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## Exploring new PET/CT capabilities and machine learning for improving the diagnosis of infective endocarditis

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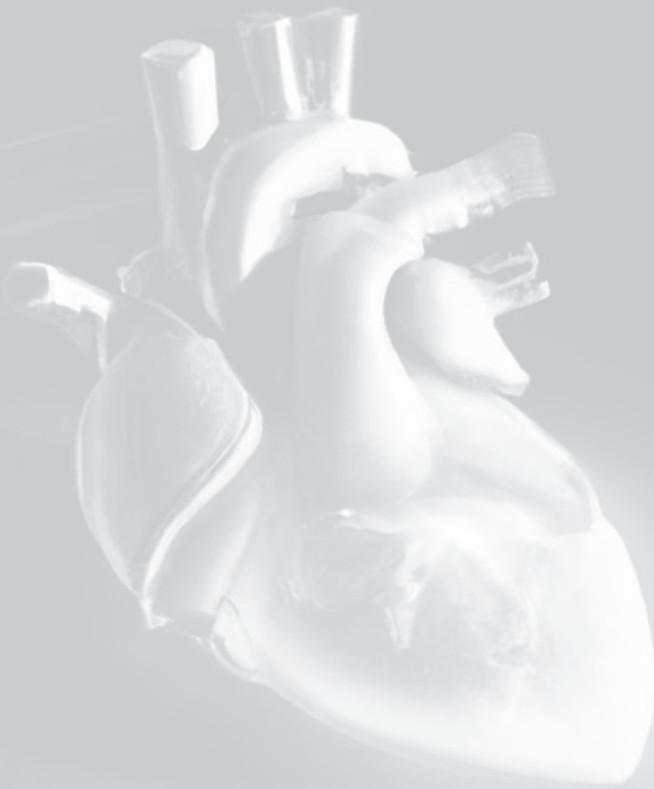
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# CHAPTER 8

## Discussion





Endocarditis is a complex disease that is difficult to diagnose and treat. Despite major advances in diagnostics and treatment for endocarditis, patients still face a severe condition with major complications and a high mortality rate. Unfortunately, the high mortality risk associated with the disease has been largely unchanged for decades. Both mainstays of the diagnosis, medical microbiology and medical imaging provide major opportunities for improvement, both technically and clinically. Since the chance of a positive patient outcome depends to a large extent on the speed at which effective treatment can be started, a fast and accurate diagnosis is of crucial importance

The objective of the studies presented in this thesis therefore was to enhance the speed and accuracy of the diagnosis of infective endocarditis. We focused on using new [<sup>18</sup>F]FDG PET/CT imaging techniques and potential new indicators for endocarditis when evaluating [<sup>18</sup>F]FDG PET/CT scans. Furthermore, we focused on a specific patient population: those with suspected LVAD infections, and evaluated a potential new use for machine learning to predict infective endocarditis. The following discussion paragraphs are a discussion about the different studies of the current thesis: where they fit in the literature, their implications for clinical practice, and future perspectives based on our findings.

## Using [<sup>18</sup>F]FDG PET/CT effectively

[<sup>18</sup>F]FDG PET/CT is increasingly applied in the diagnostic work-up in patients suspected of infective endocarditis and it is a powerful diagnostic tool for establishing the diagnosis. It can be used for the evaluation of intracardiac lesions and disseminated disease. This way, it provides clinicians information that is crucial for both diagnosis and treatment of endocarditis. This is underlined by studies that have shown how [<sup>18</sup>F]FDG PET/CT affected diagnosis and treatment decisions in 10 to 35% of cases (35,36). While the technique has shown its clinical value, two specific considerations should be kept in mind. Firstly, as described in **Chapter 2**, [<sup>18</sup>F]FDG PET/CT requires standardisation of patient preparation, scan acquisition & evaluation to achieve optimal results (21). Two specific PET procedure interventions should be highlighted because of their importance: the HFLC diet combined with fasting, the evaluation of NAC images and the use of metal artifact reduction strategies (if available) whenever prosthetic materials are located in or adjacent to the heart. Moreover, the definition for suspecting infective endocarditis and determining the appropriate timing for patients to undergo [<sup>18</sup>F]FDG PET/CT during the diagnostic process is important. Especially in the context of research focused on improving the diagnostic process for endocarditis, it is crucial that this is standardized to ensure the generalizability of any research findings.

The second important consideration is that [<sup>18</sup>F]FDG PET/CT has its strengths and weaknesses in different patient groups with suspected endocarditis, depending on the

presence and type of implanted materials such as prosthetic valves or cardiac implanted electronic devices. The significance for clinical practice is dual, impacting both how the technique is used and how it should be interpreted. Additionally, it serves as a potential starting point for future research, because the underlying reasons for these differences are currently not completely understood. If we understand better what causes the variable performance of [<sup>18</sup>F]FDG PET/CT for these different patient groups, it may significantly improve the clinical benefit of this imaging modality. This could be achieved through employing novel techniques to mitigate potential confounding factors or by using the tools already at our disposal more effectively.

