The Effect of Interventions for Atrial Arrhythmia on Physical Activity and Thoracic Impedance

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This thesis is submitted in partial fulfilment of the requirements for the degree of

Doctor of Clinical Science

October 2025

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Abstract

Introduction

Cardiac implantable electronic devices (CIEDs) store digital biomarkers (DBs). These have potential as surrogate outcome markers in research studies, and could enable more personalised treatment. We investigated the effect of clinically-indicated procedures for atrial arrhythmia (AA) on DBs.

Method

Exploratory single-site, retrospective, observational study. Procedures were either a catheter ablation (CA) or a direct current cardioversion (DCCV) for rhythm or rate control of AA. Device-measured physical activity (D-PA) and thoracic impedance (TI) measurements already stored as part of standard clinical care were retrieved.

24 months of data were analysed. For each patient, the 12 month period after the procedure (period B) was compared with the 12 months before (period A). For rhythm control patients, the change in AA burden (Δ AA), change in mean DPA (Δ DPA) and change in mean TI (Δ TI) were calculated. Δ D-PA and Δ TI were analysed for correlation with Δ AA. Patients were divided into tertiles according to the magnitude of Δ AA, and Δ D-PA and Δ TI compared between groups.

Results

30 patients were identified. 26 had a rhythm control procedure and were included in the principal analysis. Of these, 19 had TI data in addition to D-PA. 4 patients had undergone an atrio ventricular node (AVN) ablation for rate control.

There was a statically significant correlation between Δ AA and Δ TI, but not between Δ AA and Δ D-PA. Patients with a reduction in AA burden had a significant increase in TI, compared to patients with no change or an increase in burden.

Conclusion

TI is a promising DB for evaluating treatment effects. Rhythm control procedures that result in a large reduction in AA burden are associated with a reduction in pulmonary congestion that is likely to be associated with improved outcomes.

I would like to thank my academic supervisor Dr Fiona Wilkinson for her fantastic support, encouragement and friendship throughout this project

I would also like to thank my research supervisor Professor Zachy Whinnett for his mentorship over many years

Thanks also go to Dr Ahran Arnold, Dr Jagdeep Mohal, Dr Alehandro Miyazawa, Dr Matthew Shun-Shin and Edward Cajilog

Grateful thanks to all the cardiac physiologist team and to everyone involved in the treatment of arrhythmias at our institution

Finally, thanks go to my wife and daughter for putting up with me

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ACCRONYM	FULL DESCRIPTION
AA	Atrial arrhythmias
AAD	Anti-arrhythmic drug
AF	Atrial fibrillation
AFA	AF ablation
AFL	Atrial flutter
AT	Atrial tachycardia
AVN	Atrio ventricular node
BMI	Body mass index
BNP	B-type natriuretic peptide
BSc	Boston Scientific
CA	Catheter ablation
CI	Confidence interval
CIED	Cardiac implantable electronic device
CRT-D	Cardiac resynchronisation-therapy defibrillator
CRT-P	Cardiac resynchronisation-therapy pacemaker
CSP	Conduction system pacing
CTI	Cavo-tricuspid isthmus

CVD	Cerebro vascular disease
DB	Digital biomarker
DCM	Dilated Cardiomyopathy
DCCV	Direct Current Cardioversion
D-PA	Device-measured physical activity
EF	Ejection fraction
HF	Heart failure
HCM	Hypertrophic cardiomyopathy
HT	Hypertension
ICD	Implantable cardiac defibrillator
ICM	Ischaemic cardiomyopathy
IHD	Ischemic heart disease
LSPsAF	Long-standing persistent AF
LA	Left atrium
LV	Left ventricle/left ventricular
LVEF	Left ventricular ejection fraction
Med	Medtronic
MET	Metabolic equivalent of task
MICD	Minimum clinically important difference

MV	Minute ventilation
NYHA	New York Heart Association
PA	Physical activity
PAF	Paroxysmal AF
PsAF	Persistent AF
PVD	Peripheral vascular disease
RFA	Radio-frequency ablation
RM	Remote monitoring
SD	Standard deviation
SR	Sinus rhythm
TI	Thoracic impedance
TIC	Tachycardia-induced cardiomyopathy
VHD	Valvular heart disease
VT	Ventricular tachycardia

CHAPTER 1:

INTRODUCTION AND BACKGROUND

The subject of this thesis is the use of digital biomarkers recorded by cardiac implanted electronic devices to evaluate of the effect of treatments for atrial arrhythmias

1.0 Digital biomarkers

Digital biomarkers (DBs) are collected and measured by a biosensor integrated into digital technology such as wearable or implantable devices. DBs may take the form of physiological or behavioural data that are transformed into interpretable outcome measures by algorithms (Motahari-Nezhad et al., 2021). These new measures are processed largely independent of human intervention and are therefore relatively objective and resistant to bias (Dorsey et al., 2017). Furthermore, patients can be blinded to the measures so do not alter their behaviour. They facilitate continuous long-term assessment - which is usually not feasible with conventional clinical measures (Macias Alonso et al., 2024), and present an opportunity for measuring endpoints in objective and unbiased manner (Stephenson et al., 2021). Biomarkers can aid diagnosis, prognosis and improve clinical outcomes. They have the potential to give complementary information about disease progression and the effect of interventions. By

providing insights into pathophysiology, they can direct attention towards novel therapeutic targets (Bodaghi et al., 2023)

Traditional clinical trial end-points, such as morbidity and mortality can usually only be evaluated with large sample sizes over long time periods - requiring significant financial investment. In a typical clinical trial or during standard clinical practice, the researcher or medical practitioner has no knowledge of the patients' status for the vast majority of the time (outside of the brief visits to the hospital or surgery). DBs can 'fill in the gaps', and this more densely collected data has the potential to provide new insights into the temporal effects of treatment, and to act as an outcome measure in clinical trials with reduced sample sizes and timeframes. (Motahari-Nezhad et al., 2021). DBs are beginning to replace more subjective measurements collected via questionnaires, and even have the potential to replace conventional outcome measures (Macias Alonso et al., 2024). Data collected in this way can reveal behaviour in the natural environment and reach individuals who do not typically enrol in research studies (Motahari-Nezhad et al., 2021). This includes elderly people, a group who are under-represented or excluded from conventional trials (Herrera et al., 2010) and who make up a large proportion of patients with cardiac implantable electronic devices (CIEDs). DBs also have applications in diagnostics beyond clinical trials—to identify susceptible patients, to characterise people with a given condition, or to guide treatment choices (Macias Alonso et al., 2024).

Modern CIEDs measure and store a number of digital biomarkers, the most important of which are device-measured physical activity (D-PA), measured by an on-board accelerometer (Rosman et al., 2018), and thoracic impedance (TI), estimated by passing current from the lead in the heart to the implanted generator (sometimes referred to as the 'can') [Aggarwal et al., 2023]. These measurements are not integral to the core functionality of CIEDs, but are increasingly being leveraged to monitor clinical status over time in chronically sick patients (Ferrick et al., 2023). D-PA provides an estimate of functional capacity, whereas TI is an indicator of pulmonary congestion (Rosman et al., 2018; Pirrotta et al., 2021). Functional capacity and pulmonary congestion are both important measures in the assessment of the health of patients with CIEDs (Ferrick et al., 2023). D-PA and TI display many of the characteristics of ideal biomarkers (Figure 1.1) except that they have not been widely shown to be modifiable with treatment.

