mortality within the follow-up period. Adverse events were defined as IE-related adverse events during hospitalisation requiring medical intervention or prolonging hospital stay. The adverse events included were infarction (including stroke and peripheral septic emboli), bleeding, recurrent endocarditis, tachyarrhythmias and abscess formation at any location.

Statistical analysis was performed using SPSS (I.B.M. Armonk, NY, USA) and R (www.r-project.org). Student's t test was used for continuous variables and Fisher's exact test/Chi-square test for categorical variables. Multivariate logistic regression analyses were performed to determine independent risk factors for mortality and morbidity. A two-tailed p value of $p < 0.05$ or less was considered statistically significant.

As this is a retrospective study approval of the local ethics committee was not needed.

RESULTS

Patient characteristics

Between 2004 and 2011, we identified 216 cases of IE (Fig. 1). Based on the three general hospitals and the per-hospital catchment area, this would amount to an annual incidence of IE of 5.7 new cases per 100,000 persons per year [22,23]. The mean age at the time of the diagnosis was 67.5 years (22-97). Men were more affected than women: 62.5% versus 37.5%. Definite IE was diagnosed in 82.8% of the patients. Transthoracic echocardiogram confirmed the diagnosis in 19.4% of the cases and trans-oesophageal echocardiogram in 74.1%. In 6.5% no vegetation was visible. A total of 44% of the population did not have a predisposing risk factor for IE.

Figure 1: Number of patients admitted per year with endocarditis

Affected valves

One-third of the patients had prosthetic valve IE (30.1%). A pacemaker device lead located at the right side of the heart was affected in 17 cases. In these 17 cases a left-sided heart valve was also involved in 2 patients. Only 10 patients had tricuspid or pulmonary valve IE only, none of which were related to a pacemaker lead infection.

Microbiology

Positive blood cultures were found in 90.7% of the patients. A total of 30.1% of all patients had *Staphylococcus aureus* in 1 or more blood cultures, making it the most prevalent microorganism. There was only 1 patient with a MRSA positive culture. A bacterial access location was found in 115/216 (53.2%) of the patients. The most prevalent access locations were oropharyngeal (30/115, 26.0%) cutaneous (23/115 20.0%), urinary tract (12/115 10.4%) and the colon (10/115, 8.7%). There were only 2 patients with intravenous drug use as a cause of their IE.

Surgical versus conservative treatment

A total of 84 (38.9%) patients were accepted for surgical intervention. Eight underwent only pacemaker lead extraction. *S. aureus* endocarditis or prosthetic valve IE were not independent prognostic factors for receiving surgical intervention. Women were less likely to undergo a surgical intervention (OR=1.96, 95% CI 1.06-3.61, p=0.031). Also, ageing was an independent prognostic factor for not receiving surgery in a multivariate analysis (annual OR=1.04, 95% CI 1.02-1.06, p<0.001) (Table 1).

Table 1. Prognostic factors for conservative treatment, multivariate analysis

Female sex	OR = 1.96, 95% CI 1.06-3.61, p=0.031
Age (per life year)	OR = 1.04, 95% CI 1.02-1.06, p<0.001

Outcomes

All-cause mortality was 36.1%. Mortality in women was significantly higher than in men (49.3% versus 28.2%, p=0.002). Female sex was an independent prognostic factor for mortality (OR=2.35, 95% CI 1.29-4.28, p=0.005). The mean age at time of death was 76 years while the mean age for the surviving patients was 65 (p<0.001, 95% CI 4.66-12.15). Age was an independent prognostic factor for mortality as well (OR=0.95, 95% CI 0.93-0.97, p<0.001 per life year) (Table 2). Age and gender were not independent prognostic factors for adverse events.

Table 2. Prognostic factors for mortality, multivariate analysis

Age (decreased survival per life year)	OR = 0.95, 95% CI 0.93-0.97, p<0.001
Female sex (decreased survival)	OR = 2.35, 95% CI 1.29-4.28, p=0.005
Conservative treatment	OR = 3.39, 95% CI 1.80-6.38, p<0.001

S. aureus was an independent prognostic factor for adverse events (OR=2.05, 95% CI 1.10-3.84, p=0.024) but not for mortality (OR=1.90, 95% CI 0.99-3.66, p=0.054) (Table 3).

Mortality was higher in prosthetic valve IE 42/65 (66.2%) when compared with native valve IE 56/151 (37.0%) (p<0.001). In a multivariate analysis between prosthetic valve IE versus native valve IE there were no significant differences in mortality and adverse events. Mortality was higher in the conservative treatment group 62/132 (46.9%) when compared with the surgical group; 16/84 (19.0%) (p<0.001). Conservative treatment was an independent prognostic factor for mortality (OR=3.39, 95% CI 1.80-6.38, p<0.001) (Table 2). The incidence of adverse events was higher in the surgical group (62/84, 73.8%) than in the conservative treatment group (64/132, 48.4%). Surgical intervention was an independent prognostic factor for adverse events (OR=0.33, 95% CI 0.18-0.61, p<0.001) (Table 3).

Table 3. Prognostic factors for adverse events, multivariate analysis

<i>Staphylococcus aureus</i> infection	OR = 2.05, 95% CI 1.10-3.84, p=0.024
Surgical treatment	OR = 0.33, 95% CI 0.18-0.61, p<0.001

Introduction of new ESC guideline

Our study includes 126 patients before and 90 patients after the introduction of the new ESC guideline on the prevention, diagnosis and treatment of IE. Amongst these patients, we did not find an evident increase in incidence of IE before and after the introduction of the new ESC guideline. Comparing the population before and after introduction of the new guideline there was no difference in mortality (OR=1.82, 95% CI 0.97-3.50, p=0.0665) or the number of adverse events (OR=0.60, 95% CI 0.34-1.04, p=0.0698). There was no significant difference in the chance of receiving a surgical intervention before and after the introduction of the ESC guideline. Of the whole cohort only 1/216 (0.46%) patient had received prophylaxis.

DISCUSSION

To our knowledge this is the first multicentre retrospective cohort study on IE performed only in general hospitals in the Netherlands. This research shows that overall mortality associated with IE is higher than in other recent studies [16,17,18,19]. As there is no selection bias due to referral for possible surgical intervention we believe that, despite improvements in treatment, mortality still remains high and makes IE one of the most lethal infectious diseases in the Western world.

Although this study focuses on all-cause mortality it does show there might be an underestimation of IE-related mortality based on the rates from previous studies [16,17,18,19]. As stated in our introduction, patient demographics and outcomes between general hospitals and tertiary hospitals differ: more patients who are not eligible for operation will remain in a general hospital and will receive conservative treatment. Our study shows that conservative treatment is related to a higher mortality, hence a possible explanation for the high overall mortality rates. Female sex is a prognostic factor for mortality but not for adverse events. Our study shows that women are less likely to receive surgical intervention. As this study also shows that surgical intervention has a better prognosis, this may be an explanation why mortality in women is higher than in men. Earlier surgical intervention may be the key to improving survival in women with IE. Previous studies endorse our results, stating that surgical intervention improves survival and adverse event-free interval [2,24] .

Prosthetic valve IE has a higher mortality when compared with native valve IE, but our study does not show a difference in adverse events between prosthetic and native valves. This might be explained by the population in general hospitals in which patients will not be eligible for surgical intervention due to existing comorbidities and therefore will not receive surgery. As surgery is no longer an option, they may have entered a palliative setting in which there was no further recording of adverse events and as such a possible loss to follow-up. A similar mechanism may explain the difference in mortality and adverse events between surgical treatment and conservative treatment. Patients who received surgery possibly had a better preoperative physical condition and therefore had higher survival rates. As the monitoring postoperatively might be better when compared with conservative treatment, there could have been an earlier detection of

adverse events. Patients who received conservative treatment may have entered a palliative setting in which there was no further recording of adverse events.

S. aureus IE increases the risk of disease-related morbidity. As *S. aureus* spread is increasing in the population, this is a growing concern and may lead to a higher disease burden in the future. Fortunately, MRSA does not yet pose a significant problem in IE. The fact that MRSA has hardly penetrated the endocarditis population does not mean that it will not do so in the future. In a number of cases in our cohort no organism was cultured. This might be due to antibiotics having been started by a general practitioner prior to presentation in a hospital.

Although we do not see a difference in the number of new cases, mortality, adverse events and number of surgical interventions between the era before and after the introduction of the new ESC guidelines, this may be due to the small sample size. Other recent studies have shown an increase in incidence in IE related to the introduction of the National Institute of Clinical Excellence 2008 guideline and the American College of Cardiologist/American Heart Association 2007 guidelines [25,26]. We expect the Dutch population to be similar to the ones described by Pant et al. and Dayer et al. and think a similar change in the prevalence of endocarditis might have taken place in the Netherlands since the introduction of the guidelines.

The study design, a multicentre retrospective cohort study, is a limitation to this study. The difference in time of follow-up of the patients included varies widely and as such might have influenced the numbers for mortality and adverse effects.

CONCLUSION

This research shows that the endocarditis in general hospitals has a high rate of morbidity and mortality. Even when treated it ranks as one of the most lethal infectious diseases in the Netherlands, especially in women and the elderly. Further investigation is needed to determine optimal treatment and the effectiveness of the new ESC Guideline on the prevention, diagnosis and treatment of infective endocarditis.

Funding: None.

Conflict of interests: None declared.

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CHAPTER 3A

INCREASED INCIDENCE OF INFECTIVE ENDOCARDITIS AFTER THE 2009 EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINE UPDATE: A NATION-WIDE STUDY IN THE NETHERLANDS

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Eur Heart J Qual Care Clin Outcomes august 1, 2016 doi:<http://dx.doi.org/10.1093/ehjqc-co/qcw039> qcw039 (Original article)

ABSTRACT

Aims:

After the introduction of the ESC guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis (IE) in 2009 prophylaxis for patients at risk became less strict.

We hypothesise that there will be a rise in IE after the introduction of the guideline update.

Methods and Results:

We performed a nation-wide retrospective trend study using segmented regression analysis of the interrupted time series. The patient data were obtained via the national healthcare insurance database which collects all the diagnoses nationwide. We compared the data before and after the introduction of the 2009 ESC guideline.

Between 2005 and 2011 a total of 5213 patients were hospitalized with IE in the Netherlands. During this period there was a significant increase in IE from 30.2 new cases per 1,000,000 in 2005 to 62.9 cases per 1,000,000 in 2011 ($p < 0.001$). In 2009 the incidence of IE increased significantly above the projected historical trend (Rate Ratio: 1.327, 95% CI: 1.205 - 1.462 $p < 0.001$). This coincides with the introduction of the 2009 ESC guideline. After the introduction of the ESC guideline the Streptococci positive cultures increased significantly in the following years 2010-2011 from 31.1% to 53.2% ($p = 0.0031$).

Conclusion:

This observational study shows that there has been a steady increase in the IE incidence between 2005 and 2011. After the introduction of the 2009 ESC guidelines the incidence increased more than expected from previous historical trends. Furthermore there was a significant increase in Streptococci related IE cases.

Key words: Endocarditis, Prevention, Guidelines

INTRODUCTION:

Infectious endocarditis (IE) is one of the most lethal infectious diseases in the western world with mortality rates ranging from 20% to 75% (1-4). This underlines the importance of prevention of this devastating disease. The role of prophylaxis however is controversial and there is much debate on the strictness of its use in patients at risk.

In 2007 the American College of Cardiologist/American Heart Association (ACC/AHA) introduced the revised guideline on the treatment of infectious endocarditis (5). This was followed in 2008 by the National Institute of Clinical Excellence (NICE) guidelines (6,7). The European Society of Cardiology (ESC) followed in 2009 and in 2015 with the new guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis (IE) (8,9). A result of all three revised guidelines was a much less strict policy regarding the use of prophylaxis in patients at risk of developing IE. Before these revisions virtually all patients with valvular anomalies received antibacterial prophylaxis while after the revision this was only in patients with previous IE, prosthetic heart valves and cyanotic congenital heart disease indicated. The 2007 ACC/AHA and the 2009 ESC guidelines use virtually the same criteria in determining the indications for prophylaxis (5,8). Recently the ESC published a new endocarditis guideline in which the indications for prophylaxis remained unchanged (9).

In early 2015 Dayer et al demonstrated that since the introduction of the NICE guideline there has been a drop in the use of prophylaxis and at the same time there has been a rise in the incidence of IE (10). Later that year Pant et al showed a similar trend for the Streptococcus related IE incidence in the United States (11). In Europe there is scant evidence on the IE incidence after the introduction of the revised and updated IE guidelines (12).

With an aging population and an increase in the use of invasive medical techniques there is an increase in IE in the developed world (3,10-16). As the use of prophylaxis is greatly reduced we hypothesize that the increase of IE will project above the historical trend after the introduction of the 2009 ESC guideline.

Furthermore a more detailed analysis of individual patients from three general hospitals gives insight into a population which is not biased by referral to a tertiary centre which will treat patients mainly by surgical intervention.

MATERIAL AND METHODS:

We performed a nation-wide retrospective secular trend study analysed as an interrupted time series to investigate the incidence of IE in the Netherlands. Data collection took place between 2012 and 2014 and the median follow up was 4.2 years (range 0.3-8.0 years). Patients were identified using the insurance database between 2005 and 2011. Data were extracted by the Dutch Healthcare Authority (Nederlandse Zorg Autoriteit). Individual patients were anonymized but represent unique individual patients. This was done in order to exclude the possibility of duplicate entry of patients as two different hospitals could claim revenue's for treating the same patient (e.g. one hospital diagnosed and one hospital operated and treated the patient afterwards). This insurance database has a code uniquely for IE. The Dutch insurance system changed its registration after 2011 and therefore patients after this period could not be included in this analysis. Annual incidence was corrected for the annual population growth according to the National Bureau of Statistics (Centraal Bureau voor de Statistiek).

At the same time IE patients in three general hospitals in the Netherlands (Spaarne (former Kennemer) Gasthuis Haarlem, Gelre Hospital Apeldoorn, Gelre Hospital Zutphen) were used as a sample. These patients were identified using the in-hospital registration of the insurance data that was used to identify patients nationwide. All patient records were reviewed in order to determine patient characteristics such as age, gender, previous medical history, affected valves, organisms, micro-organism access location, mortality and morbidity. Patients with possible IE but treated as definite IE according to the modified Duke' criteria were included (e.g: surgical intervention or 6 weeks antibiotic treatment). A small amount of patients in our sample population (5.1%) had disease onset in 2004 but ended their hospitalisation in 2005 and were therefore coded according to insurance database. These patients were included in this research in order to achieve the largest possible sample size. In order to minimize potential selection bias which would affect a representative sample of the general population in the Netherlands the choice was made to select general hospitals only instead of tertiary centres where patients are being referred to for surgical intervention.

As this is a retrospective study, according to Dutch law (Wet Medisch-Wetenschappelijk Onderzoek met Mensen) an evaluation by a local medical ethical committee was not necessary.

Mortality was defined as all-cause mortality within the follow-up period. Adverse events were defined as IE-related adverse events during hospitalization requiring medical intervention or prolonging hospital stay. The adverse events included were thrombo-embolic events (including stroke and peripheral septic emboli), bleeding, recurrent endocarditis, tachyarrhythmias and abscess formation at any location.

Statistical analysis was performed using SPSS (I.B.M. Armonk, NY, USA) and R (www.rproject.org). Student's t test was used for continuous variables and Fishers exact test/Chi-square test for categorical variables. Multivariate logistic regression analyses were performed to determine independent risk factors for mortality and morbidity. Multivariate analysis included affected valves, micro-organism, age and sex. Furthermore, on the nation-wide data a secular trend study analysed as an interrupted time series was performed. Rate Ratios were used to determine significant changes in male to female ratios and the incidence after the introduction of the 2009 ESC guideline. A two tailed P value of $P < 0.05$ was considered statistically significant.

RESULTS:

The incidence of IE after the 2009 ESC guideline introduction.

Between 2005 and 2011 a total of 5213 patients were hospitalized with IE in the Netherlands. During this period there was a significant increase in infective endocarditis from 30.2 new cases per 1,000,000 in 2005 to 62.9 cases per 1,000,000 in 2011 ($p < 0.001$). Historically more male subjects are affected with IE; 69.9% of the patients in our population were men. The increase in IE was similar in both sexes. The male to female ratio remained consistent during the study period and was similar in the overall cohort as well as in our sample as mentioned earlier (see figure 1).

In 2009 the incidence of IE increased significantly above the projected historical trend (Rate Ratio: 1.327, 95% CI: [1.205 - 1.462] $p < 0.001$) (see figure 2). This coincides with the introduction of the 2009 ESC guideline. The rise in incidence was mainly driven by the increase in IE incidence in men in which the significant increase in incidence falls in the same year as the introduction of the ESC guidelines (Rate

Ratio: 1.360 95% CI: [1.211-1.529] $p<0.001$) (see figure 3). In the female cohort a similar significant trend was observed only this was seen one year (2008) before the introduction of the ESC guideline (RR: 1.254 95% CI: [1.053-1.496] $p=0.005$) (see figure 4).

Figure 1: Male to female rate ratios for the national cohort

Figure 2: Nation-wide retrospective secular trend analysed as an interrupted time series; (Rate Ratio: 1.327, 95%, CI: [1.205 - 1.462] p<0.001) for 2009. The horizontal line indicates the average IE incidence before and after the 2009 ESC guideline update.

Figure 3: Nation-wide retrospective secular trend analysed as an interrupted time series in men only (Rate Ratio: 1.360 95%, CI: [1.211-1.529] p<0.001) for 2009. The horizontal line indicates the average IE incidence before and after the 2009 ESC guideline update.

Figure 4: Nation-wide retrospective secular trend analysed as an interrupted time series in women only (Rate Ratio: 1.254 95% CI: [1.053-1.496] $p=0.005$) for 2008. The horizontal line indicates the average IE incidence before and after the 2009 ESC guideline update.

Patient characteristics of the sample population.

Three hospitals were chosen to analyse in detail as a representative sample of the general population. Between 2005 and 2011 we identified 216 individual cases of IE. Based on the three general hospitals and the per-hospital catchment area this would amount to an annual incidence of IE of 5.7 new cases per 100,000 persons per year. This incidence is similar to the nation-wide incidence. The mean age at the time of the diagnosis was 67.5 years (22-97). Men were more often affected than women; 62.5% versus 37.5% in our total sample population which was not statistically significantly different from the nation-wide cohort ($p=0.45$). Definite IE according to the modified Duke' criteria was diagnosed in 82.8% of the patients. Trans Thoracic Echo (TTE) confirmed the diagnosis in 19.4% of the cases and Trans Oesophageal Echo (TOE) in 74.1%. In 6.5% of the patients no vegetation was visible. A total of 40.7% of the patients had a pre-existing valvular condition predisposing for IE.

Introduction of the 2009 ESC guideline.

Comparing the population before and after introduction of the new guideline there was no difference in mortality (OR = 1.82, 95 % CI: [0.97–3.50] $p = 0.0665$) or the number of adverse events (OR = 0.60, 95 % CI: [0.34–1.04] $p = 0.0698$). There was no significant difference in the chance of receiving a surgical intervention before and after the introduction of the ESC guideline. However there was a significant difference in the mean age of the surviving patients before and after the guideline (see table 1). Furthermore the streptococci related infective endocarditis increased after the introduction of the 2009 guideline from 31.1% to 53.2% ($p=0.0031$) (see table 1). Of the whole cohort only 1/216 (0.46 %) patient had received prophylaxis.

Baseline characteristics			P value
National Cohort			
Male	69%		P=0.45 (compared to sample population)
Sample population	2005-2009 N=154	2010-2011 N=62	
Male	97 (63%)	36 (58%)	P= 0.53 P=0.45 (compared to national cohort)
Mean age	66.4 (22-97)	69.9 (40-95)	P=0.10
Pre-existing valvular disease (excluding prosthetic valves)	18 (11.6%)	12 (19.3%)	P=0.19
Pre-existing prosthetic heart valve	46 (29.9%)	19 (30.6%)	P=1.00
Mean age at time of death	72.6 (42-97)	73.5 (54-85)	P=0.75
Mean age living patients	62.7 (22–89)	68.2 (40-95)	P=0.048
Mortality	58 (37.1%)	20 (32.2%)	P=0.53
Positive culture	138 (89.6%)	58 (93.5%)	P=0.44
Streptococci positive culture	48 (31.1%)	33 (53.2%)	P=0.0031
Staphylococci positive culture	55 (35.7%)	23 (37.0%)	P=0.87
Mitral Valve IE	57 (37.0%)	19 (30.6%)	P=0.43
Aortic Valve IE	71 (46.1%)	26 (41.9%)	P=0.65
Tricuspid Valve IE	9 (5.8%)	0 (0%)	P=0.062
Pulmonary Valve IE	0 (0%)	1 (1.6%)	P=0.28
Prosthetic Aortic Valve IE	27 (17.5%)	13 (20.9%)	P=0.56
Prosthetic Mitral Valve IE	33 (21.4%)	8 (12.9%)	P=0.13
Pacemaker device lead IE	13 (8.4%)	4 (6.4)	P=0.78
Definite IE (Duke's criteria)	127 (82.5%)	52 (85.9%)	P=1.00
Possible IE (Duke's criteria)	27 (17.5%)	10 (16.1%)	P=1.00

Table 1: Baseline characteristics. Please note: various patients had multiple infected valves. One patient had an infected myxoma. Age is given in years.