### **Pitfalls, confounders and uncertainties**

Infective endocarditis is as challenging to research as it is in clinical practice. As stated in the introduction, the gold standard for the diagnosis – surgical findings – has inherent limitations. The most important one is that these are only obtained in a very selected patient population. This introduces notable challenges in terms of achieving broad generalization and is likely to remain a hurdle for anyone exploring diagnostic innovations in the field of endocarditis.

Until the moment we can obtain reliable information about microorganisms directly from the suspected areas without surgical interventions this difficulty is here to stay. Therefore, we have to be acutely aware of the associated pitfalls: the most immediate concern is that the final diagnosis as concluded by the endocarditis team in some cases may be flawed. False negative findings can sometimes be corrected by closely following up on patients after their discharge for relapses or recurrences of disease. However, confirming false positives, especially in the absence of an established definitive standard can be challenging, if not outright impossible. Moreover, when clinicians heavily rely on a specific diagnostic tool, establishing its accuracy becomes difficult in the absence of a gold standard. Over-reliance on a singular tool or dismissing it entirely can both introduce biases. While we cannot completely eliminate these risks, we assured adequate patient follow-up and we applied blinding to patient's clinical context in our studies to minimize these risks as much as possible.

### **Improving [<sup>18</sup>F]FDG PET/CT for suspected endocarditis**

PET/CT is a relatively new imaging modality, and its development since its first clinical use in 1998 has been rapid. There are many avenues for further innovations, and these include improvements of the PET/CT camera systems, improvements in the software used, new and more specific tracers, better standardised patient preparation, new acquisition and reconstruction techniques and improved criteria for image evaluation.

Two of the chapters in this thesis discussed new ways to acquire and evaluate [ $^{18}\text{F}$ ]FDG PET/CT. They underscore overall principles when it comes to developing new acquisition and evaluation methods. As demonstrated in **Chapter 3**, application of cardiac motion correction sequences showed promising results for the evaluation of endocarditis. When considering a novel acquisition method such as described in this study, it is of great importance to revisit the fundamental principles of both [ $^{18}\text{F}$ ]FDG PET/CT and the pathophysiology of endocarditis. The underlying premise for this chapter was that [ $^{18}\text{F}$ ]FDG PET/CT in clinical practice is not corrected for motion, while the lesions in endocarditis are frequently small and highly mobile throughout the cardiac cycle. We hypothesized that this might be the reason for the limited sensitivity of [ $^{18}\text{F}$ ]FDG PET/CT, in particular for NVE and CIEDIE affecting implanted leads, as described in **Chapter 2**. In these patient groups, the disease is typically located on a highly mobile structure, while in case of PVE, the most vulnerable lesion for the disease is the annulus in which the valve was implanted: a significantly less mobile structure in comparison to valve leaflets or implanted leads and generally larger in size. Whether motion correction of [ $^{18}\text{F}$ ]FDG PET/CT truly enhances the diagnostic value of PET/CT for suspected IE remains uncertain. Our study, along with another cohort study addressing a similar research question, didn't conclusively establish its effectiveness. Subsequent studies are essential for validation of our findings. Nevertheless, even if validation studies were to reveal minimal advantages for this acquisition method, it serves as a reminder: We are developing increasingly advanced scanners with improved sensitivity and dedicated tracers to support the diagnosis of endocarditis. These developments are very encouraging. Simultaneously, we should also dedicate efforts and resources to maximize the effectiveness of the tools that are already at our disposal and are the standard in most centre, to ensure that the advances of research can be applied for all patients.

Of course, when we look at potential new indicators for a disease, it is not guaranteed that they will be effective, and **Chapter 4** is a clear example of this. We hypothesized that mediastinal lymph nodes might be used as an indicator of endocarditis. Since various infections lead to activation of lymph nodes in the vicinity of the affected organs, activation of mediastinal lymph nodes might also indicate the presence of endocarditis. As discussed in the manuscript, no correlation between lymph node activity and infection was found. This was expected for the absence of lymph node activity: heart valves vascularisation is minimal to none, and lymph node activation was expected to be a late sign of infection with low sensitivity. What was unexpected is that specificity in this study was also low. The new question raised by these findings was why our results diverged so markedly from our initial expectations. This is important for two reasons: firstly, the negative findings have implications for clinical practice, as increased mediastinal lymph node activity could easily be considered as evidence for IE by nuclear physicians in clinical practice.

This study provides a warning that this may actually be a confounder in this particular situation. Secondly, the question of why the results differed from our hypothesis can lead to improved study designs. In this particular example, we realized that in our retrospective cohort, lymph nodes were registered as either negative or positive, while in practice this distinction is based on a combination of intensity of lymph node [ $^{18}\text{F}$ ]FDG uptake and lymph node diameter. Transforming this into a binary score leads to information loss. Additionally, all lymph nodes in the mediastinum were included in the analysis. This may have introduced bias, because lymph nodes more distant from the heart may become activated as a result of different pathology, such as respiratory infections or recent surgery. Future studies could benefit from this knowledge, as it allows them to avoid these potential pitfalls that may have been the basis of our negative findings. Integrating these newfound insights will significantly enhance our comprehension of the precise role, if any, that lymph nodes play in the diagnosis of endocarditis.