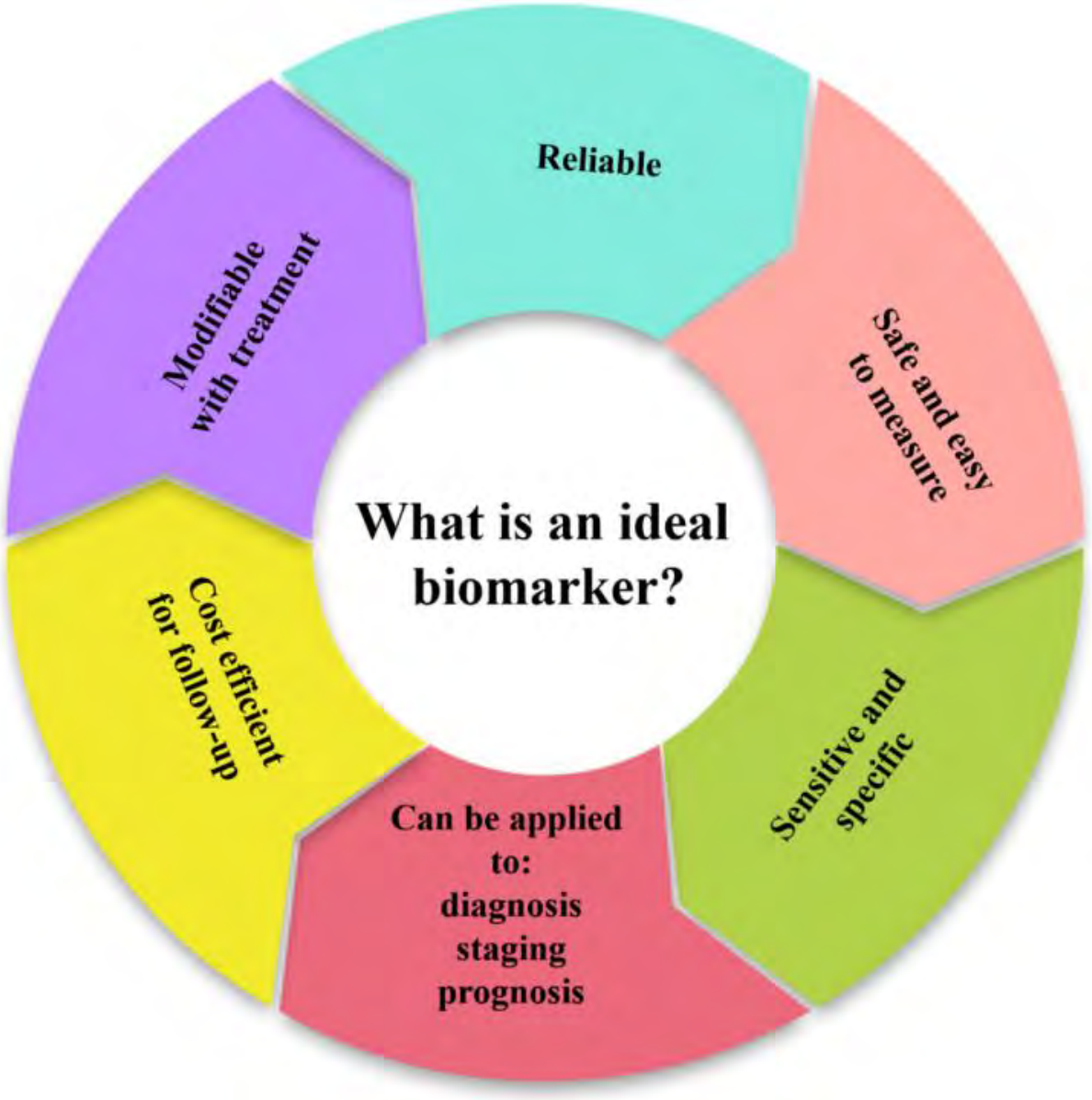


Figure 1.1 The principal features of an ideal biomarker (Bodaghi et al., 2023)

1.1 Cardiac Implantable Electronic Devices (CIEDs)

CIEDs are a class of miniature computerised medical devices with leads attached that extend into the heart. Briefly, pacemakers prevent dizziness, loss of consciousness, or in extreme cases

death from slow heart rhythms (bradycardia), whereas implantable cardiac defibrillators (ICDs) prevent sudden death by delivering shocks for a dangerous fast heart rhythm (tachycardia). Cardiac resynchronisation-therapy devices can be either pacemakers (CRT-Ps) or ICDs (CRT-Ds) – they have an extra lead to add the ability to reduce symptoms from heart failure (Wright, 2021)

1.2 Heart failure

Heart failure (HF) is a long-term, chronic condition associated with a high incidence of hospitalisation and death (Verma et al., 2017) and it is s a major healthcare cost across the world (MacFadyen et al., 2004). In HF, failure of the left ventricle (LV) to move incoming blood from the lungs onwards to the body results in increased pressure in the lung vessels, and fluid build-up in lung tissues which impairs oxygen transport, causing symptoms of shortness of breath (King and Goldstein, 2022). The use of loop diuretic medication is central in managing congestion in HF (MacFadyen et al., 2004). Diuretic medication is used for the relief of congestive symptoms and fluid retention, and titrated (up and down) according to need (NICE 2018). However, non-adherence due to side-effects, and acquired resistance to loop diuretics over time can limit their use (MacFadyen et al., 2004; Shah et al., 2017).

HF worsens in a series of discrete steps known as decompensations, which often lead to hospitalisation (Susič et al., 2022). This stepwise deterioration occurs because physiological adaptation can compensate for worsening heart function for a limited time, but eventually the

adaptation is overwhelmed, leading to a sudden deterioration and increase in symptoms. A different physiological adaptation may then come into play, and enable a new, lower equilibrium of activity to be established. Eventually however, no amount of physiological adaptation can compensate sufficiently, and ultimately the patient will die from the condition (Packer, 2020). HF decompensations are marked by sudden and significant drops in physical activity and corresponding increases in pulmonary congestion (Arrigo et al., 2020).

A high proportion of patients with CIEDs have HF. This is because impaired LV function is a key indication for ICD implantation, and because the majority of patients receiving pacemakers are elderly (HF prevalence increases with age [Coats, 2019]). It is critically important to continue to actively manage HF after implantation of a CIED (NICE, 2018).

1.3 Remote monitoring

The development of the mobile internet and secure digital communication protocols has provided the technical capability for data stored in a CIED to be transmitted directly from the patient's home to a secure website hosted by the manufacturer (Braunschweig et al., 2019, Wright, 2021). Hospital staff can log onto the manufacturer website and view this secure data in an accessible format such as graphical representation of rolling averages. The raw daily

measurements used to generate such charts are usually not presented except for the most recent values, but are stored in a data warehouse administered by the manufacturer.

Increasing attention is being paid to the use of CIED data to help in disease monitoring (Zeitler, and Piccini, 2016). Device-based sensors and algorithms produce digital biomarkers that can be utilised for continuous surveillance of a constellation of physiological parameters including heart rate, heart rate variability, physical activity, arrhythmia incidence, and thoracic impedance. These biomarkers can augment conventional clinical assessment; helping to improve long-term patient management in conditions such as HF (Aslan et al., 2024).

1.4 Physical activity and functional capacity

Functional capacity (FC) is the ability to perform activities of daily living that require sustained aerobic metabolism (Arena et al., 2007). The oxygen and nutrients needed to sustain the metabolic demands of the body are transported in the blood. The speed at which oxygen can be delivered to the tissues is in large part determined by the volume of blood which can be moved by the heart. Since physical activity requires oxygen and other substances transported by blood, the maximal efficiency of the heart limits the amount of physical activity that an individual can perform in daily life (their FC). Consequently, physical activity is impaired in patients with HF (Del Buono et al., 2019).

For many years a very simple evaluation called the 6-minute walk test (6MWT), has been used to estimate FC, although being artificial, the test is really a measure of exercise tolerance. It measures the maximum distance that a patient can walk on a flat, hard surface in a period of 6 minutes (Shah et al., 2001). The 6MWT is inexpensive, reliable, easy to perform and reproducible; but results can be affected by a variety of factors unrelated to cardiac function. Importantly, the test can be performed on only a limited number of occasions and so provides very limited time-series data. Moreover, changes in the 6MWT do not always predict outcomes (Shah et al., 2001). In recent years, techniques have evolved to capture true (i.e. ambulatory) functional capacity over extended monitoring periods under actual life conditions (Butler et al., 2017). With this approach there is the potential to provide continuous longitudinal time-series data that can be used to monitor disease progression as part of a disease management strategy, allowing vulnerable patients to be identified and triaged to an appropriate treatment.

1.5 Accelerometers incorporated in CIEDs

CIEDs and wearable physical activity monitors utilise accelerometers, which are micro-electromechanical systems that measure accelerations relative to the Earth's gravitational field (Yang and Hsu, 2010). Body movement causes a silicon sense-element to shift position, changing its capacitance, which is measured as changes in voltage. The output of these devices is a time series of accelerations expressed in gravitational units, measured in up to 3 orthogonal axes in the physical frame of reference of the device (Karas, et al., 2019). In contrast to many wearable devices, CIEDs utilise single-axis rather than tri-axial accelerometers, and are

therefore less able to differentiate different types of activity (Rossman, et al., 2019). The raw data is transformed using proprietary algorithms into a summary, which can have different labels (e.g. steps, calories, activity-counts etc), and can be presented over various time periods (e.g. minutes, hours, or days (Karas et al., 2019). Accelerometers in CIEDs produce an activity count typically presented as hours of activity per day above a threshold.