Affected Valves:

One third of the patients had prosthetic valve IE (30.1%) all of which were left sided. A pacemaker device lead located at the right side of the heart was affected in 7.9% of the cases. In 0.9% there was a combined infection of a left sided heart valve and a pacemaker device lead. Only 4.6% patients had isolated tricuspid or pulmonary valve IE, none of which were related to a pacemaker device lead infection. One patient had an infected myxoma.

Microbiology:

Positive blood cultures were present in 90.7% of the patients. In 36.1% of our population a staphylococcus was the pathogen. A total of 30.1% of all patients had Staphylococcus Aureus (SA) cultured making it the single most prevalent microorganism. Of the entire population only 0.5% of the positive cultures was a Methicilline Resistant SA. The total amount of various streptococci was 37.4%. S. Mitis was the single most prevalent streptococcus at 8.3%, S. Bovis (Galloliticus) ranked second at 6.0%. A bacterial access location was found in 53.2% of the patients. The most prevalent access locations were oropharyngic (13.8%) cutaneous (10.6%), urinary tract (5.6%) and the colon (4.6%).

OUTCOMES

Mortality:

All-cause mortality was 36.1%. The mortality in women was significantly higher than in men

(49.3% versus 28.2%, $p=0.002$). Female sex was an independent prognostic factor for mortality (OR=2.35, 95% CI: [1.29-4.28] $p=0.005$). The mean age at time of death was 76 while the mean age for the surviving patients was statically significantly lower at 65 ($P<0.001$ CI: [4.66-12.15]). Age was also an independent prognostic factor for mortality (per life year OR=1.05, 95% CI: [1.03-1.08] $p<0.001$) (see table 2). Age and gender weren't independent prognostic factors for adverse events.

Mortality was higher in prosthetic valve IE 42/65 (66.2%) when compared to native valve IE

56/151 (37.0%) ($p<0.001$). In a multivariate analysis between prosthetic valve IE versus native valve IE there was no significant difference in mortality.

Age (per life year)	OR = 1.05, 95%, CI: [1.03-1.08] $p<0.001$
Female Sex	OR = 2.35, 95%, CI: [1.29-4.28] $p=0.005$
Conservative Treatment	OR = 3.39, 95%, CI: [1.80-6.38] $p<0.001$

3A

Table 2. Prognostic Factors Mortality, multivariate analysis

Surgical versus conservative treatment

A total of 38.9% patients were accepted for surgical intervention. Mortality was higher in the conservative treatment group (46.9%) when compared to the surgical group (19.0%) ($p<0.001$). In a multivariate analysis this difference remained significant (OR = 3.39, 95% CI: [1.80-6.38] $p<0.001$) (see table 2).

SA endocarditis or prosthetic valve IE were not independent prognostic factors for receiving surgical intervention. Women were less likely to have surgical intervention performed (OR=1.96, 95% CI: [1.06-3.61] $p=0.031$). Also, aging was an independent prognostic factor for not receiving surgery in a multivariate analysis (annual OR=1.04, 95% CI: [1.02-1.06] $p<0.001$) see table 3.

The incidence of adverse events was higher in the surgical group (73.8%) than in the conservative treatment group (48.4%). Surgical intervention was an independent prognostic factor for adverse events (OR=3.03, 95% CI: [1.64-5.55] $p<0.001$).

Female Sex	OR = 1.96, 95%, CI: [1.06-3.61] $p=0.031$
Age (per life year)	OR = 1.04, 95%, CI: [1.02-1.06] $p<0.001$

Table 3. Prognostic Factors for Conservative Treatment

DISCUSSION:

To our knowledge this is the first nation-wide research that demonstrates a significant increase in the incidence of IE above the historical trend after the introduction of the ESC 2009 guidelines (8). Although there has been some research on the incidence after the introduction of the revised ESC guidelines, mainly in France, this is the first research that focuses on a country as a whole and spans a longer period of time (12). Although previous research from Pant et al already demonstrated a significant rise in *Streptococcus* IE incidence this focussed on the ACC/AHA IE guidelines. The fact that the same trend is seen after the 2009 ESC guidelines is a confirmation of Pant et al results as both the ACC/AHA and ESC use virtually similar criteria for prophylaxis (5,8,11). As Drayer et al demonstrated a similar trend in the UK the evidence seems to be tipping the scale in favour of a more strict attitude towards prophylaxis in patients at risk that are currently not covered by the IE guideline (10). However, care must be taken when interpreting these results. These are trends and not prospective studies. Furthermore, possible harm done by the abundant use of antibiotics in prophylaxis must be considered when trying to prevent a relatively uncommon disease (eg anaphylaxis, antibiotic resistance)

When looking at the temporal relationship between the publication of the ESC guideline in august 2009 and the penetration of this guideline within the healthcare profession it is important to consider the fact that the National Heart Foundation (Nederlandse Hart Stichting) published a wide spread folder in December 2008 containing the revised criteria for prophylaxis as well as communicated by its author in the *Nederlands Tijdschrift voor Geneeskunde* (17). Therefore at the time of official publication of the new endocarditis guideline this was already in wide use in the Netherlands (17).

The significant difference in mean age at time of death before and after the ESC guideline introduction could be due to increasing cohort of elderly patients at risk for IE. The cohort of the so called baby boom generation is aging and coming in the range of patients prone for IE.

Our study also showed that *Staphylococcus Aureus* is the single most frequent organism. This is probably explained by the fact that the population prone for IE is increasing. An aging population with an increase in degenerative heart valve

disease, the increased use of prosthetic heart valves and the increased incidence of pacemaker devices combined with a better prognosis in patients with congenital heart disease makes for a much larger cohort at risk (16). At the same time there is a rise in invasive procedures in just this population which is a risk factor for IE. As less than one percent of our population had a MRSA cultured this indicates that a strict use of antibiotics combined with greater awareness amongst healthcare workers may prevent the spread of MRSA in the IE population.

Before and after the 2009 ESC guideline we see a significant increase in the number of streptococci related IE cases. This could reflect the less strict indication for prophylaxis as this mainly targets streptococci. The fact that in the patients with an identified microorganism entry site the most prevalent entry site was the oropharyngeal cavity is a worrying finding as this is the main target for antibiotic prophylaxis. This is emphasized as one considers that the most prevalent *Streptococcus* is *S. Mitis*. Furthermore, the other main entry sites were the gastrointestinal and urinary tract and the skin. The former two are affected by the prophylaxis guideline as well.

In a small amount of cases no organism was cultured. This may be due to a general practitioner starting antibiotics prior to presentation in one of the sample hospitals.

The mortality due to IE is considerable in our population and higher than in various other research (1-4,13). As most research focuses on tertiary centres which have a great selection bias this may explain the higher mortality rate in our population. Patients no longer eligible for surgical intervention may enter a palliative setting and therefore may not be included in studies on IE that most of the time run in larger surgical clinics. This may indicate that the advances in survival we have made in recent history may be influenced by selection bias. To our knowledge this is one of the few studies that focuses on the general population instead of selecting patients suitable for surgical intervention as is being done in most studies (1,2,4,13).

The mortality in women is significantly higher than in men and they receive less surgical intervention what in itself is a prognostic factor for survival. The mechanism behind this is poorly understood but is confirmed by various other studies.

The difference in moment of increase in incidence between the male and female population may be explained by the fact that IE is more often underdiagnosed and treated less aggressive in women than in men. A fact that could explain the higher female mortality rate as well. Another explanation might be that men, as they are obviously more prone to endocarditis may be more susceptible for IE when prophylaxis guidelines are less strict. We hypothesise that poorer oral hygiene in men combined with less strict prophylaxis has led to the significant increase in just this population.

One third of IE patients has prosthetic valve IE. This reflects the growing incidence in the use of prosthetic material in cardiac surgery and will only increase in the future. The low incidence in right sided IE is caused by the dwindling number of intravenous drug users in the Netherlands (18). This group of patients, historically at risk for IE, is getting smaller over the course of time and may disappear altogether in the future.

The mortality in the conservatively treated group of patients is much higher than in the surgical group. This reflects a selection bias, those fit for surgery will have a better pre-operative condition than those unfit for surgical intervention. A larger number of patients will be treated in a palliative setting as they are no longer eligible for surgical intervention. As there was no selection bias in our study this may explain the high mortality rate in the entire population and even more so in the cohort that had a conservative treatment.

LIMITATIONS

There are several limitations to this study. This is a retrospective observational study and although we have demonstrated a temporal relation, causality cannot be proven. However almost all observational studies with the same study design show the same results (10,11).

Furthermore there was no correction for population composition. An ageing population is at higher risk for the development of IE. A correction for immigration of people from countries with a higher risk of rheumatic heart valve disease was also not performed and could influence the results as well.

Another limitation is the possible small sample size. However, in contrast to other studies on the subject we have detailed and verified information on our

sample patients and do not depend on discharge information which is subject to registration of discharge diagnosis and greatly depends on the physicians will to register diagnosis properly. We therefore feel that our sample populations is representative for the nation-wide cohort.

Finally we have no information on the prescription of antibiotics before and after the 2009 guideline introduction. However the National Heart Foundation (Nederlandse Hart Stichting) has been quite thorough in its education of healthcare professionals responsible for the prophylaxis in patients at risk and we expect quite rigorous adherence to these guidelines.

3A

CONCLUSION:

The incidence of IE in the Netherlands is increasing and since the introduction of the 2009 ESC guideline the increase of IE projected above the historical trend. IE is a dangerous disease with high mortality rates in women and the elderly which has hardly changed over the years. *S. Aureus* remains the single most common pathogen whereas Streptococci as a group remain the most common pathogen. After the 2009 ESC guideline we see an increase in the number of Streptococci related cases of IE. Caution is advised in interpreting these results as this is an observational study and prospective data is lacking. In order to settle the debate on the relationship between prophylaxis and IE incidence prospective studies should be performed in patients at risk.

No conflict of interest.

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CHAPTER 3B

INCIDENCE OF INFECTIVE VALVE ENDOCARDITIS AS AFTER ANTIBIOTIC PROPHYLAXIS GUIDELINES CHANGED - THERE IS A CHANGE.

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Ann Cardiothorac Surg 2019. doi: 10.21037/acs.2019.06.05 (Editorial)

From 2007 to 2009 the guidelines for endocarditis saw a major change in the prescription of antibiotic prophylaxes to preventive infective endocarditis in the United States of America, continental Europe and the United Kingdom^{1,2,3}. Antibiotic prophylaxis became much more strict and only a select group of patients was still eligible for prophylaxis^{1,2,3}. There was no evidence that chemo-prophylaxis in patients with non congenital, non prosthetic heart valve disease would prevent the occurrence of infective endocarditis which still ranks as one of the deadliest infectious diseases in the western world. We applauded ourselves that science and a lack of evidence of the effectiveness of prophylaxis had prevailed.

In the years that followed this decision, we saw the incidence of infective endocarditis rise. It rose in the USA, in the United Kingdom and in continental Europe and in many other places in the world^{4,5,6,7}. We told ourselves it was due to an aging population, more invasive medical procedures or a combination of both as age and medical treatment are two old friends walking together as risk factors for many diseases but especially infective endocarditis. And although some of us started suggesting we might be wrong in such a strict use of chemo prophylaxis for the prevention of infective endocarditis they were honed at because there was the evidence?

The year 2015 arrived and the European Society of Cardiology was preparing their new guideline for the diagnosis and treatment of infective endocarditis. Some time before the guideline came in to print two studies appeared that did show that not only the incidence of infective endocarditis was on the rise but that when prophylaxis guidelines became much more strict there was a sudden increase above the expected historical trend in Streptococci mediated infective endocarditis^{4,5}. And then a strange thing happened. Instead of trying to weighing costs and benefits of prophylaxis it was argued that evidence was at best circumstantial. More likely it was due to, again, a changing population and health care related IE. Not long afterwards a third study confirmed the results of the previous two studies using more or less the same methodology⁶.

And so we have arrived in 2019. Guidelines on chemo-prophylaxis for infective endocarditis are just as strict as they were when we designed them between 2007-2009⁸. In the meantime we have seen a rise in IE in almost all studies. Several of these studies also showed an increase in the streptococci related IE follow the

guideline changes^{4,6}. What we have not seen is a decline in IE. We have neither seen an improvement in survival of patients suffering from this devastating disease. And still, despite an increasing number of studies that show not only an increase in IE incidence but also a relation between stricter IE chemo-prophylaxis and an increase in preventable IE we still consider the evidence not to be enough to change the guideline back to what they were. Another thing that we have also not witnessed is patients suffering from chemo-prophylaxis with lethal consequence⁹. It is safe with very little patient harm or discomfort and is applied in many medical settings often with very little evidence to back it up. In fact, the evidence in the case of IE is actually quite strong when comparing it to other uses of chemo-prophylaxis.

In short, we do very little harm in giving patients chemo-prophylaxis and we probably do a lot of good in giving patients chemo-prophylaxis to prevent IE from rearing its ugly head.

We should therefore be brave and admit that we might have been wrong. We should reinstate chemo-prophylaxis for all patients with valvular anomalies to prevent IE from affecting these patients at risk. We should make all possible effort to prevent this disease from happening because we have great difficulty in treating it and the toll that patients have to pay is high.

Yes, not all evidence points in the direction of a beneficial effect of chemo-prophylaxis but a lot does. Very little evidence points in the direction of a detrimental effect of chemo-prophylaxis on patient care. We have a rare opportunity to conduct an almost world wide study in reinstating the chemo-prophylaxis as it was before 2007 and then see what happens to the incidence of IE. In doing so we can make a major step forward and hopefully settle an already very long debate. And in this way also halt an even further increase in infective endocarditis.

No conflict of interest

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CHAPTER 4

A COMBINED EPICARDIAL IMPLANTATION AND SUBSEQUENT EXTRACTION STRATEGY IN PACEMAKER DEVICE INFECTION IN PACEMAKER DEPENDENT PATIENTS

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Pacing Clin Electrophysiol . 2018 May 23. doi: 10.1111/pace.13382. (Original article)

ABSTRACT

Introduction

Treatment of pacemaker (PM) device infections is challenging in pacemaker dependent patients. We propose a novel implantation strategy for this group of patients.

Methods

Patients who were PM dependent and were admitted with a PM infection received a combined procedure of LV epicardial implantation of a PM lead and subsequent extraction of the infected system. No temporary pacing wire was used and the PM generator was placed in the left flank.

Results

Between 2012 and 2015 we treated 16 patients who were PM dependent with a PM infection. The majority of patients was male (81% (13/16)). The median age was 71 years (50-91). The cause of infection was valvular endocarditis in 38% (6/16), lead infection in 25% (4/16) and isolated pocket infection in 38% (6/16).

All patients underwent epicardial implantation of a LV lead (St Jude 1084T bipolar lead) and extraction of the infected device. There was no peri-procedural mortality and no-post procedural tamponades occurred. There was one complication in the form of a haemorrhage at the infected device extraction site. In the median follow up period of 17 months there were 4/16 deaths, none of which were attributable to epicardial LV implantation. LV lead thresholds were 1.1V (+/- 0.7V) upon implantation which increased to 1.2V (+/- 0.6V) at 0.4ms pulse duration. There were no re-infections of the epicardial lead or device.

Conclusion

Epicardial left ventricle pacemaker implantation and subsequent extraction of an infected pacemaker in pacemaker dependent patients is feasible and safe with good long term outcome.

Keywords: Pacing, Infection, Extraction

INTRODUCTION

As the use of Cardiac Implantable Electronic Devices (CIED) is increasing, so is the risk of device infection ^{1,2}. Not only are CIED's used more often, the patients undergoing implantation live longer and leads remain longer in situ ³. CIED infections are a significant cause of morbidity and mortality through a mechanism of systemic infection and the need for extraction of the device including intra-cardiac leads. Although treatment of CIED infection is well established, the timing of re-implantation is based largely on expert opinion ^{4,5-8}.

Of special consideration are patients who are pacemaker (PM) dependent and have a device infection. Although there are established guidelines on how to treat CIED infection there is little evidence on extraction and re-implantation timing and strategies in PM dependent patients ^{4,5}.

In general, three different re-implantation strategies have been described. One consists of extraction of the infected device, the subsequent use of a temporary pacing lead until the infection has subsided after which a pacemaker can be implanted on the contralateral side ⁹. Another strategy is to implant an epicardial right ventricle (RV) lead via a subxiphoid incision ^{9,10}. These two strategies have been compared in which the first strategy leads to prolonged hospitalisation while the second leads to higher long term RV-lead thresholds ^{9,10}. The third strategy is applied in case of an isolated pocket infection where during a single procedure extraction of the infected device is followed by implantation of an endocardial device on the contralateral site ¹¹.

We describe the use of an alternative fourth strategy in which a permanent left ventricular (LV) lead is implanted surgically via mini-thoracotomy and the device is placed in the left flank. This avoids the use of a temporary pacing lead which poses the possible risk of dislodging, perforating, persistent bacteraemia through bacterial colonization and various other complications ¹². Moreover it places the pacemaker outside of the bloodstream hereby minimising possible risk of continuous or recurrent infection.

MATERIAL AND METHODS

A prospective in-hospital registry on PM device extraction was kept from 1st January 2012 onwards in the St. Antonius Hospital in Nieuwegein, the Netherlands, a large volume referral centre. All patients undergoing CIED extraction were included in this database. For this specific analysis we included all PM dependent patients from this database. In 2016 we performed an analysis of all patients. The following data was collected: age, sex, PM dependency, reason for extraction (lead dysfunction, isolated pocket infection, lead infection, endocarditis), left ventricular ejection fraction (LVEF), previous cardiac surgery, in hospital death, 30 day mortality, all-cause mortality, complications, NYHA class, renal function, diabetes and duration of hospital stay ^{13, 14}. Patient data of patients who were transferred to a referral hospital were collected by contacting the consultant cardiologist treating that patient.

Pacemaker dependency was defined as more than 95% RV pacing or total Atrio-Ventricular heart block ¹⁰. Left ventricular function was determined using echocardiography ¹³. Renal function was determined per the KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification ¹⁴. A renal function of class 3 and lower (GFR<60) was considered impaired renal function. Data are shown as median +/- SD.

PROCEDURAL TECHNIQUE

Lead implantation and subsequent transvenous extraction was performed under general anaesthesia and endotracheal intubation with a dual lumen tube in the operating theatre. During the entire procedure a cardio-pulmonary bypass machine is kept standby in case of possible complications requiring urgent surgery. Prior to extraction a Trans Oesophageal Echo was placed in the oesophagus in order to monitor cardiac function, pericardial effusion and procedural progress of the extraction. A combined team consisting of a cardio-thoracic surgeon, electrophysiologist, anaesthetist, clinical perfusionist and PM-device technician performed the implantation and subsequent extraction. After appropriate antibiotic therapy the epicardial lead and device were implanted first. This was done to ensure pacing during the procedure. A St Jude Medical Myodex ® 1084T bipolar lead with screw was used. The PM generator was placed in the left axilla or flank unless this was contra-indicated. The implanted PM generator

differed per patient and was implanted at the discretion of the attending physician in view of possible future upgrade to a DDD-pacemaker, Internal Cardiac Defibrillator, Cardiac Resynchronization Therapy (CRT) Defibrillator (CRT-D) or Pacing (CRT-P) device. Afterwards extraction of the device and the endovascular leads was performed. There was no use of temporary pacing leads. Extraction of the endovascular device took place using a stylet, locking stylet, mechanical dilator sheaths, laser-sheath and laser when needed. Extracted leads and lead-tips were cultured.

RESULTS

Patient population

Between January 2012 and December 2015 a total of 129 patients underwent CIED extraction. Referred patients made up 62/129 (48%) while the rest of the patients had their infected device implanted in the St. Antonius Hospital. Of the total cohort of 129 patients 27 patients were pacemaker dependent. Of these 27 patients, 16 had a form of device related infection. The majority of these patients were male 13/16 (81%) with a median age of 71 years (50-91) at the time of extraction. Of these 16 patients 6 had a previous history of sternotomy: 2 CABG's and 2 isolated valvular surgeries (both aortic valve replacement), one Bentall procedure and one surgical repair of an atrial septal defect type 2. Of these 16 patients the infected device was a pacemaker in 10 cases (all of which were DDD pacemakers), an ICD in 2 cases, a CRT-D in 2 cases and a CRT-P in 2 cases. The indication for pacing was total AV-block in all patients. The indication for an ICD was an ejection fraction lower than 35% in two patients, a hypertrophic cardiomyopathy in one patient and idiopathic ventricular tachycardia in one patient. There were two patients with a CRT-P; one patient received a CRT-P after His-ablation and one patients had an indication for CRT-D but refused and received CRT-P only on his own request (see *table 1*). Non-cardiac previous medical history was present with respect to DM in 4 patients and with respect to impaired renal function in 11 patients. Left ventricular function was normal (>55%) in 4 patients, slightly impaired (45-54%) in 4 patients, impaired (30-44%) in 4 patients and severely impaired (<30%) in 4 patients as well. Half of the patients were NYHA class 1, 5/16 patients had NYHA class 3 and 3/16 patients were in NYHA class 3.