The studies we performed are only examples of what is possible. It is heartening to see the innovative ideas emerging in the field that may help us improving the diagnosis of this debilitating disease through various methods. In one of the studies evaluating the Duke criteria, increased [ $^{18}\text{F}$ ]FDG-uptake in the spleen (26) was mentioned as a potential indicator for the disease, and the arrival of long axial field of view (LAFOV) PET/CT camera systems will allow for further innovation. The potential of these LAFOV PET/CT camera systems to acquire the [ $^{18}\text{F}$ ]FDG PET/CT scan in a single bed position and their high sensitivity will allow for several advantages (37): 1) imaging can be performed very fast, e.g. a 3 minute acquisition, with preserved image quality. This would allow for using this technique in hemodynamically unstable patients or in patients that cannot remain supine for extended periods of time; both relevant for infective endocarditis. 2) Radiation exposure can be decreased significantly, potentially to less than 1mSv. This would expand the group for which PET/CT can be used, e.g. in pregnancy and infants. It would also decrease the threshold for repeat imaging, which could be invaluable for monitoring treatment response. LAFOV PET/CT camera systems would also allow for performing cardiac motion correction sequences without any additional patient burden, as it can be performed simultaneously with the regular acquisition. Additionally, dynamic acquisitions may be used to evaluate whether the pattern of [ $^{18}\text{F}$ ]FDG uptake over time can help distinguish between inflammation and infection.

For suspected IE, PET is combined with a low-dose CT for attenuation correction purposes, and in addition, a diagnostic contrast enhanced CT of the thoracic region can be performed for adding high resolution information about the intracardiac regions of interest. The low-dose CT may eventually no longer be necessary due to novel methods of attenuation correction. This is an area where artificial intelligence has shown great promise and this might lead to deep learning reconstruction algorithms that rely solely

on the PET signal for attenuation correction (38,39). For suspected endocarditis, the diagnostic CTA will likely remain part of the diagnostic workup. This is due to the high resolution that CTA can achieve, which complements the metabolic information gained by [ $^{18}\text{F}$ ]FDG-PET. In particular for patients who cannot undergo echocardiography or for whom echocardiography achieved insufficient image quality, CTA can provide invaluable anatomical information and literature has shown that it has superior sensitivity for valvular vegetations compared to [ $^{18}\text{F}$ ]FDG-PET. If the additional value of cardiac gated [ $^{18}\text{F}$ ]FDG-PET would be ascertained in future studies this would potentially allow for combining cardiac motion corrected [ $^{18}\text{F}$ ]FDG-PET with gated CTA, correlating the findings of both.

PET/MRI camera systems have also arrived, and they may provide a combination of high resolution anatomical and tissue characterisation to support the diagnosis. However, their use would likely be limited to those without implanted metallic materials near the heart until the issue of metal related artifacts of MRI in particular is sufficiently addressed (40).

Lastly, new tracers such as [ $^{18}\text{F}$ ]Fluorodeoxyisobutyl, [ $^{18}\text{F}$ ]Fluoromaltohexose, and [ $^{11}\text{C}$ ]-labeled para-aminobenzoic acid (PABA) are nearing their in-human testing phase (41,42). The potential advantage of these tracers is that they play a role in bacterial metabolism, whereas human cells do not metabolize them. This means that these tracers may allow for specific imaging of the offending pathogens directly. This is not possible with [ $^{18}\text{F}$ ]FDG, which is metabolised both in bacteria and in human tissues and which mostly detects infections through the FDG uptake caused by the body's own immune cells. This non-specificity of [ $^{18}\text{F}$ ]FDG uptake is why a major challenge of [ $^{18}\text{F}$ ]FDG PET/CT imaging is that a distinction must be made between physiological uptake such as in the myocardium, sterile inflammatory processes and infection. These can be very difficult to differentiate, which is why direct imaging of pathogens might significantly improve the specificity of PET/CT for the diagnosis of endocarditis (and infectious diseases in general).

### **[ $^{18}\text{F}$ ]PET/CT for suspected LVAD infections**

Two of the chapters in this thesis were aimed at a very specific patient group; those with LVADs. For these patients, the risk of device infections is ever-present due to the presence of the driveline which traverses the skin, while the diagnosis is notoriously difficult to establish. [ $^{18}\text{F}$ ]FDG PET/CT can be a valuable diagnostic tool for these device infections. During the process of composing the systematic review and meta-analysis, the considerable diversity in study methodologies became evident. While a consensus document from the International Society for Heart and Lung Transplantation addresses the prevention and management of LVAD infections, this document acknowledges the lack of randomized controlled studies regarding the management of such infections. This



encompasses also the diagnostic process. This was shown by the fact that all studies included in the meta-analysis stated as their inclusion criteria simply patients with suspected driveline or device infection, without elaborating on which symptoms led to the suspicion. Formalizing criteria for suspecting these infections can decrease the risk of inclusion bias. Therefore, LVAD infections would benefit from a standardisation similar to one performed for endocarditis: the British Society for Antimicrobial Chemotherapy (BSAC) introduced criteria for the suspicion of endocarditis (16), and these could be adapted to LVAD infections. This proposal was included in **Chapter 6** and research on LVAD infections would benefit from such standardisation. Additionally, we tried to consistently make a distinction between driveline infections and infections involved in the central (intrathoracic) device components, because they present two distinct clinical entities, with differing diagnostic and therapeutic challenges and prognosis.