This device measured daily physical activity (D PA) is objective, and is recorded continuously. The average time a patient is active each day is calculated and stored in the memory of the CIED for 12-14 months. D-PA provides a quantitative and accessible measure that reflects the functional status of an individual, and there is a strong evidence base for correlation between D-PA and adverse cardiovascular events, including death (Rosman et al., 2018). Multiple studies have shown that D-PA is associated with life expectancy and hospitalisation, and performs at least as well as established measures of FS in predicting intermediate outcomes in patients with HF (Rosman et al., 2018). A decrease in D-PA has been shown to precede worsening of HF, including episodes leading to hospitalisation and death (Rosman, et al., 2018). Indeed, Adamson et al. (2004) found that a decline in D-PA of 0.4 hours per day was a statistically significant predictor of death and hospital admission, and Jamé et al (2017) showed that a >40% reduction was predictive of a significantly increased risk of death or a HF event. Multisensory algorithms that include D-PA can predict HF events and identify patients at risk for HF hospitalisation in an ambulatory setting. D-PA is increasingly being used as an early warning indictor of patients at risk of deterioration (Rosman et al., 2018), and may have utility as a surrogate marker for assessing treatment effects (Shoemaker et al., 2019). However, D-PA has limitations: only a relatively mild or moderate level of activity is required to log hourly

activity - it therefore reflects the amount of time spent active, rather than the intensity of the activity. After treatment, the intensity of a person's activity might increase, but not the overall time spent active – such a change would likely not be reflected in CIED accelerometer data.

D-PA and TI can be incorporated into HF early warning alert systems to identify unstable or sub-optimally managed CIED patients for whom simple preventative measures may reduce hospital admission rates with benefits to both patients and healthcare systems (Tedeschi et al., 2024). Figure 1.2 shows a model of HF progression characterised by sudden drops in functional capacity that can be identified by D-PA measures in a HF alert system (Figure 1.2)

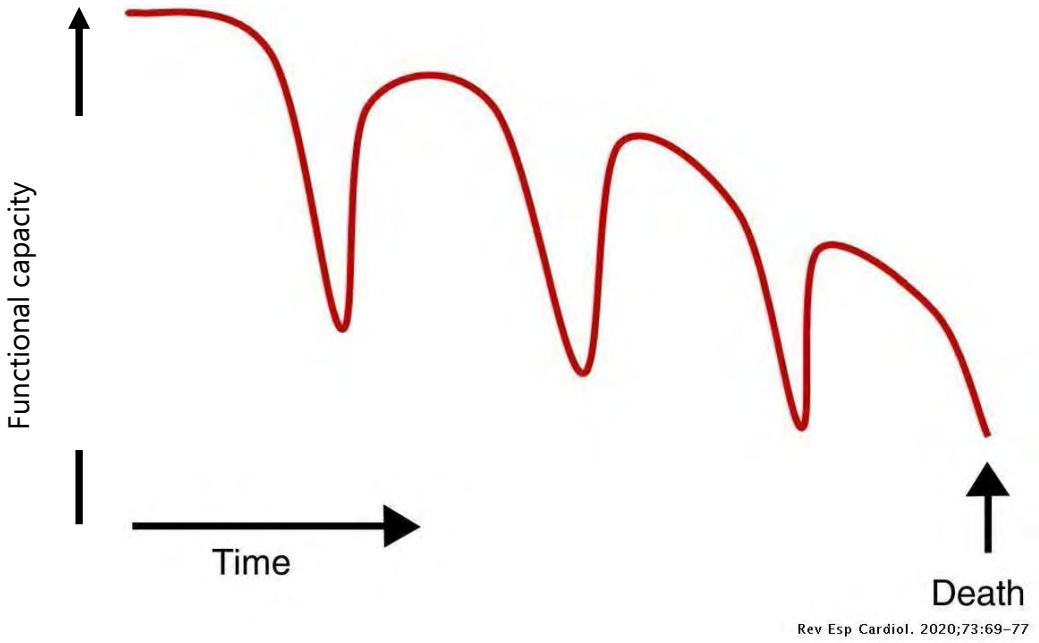


Figure 1.2 Model of heart failure progression showing drops in functional capacity (decompensations) that may lead to hospital admission and ultimately death (adapted from Manuel et al., 2019

However, despite growing interest in such early warning systems, conflicting results from randomized trials has limited uptake. The 2021 European HF guidelines (McDonagh et al., 2021) did not recommend routine remote monitoring (RM) of device-HF patients, due to a lack of evidence showing impact on admissions and mortality, whereas, the 2023 Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), Asia Pacific Heart Rhythm Society (APHRS) and the Latin American Heart Rhythm Society (LAHRS) expert consensus statement on practical management of the remote device clinic concluded, "that it is reasonable to remotely monitor HF diagnostics to detect incident HF and/or disease progression (Ferrick et al., 2023). Recently, the National Institute for Health and Care Excellence (NICE) produced guidelines for HF algorithms for remote monitoring in people with CIEDs (Nice 2024). These guidelines state that the Boston Scientific HeartLogic, and Medtronic TriageHF algorithms are options for remote monitoring in people with CIEDs which "should be used as part of a specialist multidisciplinary HF service, with alerts reviewed and acted on by specialist healthcare professionals (NICE 2024, p27)."

To interpret digital biomarkers appropriately, it is important to understand how much change in a parameter is clinically relevant, and if there are sources of variation in the measures caused by factors other than the disease state itself. HF monitoring might be improved by better

understanding of the variation in D-PA measurements, both within and between patients over time, together with novel methods for modelling and analysing this time-series data at a patient-level.

1.6 Measuring physical activity

Physical activity (PA) is a measure of FC and is a powerful predictor of mortality (Arena et al., 2007). PA may be measured to understand baseline levels in a population of interest, to motivate people to increase their activity by documenting progress, to monitor disease progression, or to assess whether an intervention has an impact (Sylvia et al., 2014). Different components of PA that can be measured include; frequency of PA, duration of that activity, and the intensity and the type of activity (Zhao et al., 2024). Duration of activity can be captured in an unbiased way, utilising CIED technology.

1.7 Thoracic impedance

Symptoms leading to HF hospitalization usually occur relatively late in the course of decompensation episodes. In one study for example, dyspnoea (shortness of breath) was noted on average only 3 days before hospital admission (Yu et al., 2005). A reliable means of monitoring chronic fluid status in ambulatory patients has therefore been sought in order to detect decompensation at a pre-clinical stage, when appropriate preventative intervention

might still be possible. It has been proposed that changes in thoracic impedance (TI) can detect pulmonary fluid retention early enough to fascilitate changes in management that might alter the clinical course and avoid negative outcomes (Yu et al., 2005).

1.8 Implanted device–based method

Impedance measurement has been used to check the electrical integrity of pacemaker and defibrillator leads for decades, but this technique can be modified to assess TI. TI reflects the fluid status of the lungs, and CIED–based TI measurement can be used to monitor clinical status over time (as a secondary function of the implanted device) [Scardovi and Boccanelli, 2024]. Current from the pacing wire is transmitted across the thorax towards the 'can' of the device (Figure 1.3) allowing changes in impedance to be determined (ibid). Positioning of the leads and the generator produce slight inter-individual variations in absolute impedance values (Tang and Tong 2009). Variation in proprietary algorithms used to analyse the signal also influence the data produced (ibid). This method produces a measure that reflects the amount of fluid in the lung extracellular space, which is comprised of both extravascular fluid and intravascular blood volume (ibid).

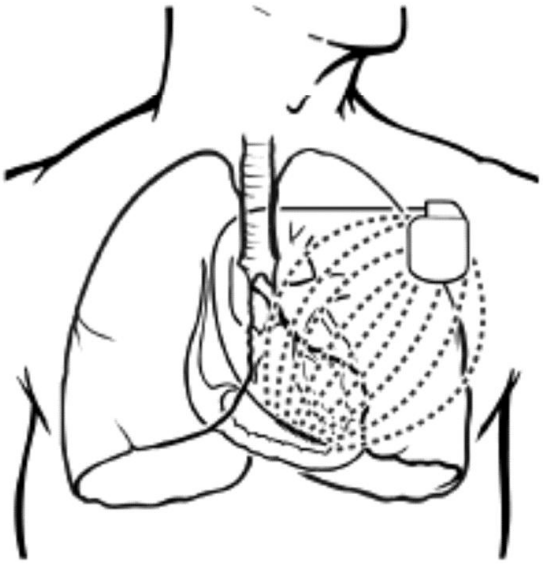


Figure 1.3. This graphic shows the placement of an implantable device system in the left pectoral region. The dotted lines represent intrathoracic impedance measurements (Taken from Yu, C. et al., 2005)

In patients with HF, blood enters the heart from the lungs faster than the LV can move it on towards the body. This imbalance generates a build-up of lung fluid, resulting in increased capillary hydrostatic pressure - with fluid accumulation in the interstitial lung tissue which impedes gaseous exchange and causes shortness of breath (Malek and Soufi, 2024). Diuretic drugs, known colloquially as 'water tablets' promote water loss through the kidneys and can reduce symptoms. Fluid provides less resistance to current flow than tissue or air, and so the electrical impedance tends to be lower in areas of higher fluid (Tang and Tong 2009). TI is thus inversely correlated with pulmonary capillary wedge pressure and fluid balance, and decreases before the onset of patient symptoms and before hospital admission for fluid overload (ibid).