Microbiology

Of the population of CIED infected patients 6/16 patients had valvular endocarditis, 4/16 patients had a lead infection and 6/16 patients had an isolated pocket infection. Cultures were positive with a single organism in 14/16 patients. One patient had multiple organisms cultured making the identification of a single pathogen difficult (patient 6) and one patient had a negative culture after antibiotic treatment by a referring physician. Most cultures were positive with commensal bacteria of the skin: 6/14 *S. Aureus*, 2/14 *S. Epidermis*, 2/14 *Propionibacterium Acnes*, 1/14 *S. Hominis*, 1/14 *S. Schleiferi* and two miscellaneous bacteria (a *Serratia Marcescens* and a *Klebsiella Oxytoca*) . There were no Methicillin-resistant *Staphylococcus aureus* (MRSA) cultured. (*see table 1*)

Extraction

Re-implantation was performed prior to transvenous extraction by placing an epicardial left ventricle lead in all 16 patients. Of these 16 patients 13/16 received epicardial implantation alone. In 2/16 patients an initial procedure with epicardial LV lead implantation and subsequent extraction was performed after which, in a second procedure, an endovascular lead was implanted in a later stage (patients nr. 15&16). One patient was implanted with an endovascular system at a later stage when the infection was subdued after which the epicardial lead was left in situ but was no longer functional (patient nr. 7). Complete extraction of the CIED was achieved in 13/16 patients. The other three patients had remaining leads or part of it in situ.

Outcome

Of the 16 patients receiving epicardial lead implantation none died during implantation and subsequent extraction. All-cause mortality was 25% (4/16) during follow up.

One patient died during hospitalisation due to progressive heart failure. This patient was a non-responder to CRT-P and did not die due to CRT-P downgrade. This patients refused CRT-D therapy and was known to have end-stage heart failure. He was planned for CRT-P re-implantation but died of aforementioned end stage heart failure before this could be achieved. The epicardial system however did not get infected within this period and assured adequate LV-pacing.

The other three patients died of natural cause more than 6 months after follow up. In all cases, there was no known relation to the pacemaker system. There was only one complication during the operative procedure in which a haemorrhage occurred on the extraction site at the subclavian vein. Four other patients had complications during hospitalisation: two patients developed heart failure, one patient developed an inflammatory response with a Systemic Inflammatory Response Syndrome (SIRS) but none of these were attributed due to PM device extraction by the treating physician. There were no complications directly attributable to the implantation of the epicardial PM system including tamponade.

PM-related outcome

Median follow up was 17 months (+/- 11.5 months). A total of 10/16 patients had a follow up of at least a year. Median duration of hospital stay was 22 days (+/- 37 days). The initial threshold of the LV lead upon implantation was 1.1V (+/- 0.7V) at 0.4ms pulse duration which increased to 1.2V (+/- 0.6V) at 0.4ms pulse duration at the last recorded LV threshold which was not significant ($p=0.63$) (see table 2). Three patients were lost to follow-up with respect to the LV lead threshold; two died before a LV threshold could be determined and one patient received an upgrade to a complete endovascular system before a LV threshold could be determined. None of the patients developed re-infection of the implanted LV endocardial lead or device after implantation. None of the patients who were downgraded from a dual chamber pacemaker to a VVI system developed clinical signs of a pacemaker syndrome due to permanent VVI LV pacing (*see table 2*). Furthermore, all patients who initially had an ICD (patients nr. 7&16) as well as the patient that had an CRT-D (patient nr. 15) received an upgrade to either a combined endovascular-epicardial system (patients nr. 15&16) or a complete endovascular system (patient nr. 7). The other patient who received a VVI system died before an upgrade was possible (patient nr. 1).

DISCUSSION

CIED related infections are becoming increasingly common as the use of CIED's is growing in an aging population with an increased life expectancy^{1-3, 6, 7, 15, 16}. This problem will only increase in the future.

We describe a strategy of implantation of a new pacemaker with an epicardial LV lead and subsequent extraction of the infected device in one surgical procedure, which to our knowledge has not been described before. The technique described has several benefits. First of all the proposed implantation-extraction strategy places the epicardial lead and pacemaker device outside of the bloodstream minimising the risk of recurrent or persistent systemic infection. Second there is no need for trans-venous (temporary) pacing leads. This minimizes the risk of possible tamponade which is reflected by our results showing the absence of tamponade as a procedural complication. These are common complications of using temporary pacing leads and in turn the use of temporary pacing wires is associated with a high complication rate in general exceeding 30%¹². In all, especially in pacemaker dependant patients this technique is well fitted to ensure continuous pacing during extraction. Combining two procedures may also reduce the risk of two separate procedures and increases patient comfort. As patients are under total anaesthesia patient discomfort is minimal. There is little evidence on timing and location of pacemaker implantation in PM dependent patients. The evidence in the guidelines is based on expert opinion. Recently Amraoui et al as well as Mountantonakis et al have described new techniques that show promising results⁹⁻¹¹. Although Amraoui and his group described a somewhat similar technique, with a subxyphoidal approach of the RV, they observed a higher complication rate mainly driven by cardiac tamponade^{9, 10}. Using a screw-in epicardial lead on the thicker LV wall, the risk of tamponade is reduced. As the results of the current study show no major complication of the epicardial implantation, the combined approach could be considered safe. In three of the patients a lead or part of a lead remained in situ. However this did not lead to infection of the epicardial system. This underlines the safety of this procedure from an infectious point of view.

The patient population in this study is diverse. The reason for extraction ranges from isolated pocket infection to full blown endocarditis. CIED vary amongst patients from single chamber pacemakers to CRT-D devices. The number of leads varies as well between the various forms of CIED. Furthermore patients varied in respect to previous medical history, presence of ischaemic heart disease, previous sternotomy, NYHA class, presence of diabetes, renal function and complete extraction of the CIED. However, we believe this reflects a real life setting and makes the feasibility of the described treatment strategy applicable to a wide variety of patients with different types of CIED infection.

The use of VVI pacing has not led to impaired left ventricular function in this population illustrating the feasibility of left ventricular pacing in pacemaker dependent patients. Patients who were in need of a CRT-D or ICD system received such a system in a later stage. Therefore this implantation strategy can be used in patients with either DDD, VVI, ICD and CRT-D systems.

A quarter of the patients in this study died. We must however state that none of the deaths was directly contributed to the described technique. A large portion of the patients suffered from infective endocarditis of which mortality ranges from 30-60%^{17,18}. Also three patients died of natural causes at home of which two were over 80 years old which is a normal life expectancy in the Netherlands. One patient developed a SIRS reaction. This has been previously described with extraction of infected CIEDs and in this case was not thought secondary to re-implantation.

The duration of hospitalization also varies greatly between patients. The relatively long mean hospital stay is mainly driven by three patients who were hospitalized for a total of 307 days because of valvular endocarditis with a need for long-term antibiotic treatment and postoperative complications, none attributable to the lead implantation and subsequent transvenous lead extraction. Of the entire cohort only 4 patients were hospitalized longer than 35 days; the three aforementioned patients and one patient who was hospitalized for 36 days. This makes the average length of stay shorter when considering hospitalization due to extraction and re-implantation alone.

The microbiological findings reflect the commensal flora of the human skin as largest source of infection. This is similar to those findings in other studies describing CIED infections^{9-11, 16}. *S. Aureus* is the most common pathogen. We did not find any MRSA. This largely reflects the strict use of antibiotics in the Netherlands which has led to relatively low MRSA rates¹⁹. All pathogens were treated after consulting a microbiologist according to the local in hospital guidelines. Complete extraction was not achieved in all patients. However, this did not account for any re-infections. The absence of re-infection suggest a benefit from the use of organism directed therapy as well as the safety of the procedure.

The LV threshold did not increase significantly during a median follow up of 18 months. As the increase in thresholds of epicardial leads is mostly seen in the first 30 days to six months after implantation, this trend should be representative of

long term lead behaviour. In none of the patients did thresholds exceed acceptable values needing re-intervention. These results are consistent with current literature. In comparison Koos et al report an increase in threshold in the first 6 months in both groups, whereas Mair et al and Buiten et al report of a stable epicardial lead threshold over up to 30 months of follow up²⁰⁻²². Garikipati et al report significantly higher thresholds in the epicardial leads as compared to transvenous LV leads²³. In three patients there was a loss of follow up concerning the LV-lead threshold and are therefore not included in the last available LV threshold.

LIMITATIONS

This is a retrospective analysis of a case series and therefore subject to limitations associated with this type of research. Furthermore our patient population is quite heterogeneous with a variety of co-morbidities as well as implanted devices. On the other hand it does show that this technique is feasible in a wide variety of patients. In addition the size of our population is relatively small making any sound statistical conclusion very difficult. Further research is needed to evaluate this technique in larger patient groups, ideally in a randomised controlled trial versus other implantation and extraction strategies. The follow up period in this study is 18 months. To make any statements on the long term outcome of LV epicardial implantation in pacemaker device infection in pacemaker dependent patients a longer follow up is needed.

CONCLUSION

In this single centre observational study left ventricular epicardial implantation of a pacemaker and subsequent transvenous extraction of the infected device and leads in pacemaker dependent patients is a safe surgical procedure. There were no complications due to implantation and only one due to extraction. LV thresholds did not increase after implantation and no re-infections were observed.

LV epicardial implantation is a safe and feasible procedure in pacemaker dependent patients with an infected CIED.

No conflict of interest reported

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Patient Number	Sex	Age	Indication	Organism	Lead Number	Complete Extraction	Indication	Device	Previous Sternotomy
1	F	74	Endocarditis	S. Epidermis	3	YES	LVEF <35%, LBBB, Total AV block	CRT-D	Yes (Bentall)
2	F	50	Endocarditis	S. Aureus	2	YES	Total AV block (His-ablation)	PM	no
3	M	69	Pocket infection	S. Hominis	2	YES	Total AV block	PM	no
4	F	71	Endocarditis	S. Aureus	2	YES	Total AV block	PM	no
5	M	81	Endocarditis	Propionibacterium acnes	2	NO	Brady-Arrhythmia, Afib, Total AV block	PM	no
6	M	71	Endocarditis	Multiple organisms	2	YES	Total AV block	PM	Yes (AVR)
7	M	56	Lead infection	S. Aureus	2	YES	Total AV block after PTSMA, ICD HOCM	ICD	No
8	M	80	Lead infection	S. Aureus	2	YES	Total AV block	PM	No
9	M	68	Lead infection	S. Schleiferi	3	YES	LBBB, CTR-P which patient, Total AV block	CRT-P	Yes (AVR)
10	M	60	Endocarditis	S. Epidermis	2	YES	Asystoly, Afib, Total AV block	PM	No
11	M	81	Lead infection	Propionibacterium Acnes	2	YES	Total AV block	PM	No
12	M	86	Pocket infection	S. Aureus	2	NO	Total AV block	PM	No
13	M	91	Pocket infection	Klebsiella Oxytoca	2	YES	Total AV block	PM	Yes (CABG)
14	M	81	Pocket infection	S. Aureus	3	NO	Total AV block (His Ablation) CRT-P	CRT-P	Yes (ASD)
15	M	66	Pocket infection	Serratia marcescens	3	YES	ICMP, LVEF<35%, Total AV-Block	CRT-D	Yes (CABG)
16	M	54	Pocket infection	Negative culture *	2	YES	Total AV block and VT's	ICD	No

Table number 1: Baseline characteristics. * Negative culture after antibiotic treatment by a referring physician (Abbreviations: F=Female, M=Male, LVEF=Left Ventricular Ejection Fraction, LBBB=Left Bundle Branch Block, Total AV block=Total Atrio-Ventricular Block, Afib=Atrial Fibrillation, PTSMA=Percutaneous Transluminal Septal Myocardial Ablation, ICD=Implantable Cardiac Defibrillator, HOCM=Hypertrophic Obstructive Cardiomyopathy, CRT-P=Cardiac Resynchronisation Therapy – Pacing, VP=Ventricular Pacing, ICMP=Ischaemic Cardio Myopathy, VT=Ventricular Tachycardia)

Patient number	Complete Extraction	Outcome	Complications	Hospitalisation Days	Follow up months	Threshold at implantaon mV at 0,4ms	Threshold, last recorded mV at 0,4ms
1	YES	Died Natural Cause	NA	152	10	1,00	0,75
2	YES	Alive	NA	16	30	0,75	1,25
3	YES	Alive	NA	22	22	0,60	0,40
4	YES	Alive	NA	73	21	2,80	1,13
5	NO	Died Natural Cause	Bleeding at extraction site	31	6	1,00	1,50
6	YES	Alive	NA	82	7	0,75	0,75
7	YES	Alive	NA	8	48	1,40	NA switch to endovascular
8	YES	Alive	NA	28	18	1,80	1,00
9	YES	Died Heart Failure	NA	36	1	1,25	NA died before first recording
10	YES	Alive	NA	18	10	0,50	1,00
11	YES	Alive	NA	10	29	0,50	1,30
12	NO	Alive	NA	10	21	0,25	1,65
13	YES	Alive	NA	18	16	1,00	1,40
14	NO	Died Natural Cause	NA	22	12	0,90	NA died before first recording
15	YES	Alive	NA	29	11	2,10	0,50
16	YES	Alive	NA	3	30	0,50	2,75

Table 2: Outcome, NA: Not Available

CHAPTER 5

INCIDENCE AND OUTCOME OF PROSTHETIC VALVE ENDOCARDITIS AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT IN THE NETHERLANDS

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Neth Heart J . 2020 Apr 24. doi: 10.1007/s12471-020-01420-2. (Original article)

ABSTRACT

Background

Transcatheter aortic valve replacement (TAVR) is increasingly being used as an alternative to conventional surgical valve replacement. Prosthetic valve endocarditis (PVE) is a rare but feared complication after TAVR, with reported first-year incidences varying from 0.57% to 3.1%. This study was performed to gain insight into the incidence and outcome of PVE after TAVR in the Netherlands.

Methods

A multicentre retrospective registry study was performed. All patients who underwent TAVR in the period 2010-2017 were screened for the diagnosis of infective endocarditis in the insurance database and checked for the presence of PVE before analysis of general characteristics, PVE parameters and outcome.

Results

A total of 3968 patients who underwent TAVR were screened for PVE. During a median follow-up of 33.5 months [interquartile range (IQR) 22.8-45.8], 16 patients suffered from PVE (0.4%), with a median time to onset of 177 days (IQR 67.8-721.3). First-year incidence was 0.24% and the overall incidence rate was 0.14 events per 1000 person-years. Overall mortality during follow-up in our study was 31%, of which 25% occurred in hospital. All patients were treated conservatively with intravenous antibiotics alone, and none underwent a re-intervention. Other complications of PVE occurred in 5 patients (31%) and included aortic abscess (2), decompensated heart failure (2) and cerebral embolisation (1).

Conclusion

PVE in patients receiving TAVR is a relatively rare complication and has a high mortality rate.

Keywords: Structural heart valve disease · Structural heart intervention · Transcatheter aortic valve replacement · Aortic valve stenosis · Prosthetic valve endocarditis

INTRODUCTION

Trans-catheter aortic valve replacement (TAVR) is increasingly being used as an alternative treatment to conventional surgery in patients with severe aortic stenosis who are considered to be inoperable or at high or intermediate surgical risk, recently even with beneficial results in low-risk patients [1–5]. One of the most feared complications after TAVR or surgical valve implantation is prosthetic valve endocarditis (PVE) [6, 7]. Known risk factors for PVE are advanced age, renal impairment, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and residual aortic regurgitation following valve surgery [8, 9]. PVE is a rare complication, with reported first-year incidences of 0.3%–1.8% after surgical aortic valve implantation (SAVR) [2, 6, 10–13], associated with high morbidity and mortality rates [10, 13]. For TAVR these incidences vary from 0.57% to 3.1%, based on small studies and a few larger nationwide registries [9, 13–17]. With the shift of TAVR indication towards lower-risk patients, it is of particularly interest how the incidence and outcome of PVE post-TAVR differs from post-SAVR. This research was performed to gain insight into the incidence and outcome of PVE after TAVR in the Netherlands.

MATERIALS AND METHODS

A multicentre retrospective registry study was performed in eight centres in the Netherlands performing TAVR, including all patients who underwent TAVR in these centres in the period 2009–2017. Data were extracted using the in-hospital TAVR registry of each participating centre.

The national insurance database (Diagnose Behandel Combinatie) was screened for the diagnosis of infective endocarditis (IE) in all post-TAVR patients. This database registers all ambulatory diagnoses and hospital admissions with main discharge diagnoses (primary and secondary) according to the International Statistical Classification of Disease and Related Health Problems (ICD-10). Every patient in the Netherlands has a unique patient identification number, which can be used for screening diagnoses in the insurance database. Patient identification numbers of all TAVR patients were screened for IE as primary or secondary diagnosis in the insurance database, using the IE-specific ICD-10 codes I33.0, I33.9, I38 and I39. Patients assigned one of the mentioned ICD-10 codes after the TAVR procedure, who were in hospital >1 week or who died before discharge were suspected of

having IE. The data of these patients were checked for correctness of the diagnosis of IE, using the modified Duke Criteria [18, 19]. Patients with possible or definite IE, based on the modified Duke Criteria, were screened for the presence of PVE using patient records.

Patients with PVE were analysed for age, gender, valve type and size, date of PVE diagnosis, organism, concomitant IE of a non-TAVR valve, presence of a cardiac implantable electronic device (CIED), concomitant IE of a CIED, re-intervention (i.e. re-TAVR, conventional surgery, conservative treatment with antibiotics or palliative care), mortality and complications according to the Valve Academic Research Consortium (VARC-2) [20]. Baseline characteristics of patients with PVE were compared with those of patients without PVE. A sample population of 848 patients without PVE and with complete baseline and hospitalisation data during transcatheter aortic valve implantation was used as a control group (confidence level of 95% with a confidence interval of 1.03, which represents a margin of error of 3%).

Complications of PVE were defined as cerebral embolisation of a vegetation, embolisation of a vegetation elsewhere, development of total atrioventricular (AV) block, root abscess, valve destruction with severe aortic regurgitation (AR) and decompensated heart failure due to AR. Investigators had the possibility to add free text remarks to the database to specify certain aspects that were not covered by the database. Left ventricular function was determined using echocardiography [21]. Renal function was determined per the KDOQI (Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification) [22]). A renal function of class 3 and lower [glomerular filtration rate (GFR) <45] was considered to be impaired renal function. Data are shown as median $\pm$ standard deviation (SD).

Normally distributed variables are reported as mean $\pm$ standard deviation (SD) and tested with the Student's *t*-test. Non-normally distributed variables are presented as median (interquartile range, IQR), and the Mann-Whitney U test was used to test for significant differences. Frequencies and percentages were calculated and used to express categorical variables. For distribution analysis of categorical variables, the chi-square test was used. Statistical analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 3968 patients who underwent TAVR between 2009 and 2017 were included in the study and screened for PVE post-TAVR. The median follow-up period was 33.5 months (IQR 22.8-45.8). Of the 3968 screened patients, 16 (0.4%) developed an episode of PVE with an incidence rate of 0.14 event per 1000 person-years. The median time to onset of PVE was 177 days (IQR 67.8-721.3). In 9 patients PVE occurred within the 1st year after TAVR (early PVE) (incidence of 0.23%) and in 7 patients (0.18%) after 1 year (late PVE).

Baseline characteristics of the PVE and control groups are shown in Table 1. Median age was 81.5 (IQR 68-86) years and just over half of the patients were male (56%) in the PVE group versus 82.1 (IQR 77-86) years and 46% in the control group. Besides impaired renal function, baseline characteristics were not significantly different between the two groups. In the PVE group, a history of diabetes was observed in 5 of 16 (31%) patients, hypertension in 7 of 16 (44%) patients and impaired renal function (GFR <45 ml/min) was present in 12 of 16 (75%) patients, which differed significantly from the control group (39 ml/min, IQR 29-57 vs 59 ml/min, IQR 64-83, $p=0.002$). None of the patients who presented with PVE after TAVR had suffered from IE prior to TAVR. Left ventricular function prior to TAVR was good (left ventricular ejection fraction >55%) in 56% (9/16), moderately impaired in 31% (5/16) and severely impaired in 13% (2/16). The affected prosthetic valves were a CoreValve CRS (Medtronic Inc., Minneapolis, MN, USA) in 25% (4/16), a Sapien XT (Edwards Lifesciences LLC, Irvine, CA, USA) in 44% (7/16), an Evolut R (Medtronic Inc.) in 13% (2/16) and a Direct Flow (Direct Flow Medical Inc., Santa Rosa, CA, USA) in 19% (3/16). The approach to implantation was transfemoral in 81% (13/16), trans-subclavian in 13% (2/16) and transapical in 6% (1/16). The mean valve diameter was 26.3 mm, ranging from 23 mm to 31 mm.