For endocarditis and LVAD infections alike, evidence for the use of semiquantitative methods to date is very limited. Therefore, we incorporated semiquantitative analysis in the dual centre study we performed and this is also a challenge to the field to validate our results. Semiquantitative methods have shown their merit in oncology, and it is unfortunate that this promising tool is not being investigated for endocarditis. A significant challenge that needs to be addressed beforehand is the standardisation of scanning procedures. Furthermore, the results and cut-off values we found in our particular cohort require external validation. Future studies are needed to establish how well these results are generalizable maybe leading to more accurate cut-off values for potential clinical use.

## Machine learning and endocarditis

In **Chapter 7**, the focus was on machine learning for predicting infective endocarditis. Over the past years, artificial intelligence and machine learning have rapidly gained recognition, including in the medical field. Machine learning models can be powerful tools for various classification and regression problems, and this makes them promising candidates also for predicting infective endocarditis. While substantial advancements are being made in nuclear medicine and radiology through the application of machine learning to imaging data, our manuscript's focus was to present the field with a distinct challenge centred around the Duke criteria. The Duke criteria, as devised in 1994, underwent multiple revisions but none of them were combined with a formal re-evaluation of how much weight should be attributed to the different features that constitute this score. This oversight has the potential to introduce bias into both clinical practice and the research domain. The situation becomes even more critical due to the inclusion of new imaging modalities in the modifications by both ESC and ISCVI (7,17), which could significantly impact the appropriate weighting of each individual feature. Even without these changes,

many of the diagnostic tools that are part of the criteria have become more refined over time and this may likewise affect the appropriate weight attributed to them.

The objectives for this study were twofold: first, it was intended as a proof-of-concept to show whether machine learning algorithms use the features of the modified Duke/ESC criteria more effectively than the traditionally applied scoring system, with major and minor criteria resulting in a rejected, possible or definite diagnosis of endocarditis. Secondly, it was intended to initiate a discussion within the field on how we keep our clinical scores aligned with clinical practice and actual patient data.

As shown in the article, when the features that constitute the modified Duke/ESC criteria were used in machine learning algorithms, the results were promising: the models achieved high predictive accuracy by using the criteria more effectively, and an inherent property of these models is that they provide a probabilistic prediction of the disease. This means clinicians get a quantification of uncertainty, which could be a marked improvement of interpretability of the scoring system compared to the modified Dukes/ESC criteria. Of course, this requires extensive external validation, which is crucial before these models can be implemented in clinical practice.

The results of this study also illustrated several important challenges and pitfalls when using machine learning in clinical practice. First and foremost, high quality data for these models is of crucial importance, and when evaluating their performance, one needs to be aware of the nuances of the underlying diagnosis. When it comes to endocarditis, this includes the difficulty that the true gold standard for the diagnosis is frequently unavailable, which translates into a risk of either under- or overreliance on a particular diagnostic modality. Predictive models could inadvertently incorporate such biases and efforts should be made to safeguard against this risk. When developed responsibly, data-driven approaches utilizing machine learning models are capable of effectively harnessing patient data, with the potential to significantly enhance the evaluation of suspected endocarditis. While we continue looking for newer, better tools to establish the diagnosis, it would be another example of making maximum benefit of the tools and information already available to us.

## Conclusion

At the end of this thesis and looking back at the results of the studies presented here, I want to end with some final thoughts.

First of all, this project has put into perspective how much of a challenge endocarditis still presents, both in the clinics and for research. Centuries after the first documented case of endocarditis, it is still a struggle to establish the diagnosis and to find the best ways to treat it. The weekly discussions with the endocarditis team in our hospital are a living testament to this: A multidisciplinary team that together represents many decades worth of clinical experience is still regularly unsure about the best course of action for a given patient. "Do we have enough evidence to conclude that this patient has (or has no) endocarditis?", "Will surgery do this patient more harm or more good?" "Should we perform surgery now or later?", "Is the infection now truly under control and is it safe to stop antibiotic treatment?" These are just examples of the difficult questions that still arise, and there is not always a clear answer. And just as the clinical work treating and caring for these patients continues, so does that of research: to help us understand the disease better, find the diagnosis earlier and treat it more effectively.

At the same time, the project has shown how far the medical field has progressed. It is encouraging to see how the combination of different imaging modalities and microbiologic diagnostic tools complement each other for finding the diagnosis and how this translates in improved patient outcomes. Likewise, it is heartening to see medical specialists across various fields combining their efforts to treat these patients on a daily basis. The research projects of this thesis were primarily aimed at [ $^{18}\text{F}$ ]FDG PET/CT, and they showed how this powerful tool can be used in the diagnostic work-up for endocarditis, both for the evaluation of intracardiac lesions and potential foci of dissemination or points of entry. They have shown potential avenues to further increase its usefulness, while the study aimed at machine learning showed us a glimpse of the potential benefits of these models for the diagnosis.