This phenomenon can be exploited to assess changes in fluid accumulation in the setting of pulmonary congestion, and can be used as part of a CIED-based diagnostic tool for detecting subclinical signs and symptoms of congestive HF (Tang and Tong 2009). At the onset of pulmonary oedema, the impedance signal decreases and can restore to baseline after diuretic therapy. Tang and Tong (2009) described a cohort of patients treated with intravenous furosemide (a loop diuretic) on a coronary care unit. They noted an increase in TI during the diuretic therapy. TI correlated with both the pulmonary capillary wedge pressure ($r=-0.91$, $P<0.001$) and net loss of fluid ($r=-0.94$, $P<0.001$). Intravenous diuretic therapy over 3.2 ± 1.8 days resulted in a significant $17.1\pm9.4\%$ increase in intrathoracic impedance from $62.0\pm9.8\ \Omega$, to $72.0\pm7.9\ \Omega$ ($P<0.001$). During this same period, the pulmonary capillary wedge pressure decreased $45.1\pm21.7\%$ from 27.7 ± 8.6 to 15.2 ± 5.1 mm Hg ($P<0.001$), and the patients lost an average of 5.2 ± 2.6 L fluid (ibid).

TI varies by relatively small amounts and so changes can be difficult to recognise. One manufacturer, Medtronic, has implemented an algorithm - OptiVol® that quantifies deviation of TI from a reference value which can be used to trigger alerts. Most research on TI has centred, not on the raw TI data itself, but on this processed information an alert. Brown et al., (2018) investigated OptiVol® data in a CRT-D cohort with over 6 years of follow-up. In this group, single OptiVol® crossings and time above the OptiVol® threshold were both associated with increased rates of mortality and hospitalisation.

Although impedance measurement has shown promise in monitoring patients with HF, clinical adoption of the concept has been slow and patchy, due to concerns about sub-optimal specificity of TI when used as a single measure, and lack of generalisability across manufacturers.

1.9 Minimum clinically important difference

Minimum clinically important difference (MICD) is defined as the smallest change in an outcome that an individual would identify as meaningful or important (Copay et al., 2007). Shoemaker et al., (2012) estimated the MICD for D-PA measurements in a large cohort of HF patients with Medtronic CIEDs. They found that an increase of 0.9 hrs/day was associated with improvement in HF status, and a drop of 0.4hrs/day signified a clinically meaningful decline. These changes in PA were associated with a change in status of one New York Heart Association (NYHA) class. This study provides a possible starting point for setting a threshold value for the change that might be expected after an effective intervention (which might be used to identify responders). The MICD has not been investigated for TI.

1.10 Seasonal variation

Seasonal variation in D-PA is well-documented (Shoemaker et al., 2024). Typically there is an increase in activity with warmer temperatures and greater daylight hours (spring and summer

months in the northern hemisphere), followed by a reduction associated with colder weather and less daylight (winter months). Seasonal variation is not seen in all individuals, but where it is evident, the pattern closely approximates a sinusoidal waveform (Shoemaker et al., 2024).

Shoemaker et al., 2024 found that people who are more active and have fewer comorbidities demonstrated a greater seasonal difference (42 min per day) than those who are inactive) and have a greater number of comorbidities (6 min per day). The greatest seasonal variation was observed in male patients with low comorbidity/NYHA core, high BMI, and who are not hospitalized. It is possible that high BMI influences the forces on the accelerometer to produce higher readings, but this association has not been studied. In patients without a clear seasonal trend, an overall declining pattern of activity has been described, with downward trajectories (40–80 mins) throughout the year. This appears to be associated with female sex and hospitalization. Seasonal variation has not been investigated for TI.

1.11 Atrial arrhythmias: atrial fibrillation, atrial flutter, atrial tachycardia

Three types of atrial arrhythmia (AA) are commonly recognised; atrial fibrillation, atrial flutter and atrial tachycardia:

Atrial fibrillation

AF is the most common sustained arrhythmia, affecting 37.5 million people worldwide in 2017 (James 2018). This arrhythmia is characterised by rapid, irregular and chaotic electrical activation of the atria. AF incidence increases with age: the world population is aging and consequently it is has been estimated that in the next three to four decades up to 18 million people in Europe will be affected by AF (Chugh 2014;James 2018;Miyasaka 2006). AF is associated with high morbidity and mortality, and presents a large burden on healthcare systems. A diagnosis of AF increases the future risk of stroke five fold, doubles the risk of heart failure, and leads to increased mortality (Calkins 2012; Kirchhof 2017). It is estimated that worldwide, 287,000 deaths were linked to AF in 2017; around 3 million years of life were lost, and another 3 million years of life were spent in disability (Haro Abad 2018; James 2018).

Historically, AF has been classified by the duration of individual episodes of arrhythmia. Consensus definitions classify paroxysmal AF (PAF) as episodes lasting less than 7 days, persistent AF (PsAF) as episodes lasting greater than 7 days, and long-standing persistent AF (LSPsAF) as continuous AF lasting greater than one year in duration. Permanent AF describes AF in which the patient and clinician have decided to stop pursuing attempts to restore sinus rhythm (Schwennesen et al., 2023).

Atrial flutter

Isolated typical right atrial flutter (AFL) is a less common arrhythmia compared with atrial fibrillation (AF) with an incidence of 88 per 100 000 person-years (Bun et al., 2014). It is

characterised by fast, regular atrial activation which is caused by a re-entrant circuit around the tricuspid valve in the right atrium. It can be treated by CA across the cavo-tricuspid isthmus (CTI) with a high success rate and low complications Because of this, and because patients with AFL are often very symptomatic, ablation is usually performed as a first-line therapy (Trines, 2017) and operators generally have a low threshold for performing CA for typical flutter (ibid).

Atrial tachycardia

Atrial tachycardia (AT) is a rhythm characterised by fast regular activation of the atria. It is usually considered separate from AFL if the rhythm originates from a focus (focal atrial tachycardia) or the re-entrant circuit is different from the one responsible for typical AFL (Liwanag et al., 2024). ATcan occur as the result of previous CA for AF.

1.12 Effect of rhythm on cardiac performance

The efficiency of the heart is influenced by the cardiac rhythm. During atrial arrhythmias, the atria contract rapidly and often chaotically, resulting in loss of AV synchrony and an irregular and often fast ventricular rate.

Optimal atrio-ventricular (AV) synchrony is important for maintaining cardiac performance. In normal hearts, AV synchrony may lower left atrial pressure and increase cardiac index by as much as 25–30%. AV synchrony has a greater contribution in patients with impaired LV function; AV synchrony is estimated to increase stroke volume by as much as 50% in some patients (Di Terlizzi et al., 2024). Myocardial contractility increases with an acute increase in heart rate, due to an increase in the calcium concentration in the sarcoplasmic reticulum of cardiac muscle cells, and its increased release into sarcoplasm (Palomeque et al., 2004). Cardiac output increases with a rate increase up to about 90-120 bpm. Above this heart rate, cardiac output is maintained until about 140 bpm in cardiac patients, or up to 180 bpm in normal healthy subjects. Above this, cardiac output falls, due to a decrease in stroke volume caused by inadequate ventricular diastolic filling (Frank–Starling law). Longer-term elevation in HR can cause progressive deterioration in LV function – known as tachycardia-induced cardiomyopathy.

The hemodynamic changes associated with an irregular ventricular rhythm are detrimental. Clark et al. (1997) assessed the hemodynamic effects of an irregular ventricular cycle length in patients with AF referred for AV node ablation. AV node ablation allows the ventricular rhythm to be controlled by a pacemaker, producing a regular rhythm despite the presence of AF. Pacing the ventricle at the same average rate as the previously conduced AF resulted in a significant increase in cardiac output, and a decrease in pulmonary capillary wedge and right atrial pressure.

1.13 Interplay between arrhythmias and heart failure

Atrial arrhythmias (AA), of which the most important is AF, are common in patients with HF, and are associated with a worse prognosis (Batul, et al., 2017). AF is both a cause and consequence of HF, with complex interactions between the two conditions. Patients with HF have a high incidence of AA, in part because the two conditions occur in the context of similar underlying pathological conditions, including ischaemic heart disease (IHD), hypertension (HT) and valvular heart disease (VHD). In addition, HF itself causes acute and long-term changes that promote arhythmogenesis. Mitral regurgitation in patients with an impaired LV contributes to atrial dilatation, a key driver of AF. Autonomic dysregulation, calcium overload, and electrolyte imbalance, brought on by diuretic use or cardiorenal syndrome, also contribute to high arrhythmic burden (Carpenito et al., 2021). In turn, AAs impact negatively on HF status. Tachycardia-induced cardiomyopathy (TIC) is the impairment of ventricular function caused by a combination of rapid, irregular or asynchronous contraction during tachy-arrhythmia. Such ventricular dysfunction can be partially or completely reversed by treating the arrhythmia. In some cases, the arrhythmia may be the only reason for ventricular dysfunction (arrhythmia-induced TIC), or the arrhythmia may exacerbate pre-existing ventricular dysfunction and/or worsen HF in a patient with concomitant heart disease (arrhythmia-mediated TIC) [Ellis and Josephson 2013].