Number of patients	PVE n=16	No PVEa n=848	p-value
Age (years), median (IQR)	81.5 (68-86)	82.1 (77-86)	0.317
Male	9 (56%)	387 (46%)	0.394
Length (cm)	169 (158-180)	168 (161-175)	0.834
Weight (kg)	78 (60-97)	73 (64-83)	0.593
Renal function (eGFR, ml/min)	39 (29-57)	59 (64-83)	0.002
Impaired renal function	12 (75%)	434 (51%)	0.058
Hypertension	7 (44%)	535 (63%)	0.116
Diabetes mellitus	5 (31%)	200 (24%)	0.472
History of endocarditis	0	2 (0.2%)	0.846
TAVR prosthesis			
First generation CoreValve	4 (25%)	336 (40%)	
Evolut R	2 (13%)	67 (8%)	
Sapien XT	7 (44%)	216 (25%)	
Sapien 3	0	26 (3%)	
Engager	0	18 (2%)	
Direct Flow	3 (19%)	23 (3%)	
Lotus Valve	0	101 (12%)	
Jena Valve	0	63 (7%)	
Left ventricular ejection fraction			0.709
Good (>55%)	9 (56%)	560 (66%)	
Moderate (35-55%)	5 (31%)	216 (25%)	
Poor (<35%)	2 (13%)	74 (9%)	

Table 1 Baseline characteristics

^aThis is a selected sample population consisting of patients without PVE after TAVR
 EF ejection fraction, eGFR estimated glomerular filtration rate, PVE prosthetic valve
 endocarditis, TAVR transcatheter aortic valve replacement

All patients had positive blood cultures, of which the most prevalent pathogen was *Enterococcus faecalis* (5/16). The other pathogens were *Staphylococcus aureus* (4/16), *Streptococcus mitis* (3/16), *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Streptococcus gallolyticus* and a diphtheroid rod which was not defined in more detail. A possible entry point for bacteria was found in 9 patients: a gastro-intestinal (GI) entry point in 5 (4 GI tract and 1 oral entry point), an infected knee prosthesis, a femoral access site, a subclavian access site, and an inguinal abscess of the ipsilateral primary access site which developed 1 month after TAVR. Microbiological characteristics including entry point and antibiotic treatment of all patients are shown in Table 2.

	Organism	Entry point	Antibiotic treatment	Duration of antibiotic treatment (days)
1	Staphylococcus aureus	Subclavian artery	Augmentin, gentamicin and after 5 days flucloxacillin	11 (patient died in-hospital)
2	Diphtheroid streptococci	Unknown	Rifampicin, vancomycin	42
3	Enterococcus faecalis	Unknown	Amoxicillin and ceftriaxone	42
4	Streptococcus mitis	Unknown	Penicillin	42
5	Enterococcus faecalis	Unknown	Amoxicillin	42
6	Staphylococcus aureus	Total knee prosthesis	Rifampicin, flucloxacillin, gentamicin	23 (patient died in-hospital)
7	Pseudomonas aeruginosa	Femoral access site TAVR	Ceftriaxone, ceftazidime	16 (patient died in-hospital)
8	Streptococcus gallolyticus	Gastro-intestinal	Penicillin, gentamicin	42
9	Staphylococcus aureus	Unknown	Flucloxacillin, gentamicin, rifampicin	7 (patient died in-hospital)
10	Enterococcus faecalis	Abscess right inguinal	Vancomycin, gentamicin	42
11	Streptococcus mitis/oralis	Unknown	Gentamicin, penicillin, vancomycin	42
12	Streptococcus oralis	Mouth	Penicillin	42
13	Klebsiella oxytoca	Gastro-intestinal	Unknown	Unknown
14	Enterococcus faecalis	Gastro-intestinal	Unknown	Unknown
15	Enterococcus faecalis	Gastro-intestinal	Unknown	Unknown
16	Staphylococcus aureus	Unknown	Unknown	Unknown

Table 2 Microbiological findings and treatment in the 16 patients who developed PVE after TAVR. TAVR transcatheter aortic valve replacement

Outcomes

Outcomes of the patients with PVE after TAVR are shown in Table 3. The mean ($\pm$ SD) length of hospitalisation was 31.2 ± 14.6 days. In the median follow-up period, mortality was 31% (5/16); 4 patients (25%) died in hospital after the diagnosis of

PVE. Three of the nine (33%) patients with early PVE died compared with 2 of 7 (29%) in the group with late PVE.

Concomitant mitral valve endocarditis was present in 25% (4/16) of patients. Of the 4 patients who developed concomitant mitral valve endocarditis 2 (50%) died. None of the patients with a pacemaker in situ developed a device-related infection.

Complications of PVE occurred in 31% (5/16) of the patients and consisted of cerebral infarction due to embolization of vegetation in 1 patient, aortic root abscess in 2 patients and decompensated heart failure in 2 patients. Moderate aortic valve regurgitation developed in 50% (8/16) of the patients. The initial treatment of choice was conservative, i.e. antibiotics alone in 88% (14/16) of patients, 2 of 16 patients entering a palliative care setting directly after the PVE diagnosis and 1 patient entering a palliative care setting shortly after starting antibiotic treatment. All antibiotic treatment was initiated after consultation with the attending microbiologist. None of the patients underwent a re-intervention of the TAVR prosthesis. Two patients died before assessment of aortic regurgitation could be performed.

Outcome	<i>n</i> =16
Mortality during follow-up	5 (31%)
In-hospital mortality after diagnosis of PVE	4 (25%)
Cerebral embolisation	1 (6%)
Aortic root abscess	2 (13%)
Decompensated heart failure	2 (13%)
None	11 (69%)
Infected pacemaker	0
Concomitant mitral valve endocarditis	4 (25%)
Time to IE (days)	177 (IQR 67.8-721.3)
Patients with IE within 1 year of TAVR	9 (56%)
Mean ($\pm$ SD) length of hospitalisation (days)	31.2 $\pm$ 14.6

Table 3 Outcomes in the 16 patients who developed PVE after TAVR. *PVE* prosthetic valve endocarditis, *IE* infective endocarditis, *IQR* interquartile range, *TAVR* transcatheter aortic valve replacement

DISCUSSION

This study investigated the incidence and outcomes in patients with an episode of PVE after TAVR in the Netherlands. We found an overall incidence of 0.4% (incidence rate of 0.13 event per 1000 person-years) with a higher incidence of early PVE after TAVR compared with late-onset PVE (0.23% vs 0.18%). In-hospital mortality in these patients was 25% and overall mortality 31%.

Several other studies have investigated the incidence of PVE post-TAVR, with conflicting results and reported first-year incidences varying from 0.57% to 3.1% [2, 9, 13–17]. When comparing our results with those of previous studies, especially other nationwide registries, we observed lower incidences (cumulative and incidence rate). In the studies of Bjursten et al. (Sweden) [17] and Butt et al. (Denmark) [13], post-TAVR patients were screened in a similar way to the procedure in our study. Both reported higher cumulative first-year incidences (1.4% [17] and 2.3% [13] vs 0.23% in our study), while incidence rates were more comparable (0.16 versus 0.13 events per 1000 person-years [13]). This discrepancy in incidence can be explained by the different definitions of IE used across these studies. In some studies, only cases of PVE or definite IE, as defined by the modified Duke criteria, were included, whereas other studies also include possible IE or all patients with IE. We examined only patients with PVE, resulting in a lower incidence as compared to that in other studies using other definitions. Other possible explanations could be a difference in predisposing factors and risk profiles or the small number of patients in most studies.

With the ongoing shift in TAVR indication from high-risk towards intermediate- to low-risk patients, the comparison between PVE after SAVR versus TAVR becomes even more interesting. Reported incidences of PVE post-SAVR are low and comparable to those after TAVR, with incidences varying from 0.3% to 1.8% per year [2, 6, 11–13], while bioprosthetic surgical valves were more prone to PVE than their mechanical equivalents [12].

PVE has been associated with a grave outcome and high mortality rates. In-hospital mortality rates reported from previous studies ranged from 11% to even 67% [13, 15, 17, 23–25]. In our study, we observed an in-hospital mortality rate of 25%. In contrast with these findings, SAVR patients who develop PVE seem to have better outcomes, with reported in-hospital mortality rates of 14–25% [10, 13]. The

more advanced age, frailty and presence of more comorbidities in TAVR patients compared with SAVR patients could explain this difference in mortality.

All patients who developed PVE following TAVR were treated conservatively with antibiotics, and even after prolonged antibiotic treatment the attending physicians did not consider any surgical re-intervention (SAVR or re-TAVR). Even patients having a *Staphylococcus aureus* PVE (25%), known for its high complication rate, did not undergo re-intervention. This finding may be explained by the high to prohibitive surgical risk of this frail patient population added to the surgical difficulties of transcatheter aortic valve explantation. Re-intervention in patients with PVE after TAVR has been reported previously. However, it was still associated with high in-hospital mortality rates [9]. The number of re-interventions in patients with PVE after TAVR will probably rise in the future, due to the shift towards younger and lower-risk patients with fewer co-morbidities. The role of valve-in-valve TAVR in patients with PVE is still unclear, and future research investigating the feasibility and safety of valve-in-valve TAVR in treating PVE is necessary.

There were differences in baseline characteristics (i.e. more frequent impaired renal function in the PVE group) between the two groups. We were, however, unable to test for independent risk factors, due to the low number of patients with PVE. On the other hand, renal impairment was previously described as a risk factor for PVE post-TAVR [9, 17]. Other identified risk factors include older age, male sex, diabetes, COPD, vascular complications and residual aortic regurgitation post-TAVR [9]. PVE was more often observed in patients with a first-generation TAVR valve (i.e. Sapien XT, Direct Flow and CoreValve), compared to newer-generation TAVR devices. The use of the newer-generation devices has reduced procedural complications such as residual aortic regurgitation and vascular complications, which may have resulted in a lower risk of PVE. However, more data on the incidence of PVE related to device type are necessary.

The most frequent entry point for bacteria was the GI tract, but second came the TAVR access site, with one patient developing PVE just weeks post-TAVR. Thus, despite TAVR being a minimally invasive procedure, there is still a chance of it being the source of potentially life-threatening infections. A temporary pacing lead may also be an entry point for bacteria into the bloodstream. *Staphylococcus aureus* was the cause of PVE in 25% of the patients, which was comparable with the findings of other studies [17, 23].

LIMITATIONS

This is a retrospective study with inherent limitations. The number of patients with actual PVE is small, limiting statistical analysis. As this study relies on an insurance database for identification of patients with IE it depends on correct registration of these data. It is possible that patients were missed due to inappropriate code registration on hospital admission. The relatively short follow-up of this patient population who developed PVE after TAVR in this study makes it difficult to draw any conclusions on long-term outcome. PVE is a rare disease, making prospective research very difficult. We therefore have to rely on data from retrospective studies for diagnosis, treatment and prognosis of this often-lethal disease.

CONCLUSION

This was the first study investigating the incidence of PVE after TAVR in the Netherlands. The incidence of PVE after TAVR was low, but it had a grave outcome with a high mortality rate.

Conflict of interest J. Brouwer, F.S. van den Brink, V.J. Nijenhuis, T.N. Vossenbergh, R. Delewi, M.S. van Mourik, P. den Heijer, W. Tanis, P.C. Kievit, W. Holvoet, R.S. Hermanides and J.M. ten Berg declare that they have no competing interests.

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CHAPTER 6A

VENO ARTERIAL-EXTRA CORPORAL MEMBRANE OXYGENATION FOR THE TREATMENT OF CARDIAC FAILURE IN PATIENTS WITH INFECTIVE ENDOCARDITIS

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Perfusion. 2019 Apr 26;26:267659119842807. doi: 10.1177/0267659119842807
(Original article)

ABSTRACT

Introduction

Surgery for Infective Endocarditis (IE) imposes great challenges in post-operative circulatory and pulmonary support but the role of Venous-Arterial Extra-Corporeal Membrane Oxygenation (VA ECMO) in this respect is unclear.

Methods

All patients undergoing VA-ECMO after IE surgery were analysed for age, gender, medical history, microorganisms, clinical outcome, complications and surgical procedure.

Results

Between 2012 and 2016, 13 patients received VA-ECMO following IE surgery. The median age was 62 years (33-73) and 8/13 were male. Previous cardiac surgery was present in 9 patients. Surgery for infective endocarditis consisted of a Bentall procedure in 10 patients, 2 of which received concomitant mitral valve surgery and 2 received concomitant CABG. Valvular surgery alone was performed in 3 patients. Mortality on VA-ECMO was 62% (8/13). Mortality during ICU stay was 77% (10/13). Survival to discharge was 23% (3/13). One patient reached the one year survival point. Two patients who survived to discharge have not yet reached the one year survival point. Patient related complications occurred in 54% (7/13) of patients and consisted of haemorrhage at the cannula site in 4 patients, leg ischaemia in 1 patient, haemorrhage at another site in 1 patient and infection of the cannula in 1 patient. ECMO hardware related complications occurred in 1 case consisting of clot formation in the oxygenator.

Conclusion

VA-ECMO in post-cardiotomy patients who were operated on for infective endocarditis is feasible but outcome is poor.

Key words: VA-ECMO, Infective endocarditis, Surgery

INTRODUCTION

Infective endocarditis (IE) is one of the most lethal infectious diseases in the western world with mortality rates ranging from 20% to 60% depending on patient characteristics, affected valves and organisms involved (1-6). The incidence of IE is on the rise (7-9). More and more patients contract this disease due to a change in the use of antibiotic prophylaxis, aging population, increase in prosthetic valve implantation and increase in invasive medical procedures such as haemodialysis (7,8,10-12). Treatment is often difficult and long. Antibiotic courses of up to six weeks in combination with possible surgical intervention are the cornerstones of IE treatment (12). Surgical intervention will be the treatment of choice in about one-third of the patients with IE (2,6). Surgery for IE is often difficult with great challenges in post-operative circulatory and pulmonary support, especially in those patients who have a history of cardiac surgery in the form of prosthetic valve implantation or concomitant or isolated aortic surgery.

Since the mid 1990's veno-arterial extra-corporeal membrane Oxygenation (VA ECMO) has been recognised as a possible life saving technique in the treatment of cardiac failure in post-cardiotomy patients (13). It's use is increasing in the adult population and has proven successful in the treatment of cardiogenic shock due to, for example, ST-elevation myocardial infarction (14). However there are no well established guidelines for the indication of VA-ECMO post-cardiotomy (13). Literature suggests that about one third of the patients with cardiac failure post cardiotomy may benefit from VA-ECMO treatment (13). When considering VA-ECMO post-cardiotomy for patients who were operated on for IE there is only anecdotal data on the subject but no larger case series exist (15-17). The purpose of this study is to present a larger cohort of patients who underwent cardiac surgery for IE and received subsequent VA-ECMO treatment as data in this field is virtually non-existent. It could provide a proof of concept on the subject and may be the starting point for future research and could help in establishing guidelines for the indication for VA-ECMO support in post-cardiotomy patients. The aim of this study was to gain insight in outcome of patients undergoing surgery for IE and subsequent treatment with VA-ECMO for circulatory support.

METHODS

An in-hospital registry was kept between 2009 and 2016 on all patients receiving VA ECMO for circulatory support in the St. Antonius Hospital, Nieuwegein, the Netherlands, a larger tertiary referral centre. ECMO was introduced in 2009. The following data were collected: age, sex, medical history including New York Heart Association (NYHA) functional class and left ventricular function, previous endocarditis, procedural characteristics including mode of cannulation and concomitant use of other circulatory support (e.g. intra-aortic balloon pump (IABP)), left ventricular function prior to admission, survival, complications related to the patient (e.g. bleeding at the cannula site, limb ischaemia), complications related to the ECMO hardware (e.g. pump failure, clot formation), length of ECMO treatment and length of stay on the intensive care unit (ICU) and in hospital, haemodynamic parameters, C-reactive protein (CRP) as an inflammatory marker mortality and neurological outcome. Heart failure was defined according to the NYHA scale.. A normal LVEF was defined as more than 50% ejection fraction (EF), a mildly impaired LVF was defined as 40-50% EF, a moderately impaired LVF was defined as 30-40% EF and severely impaired LVF was defined as an EF of less than 30%. Neurological outcome was defined using the Cerebral Performance Categories Scale (CPC) where a CPC score of 1 and 2 was deemed a good neurological outcome (18). The Euro-SCORE I was calculated for all patients to assess the chance of peri operative mortality.

Statistical analysis was performed using chi-square test for categorical variables and Student's t test for continuous variables when applicable. Continuous variable are given as median +/- SD.

Although according to Dutch law (Wet Medisch Wetenschappelijk Onderzoek met Mensen) there is no need for evaluation by a Medical Ethical Committee (MEC) in retrospective cohort research as this is an evaluation by a MEC was performed nonetheless in which there was no objection to this study.

RESULTS

Baseline Characteristics

Between 2009 and 2016 there were 118 patients who were treated with VA-ECMO for various reasons such as pulmonary embolism, cardiogenic shock following ST-elevation myocardial infarction and post-cardiotomy. In the same period 243

patients underwent surgery for IE. Between 2012 and 2016, 13 patients were treated with VA-ECMO following surgery for IE.

Most patients were male (8/13). The median age was 62 years (33-73) with four patients being over 70 years old. A medical history concerning cardiac surgery was present in nine patients: eight had previous valvular surgery of whom two received concomitant coronary bypass surgery graft (CABG) as well, one patient had undergone coronary artery bypass graft surgery alone. Aortic surgery prior to admission with IE was performed in 54% (7/13) patients all of whom had undergone a Bentall procedure. Only one patient had a history of a previous case of endocarditis. Functional status was NYHA class 1 in 31% (4/13) of the patients, NYHA class 2 in 38% (5/13) of the patients and NYHA class 3 in 31% (4/13) of the patients. There were no patients in NYHA class 4 or with known end stage heart failure. The left ventricular function was good in 31% (4/13), mildly impaired in 38% (5/13), moderately impaired in 23% (3/13) and severely impaired in 8% (1/13). Neurological events in the form of a previous cerebrovascular event was present in 31% (4/13) of the patients: There were two patients who had neurological impairment prior to surgery both consisting of a CPC score of 3. Of the other patients there were two patients with CPC score 2 and nine patients with CPC score 1. CRP levels prior to surgery were 57.7 (8-169). A history of diabetes was observed in 23% (3/13) of the patients, atrial fibrillation in 31% (4/13) of the patients and hypertension in 62% (8/13) of the patients. The Euro-SCORE prior to surgery was 41.7% (12.8%-61.5%) (See table 1: Baseline characteristics)

Baseline Characteristics	Number
Male	62% (8/13)
Median Age (years)	62 (33-73)
Previous Endocarditis	8% (1/13)
Previous Bentall	62% (8/13)
Previous CABG	23% (3/13)
Previous CVA/TIA	31% (4/13)
COPD	NA
Peripheral Artery Disease	8% (1/13)
Impaired Neurological Function (CPC 3-4)	15% (2/13)
Median EURO-SCORE	41.7% (Range 12.8%-61.5%)

Table 1: Baseline Characteristics

Abbreviations : CABG: Coronary Artery Bypass Graft. CVA: Cerebrovascular Accident. TIA: Transient Ischaemic Attack. COPD: Chronic Obstructive Pulmonary Disease. CPC:Cerebral Performance Category.

Procedural characteristics

Surgical intervention consisted of a Bentall procedure in 10 patients (77%), two of which received concomitant mitral valve surgery and another two received concomitant CABG. In total 21 patients received ECMO support after a Bentall procedure in our institution of which 10 received it for infective endocarditis. Isolated valvular surgery without aortic involvement or concomitant CABG was performed in 3 patients: 1 mitral valve replacement, 1 aortic valve replacement and 1 combined procedure. All patients had positive cultures: *Staphylococcus aureus* in three cases, *Enterococcus faecalis* in three cases, *Enterococcus faecium* in two cases, *Escherichia coli* in one case, *Staphylococcus epidermis* in one case, *Streptococcus mitis* in one case, *Haemophilus parainfluenzae* in one case and *Candida albicans* in one case. All patients were on maximum inotropic and vasopressor support after surgery. In all patients this was done by using noradrenaline and milrinone as is customary in our institution. None of the patients were able to wean of ECC and all were put on VA-ECMO support post-cardiotomy. The indication for ECMO was impossibility to wean from cardiopulmonary bypass following cardiac surgery in all patients. None of the patients received concomitant mechanical circulatory support by another device than ECMO (e.g.: Intra-Aortic Balloon Pump or Impella (Abiomed Europe GmbH, Aachen, Germany)). The arterial mode of cannulation was in the right subclavian artery in 3/13 patients whereas in the other ten it was placed in the femoral artery.