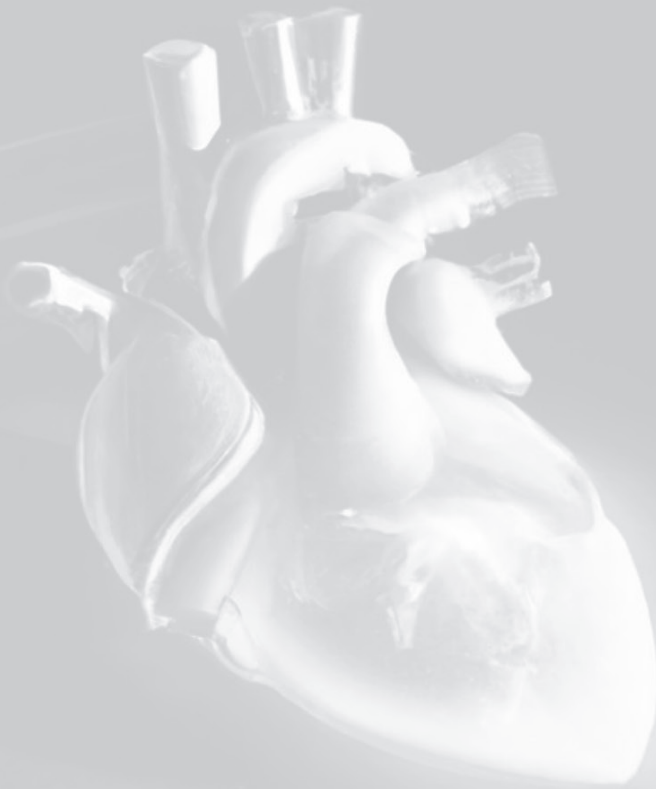
Above all, the time working on this project has shown me that research is a shared pursuit, where every research project deepens our collective knowledge and understanding. Our combined efforts, the challenges we encounter and the successes and failures we have, all pave the way for future advancements. I hope this work stands as a valuable contribution in this collective goal to better diagnose and treat patients with (suspected) endocarditis and to improve the lives of those affected by it.

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# English Summary





The goal of this thesis is improving the diagnosis of infective endocarditis. This disease is defined as an infection of the inner lining of the heart or of materials that are implanted intracardially, such as prosthetic valves or cardiac implanted electronic devices (CIEDs). It is a notoriously difficult disease to diagnose and treat, and consequently it is associated with high morbidity and mortality. For the improvement of the diagnosis of infective endocarditis, this thesis is aimed primarily on the role of [ $^{18}\text{F}$ ]FDG PET/CT. Additionally, the final chapter focuses on machine learning models and a potential way in which these could be used to improve the diagnosis of IE, by optimizing the modified Duke criteria.

**Chapter 1** is an introductory chapter that offers an overview of the history, diagnosis and treatment of infective endocarditis and the challenges this disease presents us with. It includes an overview of the myriad diagnostic tools that can be used to diagnose the disease and the potential improvements to these diagnostic tools that are discussed in the following chapters.

In **Chapter 2** we provide an overview of the value of [ $^{18}\text{F}$ ]FDG PET/CT for the diagnosis of infective endocarditis as it is currently used in clinical practice. Since the publication of the 2015 ESC guideline, findings on [ $^{18}\text{F}$ ]FDG PET/CT that are consistent with intracardiac infection are considered major criteria for the diagnosis in patients with prosthetic valves according to the European Society of Cardiology. This came alongside with the incorporation of diagnostic CTA and WBC scintigraphy. These substantial changes to the Duke criteria lead to questions regarding the exact place of [ $^{18}\text{F}$ ]FDG PET/CT in the diagnosis of endocarditis: its indications and the preferred timing of this technique. This review article starts with an overview of indications for [ $^{18}\text{F}$ ]FDG PET/CT. A distinction was made based on the presence of either artificial valves (PVE) and/or CIED's such as pacemakers or ICDs. The role of [ $^{18}\text{F}$ ]FDG PET/CT is different for these patient groups as its accuracy in evaluating suspected intracardiac lesions varies depending on the presence of implanted intracardiac materials. The need for further standardisation, a discussion regarding the optimal timing of PET/CT in the diagnostic workup and considerations how best to perform the scan as well as future perspectives for [ $^{18}\text{F}$ ]FDG PET/CT and potential new radiopharmaceuticals are subsequently discussed.

**Chapter 3** investigates the benefit of applying cardiac gating to [ $^{18}\text{F}$ ]FDG PET/CT to correct for cardiac motion. In this case series, motion correction of [ $^{18}\text{F}$ ]FDG PET/CT using either conventional single-gate gating, Cardiofreeze™ or a combination of the two improved interpretability in four out of five cases with valvular IE lesions, confirming the diagnosis in one case where non-gated PET had missed the diagnosis. Both motion correction methods performed equally well. Cardiac motion correction can help differentiate between physiological uptake and infectious processes based on movement patterns of areas with increased [ $^{18}\text{F}$ ]FDG uptake, leading to higher image quality scores given to



the gated images. We conclude that, while preliminary, these results are promising and warrant further investigation.