Patients with both AF and HF have a higher morbidity and mortality than people with either condition alone. Chelu et al., (2016) found that D-PA decreases and mortality increases after the onset of PsAF in patients with ICDs, and conversely, that most patients who returned to

normal sinus rhythm eventually also returned to baseline levels of activity, whereas patients who remained in AF did not. However, this study did not report if the return to normal rhythm was spontaneous or achieved by interventions. Treatments can restore normal rhythm (rhythm control interventions), but whether doing so results in a reduction in mortality in HF patients is contested (Packer & Kowey 2018) and the treatments carry risks.

1.14 Procedures to treat atrial arrhythmias

AF can be treated by getting patients back into a normal rhythm - *rhythm control*, or by accepting the presence of the arrhythmia and preventing the heart rate from going too fast - *rate control* (Verma et al., 2017). There is clear evidence that being in normal rhythm (known as sinus rhythm) is associated with improved survival compared to AF (Batul, et al., 2017). This suggests that rhythm-control approaches ought to confer a survival benefit, and numerous studies have demonstrated improvements in surrogate outcomes after restoration of sinus rhythm, including in exercise tolerance and LV function (Pfeffer, et al., 2019). Studies using anti-arrhythmic drugs (AADs) to restore sinus rhythm (SR), alone or in combination with direct current cardioversion (DCCV), have not shown superiority of rhythm control over rate control in patients with established AF (Van Gelder et al, 2002; Wyse et al., 2020; Carlsson et al., Roy et al., 2008). The AFFIRM trial (**A**trial **F**ibrillation **F**ollow-up **I**nvestigation of **R**hythm **M**anagement) showed no difference in mortality in patients with AF when comparing rate control with rhythm control using medical therapy (Corley et al., 2004). However, an on-treatment analysis of the AFFIRM data showed that the presence of sinus rhythm at follow-up

was associated with a decreased risk of death (adjusted HR 0.53, 99% CI 0.39-0.72, p < 0.0001) (Corley et al., 2004). AADs are associated with significant adverse effects, therefore it has been proposed that any survival benefit of restoring SR may be counteracted by the increased mortality associated with the AADs employed (Batul, et al., 2017). This hypothesis has driven a search for an effective and safe method to maintain sinus rhythm that might improve survival in addition to improving AF-related symptoms.

DCCV

In some patients, rhythm control can be achieved by using AADs, either alone but more often in combination with DCCV. DCCV involves the delivery of a controlled, synchronized, direct current (DC) electric shock through the chest from patches applied to the skin. DCCV is a cornerstone of rhythm control strategies in the management of AF and AFL in symptomatic patients. The high voltage shock stops the multiple circulating electrical wavefronts that are responsible for AF by rendering the majority of the atrial tissue refractory at the same time, allowing a normal beat to then emerge. Cardioversion is recommended as part of rhythm control therapy in symptomatic patients with persistent or long-standing persistent AF (Kwon, 2020). Cardioversion has a high (90%) acute success rate, and is the treatment of choice for patients with new-onset AF or AFL who are severely haemodynamically compromised (Brandes et al., 2020).

DCCV may also be used to establish if apparently asymptomatic patients with persistent AF are truly asymptomatic - to see if they show improved exercise tolerance during sinus rhythm (Kwon, 2020). This is often referred to as a 'trial of sinus rhythm'. DDCV may also be used to treat recurrence of arrhythmia early after catheter ablation of AF.

Although effective at stopping AF and other atrial arrhythmias, DCCV alone does nothing to prevent recurrence. The chances of maintaining sinus rhythm after DCCV, particularly in patients with HF, can be increased by the use of the anti-arrhythmic drug amiodarone (Camm et al., 2022). This drug has significant side effects however, due in part to the accumulation of the drug in various tissues over time, and the use of amiodarone is often avoided in younger people with fewer co-morbidities. If patients go back into AF after DCCV, they may require the more complex intervention of catheter ablation to increase the likelihood that they will maintain sinus rhythm for more extended time periods.

Catheter ablation

Catheter ablation (CA) is a treatment that has the potential to reduce AF-associated morbidity and mortality by establishing and maintaining sinus rhythm without the significant adverse effects associated with AAD therapy.

Catheter ablation (CA) is a procedure involving the insertion of catheters into the heart - to heat or freeze specific areas of tissue thought to be important in causing or maintaining an arrhythmia. CA has been used to treat AAs such as AFL since the 1990s, and has been used more widely in the treatment of AF since the beginning of the 21st century. AF ablation (AFA) has gained interest due to evidence of improvements in LV function, functional capacity and quality of life in comparison to rate control in HF patients (Anselmino et al., 2014; Batul, et al., 2017). Unfortunately, complete success with CA (i.e, no recurrence and no need for AADs) is uncommon, and the rate of complications is not trivial (Packer & Kowey, 2018).

Multiple trials have shown a significant reduction in AF burden and lower rates of arrhythmia recurrence with CA compared to AAD therapy, with similar rates of adverse safety events (Schwennesen et al., 2023). Moreover, CA delays the progression from PAF to PsAF more effectively than pharmacological therapy (Kuck et al., 2021).

Mortality benefit from AFA has not yet been conclusively demonstrated in the general population of AF patients. In 2012, a Cochrane review of 32 randomized controlled trials (RCT) revealed that patients treated with AFA were significantly more likely to maintain normal sinus rhythm, but that there was no significant difference in mortality compared to medical therapy (Chen et al., 2012). Subsequently, the CABANA trial reported no significant difference in its primary end point (composite of death, disabling stroke, serious bleeding, or cardiac arrest) in symptomatic AF patients treated with CA compared to patients treated with AAD therapy (Crawford et al., 2024).

Success rates after AFA in randomized studies of patients with HF vary from 50% to 88% (Mukherjee et al., 2018). Ullah et al., (2016) reported registry data demonstrating that the presence of HF is associated with lower success from AFA in patients with PsAF (57.3% vs 75.8%). However, there is emerging evidence of a survival benefit for AFA in the sub-population of patients with HF and AF who are at high risk of adverse outcomes. The AATAC study (Di Biase et al., 2016) was the first randomised controlled trial (RCT) to suggest a survival benefit from AFA in patients with HF. This study compared AFA to amiodarone and demonstrated a significantly lower mortality in the ablation group (8% versus 18%; P=0.037). The authors concluded that AFA is superior to amiodarone in achieving freedom from AF and at reducing mortality; but all-cause mortality was a secondary end point in the study. Subsequently, the CASTLE-AF RCT (Marrouche et al, 2018) also reported that AFA reduced the risk of death and HF hospitalization in patients with AF and HF by 40%, where a combination of risk of death and HF hospitalization was the primary end point in this study. Rather than settle the matter of survival benefit from CA of AF in HF, the CASTLE-AF trial has come under intense criticism over its methodology - including that its conclusions were based on a small a number of events, that it was not blinded, and that the trial population was very highly selected and not representative of the real-world clinical population (Packer & Kowey, 2018). Packer & Kowey (2018, p753) comment that "*…the results of the CASTLE-AF trial are hypothesis-generating. It is impossible to have confidence that the findings will be reproduced in properly designed trials".* Patients in CASTLE-AF all had CIEDs but did activity data from the devices was not analysed. Following this, Kirchhoff et al., (2020) published the results of EAST-AFNET (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), a large, international,

blinded-outcome-assessment trial, in which patients who had recently-diagnosed AF (diagnosed ≤1 year before enrolment) and cardiovascular conditions were randomly assigned to receive either early rhythm control (with AADs or CA) or usual care. The authors concluded that rhythm-control therapy delivered early after the discovery of AF is associated with a lower risk of adverse cardiovascular outcomes than usual care. This study emphasised the *timing* of treatments for AF - that interventions delivered early after the onset of AF may be more likely to be successful. Subsequently, the EAST-AFNET 4 trial showed benefit from an early rhythm control strategy in patients with a recent diagnosis of AF (Kirchhof et al. 2020). In this study, when compared to usual care, patients randomized to early rhythm control had lower rates of stroke, hospitalization for worsening HF or acute coronary syndrome, and death from cardiovascular causes. The effectiveness of early rhythm control was associated with the presence of sinus rhythm at follow-up. The majority of sinus rhythm was achieved with AAD therapy, but AFA was also utilised in the trial. Although D-PA has been widely associated with mortality, it has not yet been demonstrated to be affected by AFA.