Outcome

Mortality while on VA-ECMO was 62% (8/13). The cause of death while treated with ECMO was severe left ventricular failure in 2/13 patients, severe right ventricular failure in 2/13 patients, multi-system organ failure in 3/13 patients and severe brain damage in 1/13 patient. Mortality during ICU stay was 77% (10/13) of which one patient died due to aspiration pneumonia and one patient was successfully weaned from ECMO but had a CPC of 4 which was deemed not recoverable. Survival to the ward was 23% (3/13) and all these patients had survival to discharge. One patient reached the one year survival point. The other two patients who have survived to discharge have not yet reached the one year survival point but are still alive. The patients that survived all had good neurological outcome in the form of CPC 1 as by clinical observation. Patient related complications occurred in 54% (7/13) of the patients and consisted of haemorrhage at the cannula site in four patients,

leg ischaemia in one patient, haemorrhage at another site in one patient and infection of the cannula in one patient. The ECMO related haemorrhage occurred at the subclavian artery in 15% (2/13) and at the femoral artery in 15% (2/13). In all cases it was treated conservatively by applying pressure at the cannula site. All patients who received femoral cannulation received antegrade leg perfusion as is customary in our institution. On patient who developed leg ischaemia underwent cannula repositioning which solved this problem. ECMO hardware related complications occurred in one case consisting of clot formation in the oxygenator possibly due to a strongly elevated platelet count of 657.000mm³ in this patient. The oxygenator of this patient was replaced. The median time on VA-ECMO was 5 (1-15) days, the median time spent on ICU was 6 (2-29) days and the median time spent in hospital was 16 (5-78) days. (See table 2: Outcome)

Outcome	Number
Mortality on ECMO	62% (8/13)
Mortality on ICU	77% (10/13)
Survival to Discharge	23% (3/13)
Survival >1 Year*	8% (1/13)
All patient related complications	54% (7/13)
ECMO hardware related complications	8% (1/13)
Good Neurological outcome (CPC 1-2)	23% (3/13)

Table 2: Outcome

Abbreviations: ECMO: Extra Corporal Membrane Oxygenation. ICU: Intensive Care Unit

*Of the three patients that have survived two have not yet reached the one year survival point but are alive at the time of the manuscript draft.

When analysing the three patients that survived; they were relatively young with a median age of 46 (range 33-51). This is significantly lower than in the group of no survivors 66 (range 54-73) $p=0.0035$. Furthermore valvular surgery only was performed in 2/3 surviving patients.

DISCUSSION:

This study shows that VA-ECMO in patients with cardiac failure post-cardiotomy following IE surgery is feasible but has a high mortality rate. To our knowledge this is the first case series published on this matter with a larger number of patients.

A large portion of the patients described in this study are patients who underwent previous aortic surgery. This could complicate surgery through a mechanism of altered anatomy making surgery for IE difficult. Previous cardiac surgery can impair left ventricular function which can greatly hamper cardiac recovery after redo surgical intervention and regain enough cardiac output to be weaned of mechanical support post-surgery. A somewhat similar mechanism may be the active inflammation and immune response of the patients with infective endocarditis. Active infection can impair cardiac function, again, making it difficult to come off mechanical support post-surgery.

The surgical procedure that was performed consisted of a Bentall procedure in more than three quarter of the patients. This is major cardiac surgery and may compose a larger risk on cardiac failure than isolated valvular surgery. Selection of patients for possible VA-ECMO treatment might optimise these results.

The NYHA class of patients was NYHA class 2 or higher in 69%. A NYHA class of 2 and higher is a known predictor for mortality (19). Selection of patients for VA-ECMO using the EURO-SCORE is not validated but may be usable for this group of patients (19). Future studies might be able to validate the EURO-SCORE for this group of patient.

Over half of the patients suffered a complication of the treatment, most of these being a haemorrhage. This could have led to haemodynamic instability through blood loss. It is possible that that may have led to inadequate organ perfusion which may impair survival. Strict haemodynamic monitoring and possibly a more aggressive approach to possible complications may prevent this and improve survival.

Four of the patients presented in this study were over 70 years old. Patients over 70 years old generally perform poorly on VA-ECMO and are currently no longer eligible for VA-ECMO treatment in our centre. This could have influenced outcome and be a possible explanation for the high mortality rate in this study. Moreover this is reflected in the significantly lower age of patients who survived. Strict adherence to selection of patients of a younger age and forgoing patients over 70 may improve outcome in this population.

The neurological outcome is, albeit the low survival rate, good. This illustrated the possibility of VA-ECMO to ensure adequate end-organ perfusion.

There was only one ECMO related complication. This consisted of clot formation in the oxygenator. This is a known complication and may be prevented with strict adherence to anticoagulation protocols. However, this is often difficult in septic patients in which the septicaemia could influence the anticoagulation.

The mode of cannulation differs between the patients. This could influence survival. Femoral cannulation increases afterload for the left ventricle and could influence outcome. Central cannulation could overcome this but has the drawback of being much more invasive and possibly increasing the risk of infection. The use of left ventricular unloading using an intra-aortic balloon pump has been suggested but the effect on outcome is uncertain (6,14,20).

Survival to discharge is low in this study, yet in three patients has led to a favourable outcome. VA-ECMO is a costly therapy which needs not only expensive hardware but also continuous schooling of staff. If the applicability of this technique is in the post-cardiotomy patient who was operated on for infective endocarditis, an ethical discussion must be held if it is desirable to spend such a large amount of funds and resources on a relatively rare disease with poor outcome. This discussion is however beyond the scope of this article but must be held on an international, national and individual level with doctors, patients, nurses, allied staff and medical ethicists.

6A

LIMITATIONS

This study has several limitations. It is a small cohort making any statistical analysis virtually impossible. It is a retrospective study, with all the associated shortcomings of such. The decision to put patients on VA-ECMO post-cardiotomy may have led to a selection bias. As this is an observational study there is no control group making comparison impossible. Possibly a future randomised controlled trial may solve this issue, however, there are many medical and ethical barriers in doing this.

CONCLUSION:

VA-ECMO for the treatment of cardiac failure in post-cardiotomy patients who were operated on for infective endocarditis is feasible but outcome is poor. It could improve survival in selected patients. Further research is needed to identify

patients eligible for VA-ECMO treatment for cardiac failure post-cardiotomy in infective endocarditis.

The authors received no funding for this research

Conflict of interest: none declared

Research material is available by contacting the corresponding author

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6A

CHAPTER 6B

SUCCESSFUL USE OF PLAIN SUBCOSTAL TTE IN VV-ECMO CANNULA REPOSITIONING

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Netherlands Journal of Critical Care, volume 25 – no 5 –sep 20i7; 186-187 (*Case report*)

A previously healthy 62 year old male with recently diagnosed rapidly progressive pulmonary fibrosis was hospitalized and accepted for lung transplantation. During admission his pulmonary function critically deteriorated due to an intercurrent pneumonia which necessitated additional respiratory support. In order to avoid physical deconditioning inherent to invasive mechanical ventilation and analgesedation the patient was not intubated. Instead it was decided to follow an 'awake Extra Corporal Membrane Oxygenation (ECMO)' strategy, which is increasingly used as a bridge to lung transplant and allows active participation of the patient including physical therapy and training(1). He was put on Venovenous ECMO (VV-ECMO) using a single site double lumen cannula (Avalon Elite®) in the right jugular vein (RJV)(2). During daily care the VV-ECMO flow suddenly dropped from 4.3 litres per minute to 2.7 litres per minute. This was followed by a significant desaturation in oxygen levels from 99% to around 75%. Patient became unresponsive and to avoid possible aspiration of stomach content a trans oesophageal echocardiography was deemed too dangerous. Trans thoracic echocardiography only produced proper subcostal views due to patient's supine position.

Image A shows a subcostal view. The right atrium (RA in red) right ventricle (RV in red) left atrium (LA in red) and left ventricle (LV) are indicated as well as the tricuspid valve in blue and the liver and the diaphragm. The cannula position (white arrow) is in front of the right atrium passing from superior caval vein to inferior caval vein during the initial echo images. The ECMO flow is indicated by the yellow arrow. Image B shows the same image with colour Doppler in which the VV-ECMO cannula is retracted and turned directing the flow towards the inferior caval vein. Image C shows the cannula after slight twisting and pushing it somewhat deeper in the RJV with colour Doppler signal aimed more towards the tricuspid valve (red arrow). Image D shows the ECMO colour Doppler signal directed towards the tricuspid annulus and across after further repositioning (red arrow). The images are an example of so-called re-circulation(3). A situation in which part of the ECMO flow from the exit cannula containing oxygen rich blood is being directed towards the entry cannula and thus re-circulates within the ECMO circuit. This was caused by the shift in cannula position due to daily care. In the process the patient is being derived from this oxygen rich blood. This together with the decrease in flow caused the sudden deterioration in oxygen saturation.

After repositioning of the VV-ECMO cannula using only subcostal views due to patient and technique related circumstances flow of the VV-ECMO circuit normalised completely and the patient recovered. He was transferred to a designated lung transplantation centre in order to receive a lung transplantation.

Plain subcostal trans thoracic echocardiography can be successfully used in double lumen Avalon cannula repositioning in VV-ECMO when placed in the right internal jugular vein.

6B

No conflict of interest

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CHAPTER 7

VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION IN ADDITION TO PRIMARY PCI IN PATIENTS PRESENTING WITH ST-ELEVATION MYOCARDIAL INFARCTION

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Netherlands Heart Journal DOI : 10.1007/s12471-017-1068-y NEHJ-D-17-00146.3
(Original Article)

ABSTRACT

Introduction

Primary percutaneous coronary intervention (pPCI) in ST-elevation myocardial infarction (STEMI) can cause great haemodynamic instability. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can provide haemodynamic support in patients with STEMI but data on outcome and complications are scarce.

Methods: An in-hospital registry was conducted enrolling all patients receiving VA-ECMO. Patients were analysed for medical history, mortality, neurological outcome, complications and coronary artery disease.

Results

Between 2011 and 2016, 12 patients underwent pPCI for STEMI and received VA-ECMO for haemodynamic support. The majority of the patients were male (10/12) with a median age of 63 (47-75) years and 4 of the 12 patients had a history of coronary artery disease. A cardiac arrest was witnessed in 11 patients. The left coronary artery was compromised in 8 patients and 4 had right coronary artery disease. All patients were in Killip class IV. Survival to discharge was 67% (8/12), 1-year survival was 42% (5/12), 2 patients have not yet reached the 1-year survival point but are still alive and 1 patient died within a year after discharge. All-cause mortality was 42% (5/12) of which mortality on ECMO was 33% (4/12). Patient-related complications occurred in 6 of the 12 patients: 1 patient suffered major neurological impairment, 2 patients suffered haemorrhage at the cannula site, 2 patients had limb ischaemia and 1 patient had a haemorrhage elsewhere. There were no VA-ECMO hardware malfunctions.

Conclusion

VA-ECMO in pPCI for STEMI has a high survival rate and neurological outcome is good, even when the patient is admitted with a cardiac arrest.

Keywords: ECMO, STEMI, Cardiogenic Shock, Circulatory Support

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the cornerstone in the treatment of ST-elevation myocardial infarction (STEMI). STEMI can cause great haemodynamic instability through a mechanism of cardiac failure and subsequent low output state [1-7]. Haemodynamic support following STEMI is quintessential for survival and preservation of cardiac function [6]. Historically, this consisted of medical support with inotropes and vasopressors, and mechanical circulatory support by an intra-aortic balloon pump [1,3,8,9]. Recently more advanced devices have been introduced such as the Impella device, but data on its safety and efficacy are inconclusive [10,11].

Another form of haemodynamic support is veno-arterial extracorporeal membrane oxygenation (VA-ECMO) [12,13]. VA-ECMO can provide haemodynamic support in patients with STEMI with cardiac failure and possible concomitant respiratory failure due to pulmonary congestion [13-15]. Its mechanism is based on the combined possibility of circulatory support through laminar flow of blood in the aorta and simultaneous oxygenation of the patient's blood. Blood flow of up to 7 litres/min can be generated in ideal circumstances.

Data on outcome and complications in the use of VA-ECMO in pPCI for STEMI are scarce but first reports on this therapy show promising results [6,14-16]. This study was performed to gain insight into the outcome and complications of the use of VA-ECMO in pPCI for STEMI with subsequent haemodynamic instability.

METHODS

An in-hospital registry was kept at the St Antonius Hospital, Nieuwegein, the Netherlands involving all patients who received treatment with VA-ECMO for haemodynamic support from 2009 onwards. Data were collected retrospectively and included those patients who received VA-ECMO in addition to pPCI for STEMI. All patients were analysed at baseline for age, sex, medical history, previous coronary artery disease, coronary artery occlusion in STEMI, concomitant coronary artery disease, SYNTAX score, concomitant chronic total occlusion, Survival After VA-ECMO (SAVE) score, procedural characteristics including mode of cannulation and concomitant use of other circulatory support (e.g. intra-aortic balloon pump (IABP)), left ventricular function prior to admission, survival, complications related

to the patient (e.g. bleeding at the cannula site, limb ischaemia), complications related to the ECMO hardware (e.g. pump failure, clot formation), length of ECMO treatment and length of stay on the ICU and in hospital, haemodynamic parameters, mortality and neurological outcome [17-19].

Shock was defined according to the Killip class [20]. The SYNTAX score was calculated using the online SYNTAX score calculator (<http://www.syntaxscore.com/calculator/start.htm>) [17]. The SAVE score, an Extracorporeal Life Support Organisation (ELSO) endorsed and validated score, was calculated to compare predicted mortality with actual mortality [18]. This was done by using the online SAVE score calculator (<http://www.save-score.com/>). Neurological outcome was defined using the Cerebral Performance Categories Scale (CPC) where a CPC score of 1 and 2 was deemed a good neurological outcome [19].

RESULTS

VA-ECMO using the Maquet Cardiohelp, which is a system using an integrated rotational pump and oxygenator, was introduced at the St Antonius Hospital in Nieuwegein, the Netherlands, a large referral centre, in 2009. From 2009 until 2016 a total of 118 patients received VA-ECMO for circulatory support for various conditions such as post cardiectomy, pulmonary embolism and septic shock. Between 2009 and 2016 a total of 19,116 patients underwent coronary intervention of which 3673 underwent a PCI for an acute ischaemic event; 12 patients underwent pPCI for STEMI and received additional VA-ECMO treatment for haemodynamic support. The first VA-ECMO in addition to STEMI was performed in 2011.

Baseline characteristics

The majority of patients were male (83%,10/12) with a median age of 63 (47-75) years with only 1 patient over the age of 70 years. A history of coronary artery disease in the form of a previous PCI was present in 33% (4/12) of the patients of whom 1 patient had recently diagnosed left main disease. None of the patients had undergone previous cardiac surgery and none had known left ventricular impairment prior to admission. None of the patients had a history of neurological events in the form of either a transient ischaemic attack or a cerebrovascular accident. Only 1 patient had known pulmonary disease in the form of chronic obstructive pulmonary disease GOLD class 1/4. Two patients had a history

of diabetes mellitus type 2 and 42% (5/10) were known to have a history of hypertension. There was 1 patient with a history of peripheral artery disease in the form of implantation of an aortic bifurcation prosthesis 11 years prior to primary pPCI for STEMI. All patients were in cardiogenic shock, Killip class 4 prior to and after pPCI (Table 1).

Baseline Characteristics	N=12
Male	83% (10/12)
Age	63 (47-75) years
Previous Coronary Artery Disease	33% (4/12)
Diabetes	17% (2/12)
Hypertension	42% (5/12)
TIA/Stroke	NA
COPD	8% (1/12)
Per peripheral artery disease	8% (1/12)
Shock upon admission, Killip class IV	100% (12/12)

Table 1 Baseline Characteristics. Abbreviations: TIA: Transient Ischaemic Attack, COPD: Chronic Obstructive Pulmonary Disease, NA: Not Available

Procedural characteristics

The indication for VA-ECMO was determined by the attending interventional cardiologist and intensivist. An out-of-hospital cardiac arrest (OHCA) prior to presentation was witnessed in 9 of the 12 patients. Two patients suffered an in-hospital cardiac arrest. The left coronary artery was involved in 67% (8/12) of the patients: 3 left main coronary arteries, 5 left anterior descending arteries and the other 4 patients had right coronary artery disease. The mean SYNTAX score was 23.7 (4-40). A total of 8 patients had concomitant coronary artery disease, 3 of which had a chronic total occlusion of another coronary artery than the culprit lesion. Culprit lesion revascularisation was achieved in 92% (11/12). One patient had an unsuccessful evacuation of thrombus in the right coronary artery. One patient had successful revascularisation of the culprit lesion but received a coronary artery bypass graft (CABG) after pPCI.

Mean systolic blood pressure was 70 (53-80) mmHg upon admission while mean pH was 7.2 (6.97-7.40) and mean lactate was 6.4 (1.6-12.0) mmol/l. Mean blood bicarbonate levels were 16.5 (5.7-22.2) mmol/l and mean creatinine was 134 (72-333) mmol/l.

All patients were cannulated at the Cathlab. The cannula was inserted in the femoral artery in 9 of the 12 patients. In 3 patients the cannula was placed in the subclavian artery by the attending cardiothoracic surgeon. The venous cannula was placed in the femoral vein in all but 1 patient, where it was placed in the internal jugular vein. Two patients had an IABP in situ at the time of cannulation. The mean SAVE score was -5.5 (-2 - -11) which represents an estimated survival of 30% (25%-35%) (Table 2).

Initially the patients were weaned off the device according to the clinical judgement of the attending physician. However, after 2015 the patients were weaned off the device using the local weaning protocol, which is a modification of an existing protocol [21].

Procedural characteristics	N=12
Out of hospital cardiac arrest	75% (9/12)
In hospital cardiac arrest	17% (2/12)
Left coronary artery	67% (8/12)
Right coronary artery	33% (4/12)
Culprit revascularisation	92% (11/12)
SYNTAX Score	23.7 (4-40)
Intra-Aortic Balloon Pump	17% (2/12)
Subsequent CABG after PCI	8% (1/12)
SAVE Score	-5.5 (-2 - -11)

Table 2 Procedural Characteristics. Abbreviations: CABG: Coronary Artery Bypass Grafting. PCI: Percutaneous Intervention

Outcome

Survival to discharge was 67% (8/12), 1-year survival was 42% (5/12), and 2 of the 12 patients have not yet reached the 1-year survival point but are still alive. Mortality on VA-ECMO was 33% (4/12) and this was also the 30-day mortality. All patients who survived VA-ECMO survived to discharge. All-cause mortality was 42% (5/12); The aforementioned 33% (4/12) of patients who died on VA-ECMO and 1 patient who died within a year after discharge due to aspiration pneumonia caused by poor neurological status after prolonged cardio-pulmonary resuscitation.

Both the patients who received IABP and ECMO survived to discharge. The patient who suffered unsuccessful evacuation of the thrombus in the right coronary

artery did not survive. The patient who underwent subsequent CABG did survive to discharge.

Patient-related complications occurred in 6 of the 12 patients: 2 patients suffered haemorrhage at the cannula site and 1 patient had a haemorrhage elsewhere in the form of a venous haemorrhage of the liver due to the venous cannula position while on VA-ECMO. Limb ischaemia occurred in 3 of the 12 patients; in 1 of these patients the right leg was eventually amputated due to clot formation between the ECMO cannula and antegrade leg perfusion. One patient suffered major neurological impairment; however, this was not due to intracranial haemorrhage but due to prolonged resuscitation prior to receiving the VA-ECMO treatment. There were no malfunctions regarding the VA-ECMO hardware. The median time spent on VA-ECMO was 5 (1-10) days, the median time spent on the ICU was 14 (1-68) days and the median time spent in hospital was 23 (1-82) days (Table 3).

Outcome	N=12
Survival to discharge	67% (8/12)
Survival with >1 year follow up	42% (5/12)
All-cause mortality	42% (5/12)
Mortality on ECMO	33% (4/12)
30 days mortality	33% (4/12)
Mortality after discharge	8% (1/12)
All Complications	50% (6/12)
Major Neurological impairment	8% (1/12)
Haemorrhage cannula	17% (2/12)
Haemorrhage elsewhere	8% (1/12)
Limb ischaemia	25% (3/12)
Median time on ECMO	5 (1-10) days
Median time on ICU	14 (1-82) days

Table 3 Outcome: Abbreviations: ECMO: Extra Corporal Membrane Oxygenation. ICU: Intensive Care Unit

Follow-up after VA-ECMO in pPCI for STEMI

Of the 12 patients who received VA-ECMO in pPCI for STEMI, 1 patient received a CABG for concomitant coronary artery disease. Another patient underwent implantation of a left ventricular assist device (LVAD) in a designated LVAD centre. Both of these patients survived to discharge and are neurologically well.