In **Chapter 4** the role of mediastinal lymph nodes as an indicator for infective endocarditis was evaluated, given that their activation is an indicator for various different infectious conditions. We evaluated the predictive value of mediastinal lymph nodes in an existing retrospective cohort of patients suspected of prosthetic valve endocarditis. Our results showed that mediastinal lymph node activity was neither sensitive or specific for prosthetic valve endocarditis, even though it was predictive of worse patient outcomes in those with confirmed infection. Based on our findings, we conclude that mediastinal lymph node activity cannot be relied upon for predicting infective endocarditis, neither for its absence or its presence. However, more precise documentation of which exact lymph node stations show increased [<sup>18</sup>F]FDG uptake and quantification of this uptake might still be of use for this indication and could be an interesting avenue for future studies.

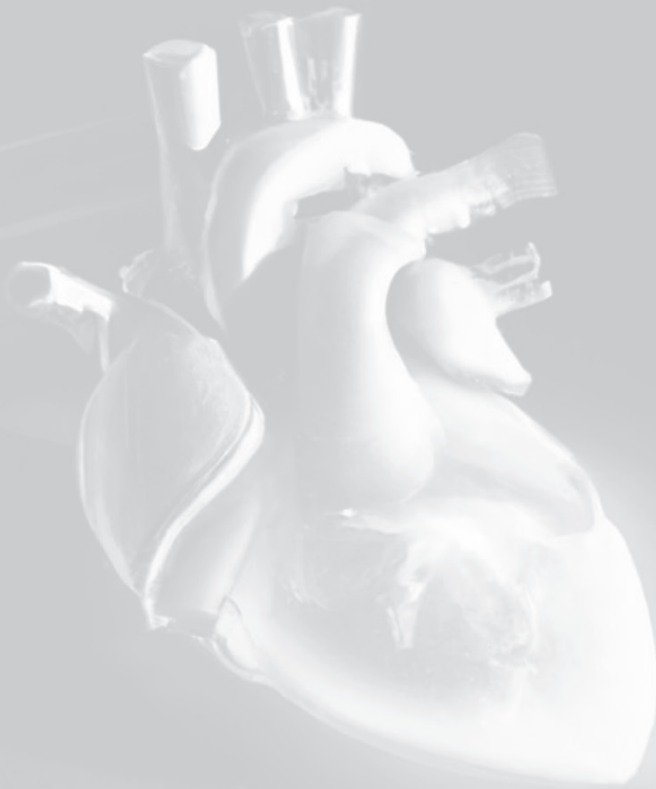
**Chapter 5** is a systematic review and meta-analysis of the value of [<sup>18</sup>F]FDG PET/CT for diagnosing infections Left ventricular assist devices. The analysis was split to include both infections of the driveline and infections of the intrathoracic central device components and included 8 studies aimed at this research question. Their findings demonstrate that [<sup>18</sup>F]FDG PET/CT is a valuable tool for establishing or excluding the diagnosis of device specific infection in patients with a Left Ventricular Assist Device with a high sensitivity and a high, albeit variable, specificity. Future studies, in which criteria for suspecting device infection and scan procedures are standardised, are needed to confirm these findings. Current evidence strongly supports implementation of [<sup>18</sup>F]FDG PET/CT in the standard work-up of patients with suspected LVAD related infections, in particular when initial clinical investigations are inconclusive.

In **Chapter 6** we evaluated the value of [<sup>18</sup>F]FDG PET/CT for suspected LVAD infections in a dual centre patient cohort. Here we also placed particular emphasis on the potential role of semiquantitative analysis in enhancing the diagnostic performance of [<sup>18</sup>F]FDG PET/CT. Our results show that [<sup>18</sup>F]FDG PET/CT is effective in identifying LVAD infections, when both normal and abnormal [<sup>18</sup>F]FDG uptake patterns surrounding these devices are correctly weighed. Visual analysis and semi-quantitative analysis complement each other to reliably establish the presence of driveline infections. For central device component infection, visual analysis achieves moderate sensitivity and specificity. Using both Attenuation corrected and Non Attenuation Corrected images is pivotal for achieving sufficient specificity for this indication, while semi-quantitative analysis may be of additive value for further increasing [<sup>18</sup>F]FDG PET/CT specificity for these infections.

**Chapter 7** takes a step back from the imaging and focuses on the overall diagnostic process for suspected endocarditis: in this chapter, we set up a proof-of-concept to show how the Duke criteria and their subsequent modifications could benefit from the application of machine learning. For this, we used data from an existing retrospective cohort study of suspected prosthetic valve endocarditis. Our results indicate that machine learning approaches can be powerful tools for predicting endocarditis using the same features that constitute the modified Duke/ESC criteria. However, the results also showed potential pitfalls for using these models for clinical predictions, in particular the inherent difficulty of evaluating a new diagnostic paradigm when the gold standard for the diagnosis is not available, which for IE is unfortunately frequently the case. Larger, prospective studies are crucial for validating our results before these models could be incorporated into clinical practice.