1.14 AF Burden

Conventional AF classifications may be useful in clinical practice but are imperfect. They rely on a patient's subjective reporting of symptoms, which is used to infer persistence and duration of AF episodes. The amount of time spent in AF (AF burden) can significantly overlap between clinical classifications. Even in patients within the same clinical AF classification, AF burden can vary considerably. Some "paroxysmal" patients with frequent short episodes may in fact spend more time in AF than a "persistent" patient with rare longer episodes (Al-Turki and Essebag 2024).

The CASTLE-AF trial did not demonstrate a relationship between AF recurrence and the primary outcome (composite of all-cause mortality and hospitalization for worsening HF). However, there was a clear relationship between AF *burden* and outcomes (Marrouche et al, 2018). The study could assess AF burden accurately because subjects all had CIEDs which record time spent in atrial arrhythmia per day. Long-term AF burden was reduced with CA but not with medical therapy. Among patients treated with CA, those with AF burden <50% at 6 months had a significantly reduced risk of the primary outcome and all-cause mortality, as well as a non-significant reduction in HF hospitalisation. The findings of this trial point to AF burden after AFA as a more important outcome with greater clinical significance than AF recurrence. Figure 1.4 shows the relationship between AF burden and clinical impacts.

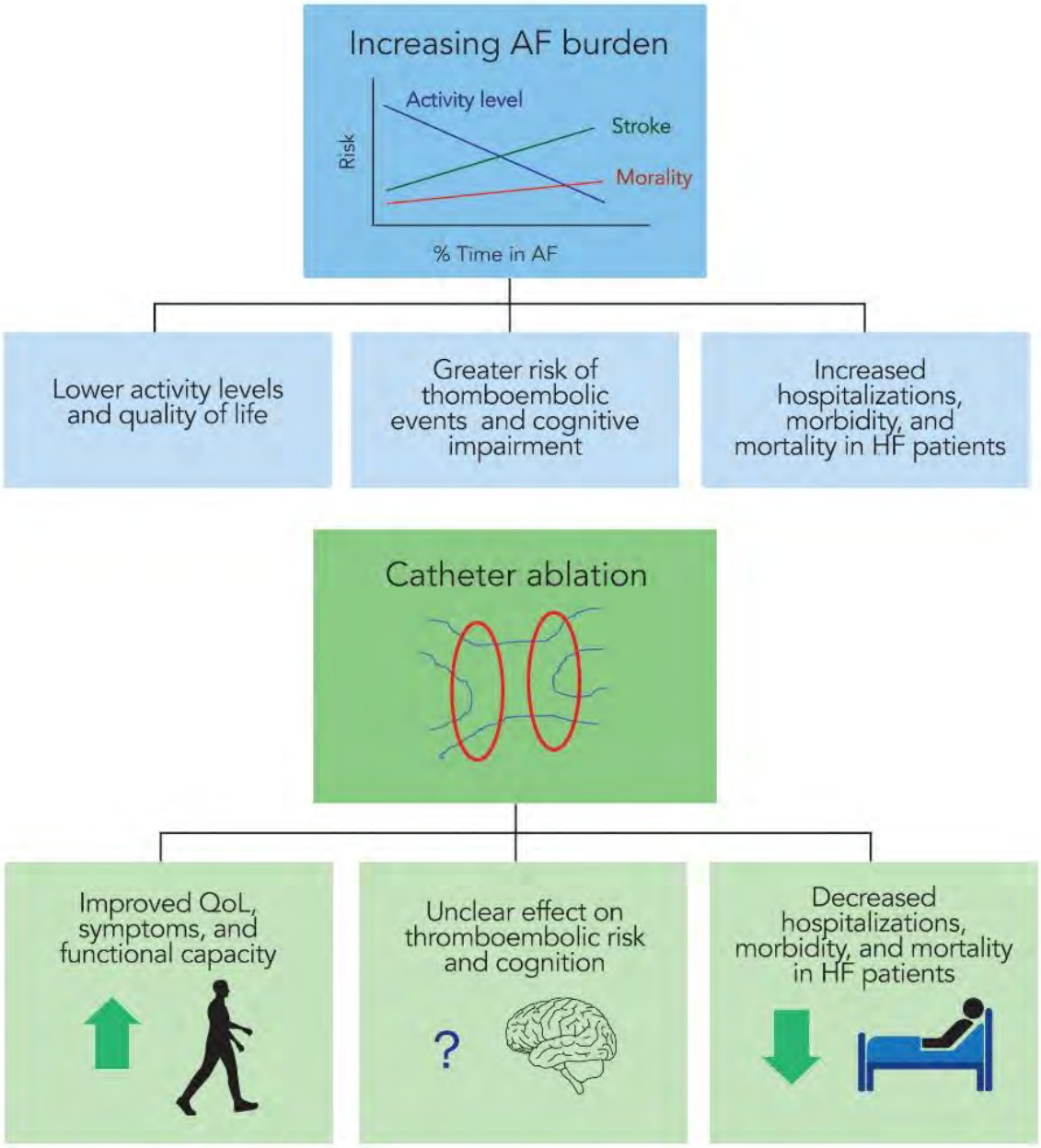


Figure 1.4. A schematic diagram showing impact of atrial fibrillation (AF) on patient outcomes after ablation. (Taken from Schwennesen et al., 2023).

1.15 Current challenges

Asymptomatic AF can be detected by CIEDs and clinicians face significant challenges determining the appropriate treatment of such subclinical arrhythmia (Schwennesen et al., 2024). Many questions remain about the relationship between AF burden, cardiovascular outcomes, and rhythm control with DCCV or CA (Schwennesen et al., 2024).

The current definition of recurrence (the presence of any AF episodes greater than 30 seconds) does not correlate with adverse clinical outcomes. In order to better assess the clinical success of AFA, it has been suggested that recurrence should be defined as a burden of AF that is associated with lower quality of life, higher healthcare utilization, and higher risk of hospitalization or death (Schwennesen et al., 2024).

There are significant gaps in knowledge regarding the inter-relationship between AF and HF. Atrial arrhythmias are associated with a worse outcome and prognosis in patients with HF (Verma et al. 2017) but it is not clear if the AF is the root cause of this poor outcome, or simply a marker for more severe disease (Kotecha, & Piccini, 2015). Furthermore, controversy continues regarding the best approach to treating AF in patients with HF, and if doing so improves their survival (Packer & Kowey 2018). Both rate and rhythm control treatment strategies have been associated with improvement in quality of life but until recently both approaches have reported mostly neutral effects on stroke and mortality (Crawford et al., 2024). However, the EAST-AFNET 4 trial has shown that early rhythm–control therapy was associated with a lower risk of cardiovascular outcomes (ibid)

Current recommendations state that rhythm control therapy is indicated to improve symptoms (Camm et al., 2022; Yamane 2022), but in clinical practice a significant proportion of asymptomatic patients are also treated by rhythm control procedures. For example Ferre-Vallverdu et al., 2021 were surprised that 41.8% of patients who underwent DCCV were asymptomatic. Other studies have reported a high proportion of asymptomatic patients undergoing AFA (Yamane 2022). This may reflect the perception among clinicians that rhythm control therapy has favourable effects on cardiovascular haemodynamics, and therefore they would argue that rhythm control must also have a beneficial effect on outcomes such as survival and hospitalisation, even if direct evidence for this is still somewhat lacking.

It is possible that digital biomarkers from CIEDs might be useful as endpoints in future clinical trials for the treatment of AAs and other cardiac conditions. However, to define a primary or secondary endpoint, exploratory digital biomarkers need to be tested and validated. Measured data only becomes a useful biomarker when it connects to an important health-related outcome. To have operational value, DBs need to be tightly linked to disease and its modification by interventions (Motahari-Nezhad et al., 2021). Only one study has so far evaluated the change in D-PA following a cardiac intervention (Peigh et al., 2022). This retrospective analysis of patients undergoing AFA failed to show any significant difference before and after treatment, despite the procedure having a good effect on the target condition. After ablation, significant reductions in AF burden were recorded. However,

somewhat surprisingly, no significant changes in activity minutes per day were observed following the procedure. The study did not evaluate TI measurements.

The clinical use of intrathoracic impedance monitoring remains limited. There is no consensus as to which clinical actions might avoid adverse outcomes in response to changes in readings, or whether device-measured information should be used alone or in combination with an in-person clinical evaluation (Abraham 2007). Long-term data demonstrating the independent impact of clinical procedures on TI monitoring in a real-world cohort would be an important addition to the current knowledge base.