DISCUSSION

This study shows that VA-ECMO is feasible in selected patients. It could potentially improve survival in patients undergoing primary PCI for STEMI with cardiogenic shock. As all patients were in cardiogenic shock, VA-ECMO could be considered a last resort therapy. There are no randomised trials on VA-ECMO in pPCI in STEMI; observational studies proving the concept of circulatory support with VA-ECMO in pPCI in STEMI are crucial in facilitating future research in this field [13-16]. In this observational study VA-ECMO was feasible, safe and with a relatively low complication rate in a very high-risk group of patients with great haemodynamic instability. As our research shows, the applicability of this possibly life-saving technique in patients undergoing pPCI for STEMI can be the start of a future randomised controlled trial proving its use in pPCI in STEMI.

Although the SAVE score is not a substitute for clinical assessment of patients, the difference between the predicted mortality and the actual mortality may illustrate that VA-ECMO is especially useful in the treatment of cardiogenic shock caused by STEMI.

Only 1 patient suffered a poor neurological outcome due to prolonged resuscitation prior to pPCI and VA-ECMO cannulation. This illustrates the safety of using VA-ECMO in haemodynamic support with respect to possible neurological injury. Three patients suffered limb ischaemia. This is a known complication of VA-ECMO due to occlusion of the femoral artery distal of the cannula and the cannula itself. The correct use of antegrade leg perfusion via insertion of an extra small diameter cannula can prevent this (known as leg-ECMO or L-ECMO). However, 1 patient had adequate leg perfusion but developed clot formation between the retrograde ECMO cannula and antegrade leg perfusion. Surgical exploration during decannulation could prevent this. Studies in this regard are lacking and a standardised procedure of decannulation might prevent this complication. No intracranial haemorrhages were reported, although patients on VA-ECMO received dual antiplatelet therapy and heparin infusion for the ECMO circuit. This indicates the safety of the described procedure from a neurological point of view.

One of the possible drawbacks of VA-ECMO in pPCI for STEMI is the increase in afterload of the heart. This is a direct result of competitive flow of the ECMO circuit with the cardiac circulation [22]. However, as one of the major problems

of cardiogenic shock is poor organ perfusion with subsequent organ failure, adequate organ perfusion is pivotal in improving patient survival and may outweigh the problem of increased afterload. In our study increased afterload did not lead to a worsening of the outcome for patients. If increasing afterload poses a problem in the treatment of patients on VA-ECMO, the use of an IABP or Impella device for left ventricular unloading may be considered. However, the possible benefit of left ventricular unloading is purely theoretical and not yet proven in a clinical setting. Furthermore, the use of an IABP or Impella or other left ventricular unloading device may increase the risk of possible complications, the complexity of the procedure as well as the cost of treatment. In this study, 2 patients received concomitant IABP therapy during VA-ECMO treatment and survived to discharge. This illustrates the technical feasibility of these two combined techniques.

Two of the described patients underwent VA-ECMO treatment in pPCI for STEMI and received additional therapy after pPCI in the form of a CABG and LVAD placement. This underlines the possibility of using VA-ECMO as a bridge to LVAD, treatment or recovery.

In this study, all patients were placed on VA-ECMO after PCI. In future studies patients could be placed on VA-ECMO prior to PCI. The first strategy has the benefit of earlier revascularisation, but it prolongs poor organ perfusion and haemodynamic shock. The second strategy may delay revascularisation by several minutes but allows early haemodynamic support and stabilisation as VA-ECMO therapy can be administered directly in the Cathlab. Future research must establish the ideal timing of VA-ECMO placement.

The absence of ECMO-related hardware failure is a possible indication of the reliability of the Maquet Cardiohelp. It can be safely used in this group of patients.

LIMITATIONS

Our study has several limitations. It is an observational study comprising only a small number of patients. As patients were selected for VA-ECMO by the attending physicians, selection bias is present. Furthermore, there was no control group; future studies may be able to randomise patients undergoing pPCI for STEMI with subsequent cardiogenic shock to VA-ECMO treatment versus medical treatment.

The small number of patients in this study makes any sound statistical conclusion impossible, In future registries with larger numbers of patients this can be overcome.

CONCLUSION

In our group, VA-ECMO in pPCI for STEMI had a survival to discharge rate of 67% and even when patients were admitted with an OHCA this outcome was favourable. The complication rate was relatively low and neurological outcome was good. Further research is needed to identify the patients most likely to benefit from VA-ECMO treatment in pPCI for STEMI. Randomised controlled trials are needed to prove the efficacy of this new and promising technique.

DISCLOSURES

No conflict of interest.

There was no funding for this research.

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CHAPTER 8

PROPHYLACTIC VENO-ARTERIAL EXTRA CORPORAL MEMBRANE OXYGENATION IN PATIENTS UNDERGOING HIGH RISK PERCUTANEOUS CORONARY INTERVENTION

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Neth Heart J . 2020 Mar;28(3):139-144. doi: 10.1007/s12471-019-01350-8.
(Original article)

ABSTRACT:

Purpose

Complex high risk percutaneous coronary intervention (PCI) is challenging and frequently accompanied by haemodynamic instability. Veno-arterial extra corporal membrane oxygenation (VA-ECMO) can provide cardiopulmonary support in high risk PCI however outcome is unclear.

Methods

A two-centre registry of all patients undergoing high risk PCI and receiving VA-ECMO for cardiopulmonary support.

Results

A total of 14 patients (92% male, median age 69 (53-83)) years of which 50% had previous coronary artery disease in the form of a CABG (36%) and a PCI (14%) underwent high risk PCI and received VA-ECMO support. The main target lesion was a left main in 78%, a LAD in 14%, a RCA in 7% and 71% underwent multi vessel PCI in addition to main target vessel PCI. The median Syntax score was 27.2 (8-42.5) and in 64% (9/14) there was a CTO lesion. LV function was mildly impaired in 7% (1/14), moderately impaired in 14% (2/14) and severely impaired in 64% (9/14). Cannulation was femoral-femoral in all patients. Median ECMO run was 2.57 hours (1-4)

Survival was 93% (13/14). One patient died during hospitalisation due to refractory cardiac failure. All other patients survived to discharge. Complications occurred in 14% (2/14) with one patient developing a transient ischaemic attack post ECMO and one patient developing a thrombus in the femoral vein used for ECMO cannulation.

Conclusion

VA-ECMO in high risk PCI is feasible with good outcome. It can be successfully used for cardiopulmonary support in selected patients.

Keywords: Veno-arterial extracorporeal membrane oxygenation · Percutaneous coronary intervention · High-risk percutaneous coronary intervention · Chronic total occlusion

INTRODUCTION

Patients with stable complex coronary artery disease, e.g. three vessel disease, left main disease or one or more chronic total occlusions (CTO) who need revascularisation can be treated with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [1]. Usually these patients are discussed in a Heart Team where several risk stratification scores can be used to determine the risk of either form of revascularisation and make a well-considered decision about the most appropriate revascularization strategy [1]. Examples of these score are the Syntax, Syntax II, EURO-score and for CTO's the J-CTO score [1-4]. For many years, CABG was the treatment of choice for multi-vessel coronary artery disease, especially in diabetic patients [2,5]. In the last decade or so studies have shown that for noncomplex multi-vessel coronary artery disease, CABG and PCI have equal outcomes [3]. For complex multi-vessel disease however, guidelines still advise CABG over PCI [1].

Nonetheless, a considerate group of patients is not suitable for surgical revascularization. This group comprises patients with advanced age, multiple comorbidities, poor left ventricular function, earlier cardiothoracic surgery, or a combination of these factors. Until recently, treatment for these patients was either conservative or very high risk PCI with a high chance of peri-procedural mortality.

Complex high risk PCI can cause hemodynamic instability through a mechanism of procedure induced ischemia of the heart. This can cause acute heart failure and lead to detrimental outcome of elective percutaneous interventions.

Historically high risk PCI could be performed under mechanical circulatory support using the Intra Aortic Balloon Pump (IABP) but its use has seen a decline and downgrade in this regard as studies have failed to display a clear benefit of this form mechanical circulatory support [6-8]. Recently, high risk PCI under mechanical support, especially extracorporeal membrane oxygenation (ECMO) and Impella, has been established as a possible alternative for this group of high risk patients [9-12]. Initial reports on the use of VA-ECMO showed promising result in the treatment of cardiogenic shock due to myocardial infarction [13-15]. Patients with stable coronary artery disease have also been re-vascularised with mechanical support using VA-ECMO however data on outcome and procedural characteristics is scarce [9,10].

The current study aims at describing patient characteristics, procedural findings and outcome in the of VA-ECMO for mechanical circulatory support in elective high risk PCI.

METHODS

A two-centre retrospective study, including all patients that underwent elective very high risk PCI under ECMO for stable coronary artery disease in the past 18 months was performed. All patients were analysed for age, gender, previous medical history including diabetes, hypertension, peripheral artery disease, tobacco use, renal function where a eGFR<60 (stage 3) was considered an impaired renal function and the presence of a malignant proliferative disease [16].

Patients were selected by the attending interventional cardiologist who would also perform the ECMO assisted PCI. In none of the two participating centres another form of mechanical circulatory support capable of providing full mechanical circulatory support was available at the time other than VA-ECMO.

Cardiac status was analysed in regard to previous coronary artery disease, previous cardiac surgery which was divided into previous CABG and valvular surgery. Left ventricular function was assed using the available imaging modalities for each patients including trans thoracic echo and nuclear imaging when available. Left ventricular function was defined as good (>55%), mildly impaired (45-55%), moderately impaired (35-45%) or severely impaired (<35%) [17].

Procedural characteristics were analysed on number of target vessels that were re-vascularized in which all separate braches were counted as one separate vessel, achievement of complete revascularization, duration of ECMO run in hours, limb ischemia, post-procedural admission to the intensive care unit, thromboembolic complications, acute renal failure defined as a increase of >1 stage of renal failure above baseline, the need for haemodialysis, drop in haemoglobin post procedure, drop in thrombocytes count post procedure, neurological outcome where a cerebral performance category (CPC) scale of 1 and 2 was deemed a good neurological outcome, major adverse cardiovascular events (MACE) during admission, re-infarction and mortality at discharge [18].

For all patient the Syntax score I and II were calculated in order to asses coronary anatomy using the on-line calculator (<http://www.syntaxscore.com/calculator/>

[start.htm](#)) and for all patients the J-CTO score was also calculated when appropriate to assess lesion anatomy and complexity using the on-line J-CTO score sheet (<https://www.incathlab.com/files/COURSES/CTO/jcto-score-sheet.pdf>). Furthermore, for all patients the EURO-score I and II were calculated to assess the risk of peri-procedural mortality using the on-line calculator (<http://www.euroscore.org/calc.html>).

RESULTS

Baseline clinical characteristics

Between January 2017 and August 2018, a total of 14 patients underwent high risk PCI under prophylactic VA ECMO support in two hospitals in the Netherlands. The majority was male (92%) with a median age of 69 (53-83) years and with 50% of all patients being over 70 years old. A previous history of hypertension was present in 57%, diabetes mellitus in 21%, documented hypercholesterolemia in 29% and 43% was known to have peripheral artery disease. No patients had an active malignancy at the time of this study. Renal function was impaired (eGFR <60, stage ≥3) in 21%. Median haemoglobin levels prior to mechanical circulatory support was 8.2 (6.9-9.8) mmol/L and median thrombocyte count was 271 (166-594) mmol/L. (see table: 1)

Baseline characteristics (demographics, risk factors and biochemical values)

Age (years)	69 (53-83)
Male sex	92% (13/14)
Diabetes mellitus	21% (3/14)
Hypercholesterolemia	29% (4/14)
Hypertension	57% (8/14)
Peripheral arterial disease	43% (6/14)
Malignancy	0% (0/14)
Smoker	29% (4/14)
Impaired renal function (eGFR <60, stage ≥3)	21% (3/14)
Hemoglobin (mmol/L)	8.2 (6.9-9.8)
Thrombocytes (mmol/L)	271 (166-594)

Table 1 Baseline characteristics (demographics, risk factors and biochemical values)

Assessment of cardiac anatomy and function

Half of the patients had undergone previous coronary revascularisation in the form of CABG (36%) or PCI (14%). Left ventricular function was severely impaired (ejection fraction <30%) in most patients, 71% in total. In 21% the left ventricular ejection fraction was moderately impaired and in 7% mildly impaired. Main target vessel was left main in 71% of cases, LAD in 21% of cases, and RCA in 7%. Additional PCI of the non target vessel was performed in 71%. Target vessel was a CTO in 79% of the lesions. Median syntax I score was 34, median J-CTO score was 1 (0-3) (mean 1.55 SD 0.93). The median Syntax score was 34 (8-42.5), the median Syntax score II (PCI) was 53.5 (26.2-79.5) and the median Syntax score II (CABG) was 40.1 (16.2-57.2). (see table 2)

Baseline characteristics (cardiac history, anatomy and risk scores)

Prior coronary artery disease	57% (8/14)
Prior CABG	36% (5/14)
Previous valvular surgery	0% (0/14)
Number of target vessels	3 (1-4)
LM	71% (10/14)
LAD	57% (8/14)
RCA	64% (9/14)
RCx	57% (8/14)
CTO	79% (11/14)
LVEF >55%	0% (0/14)
LVEF 45%-55%	7% (1/14)
LVEF 35%-45%	21% (3/14)
LVEF <35%	71% (10/14)
EURO-score I	7.1 (3.6-34.1)
EURO-score II	3.2 (0.9-16.8)
Syntax score I	34 (8-42.5)
Syntax score II (PCI)	53.5 (26.2-79.5)
Syntax score II (CABG)	40.1 (16.2-57.2)
J-CTO score (median for all CTO lesions)	1 (0-3)

Table 2 Baseline characteristics (cardiac history, anatomy and risk scores) abbreviations: CABG: Coronary Artery Bypass Graft, LM: Left Main, LAD: Left Anterior Descending, RCA: Right Coronary Artery, RCx: Ramus Circumflex, CTO: Chronic Total Occlusion, LVEF: Left Ventricular Ejection Fraction.

Procedural characteristics

Prior to cannulation all patients were intubated and put on mechanical ventilation. Cannulation was femoral-femoral in all patients. None of the patients received

ante-grade perfusion of the leg during the procedure. All patients were cannulated by the attending cardiothoracic surgeon. Median ECMO run was 2.57 hours (1-4). All patients were decannulated at the catheterisation laboratory without complications by the cardiothoracic surgeon in an open procedure. None of the patients was admitted to the ICU after the procedure. All patients were transferred to the coronary care unit uneventfully.

Outcome

PCI was successful in 100% of patients with revascularization of all target and additional lesions. Survival to hospital discharge was 93%. One patient died during hospitalization due to refractory cardiac failure due to end stage heart failure which was not attributed to either the PCI or the VA-ECMO support by the attending physician. All other patients were discharged neurologically intact with a CPC of 1. ECMO related complications occurred in 14% of patients, with one patient developing a transient ischemic attack after the procedure and one patient developing a thrombus in the femoral vein used for cannulation several days after decannulation. One patient was re admitted after several months with a re-infarction. The median drop in haemoglobin was 2.0 (0.4-3.0) mmol/L and the median thrombocyte count drop was 82 (16-107) mmol/L. (*see table 3*)

Procedural characteristics and outcomes

Complete revascularisation	100% (14/14)
Duration of ECMO (hours)	3 (1-4)
Limb ischemia	0% (0/14)
Postprocedural admission to ICU	0% (0/14)
Thromboembolic complication	14% (2/14)
Renal insufficiency post-procedural (increase ≥ 1 stage above baseline)	21% (3/14)
Need for haemodialysis	0% (0/14)
Hemoglobin drop (mmol/L)	2.0 (0.4-3.0)
Thrombocytes drop (mmol/L)	82 (16-107)
MACE during admission	14% (2/14)
Re-infarction	7% (1/14)
Mortality at discharge	7% (1/14)

Table 3 Procedural characteristics and outcomes. Abbreviations: ECMO: Extra Corporal Membrane Oxygenation, ICU: Intensive Care Unit. MACE: Major Adverse Clinical Events

DISCUSSION

The present study reports patient and procedural characteristics and short term outcome of 14 patients who underwent high risk PCI for stable coronary artery disease under prophylactic VA ECMO support. Mortality and complications were low and despite the highly complex and mostly extensive coronary artery disease of these patients, PCI was successful in all cases.

PCI under ECMO in unstable patients with STEMI and/or cardiogenic shock has been reported as relatively safe with good outcome [9,13]. Literature about high risk PCI under ECMO support in stable patients, however, is scarce up to date. Tomasello et al. have shown excellent 6 month outcome in a prospective study with 12 patients with stable coronary artery disease, however complete revascularization was accomplished in only 50% of these patients [19]. The present retrospective study shows similar short term outcome however with complete revascularization in all patients. This might be explained by operator experience. A large portion of the patients had known CTO lesions and it is in this specific group of patients that results are operator dependent. Highly skilled and experienced operators as well as clear revascularization strategies heighten the chance of success.

Decision-making about whether or not a specific patient requires hemodynamic support during high risk PCI is not easy. Several factors are to be considered, such as left ventricular function, comorbidities, previous revascularizations, expected duration and complexity of PCI and expected ischemic burden during PCI. For example, PCI of unprotected left main, especially when accompanied with significant RCA disease - or even CTO, can lead to massive ischemia. Expected duration of balloon inflation and risk of complications such as dissection have to be estimated beforehand. Ostial LM lesions might lead to shorter duration of ischemia than complex Medina 1,1,1 distal LM lesions, for example. Coronary anatomy must be taken into account when selecting patients for ECMO assisted revascularization.

In the present study, patient characteristics and extent of coronary artery disease vary widely. This is reflected by the EURO I and II score and Syntax I and II score. This emphasizes the fact that high risk factors are partially incorporated in these risk stratification scores, but individual assessment and tailored decision making stays of the utmost importance.

Local expertise with VA-ECMO and availability of trained personnel is also a key factor applying this new technique. In the participating hospitals, the majority of patients have been referred from another hospital. This includes hospitals with cardiac interventional facilities but without expertise and availability of ECMO. In the future, increase of experience with this new strategy in hemodynamic support may increase favourable outcome and further reduce complications.

In prolonged ECMO therapy one of the major complications that can arise is leg ischemia due to occlusion of the femoral artery due to the arterial cannula. None of the patients in this study received ante-grade perfusion of the leg (so called Leg-ECMO or L-ECMO) yet none of the patients developed leg ischemia. This underlines the safety of the procedure in respect to distal limb perfusion.

Use of femoral- femoral VA-ECMO increases afterload for the left ventricle which is already being stressed by the PCI itself. This may cause a less optimal outcome. Simultaneous use of either the intra-aortic balloon pump (IABP) or Impella device has shown to improve outcome in cardiogenic shock and may be considered to reduce afterload [20]. However this does make the procedure more complex, the aorta crowded with several devices which may hamper catheter placement as well as femoral access being unavailable for catheter access. It will also greatly increase the costs. In this study, ECMO use alone has shown good outcome and no form of afterload reduction was used. Possibly the short duration of the use of ECMO as mechanical circulatory support may not necessitate afterload reduction.

All patients were cannulated and decannulated by the attending surgeon. This may increase safety of the procedure but it will also stretch resources that could be otherwise put to good use. As experience with large bore cannula's is increasing (e.g. TAVI) and closure devices are more and more being used successfully (e.g. Manta closure device®, Perclose closure device®) future procedures could be done fully percutaneous with surgical expertise on-site. This may increase patient comfort, reduce scarring and also reduce cost of the procedure.

In the application of VA-ECMO in the treatment of cardiogenic shock regardless of its cause age plays a major role in outcome. Patients of over 70 are generally excluded from this form of mechanical circulatory support as they do quite poorly in respect to outcome and complications [13]. In the study however half of the patients is over 70 years old with some being even over 80 years old and they

do very well. This might be an indication that this revascularization strategy with mechanical circulatory support is applicable to a much higher age group than ECMO support for cardiogenic shock is.

Next to prophylactic ECMO support, as was used in all patients in our present study, one might also consider provisional ECMO support. In this strategy, ECMO equipment and trained personnel will be readily available when needed, but only used when hemodynamic problems occur during the PCI procedure. An ECMO circuit will be present in the catheterisation laboratory, ready for use when needed. This might lead to less ECMO related complications, reduce cost but on the downside, this strategy might lead to a delay in the treatment of cardiogenic shock and may increase poor outcome when cardiogenic shock occurs. Literature on provisional ECMO support is virtually absent when compared to prophylactic ECMO support. In the future, randomized trials will be necessary to answer this question and determine the best strategy in revascularization with mechanical circulatory support.