# Nederlandse samenvatting





Het doel van dit proefschrift is het verbeteren van de diagnose van infectieuze endocarditis. Bij infectieuze endocarditis is sprake van een infectie van de binnenbekleding van het hart of van materialen die intra-cardiaal zijn geïmplant, zoals kunstkleppen of CIED's (cardiaal geïmplanteerde elektronische apparaten). Het is een notoir moeilijke ziekte om te diagnosticeren en te behandelen en daarom heeft de ziekte een hoge morbiditeit en mortaliteit. Voor de verbetering van de diagnostiek naar endocarditis is dit proefschrift met name gericht op de rol van [<sup>18</sup>F]FDG PET/CT, met daarnaast nog een hoofdstuk dat gericht is op machine learning modellen en een potentiële manier waarop deze kunnen helpen de diagnose te verbeteren, door een optimalisatie te geven van de zogenoemde modified Duke criteria.

**Hoofdstuk 1** is een inleidend hoofdstuk dat een overzicht biedt van de geschiedenis, diagnose en behandeling van infectieuze endocarditis en de uitdagingen waarmee deze ziekte ons confronteert. Het bevat een overzicht van de talloze diagnostische hulpmiddelen die gebruikt kunnen worden om de ziekte te diagnosticeren en de mogelijke verbeteringen van deze diagnostische hulpmiddelen die in de volgende hoofdstukken worden besproken.

In **Hoofdstuk 2** geven we een overzicht van de waarde van [<sup>18</sup>F]FDG PET/CT voor de diagnose van infectieuze endocarditis zoals het momenteel in de klinische praktijk wordt gebruikt. Sinds de ESC-richtlijn van 2015 worden bevindingen op [<sup>18</sup>F]FDG PET/CT die consistent zijn met intracardiale infectie beschouwd als belangrijke criteria voor de diagnose bij patiënten met kunstkleppen volgens de Europese Vereniging voor Cardiologie. Dit ging gepaard met de opname van diagnostische CTA, WBC-SPECT/CT en [<sup>18</sup>F]FDG PET/CT in de richtlijn als criteria voor de diagnose van endocarditis. In dit overzichtsartikel werden indicaties voor [<sup>18</sup>F]FDG PET/CT besproken. Er werd onderscheid gemaakt op basis van de aanwezigheid van kunstkleppen (PVE) en/of cardiaal geïmplanteerde apparaten zoals pacemakers of Implanterbare Cardioverter Defibrillators. De rol van [<sup>18</sup>F]FDG PET/CT verschilt voor deze patiëntengroepen omdat de nauwkeurigheid bij het evaluatie van intracardiale laesies varieert afhankelijk van intracardiale materialen. De behoefte aan verdere standaardisatie, overwegingen bij het uitvoeren van een [<sup>18</sup>F]FDG PET/CT scan en de toekomstperspectieven voor de techniek werden ook besproken.

In **Hoofdstuk 3** wordt het voordeel onderzocht van het toepassen van gating op [<sup>18</sup>F]FDG PET/CT om te corrigeren voor cardiale beweging. In deze patiëntengroep verbeterde bewegingscorrectie van [<sup>18</sup>F]FDG PET/CT met behulp van conventionele single-gate gating, Cardiofreeze™ of een combinatie van beide de interpreteerbaarheid van de scans in vier van de vijf patiënten met valvulaire IE-laesies. In één geval werd de diagnose bevestigd waar PET zonder gating de diagnose had gemist. Beide bewegingscorrectiemethoden presteerden even goed. Cardiale bewegingscorrectie kan helpen om onderscheid te maken tussen fysiologische opname en infectieuze processen op basis van bewegingspatronen

van gebieden met verhoogde [<sup>18</sup>F]FDG-opname, wat leidt tot hogere beeldkwaliteitsscores voor de gecorrigeerde beelden. Hoewel voorlopig, zijn deze resultaten veelbelovend en verdienen ze verder onderzoek.

In **Hoofdstuk 4** werd de rol van mediastinale lymfeklieren als indicator voor infectieuze endocarditis geëvalueerd, aangezien hun activering een indicator is voor verschillende infectieuze aandoeningen. Voor infectieuze endocarditis was een verhoogde [<sup>18</sup>F]FDG-opname in de mediastinale lymfeklieren noch gevoelig noch specifiek voor infecties. Deze resultaten toonden aan dat de activiteit van de mediastinale lymfeklieren niet kan worden vertrouwd voor het voorspellen van infectieuze endocarditis. Het is mogelijk dat een nauwkeuriger beeld van welke exacte lymfeklierstations verhoogde activiteit laat zien en kwantificatie van de precieze mate van activiteit zou helpen om lymfeklieractiviteit een betere voorspellende waarde te geven en dit zou een veelbelovende richting kunnen zijn voor vervolgonderzoek.