Treatments likely to have mortality benefit might be expected to increase functional capacity and reduce pulmonary congestion. CIEDs routinely and continuously record digital biomarkers that are known to reflect these quantities. Patients with CIEDs (which include pacemakers and implantable defibrillators), often have underlying HF, and frequently develop AAs including AF (Verma et al. 2017). Front-line clinicians, including cardiac scientists, currently have no objective way of knowing whether any given patient is likely to derive survival benefit from restoring normal rhythm. A tool that would allow clinicians to monitor the effect of treatments on FC or pulmonary congestion might enable better and more personalised treatment decisions and the development of more effective therapies. D-PA and TI exhibit many of the characteristics of an ideal biomarker but better understanding of their characteristics are required before they can be utilised in the assessment of the outcome of procedures or other changes in treatment (such as changes in CIED programming). The current study will help to

inform methods of analysing D-PA and TI data for on-going and future clinical trials, as well as providing insights for clinical management of CIED patients.

1.16 Research Aim

Digital biomarkers could be used to monitor cardiac improvement after therapeutic procedures and so augment conventional clinical and research evaluation of patient outcomes. The use of different parameters recorded by CIEDs as potential digital biomarkers for assessing such outcomes has not been widely investigated. The aim of this thesis was to investigate the potential suitability of two parameters, D-PA and TI, for use as digital biomarkers, by comparing these variables from 12 months before to 12 months after DCCV and ablation procedures for AAs in patients with CIEDs.

1.17 Research Objective

1. Develop methods for comparing the pre and post procedure periods
2. Assess if any observable changes are associated with rhythm correction
3. Investigate the influence of device manufacturer on D-PA and TI values and trends.
4. Explore the relationship between season and D-PA and TI trends.
5. Explore the relationship between D-PA and TI and whether they affect each of other
6. Examine the influence of factors other than the procedure on the data
7. Identify changes in D-PA or TI that are linked to the clinical course of individual patients

CHAPTER 2:

PROJECT METHODS

2.0 Study design, setting, and participants

The study was an exploratory feasibility/pilot study to investigate the potential use of DBs measured by CIEDs in assessing the health benefits of procedures to treat AAs such as AF. The investigation was a retrospective, single-site, observational study - utilising data routinely collected during standard clinical care, and a repeated measures quasi experimental (AB) design.

The study took advantage of a natural experiment - patients had received a clinically indicated procedure to treat an atrial arrhythmia (either a CA or DCCV). Each patient acted as his or her own control for demographic and clinical variables, and the study was therefore a within-subjects design with repeated measures. Using a within subject design controls for individual differences that could confound the results, such as age, baseline health, or pre-existing co-morbidities.

No data were collected over and above that required for clinical purposes, and no additional study visits were imposed on patients. Physiological parameter data were collected continuously by the implanted device as part of standard care. Participants were not asked to complete any type of survey or questionnaire, and did not undergo any additional tests or investigations. No changes in medication or other therapy were instigated as part of the study. The investigator had access to the relevant data as part of their clinical role. Institutional ethical approval was in place for the retrieval and processing of numerical data from the Carelink and Latitude remote monitoring systems. This current sub-study will help to inform data-analysis methodology for on-going and future clinical trials.

Each patient received a sequence of two 12 month "treatment" periods for atrial arrhythmia as part of their standard care. The first 12 m period was the baseline treatment and the second period followed on from a procedural intervention of either DCCV or CA. The same measures, D-PA and TI, were collected multiple times for each subject as part of routine clinical care. Figure 2.1 shows example data indicating the baseline and intervention periods. An entire 12 month period before and after the procedure was chosen to account for seasonality.

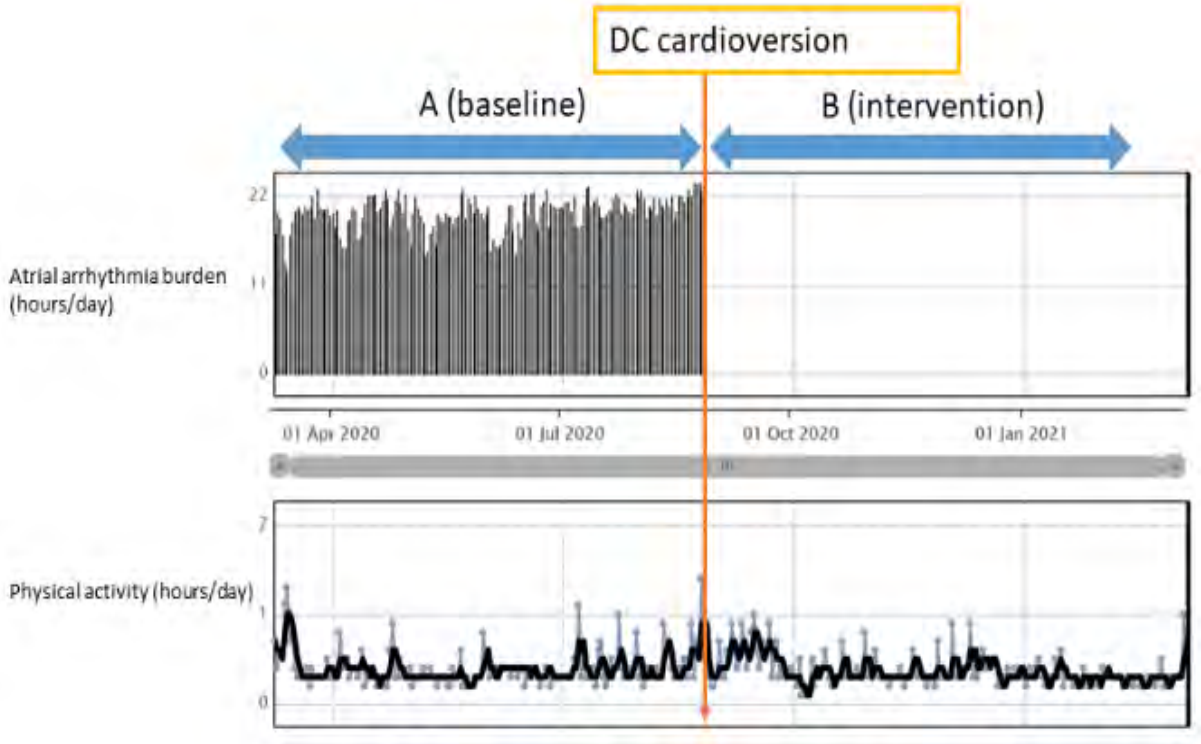


Figure 2.1 Example CIED data (in this case D-PA) demonstrating a reduction in AF burden after DCCV, and illustrating the AB design.

To balance treatment assignments, trials usually employ multiple-period crossover experiments (ABAB) using randomisation and counterbalancing (Kravitz & Duan, 2014; Duan et al., 2013). However, it would be difficult to use this approach for rhythm control interventions for AAs, even in prospective trials, because the treatment terminates the condition of interest, and it would be difficult (and unethical) to re-introduce it artificially (i.e. re-induce the AA). This factor limits repeated measures investigations of procedures for AAs to a quasi-experimental approach, regardless of whether prospective or retrospective. Because the treatment terminates the condition of interest, the order of treatments also cannot be

randomised. This means that the effect of time cannot be controlled for – in the current study the active treatment was always the second 12 month period. Patients might be expected to deteriorate over time without treatment (Sankaranarayanan et al., 2015) so this would be unlikely to produce an artefactual appearance of improvement.

2.1 Choice of device manufacturer

Many studies involving CIEDs focus on devices from only one manufacture (Powell et al., 2013; Shoemaker et al., 2021). This is almost always the case with large multicentre trials involving CIEDs. The principal reason appears to be that the manufacturer is a sponsor of the research. There are also differences in algorithms and other aspects of device functioning that may differ between manufacturers which could be confounders. Previous studies of D-PA and TI measurements have tended to be single manufacturer studies, which limits the generalisability of these studies. For equitable treatment of the CIED population as a whole it is desirable that where possible, patients with devices from different manufacturers can all benefit from research findings. In the case of the present study, CIEDs from both Medtronic and Boston Scientific were utilised. These manufacturers store D-PA data continuously even during AA episodes and store daily TI data in Ohms for many of their devices. This can be retrieved as raw numerical from their remote monitoring systems.

The setting for this research was the tertiary referral centre for CIED implantation and follow-up that serves a local population and the wider conurbation. The study sample was drawn from

all ambulatory adult patients (aged ≥ 18 years) with Medtronic or Boston Scientific CIEDs being monitored remotely by the Hospital Trust. The types of CIEDs included cardiac resynchronization therapy devices [CRT-D (with defibrillator), CRT-P (with pacemaker)], implantable cardioverter-defibrillators (ICDs) and dual chamber pacemakers; all devices with a functioning atrial lead to facilitate detection of AA.