Besides ECMO, other hemodynamic support systems are also available. This comprises Impella, IABP, Tandemheart and PulsCath. Of these devices, IABP gives a relatively low increase in cardiac output but has shown an improvement in outcome in the BCIS-1 trial [21]. In a prospective study by Kovacic et al, direct comparison in stable patients with 3 vessel disease and impaired left ventricular function shows that Impella is associated with a significant lower incidence of major adverse events in 90 days than IABP [11]. The advance of Impella is that it is less invasive. The disadvantage is that it only provides flow but does not ensure end organ perfusion. Furthermore the presence of the Impella device might hamper catheter placement in the aorta. ECMO is more invasive but will ensure end organ perfusion and will not disturb catheter placement in the aorta. Direct comparison of prophylactic Impella and VA-ECMO support in high risk PCI patients has not yet been performed to our knowledge. Local availability and expertise will largely guide the choice for which hemodynamic support device to use until there is a head to head comparison of these two techniques. Two other devices have been used for mechanical support during high risk PCI. The Tandemheart shows similar results to the Impella [22]. The PulsCath has demonstrated feasibility and safety in this group of patients and first reports on outcome show promising

results [23,24]. A future head to head comparison between the different support modalities must show which of these is most suited in this group of patients.

CONCLUSION:

Our study shows good feasibility and good short term outcome of prophylactic VA-ECMO supported PCI in stable high risk patients. Mortality and complication rate is low. It can be safely used to provide mechanical circulatory support in patients undergoing high risk PCI.

However, more prospective research and head to head comparison with other support devices is indicated to determine the best strategy in this vulnerable and high risk group of patients

No conflict of interest

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CHAPTER 9

IABP AND VA-ECMO IS ASSOCIATED WITH BETTER OUTCOME THAN VA- ECMO ALONE IN THE TREATMENT OF CARDIOGENIC SHOCK IN ST-ELEVATION MYOCARDIAL INFARCTION

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J Invasive Cardiol. 2021 May;33(5):E387-E392. Epub 2021 Apr 20 (*Original Article*)

OBJECTIVE

To assess if combining VA-ECMO with IABP improve outcome in STEMI over ECMO alone

BACKGROUND

VA-ECMO is an upcoming technique in the treatment of cardiogenic shock however it increases afterload. IABP in addition to VA-ECMO has been suggested to reduce afterload and increase survival.

METHODS

A multi-center in-hospital registry was kept on all patients undergoing VA-ECMO or VA-ECMO and IABP treatment for cardiogenic shock in STEMI.

RESULTS

Between 2015 and 2018, 18 patients with STEMI underwent VA-ECMO +/- IABP treatment for cardiogenic shock. The majority was male (78% (14/18)), median age of 59 (47-75) years. VA-ECMO+IABP was performed in 39% (7/18) and 61% (11/18) received VA-ECMO alone.

The ECMO+IABP group had more complex coronary anatomy with a higher number of patients with left main (LM) disease, LM + 3-vessel disease or 3-vessel disease (ECMO+IABP 86% vs ECMO alone 18% $p=0.03$). The SAVE score did not differ between the groups (ECMO alone -5.9 ± 2.4 vs ECMO+IABP -6.1 ± 2.6 $p=0.88$). The Syntax score was higher in the ECMO+IABP (ECMO alone 22 ± 14 vs ECMO+IABP 32 ± 13). In the total group, a SAVE score of -6 had a predicted survival of 25-35%.

Survival in the VA-ECMO+IABP group was 100% (7/7), survival in the VA-ECMO group was 55% (6/11) $p=0.035$. Good neurological outcome was achieved in more patients in the ECMO+IABP group (ECMO alone 45% vs ECMO+IABP 100% $p=0.037$).

CONCLUSION

In STEMI complicated by cardiogenic shock VA-ECMO combined with IABP leads to a lower observed mortality and higher observed good neurological outcome.

Abbreviations: VA-ECMO: Venous-arterial extra corporeal membrane oxygenation. IABP: intra-aortic balloon pump. STEMI ST: elevation myocardial infarction. pPCI: primary percutaneous intervention. BMI: body mass index. LVEF: left ventricular ejection fraction. CPC: cerebral performance categories. GFR: glomerular filtration rate

Keywords: Extra Corporeal Membrane Oxygenation, Intra-Aortic Balloon Pump, ST-elevation Myocardial Infarction

INTRODUCTION

ST elevation myocardial infarction (STEMI) can cause great hemodynamic instability due to acute heart failure and this is associated with poor outcome [1-3]. Traditionally intra-aortic balloon pump (IABP) was used for mechanical circulatory support but it has seen a decline in indication [4-8]. Venous-arterial extra corporeal membrane oxygenation (VA-EMCO) is an upcoming technique in the treatment of cardiogenic shock and the first results with this technique have shown promising results [9-12]. It has recently been introduced in the European Society of Cardiology guideline as a IIB indication for the treatment of cardiogenic shock [7, 13]. One of the drawbacks of VA-ECMO, however, is the increase of afterload for the left ventricle, especially in femoral-femoral percutaneous cannulation which is almost always the case in the setting of STEMI [9]. This increased afterload causes a higher oxygen consumption by the myocardium as well as increased left ventricular (LV)-pressures leading to injury upon insult of the already infarcted myocardium [14, 15]. Currently there is much debate if left ventricular unloading is necessary. The use of Impella (Abiomed) (the so-called Ecmella), left ventricular venting and concomitant ECMO and IABP use have all been suggested to achieve this, but evidence on the best strategy is lacking [14, 15]. There are no physiological studies in this area and currently only computer simulations are available to give insight in the role of left ventricular unloading during ECMO for cardiogenic shock [14]. Combination of VA-ECMO and IABP has been suggested to reduce afterload and increase survival but there is very little real world evidence [9].

METHODS

A multi-center in hospital registry was kept on all patients undergoing VA-ECMO or VA-ECMO and IABP treatment for cardiogenic shock in addition to primary

percutaneous intervention (pPCI) in STEMI in four different hospitals in Europe . All patients were analysed at baseline for age, sex, medical history, previous coronary artery disease, renal function, diabetes, body mass index (BMI), culprit lesion and target vessels, concomitant coronary artery disease, procedural characteristics including mode of cannulation, left ventricular ejection fraction (LVEF) before admission and after admission, patient related complications (e.g. bleeding at the cannula site, limb ischaemia), ECMO hardware related complications (e.g. pump failure, clot formation), length of ECMO treatment and length of stay on the ICU and in hospital, haemodynamic parameters including cardiac arrest, mortality and neurological outcome. Haematological parameter were also observed and included haemoglobin, haematocrit, platelet count and lactate levels.

Cardiogenic shock was defined using the Killip class system [3].

In order to assess coronary anatomy the SYNTAX score was calculated using the online SYNTAX score calculator (<http://www.syntaxscore.com/calculator/start.htm>) [16, 17]. The SAVE score, an Extracorporeal Life Support Organisation endorsed and validated score, was calculated to compare the predicted mortality with the actual mortality [18]. This was done by using the online SAVE score calculator (<http://www.save-score.com/>). Neurological outcome was defined using the Cerebral Performance Categories Scale (CPC) where a CPC score of 1 and 2 was considered good neurological outcome [19]. Renal function was assed using the glomerular filtration rate (eGFR) [20].

Statistical analysis was performed using chi-square and T-test to compare categorical and continuous variables.

Although according to Dutch law (Wet Medisch Wetenschappelijk Onderzoek met Mensen) no approval of a medical ethical committee is needed this was performed anyway which saw no ethical conflict regarding this study. All patients were treated using the Maquet Cardiohelp ®, an integrated pump system which can generate flows of up to 7 liter per minute and the Maquet CS300™ IABP which has a pulsatile volume of 50cc (Maquett/Gettinge group, Rastatt Germany).

RESULTS

Between 2015 and 2018, 18 patients with STEMI underwent VA-ECMO +/- IABP treatment for cardiogenic shock. The majority was male (78% (14/18)) with a

median age of 59 (47-75) years. VA-ECMO and IABP was performed in 39% (7/18) and 61% (11/18) received VA-ECMO alone. All patients were in Killip class IV prior to admission, were on vasopressors and inotropes and all patients received VA-ECMO support in the cathlab in addition to pPCI for STEMI. The patients in the IABP+ECMO group received IABP support in the catheterization laboratory prior to PCI. Both the patients in the ECMO alone group and the ECMO+IABP group received ECMO cannulation in the catheterization laboratory after PCI was performed. Indication for either procedure was made by the attending cardiologist. All patients underwent femoral-femoral cannulation.

Baseline

When comparing the ECMO alone group vs the ECMO+IABP group there was no significant difference in age (59 ± 7 vs 59 ± 7 $p=0.89$), diabetes (9% vs 43% $p=0.09$), known coronary artery disease (36% vs 0% $p=0.07$), hypertension (45% vs 14% $p=0.31$), known reduced LVEF (0% vs 0% $p=1.0$) or eGFR (56 ± 27 vs 59 ± 7 $p=0.88$). There was however a difference in BMI with patients in the ECMO alone group being significantly heavier (29.1 ± 3.8 vs 24.5 ± 1.98 $p=0.02$). In both groups a large number of patients suffered a cardiac arrest prior to or during admission (ECMO alone 91% vs ECMO+IABP 71% $p=0.52$). The SAVE score did not differ between the groups (ECMO alone -5.9 ± 2.4 vs ECMO+IABP -6.1 ± 2.6 $p=0.88$). A SAVE score of -6 has a predicted survival of 25-35%. (see table 1. Baseline)

	ECMO alone (n=11)	ECMO + IABP (n=7)	p Value
Age	59 ± 7	59 ± 11	0.98
Male Gender	9 (82%)	6 (86%)	0.99
BMI	29.1 ± 3.8	24.5 ± 1.98	0.02
Diabetes	1 (9%)	3 (43%)	0.09
CAD	4 (36%)	0	0.07
Hypertension	5 (45%)	1 (14%)	0.31
LVEF <55%	0	0	1.0
eGFR	56 ± 27	59 ± 7	0.88
Cardiac Arrest	10 (91%)	5 (71%)	0.52
SAVE score	-5.9 ± 2.4	-6.1 ± 2.6	0.84

Table 1 Baseline Characteristics

Abbreviations: BMI: Body Mass Index, CAD: Coronary Artery Disease, LVEF: Left Ventricular Ejection Fraction, eGFR: estimated Glomerular Filtration Rate

Coronary anatomy

There was a significant difference in the coronary anatomy between the two groups. The ECMO+IABP group tended to have more complex coronary anatomy when compared to the ECMO alone group. This is represented by a higher amount of either left main disease, left main plus three vessel disease or three vessel disease (ECMO alone 18% vs ECMO+IABP 86% $p=0.03$). This also represented by the higher SYNTAX score (ECMO alone 22 ± 14 vs ECMO+IABP 32 ± 13). (See table 2: *Coronary anatomy*)

	ECMO alone (n=11)	ECMO + IABP (n=7)	p Value
Culprit lesion			0.03
LAD	6 (54%)	0	
LCx	0	0	
RCA	3 (27%)	1 (14%)	
LM	2 (18%)	2 (29%)	
3-vessels PCI	0	2 (29%)	
LM+3 vessels disease	0	2 (29%)	
Syntax Score	22 ± 14	32 ± 13	

Table 2 Coronary anatomy

Abbreviations: PCI: Percutaneous Coronary Intervention, LAD: Left Anterior Descending artery, LCx: Left Circumflex artery, RCA: Right Coronary Artery, LM: Left Main

Outcome

Survival to discharge was 72% (13/18) in the overall cohort. Survival to discharge in the ECMO+IABP group was significantly higher with 100% (7/7) when compared to the ECMO alone group where survival to discharge was 55% (6/11) $p=0.035$. A greater number of patients in the ECMO+IABP group have reached the one year survival point in the follow up period (ECMO alone 36% vs ECMO+IABP 86% $p=0.04$). Of the patients that died, most died on ECMO and in the hospital (80% (4/5)). One of the patients in the ECMO alone group suffered major neurological impairment due to prolonged resuscitation and died after discharge due to aspiration pneumonia. Good neurological outcome was achieved in more patients in the ECMO+IABP group (ECMO alone 45% vs ECMO+IABP 100% $p=0.037$). However if this is calculated for the survivors only, leaving out deceased patients

this difference was not significant (ECMO alone 83% vs ECMO+IABP 100% $p=0.26$). Complete revascularization was achieved equally in the two groups (82% vs 86% $p=0.99$). LVEF did not differ between the two groups, with only a small amount of patients having a preserved ejection fraction after treatment (9% vs 14% $p=0.34$). (See table 3: Outcome)

	ECMO alone (n=11)	ECMO + IABP (n=7)	p Value
Survival total	6 (55%)	7 (100%)	0.035
Survival at 1-year	4 (36%) [^]	6 (86%)	0.04
Follow-up			
In-hospital Death	4 (36%)	0	0.12
Death on ECMO	4 (36%)	0	0.12
Good Neurological Outcome (CPC 1-2)*	5 (45%)	7 (100%)	0.037
Complete revascularization	9 (82%)	6 (86%)	0.99
LVEF post procedure			0.34
Preserved (>50%)	1 (9%)	1 (14%)	
Moderate Dysfunction (35-40%)	3 (27%)	4 (57%)	
Severe Dysfunction (<35%)	7 (64%)	2 (29%)	

Table 3 Outcome

*If calculated for survivors alone $p=0.26$, [^]One patient died during follow up period after reaching 1 year survival point.

Length of stay and laboratory findings

With regard to length of ECMO treatment (4.9 ± 2.8 vs 4.5 ± 2.1 $p=0.77$), days spent in the Intensive care unit (21.5 ± 23.8 vs 17.3 ± 12.6 $p=0.70$) or length of hospitalisation there was no difference between the ECMO alone group and the ECMO+IABP group. There was also no difference in the haematocrit (0.39 ± 0.05 vs 0.45 ± 0.06 $p=0.18$), platelet count ($205 \pm 53 \times 10^9/L$ vs $267 \pm 10 \times 10^9/L$ $p=0.14$), Ph (7.14 ± 0.16 mmol/L vs 7.31 ± 0.11 mmol/L $p=0.42$) and lactate levels (8.57 ± 5.5 mmol/L vs 3.7 ± 1.7 mmol/L $p=0.06$) post procedurally. There is was however a higher haemoglobin count in the ECMO alone group (8.2 ± 1.1 mmol/L vs 10.1 ± 1.5 mmol/L $p=0.009$). (See Table 4: Length of stay and laboratory findings)

	ECMO alone (n=11)	ECMO + IABP (n=7)	p Value
Days on ECMO	4.9±2.8	4.5±2.1	0.77
Days in ICU	21.5±23.8	17.3±12.6	0.70
Days in hospital	27.3±29.2	34.3±26.9	0.65
Haemoglobin (mmol/L)	8.2±1.1	10.1±1.5	0.009
Haematocrit	0.39±0.05	0.45±0.06	0.18
Platelets (x109/L)	205±53	267±10	0.14
pH	7.14±0.16	7.31±0.11	0.42
Lactate (mmol/L)	8.57±5.5	3.7±1.7	0.06

Table 4 Length of stay and laboratory findings.

Safety aspects

From a safety perspective there was no statistical difference between the two groups. Thromboembolic complications occurred in 27% of the ECMO alone group and one patient in that group also had an infected cannula. In the ECMO+IABP group there were no observed thromboembolic complications. However this was not statistically significant ($p=0.55$). Haemorrhagic complications occurred in 28% in the ECMO alone group, compared to 43% in the ECMO+IABP group ($p=0.28$). In neither of the groups was there any ECMO hardware malfunction observed. (see table 5: Safety aspects)

	ECMO alone (n=11)	ECMO + IABP (n=7)	p Value
Complications			0.55
Embolism peripheral	0	0	
Embolism central	0	0	
Embolism air	0	0	
Leg-ischemia	3(27%)	0	
Infection	1(9%)	0	
Bleeding	2(18%)	3(43%)	0.28
Surgical Site	2(18%)	2(29%)	
Cannula Site	0	1(14%)	
Cerebral bleeding	0	0	
Hardware failure	0	0	1.0

Table 5 Safety Aspects

DISCUSSION

This study suggests that the combination of IABP and ECMO is associated with better outcome than ECMO alone in the treatment of cardiogenic shock.

The difference in outcome between the two groups could be a result of the LV unloading by the IABP. As all other organs are perfused by the ECMO circuit the IABP reduces the afterload for the LV and this may reduce infarct size. There is however no difference in the post procedural EF in this study. It could also improve survival through a mechanism of increased coronary perfusion with oxygenated blood from the ECMO circuit. In the absence of an IABP blood ejected from the heart goes through the pulmonary circulation. In the case of cardiogenic shock there may be overt pulmonary congestion causing desaturated blood being ejected from the LV into the coronary arteries. This can cause a harlequin effect and inadequate coronary perfusion. The use of an IABP may lead to better dispersion of oxygen rich blood through the aorta facilitating adequate coronary artery perfusion. This same mechanism may apply to cerebral perfusion. Concomitant IABP in addition to ECMO may increase cerebral perfusion and increase a good neurological outcome. Although no statistical proof-of-principle in this study all patients who received this technique had good neurological outcome.

The Syntax score in the ECMO+IABP group is higher than in the ECMO alone group. A higher syntax score aids in decision making between either PCI or coronary artery bypass surgery. In the case of STEMI, especially when there is profound cardiogenic shock, primary PCI is the treatment of choice. The more complex anatomy in the ECMO+IABP group did not lead to either worse outcome nor did it lead to less complete revascularization. This may be explained through the mechanism that while a patient is on ECMO there is adequate hemodynamic support which may facilitate a more complex coronary intervention. A higher SYNTAX score is also a predictor for major adverse cardiovascular and cerebral events with a cutoff of 34. Yet in this study there is no observed difference between the two groups in regard to safety outcome. A possible explanation may be that concomitant use of ECMO and IABP may lead to better overall hemodynamics and so prevents complications.

The predicted mortality as assessed by the SAVE score in this study was equally high in both groups. All patients were in Killip class 4. Both these findings suggest a

low predicted survival rate of between 15-35%. Yet in both groups actual survival is much higher. This may be an indication that both techniques may be successfully used in the treatment of cardiogenic shock in STEMI. A large number of patients suffered a cardiac arrest prior to receiving mechanical circulatory support. Yet outcome is still good in the overall group and more specifically in the ECMO+IABP group. This underlines that after the finding that routine IABP implantation alone did not improve survival, ECMO and concomitant IABP implantation may be the way forward in treating cardiogenic shock associated with STEMI.

The form of LV unloading in this study is IABP. As mentioned before, other strategies are also possible. The advantage of using the IABP is that its use and availability is wide spread and it is therefore readily available in many hospitals around the world. It is also relatively cheap compared to, for example, Impella. Also, Impella is not reimbursed in various countries making this a costly approach to LV unloading. Furthermore IABP is less invasive, specifically when compared to surgical LV venting, and can even be used through the ECMO cannula with the use of a Y-connector. It can be used if there is severe aortic stenosis and it is difficult to pass the aortic valve.

The length of hospitalization and treatment did not differ between the groups. Yet time spent in hospital was considerable for both groups of nearly a month. This implicates that these high complex patients with serious acute life threatening disease should ideally be treated in dedicated tertiary care centers with not only expertise on ECMO, IABP and PCI but also in patient and family guidance as these treatments can be very traumatizing for patients as well as their next of kin. In regard to the laboratory findings there is a lower Hb level in the ECMO alone group. ECMO can cause haemolysis and reduce Hb which could explain this finding. It was however not observed in the ECMO+IABP group. There is a trend towards lower lactate levels in the ECMO+IABP group which could be explained by the better hemodynamic support of this combined form of mechanical circulatory support. However, it could also be that the patients in the ECMO+IABP group were just less sick.

The complication rate is relatively low in this group. Limb ischemia is a known complication and can be prevented by several things. First, cannulation should ideally be performed in both groins. Where the arterial and venous cannula are each at a different groin preventing simultaneous decreased perfusion of the leg

due to arterial blockage and stasis of the blood due to venous occlusion by the cannula. Second, antegrade perfusion of the leg should be routinely performed to insure perfusion of the leg. Distance between antegrade and retrograde arterial cannula's should be as short as possible to prevent clot formation at this site.

Recently a meta analysis was published by Russo et al demonstrating a benefit of LV unloading for the outcome in the treatment of cardiogenic shock. This study showed a benefit of all forms of unloading. However it did not discern between the different etiologies of cardiogenic shock. Our studies corroborates this data but adds to this that in the specific case of STEMI, LV unloading using the IABP in the setting of VA-ECMO support is beneficial [21].