**Hoofdstuk 5** is een systematische review en meta-analyse van de waarde van [<sup>18</sup>F]FDG PET/CT voor het diagnosticeren van infecties van LVADs. De analyse werd opgesplitst in twee delen: 1) infecties van de draad die de pomp voorziet van elektriciteit, de driveline en 2) infecties van de intra-thoracaal gelegen apparaat componenten. Onze bevindingen tonen aan dat [<sup>18</sup>F]FDG PET/CT een waardevol hulpmiddel is voor het vaststellen of uitsluiten van de diagnose van LVAD specifieke infecties bij patiënten met een LVAD. De gevoeligheid van [<sup>18</sup>F]FDG PET/CT voor de diagnose is hoog en hetzelfde geldt voor de specificiteit, al is deze over de verschillende onderzoeken wel meer variabel. Toekomstige studies zijn nodig om deze bevindingen te bevestigen. Hierbij is belangrijk dat criteria voor het vermoeden van LVAD infectie en de scanprocedures rondom [<sup>18</sup>F]FDG PET/CT worden gestandaardiseerd. De onderzoeken tot nu toe ondersteunen sterk de implementatie van [<sup>18</sup>F]FDG PET/CT in de klinische praktijk voor patiënten met vermoedelijke LVAD-gerelateerde infecties, met name wanneer initiële klinische onderzoeken niet eenduidig zijn.

In **Hoofdstuk 6** evalueerden we de waarde van [<sup>18</sup>F]FDG PET/CT voor vermoedelijke LVAD-infecties in een cohort van twee centra; het UMCG en het Erasmus MC. Hier legden we ook bijzondere nadruk op de mogelijke rol van semi-kwantitatieve analyse bij het verbeteren van de nauwkeurigheid van [<sup>18</sup>F]FDG PET/CT. Onze resultaten tonen aan dat [<sup>18</sup>F]FDG PET/CT effectief is bij het identificeren van LVAD-infecties, wanneer zowel normale als abnormale [<sup>18</sup>F]FDG-opnamepatronen rond deze apparaten correct worden ingeschat. Visuele analyse en semi-kwantitatieve analyse vullen elkaar aan om betrouwbaar de aanwezigheid van aandrijflijninfecties vast te stellen. Voor infecties van de intra-thoracaal gelegen LVAD onderdelen bereikt visuele analyse een matige gevoeligheid en specificiteit. Het gebruik van zowel gecorrigeerde als niet-gecorrigeerde beelden is essentieel om

voldoende specificiteit voor deze indicatie te bereiken, terwijl semi-kwantitatieve analyse van toegevoegde waarde kan zijn voor het verder verhogen van de specificiteit van [<sup>18</sup>F] FDG PET/CT voor deze infecties.

**Hoofdstuk 7** neemt afstand van de beeldvorming en focust zich op het algemene diagnostische proces voor vermoedelijke endocarditis: in dit hoofdstuk hebben we een proof-of-concept opgezet om te laten zien hoe de Duke-criteria en hun latere wijzigingen zouden kunnen profiteren van de toepassing van machine learning. Hiervoor gebruikten we gegevens uit een bestaande retrospectieve cohortstudie van patiënten die analyse in het ziekenhuis ondergingen i.v.m. een vermoeden op kunstklependocarditis. Onze resultaten geven aan dat machine learning modellen krachtige hulpmiddelen kunnen zijn voor het voorspellen van endocarditis, zelfs bij gebruik van precies dezelfde criteria die de aangepaste Duke/ESC-criteria gebruiken om tot hun score te komen. De resultaten toonden echter ook potentiële valkuilen aan voor het gebruik van deze modellen voor klinische voorspellingen. Grotere, prospectieve validatiestudies zouden cruciaal zijn voordat deze modellen in de klinische praktijk kunnen worden geïmplementeerd.





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## About the author

Dik ten Hove was born on the first of January 1990 in Rijssen, a small town in Twente, Overijssel, The Netherlands. He grew up in a warm, large family that has been and remains in his heart, even as the road led around the country.

He left Rijssen for Groningen in 2008 to study Medicine and finished the study in 2015. Afterwards he started as a physician in intensive care Medicine at Elkerliek hospital Helmond, and then at the department of Cardiology at Medisch Spectrum Twente in Enschede. While these positions came with invaluable life experiences, they were not a career home, and after a year of reconsideration a new position brought him back to Groningen. A position at the Faculty of Medicine opened up, this time not as a student, but as a physician-teacher of clinical reasoning for the faculty of Medicine.

Research had always had his interest and in March 2019 began the project that would lead to the thesis that lies before you: a PhD study aimed at improving the diagnosis of infective endocarditis. With Andor, Bhanu and Riemer as his main supervisors, the project steadily progressed over the years and between the publications and conferences, time truly flew.

In his free time, Dik enjoys bouldering, skating, skiing, singing, reading, gaming, cycling and making long walks; be it in the city, a forest or along the water.

Together with his love, Samiksha, he lives in Groningen, with a direct view of Martini tower and on walking distance from the UMCG, where he still works: Towards the end of the research project he realized that he missed the work in the clinic more and more. A new chapter of his career began at the department of psychiatry, where he is currently training to become a psychiatrist, feeling very much at home. The heart always finds a way.