LIMITATIONS

There are several limitations to this study. It is an observational study with a limited number of patients. Bias and unknown confounders may have caused the lower observed mortality in the ECMO + IABP group. However, the lower mortality was observed even with the patients in the ECMO + IABP group having more severe coronary artery disease. There is also operator bias in selecting patients eligible for mechanical circulatory support. Only comparative statistics were used in this study making it difficult to establish causality

However, to our knowledge this is the first study demonstrating a possible survival benefit of ECMO with concomitant IABP in the setting of STEMI complicated by cardiogenic shock. Future studies are required to establish the benefit of this technique in this group of patients, preferably in a randomized controlled design. Interpretation of this study must be done with caution. It is hypothesis generating but it is difficult to apply in daily practice. Hopefully it will be possible to perform a randomized controlled trial in the future to establish a true survival benefit.

CONCLUSION

In this small observational study it is shown that VA-ECMO might be able to improve survival in patients with cardiogenic shock due to STEMI even when in cardiac arrest. This observation suggests that VA-ECMO in combination with IABP is associated with higher survival than VA-ECMO alone and is also associated with good neurological outcome. It is also associated with better outcome in

more complex coronary artery anatomy. However, the data presented is purely exploratory and warrants cautiousness in its interpretation. Physiological studies are required to prove the effectiveness of this technique and to facilitate a future randomized controlled trial.

No conflict of interest.

There has been no funding whatsoever in regard to this study, it's author or this manuscript. There is no relationship to the industry or any of the products named in this paper by any of the authors.

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CHAPTER 10

FUTURE PERSPECTIVES EN NEDERLANDSE SAMENVATTING VAN HET PROEFSCHRIFT

FUTURE PERSPECTIVES

This thesis has demonstrated that the incidence of infective endocarditis is rising. Despite great advances in imaging modalities, antibiotic treatment and surgical technique we have not been able to reduce mortality in this devastating disease and it still ranks amongst the most lethal infectious diseases in the western world. Future studies should focus on early detection and novel imaging modalities. An example of this is the use of Positron Emission Tomography (PET). The PET scan is increasingly being used to detect prosthetic valve endocarditis at an early stage. Hopefully this will develop further and as such will influence prognosis through a mechanism of early detection of possible complications and prompt surgical intervention.

The ever ongoing debate on whether chemoprophylaxis is useful in preventing infective endocarditis should also be settled. However, as this debate has been going on for many years already I greatly fear it might never be completely settled at all. The evidence in favor of chemoprophylaxis is robust. The evidence against chemoprophylaxis is robust as well. Possibly a future randomized controlled trial will bring forth enough evidence to make sound recommendations on this subject.

Infectious endocarditis has a very high mortality, even more so in the population affected in general hospitals. The reasons for this phenomenon are unclear. As most studies concentrate on tertiary centers, general hospitals are underrepresented in previous literature and there is selection bias. This may be the key in improving outcome; perform more studies in general hospitals in an all-comer real world population.

The treatment of cardiogenic shock is difficult. VA-ECMO may be a solution for this problem. A randomized controlled trial in a similar fashion as the IABP-SHOCK trial may provide answers. In facilitating high risk percutaneous intervention it can be used safely and effectively. A head to head comparison with other mechanical circulatory support devices, such as the Impella device, may determine the best strategy. Future studies should concentrate on drawing conclusions from making such a comparison.

Another issue that needs to be addressed is how to reduce afterload for the left ventricle when patients are on VA-ECMO. Current strategies are the concomitant

use of ECMO and Impella or ECMO and IABP. Both seem to influence outcome in a positive way. Animal studies, preferably with LV pressure volume loops should (could?) confirm the best strategy. Future human studies should confirm the animal results and provide an answer to the question: what is the best strategy in mechanical circulatory support?

However we must not forget that it is not all roses when it comes to ECMO as a means for circulatory support. The outcome in patients who receive ECMO support after cardiac surgery for infective endocarditis is disappointing, to put it mildly. This echoes the result of other studies in this thesis that despite medical progress we still struggle to treat this devastating infectious disease.

In all, this thesis answers some question but raises more. It is my great desire to answer these questions in the future.

NEDERLANDS SAMENVATTING

Het voor u liggende proefschrift getiteld “Intra-cardiale infecties, coronaire interventies en mechanische circulatoire ondersteuning” handelt over de volgende zaken:

In het eerste hoofdstuk wordt de opbouw van het proefschrift uitgelegd. Daarna wordt in het tweede hoofdstuk van het proefschrift beschreven hoe de uitkomst is van patiënten met infectieuze endocarditis die zich in een algemeen ziekenhuis presenteren. Het meeste onderzoek naar endocarditis vindt plaats in tertiaire centra en dat kan de uitkomst in deze groep patiënten vertekenen. We zien dat patiënten in algemene ziekenhuizen die zich presenteren een veel hogere mortaliteit hebben dan vergelijkende studies in tertiaire ziekenhuizen. Ook zien we dat vrouwelijke patiënten, patiënten met een kunstklep en oudere patiënten het aanzienlijk slechter doen. Daarnaast toont deze studie aan dat een infectieuze endocarditis met een *Staphylococcus Aureus* bacterie een gecompliceerder beloop kent dan endocarditis veroorzaakt door andere bacteriën.

Het derde hoofdstuk is opgedeeld in twee delen. In het eerste deel wordt aangetoond dat sinds de versoepelingen van een endocarditis profylaxe richtlijnen in 2009 we een toename zien van het aantal gevallen van infectieuze endocarditis.

Deze toename is meer dan op de eerdere historische trend te verwachten was en zou dus verband kunnen houden met de versoepeling van die eerder genoemde profylaxe richtlijnen. Daarnaast zien we gelijktijdig met deze versoepeling een toename van het aantal Streptokok remedieerde endocarditis en dit is juist de bacterie waarvoor de profylaxe wordt gegeven. In het tweede deel van hoofdstuk drie wordt een pleidooi gehouden voor het opnieuw overwegen van de indicatie van en profylaxe om zo de stijging van het aantal gevallen van endocarditis tot staan te brengen.

In hoofdstuk vier wordt een nieuwe strategie beschreven om patiënten te behandelen met een pacemaker infectie die gelijktijdig van deze pacemaker afhankelijk zijn. Bij deze patiënten wordt in een sessie de geïnfecteerde endovasculaire pacemaker verwijderd waarna er een epicardiale pacemaker draad op het hart wordt geplaatst om zo de pacing te borgen. De peri-procedurele complicaties zijn laag en deze techniek blijkt effectief, veilig en toepasbaar te zijn.

In hoofdstuk vijf wordt een studie beschreven naar de incidentie en uitkomst van endocarditis van de aortklepprothese na trans-katheter aortaklep vervanging. Deze studie, uitgevoerd in negen ziekenhuizen laat zien dat hoewel de incidentie laag is de uitkomst in deze groep patiënten slecht is.

Hoofdstuk zes is wederom opgedeeld in twee delen. In het eerste deel wordt een groep patiënten beschreven die infectieuze endocarditis hebben en ten gevolgen van ernstig acuut hartfalen behandeld moeten worden met extra corporele membraan oxygenatie. De uitkomst in deze groep patiënten is slecht en het is de vraag of deze nieuwe techniek toepassing heeft in deze specifieke populatie. Het tweede deel van hoofdstuk zes laat een patiënt zien waarin door middel van trans thoracale echo een repositie van de veno veneuze extra corporele membraan oxygenatie canule heeft plaatsgevonden met verbetering van de klinische conditie van de patiënt.

Hoofdstuk zeven beschrijft hoe veno-arteriele extra corporele membraan oxygenatie gebruikt kan worden bij patiënten in cardiogene shock tijdens een ST-elevatie myocard infarct. Door het toepassen van deze techniek kan een hogere overleving dan voorspeld worden bereikt, zelf als patiënten in een reanimatie setting komen. Mogelijk is de beschreven techniek en strategie een alternatief voor de intra-aortale ballon pomp die inmiddels een groot deel van zijn indicatie is kwijt geraakt in de behandeling van cardiogene shock.

Hoofdstuk 8 beschrijft het gebruik van veno-arteriele extra corporele membraan oxygenatie als ondersteuning van het hart gedurende electieve hoog risico percutane interventies aan de coronair arteriën. De uitkomst in deze groep patiënten is goed en deze strategie van mechanische ondersteuning is veilig en effectief.

Het laatste hoofdstuk behandelt het gebruik van veno-arteriele extra corporele membraan oxygenatie in combinatie met een intra-aortale ballon pomp en vergelijking met veno-arteriele extra corporele membraan oxygenatie alleen in de behandeling van cardiogene shock bij ST-elevatie myocardinfarct. Omdat veno-arteriele extra corporele membraan oxygenatie de afterload van de linker kamer verhoogd zou de dit uitkomst negatief kunnen beïnvloeden bij deze groep patiënten. Als er gelijktijdig een intra-aortale ballon pomp gebuikt wordt verlaagt dit de afterload van de linker kamer en zou dit de uitkomst positief kunnen beïnvloeden. Dit blijkt dan ook uit de laatste studie van dit proefschrift.

CHAPTER 11

IMPACT PARAGRAPH

In this section the impact of the research describe in this thesis will be discussed. It will also include a summary of its main findings for the non-medical reader, the implications for patients and medical professionals and the contribution of this thesis to the scientific field.

SUMMARY OF THE FINDINGS FOR THE NON-MEDICAL READER

Infective endocarditis is a disease where part of the inner side of the heart is infected with bacteria. This can be a native structure (like a heart valve) but it can also be prosthetic material (like a pacemaker lead or a prosthetic heart valve). It is a dangerous disease with high mortality, as demonstrated in this thesis. One of the ways infective endocarditis can be prevented is by administering antibiotics prior to certain procedures (like dental procedures) when you have an abnormal heart valve. In 2009 the indication for this prophylaxis was changed. The result was that less patients were eligible for this prophylaxis. Since that time there has been an increase in infective endocarditis above the expected historical trend.

It is possible for patients to not have a heart rhythm of their own. If this is the case they need a pacemaker. This pacemaker is usually placed in the venous system on the right side of the heart. A possible complication of having a pacemaker is that it gets infected with a bacteria. In that case the pacemaker will have to be removed. However, if a patient has no underlying heart rhythm they cannot live without a pacemaker. If you place a pacemaker on the outside of the heart and the remove the infected pacemaker you will ensure pacing of the heart. This technique is safe and feasible.

Infective endocarditis can also affect prosthetic heart valves that have been implanted via a catheter through the arteries in the groin. This is a rare complication and it is rarer than endocarditis of a surgically implanted heart valve. Yet when you do attract it, outcome is poor.

Patient who contract endocarditis can be very sick. They can be so sick that their heart is no longer possible to keep them alive. A possible treatment for this is veno-arterial extra corporeal membrane oxygenation (VA-ECMO). This is a kind

of heart lung machine for prolonged use. It can be used in patients with infective endocarditis, however, outcome is poor.

The same VA-ECMO technique can be used in patients who suffer from an acute heart attack. These patients can develop acute heart failure due to occlusion of one of the arteries of the heart. They can even develop cardiac arrest. VA-ECMO can improve survival in these patients and ensure adequate blood flow to the organs when the heart is no longer able to do so.

If patients need to undergo an elective procedure in which a stent is placed in one of the arteries of the heart and they have poor contractility of the heart muscle they can develop acute heart failure during the procedure. The use of VA-ECMO prior to this procedure in a prophylactic fashion is safe and can be effectively used to prevent acute heart failure and ensure organ perfusion during these procedures. Finally we demonstrate that the combined use of VA-ECMO and the intra-aortic balloon pump improves survival in acute myocardial infarction when compared to the use of VA-ECMO alone.

SCIENTIFIC IMPACT AND IMPACT FOR PATIENTS

This thesis has made it clear that mortality from infective endocarditis is high and that early referral may improve survival. It also demonstrates that there may be need to expand the indication for chemoprophylaxis in preventing infective endocarditis. Patients who are pacemaker dependent and have an infected device now have a safe extraction and re-implantation strategy which ensures permanent pacing. Patients who have undergone a transcatheter aortic valve implantation are now assured that the risk of infective endocarditis is low. However, if they do contract it outcome is poor.

Patients who are in cardiogenic shock, especially when suffering from ST-elevation myocardial infarction can be safely treated with VA-ECMO. This can improve survival and could be considered by interventional cardiologists when encountering these patients in clinical practice. They could also consider using VA-ECMO when they perform high risk percutaneous interventions in order to prevent cardiogenic shock. However, if prolonged use of VA-ECMO is indicated in patients who have developed cardiogenic shock due to ST-elevation myocardial infarction afterload reduction with the intra-aortic balloon pump as an afterload device is advisable.

DISSEMINATION OF KNOWLEDGE.

In order to share our knowledge presented in this thesis we have published all research in this thesis in peer reviewed national and international scientific journals. In addition to these scientific publications we have presented all original studies at national and international congresses including the European Society of Cardiology congress, American Heart Association/American College of Cardiologists scientific sessions, Cardiovascular Research Foundation Trans Catheter Therapeutics, EuroPCR congress and Euro-Extra Corporeal Life Support Organization congress as well as during the congress of the Nederlandse Vereniging voor Cardiologie.

CHAPTER 12

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CHAPTER 13

DANKWOORD

DANKWOORD

Zeer geachte Prof. Dr. J.M. ten Berg, beste Jur. Het eerste dankwoord is voor jou als mijn promotor, opleider en begeleider tijdens het vervaardigen van dit proefschrift. Ik wil je danken voor de mogelijkheid die je me hebt gegeven om mezelf te ontwikkelen tot cardioloog en hoe je me hebt aangespoord in het doen van wetenschappelijk onderzoek.

Zeer geachte Prof. Dr. A. van't Hof, beste Arnoud. Dank voor de mogelijkheid om bij jou te promoveren. Het is grote eer om mijn proefschrift te mogen verdedigen bij zo'n vooraanstaand cardioloog.

To the esteemed dr. C. Zivelonghi. Dear Carlo! How lucky is a man who has a friend who shares not only his professional interest but also his personal ones. You are by far one of the best cardiologists I have ever encountered and I am humbled to to stand in your shadow. May the force be with you!

Zeer geachte drs. V.L. Winia. Lieve Viv. De enige die twee keer in dit proefschrift wordt bedankt en niet zonder reden. Je substantiële bijdragen aan mijn werk hebben geleid tot mijn eerste stappen in het vervaardigen van dit proefschrift en dat terwijl je zwanger was van Annie. Dank. Zonder jou was dat nooit gelukt.

Ik wil graag alle cardiologen van het Medisch Centrum Leeuwarden bedanken voor de mogelijkheid die ik heb gekregen om mijzelf te ontwikkelen als interventie cardioloog. Nadrukkelijk wil ik Sjoerd Hofma, Krischan Sjauw, Jan Brouwer, Kees Jan de Vries, Tessel Vossenbergh, Ad van Boven en Joost Haeck bedanken voor de moeite die ze hebben genomen om mij te leren dotteren.

Mijn dank gaat uit naar de arts-assistenten van de cardiologie van het Antonius Ziekenhuis te Nieuwegein. Zonder alle lol, steun en vrijdagmiddagborrels zou de assistententijd een stuk minder mooi zijn.

De cardiologen van het St. Antonius ziekenhuis en het Gelre Ziekenhuis wil ik danken voor de moeite die ze hebben genomen om mij op te leiden.

To all the staff of the Royal Brompton NHS trust I would like to express my deepest gratitude for not only educating me in the field of ICU and ECMO but also showing me how a center can strive for excellence. In particular I would like to thank dr. Jeremy Cordingley for accepting my application and teaching me and Prof. Dr.

Suzanna Price for showing me how to be brilliant and also giving me some of the best advise ever.

Aan de cardiologen van het Kennemer Gasthuis: Bob van Vlies, Raymond Tukkie, Gerard Verdel, Maarten Janssen en Mitran Keijzers: Dank dat ik bij jullie mijn eerste stappen in de wereld van de cardiologie heb kunnen zetten. Met nadruk wil ik hierin Jon Funke Kupper bedanken voor je steun en wijze woorden en dat je mij hebt laten zien hoe een cardioloog hoort te zijn.

Aan Prof. dr. Marja Boermeester. Niet elke les wordt geleerd op het moment dat die onderwezen wordt. Dank voor de les, ik heb het eindelijke begrepen.

Aan de cardiologen en assistenten van het Leids Universitair Medisch Centrum wil ik mijn dank uitspreken voor het in hun midden opnemen van deze aan lager wal geraakte interventie cardioloog en de kansen die ze mij bieden om mijn carrière een vervolg te geven.

Aan de stad Amsterdam wil ik mijn onnoemlijke dank uitspreken daar zij de mooiste stad ter wereld is en mijn liefde voor haar nog immer brandt. Ik prijs mij gelukkig een Amsterdammer te zijn.

To Otto Berchem. A cyclist may become an artist but is ever a cyclist.

Mijn dank gaat uit naar mijn peers binnen de interventie cardiologie: Roel Snijder, Fatih Arslan, Bastiaan Zwart en Erik-Jan Bakker. Ik hoop nog vele jaren met jullie samen te mogen werken.

Zeer geachte dr. M. Klomp, lieve Go! Wat is het toch fijn dat een van mijn co-auteurs ook een van mijn beste vriendinnen is. Dank voor je hulp bij mijn eerste stappen op weg naar voltooiing van dit proefschrift. En dank voor de dagen bij de fontein, in het park, op congres en in Amsterdam. Dat onze kinderen nog maar vaak samen mogen spelen.

Lieve Jennifer. Dank voor al je hulp bij het aanvangen van dit proefschrift. Ik hoop dat we nog vele rondjes in Artis mogen delen.

Aan zij die zijn geslachtofferd op het aambeeld van mijn ego en ambitie: Ruurt Staverman en Floris Hekster. Onze wegen hebben zich gescheiden maar jullie zijn niet vergeten.

Lieve Laetitia en Astrid. Dank. Voor alle rondjes in Artis en dat we ons eigen feestje maken.

Lieve Sophie en Rene, dank voor jullie warmte en gezelligheid.

Lieve Myrthe, dank voor alle avonden bij het vuur en alle steun bij deze onderneming. En dank voor alle boks trainingen, helemaal toen het wat minder ging.

Lieve Tijmen, dank voor alle relativering en steun. En alle chinezen met de witte pet om stoom af te blazen.

Lieve moeder, dank voor het op de wereld zetten en alle andere dingen die je voor me hebt gedaan.

Lieve vader, eindelijk ook doctor. De tweede in de familie. Dank voor al je steun.

Mijn liefste Julia en Anna, jullie zijn het licht in mijn bestaan. Elke dag met jullie is een feestje en ik kan geen woorden vinden om te beschrijven hoe veel ik van jullie hou. Ik kijk er naar uit om jullie samen op te zien groeien. Mijn liefste derde kleintje. Wat kijk ik uit naar je komst. Eindelijk is ons gezin compleet.

Lieve Vivian. De laatste woorden van dit proefschrift zijn voor jou. Wat heb je toch met mij te stellen. En wat ben ik je dankbaar voor alles wat je me geeft. Ik hou van je met heel mijn hart.

CHAPTER 14

CURRICULUM VITAE

Floris Stefan van den Brink werd geboren op 4 september 1978 te Apeldoorn als kind van dr. ing Steven van den Brink en Mary den Haring. Na het behalen van zijn VWO diploma ging hij eerst medisch biologie en kunstgeschiedenis studeren aan de Universiteit van Amsterdam om een jaar later de overstap naar Geneeskunde te maken. Tijdens zijn studie roeide en fietste hij fanatiek. Na het behalen van zijn artsentitel werkte hij in verschillende ziekenhuizen voordat hij in 2012 aan de opleiding cardiologie begon (opleider Prof. dr. J. ten Berg). De opleiding ving aan met een B jaar bij het Gelre Ziekenhuis te Apeldoorn (opleider dr. B. Groenemeijer) en werd gevolgd door de vooropleiding interne geneeskunde bij het Kennemer gasthuis te Haarlem (opleider prof. Dr. R. Ten Kate en dr. P. De Ronde). Gedurende zijn opleiding volgde hij een fellowship aan the Royal Brompton and Harefield NHS trust te London en specialiseerde zich daar in het gebruik van extra-corporele membraan oxygenatie, een vorm van mechanische circulatoire ondersteuning. Tevens startte hij gedurende deze tijd op eigen initiatief met het onderzoek dat uiteindelijk tot deze promotie heeft geleid. Na zijn opleiding tot cardioloog werkte hij kortstondig in het Rode Kruis Ziekenhuis te Beverwijk. Medio 2018 startte hij met zijn fellowship interventie cardiologie bij het Medisch Centrum Leeuwarden te Leeuwarden (opleider dr. S.H. Hofma) welke hij in mei 2020 afrondde. Na het afronden van dit fellowship is hij nog 6 maanden interventie cardioloog geweest in het MC. Momenteel werkt hij als cardioloog in het Leids Universitair Medisch Centrum waar hij in 2023 zal beginnen met de opleiding tot Intensivist.

Hij is getrouwd met Vivian Winia, anesthesioloog-intensivist en heeft twee prachtige dochters; Julia en Anna. Een derde kind is op komst. Ze wonen in Amsterdam.