Pacemakers are implanted into patients who experience symptomatic bradycardia (slow heart rhythms). Implantable cardiac defibrillators (ICDs) are implanted to prevent sudden death from life-threatening ventricular arrhythmias, usually in people with severe structural heart disease. CRT aims to reduce symptoms from HF by optimising the synchronisation of the heart chambers (Jafferani et al., 2019)

2.2 Population of patients with CIEDs from which the sample population was drawn

The sample for this study was drawn from a local CIED population of approximately 4,500 adult patients with a pacemaker, CRT (P or D) or ICD remotely monitored by the hospital. The median age of this CIED population was investigated recently as part of a service evaluation, and was fond to be 79.5 years (Wright, 2020). Of those with a pacemaker, the median age was 81 years. The ICD population is younger, with a median age of 75 years. Published data on the characteristics of patients with CIEDs are somewhat misleading, as most studies recruit patients

at the time of their first device implantation. This leads the age and comorbidities in these studies to not being representative of the real-world ambulatory CIED population as a whole – some patients live for decades after the initial implantation and acquire co-morbidities as they age. For example, the median age of ICD patients reported in the DANISH study was 63 years (- Køber et al., 2016) - but this was age at implantation and is therefore unrepresentative of the follow-up population.

2.3 Data sources: Inclusion and exclusion criteria, missing AF burden, Covid lockdowns

Data was acquired from two sources used in routine clinical care: hospital-based electronic health records on site, and transmission data from the CIED manufacturer's cloud service; the CareLink network for Medtronic devices and the Latitude network for Boston Scientific. Daily data is stored in the on-board memory within the implanted device until a data transmission (download) occurs - either as an alert triggered by detection of new information, or as a routine scheduled transmission that occurs at 3-12 monthly intervals (for most patients as per guidelines). When a transmission is triggered, measured parameters for each day are uploaded to the CIED manufacturer's cloud service. The hosted cloud service collates all device transmissions and produces data reports that can be accessed by local care providers (cardiac physiologists) using a secure login as part of standard care.

Inclusion criteria

- Age over 18 years. No upper age limit.
- CIED with functioning atrial lead registered on either the Medtronic Carelink or Boston Scientific Latitude remote monitoring system
- CA or DCCV for rhythm or rate control of atrial arrhythmia

Exclusion criteria

- CIED implanted <15m prior to procedure

15m (rather than 12m) was selected to allow at least a 3m lead-in period for stabilisation of measurements post implantation. This is because patient activity may be reduced post implantation due to pain, anxiety and medical advice regarding convalescence, and TI is known to decrease initially post implant (due to build-up of fluid in the space surrounding the CIED during wound healing) before then subsequently rising gradually to an equilibrium level (Figure 2.2) as a stable fibrous pocket forms around the device.

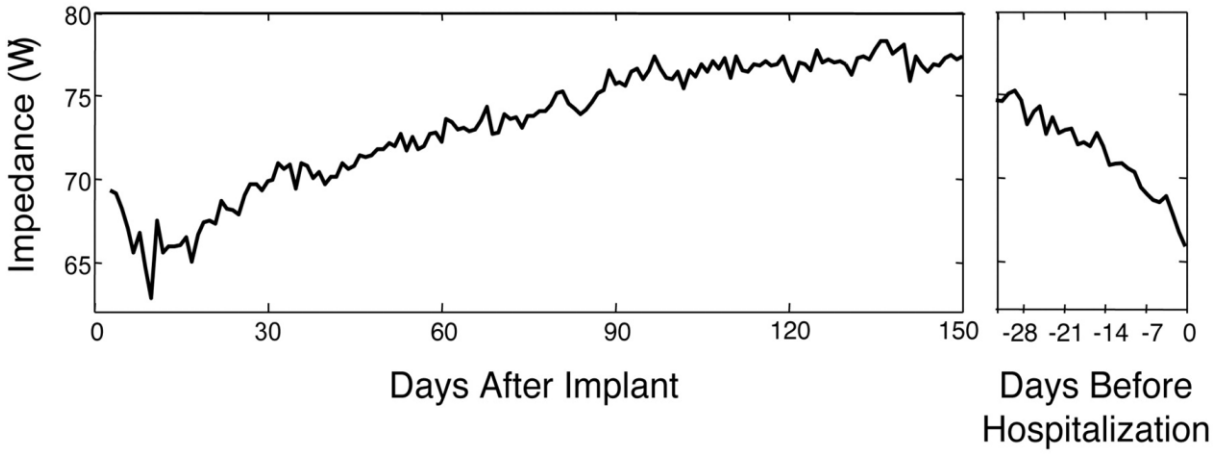


Figure 2.2: Thoracic impedance after device implantation. There is an initial rapid fall followed by gradual rise to a stable baseline level (Yu, C. et al., 2005)

CIED replaced <12m after procedure

In some cases, the CIED might be replaced with another device before the end of the 12m post-procedure, period because of the battery. In this case the patient would receive a new CIED, but D-PA and TI data from a different device could not easily be compared, and this would add a confounder. Patients with >10% of the 24m monitoring period missing were excluded at this stage (Figure 2.3).

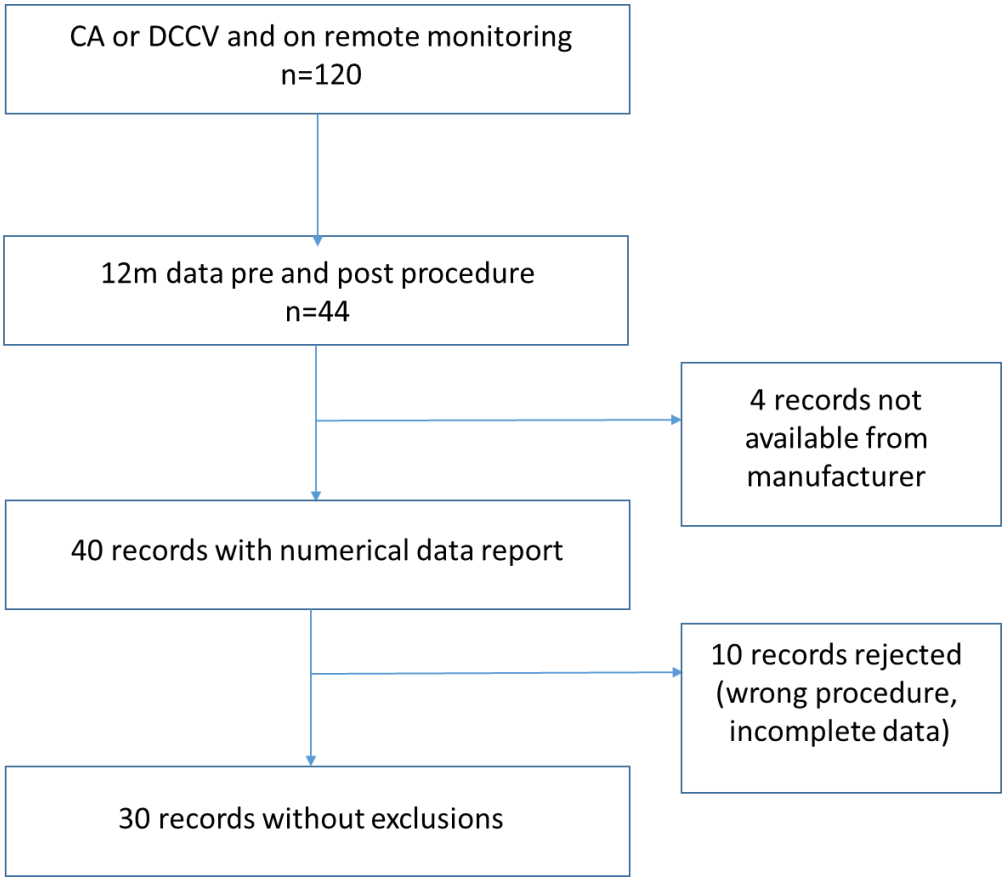


Figure 2.3: Flow diagram of identification of the patient population.

Three patients with < 10% missing data were found to have had the CIED implanted <15m prior to the procedure due to incorrect procedure details. Consequently, some data immediately after implant needed to be excluded from analysis to ensure measurements had reached a stable equilibrium level. This resulted in an increase in missing data at the start of

the pre-implant year in these three patients; 78, 93 and 139 days of data were missing or excluded at the start of the pre-procedure 12m period in these patients, representing 10.7%, 12.7% and 19% of the total 24m period respectively (21.4%, 25.5% and 38% of the pre-implant 12m baseline period). Due to the small number of available records, it was decided to include these patients in some of the analyses - depending on the amount of missing data and the likely impact on the specific question. All patients were included in evaluations that did not involve comparing the pre and post procedure time periods (for example correlation between D-PA and TI). Patients with >25% of the baseline year missing (2 patients) were excluded from analysis of measures pre verses post procedure, as a seasonal effect could not be adequately accounted for.

In a large study, seasonal effects could be accounted to some extent by a subgroup analysis of patients with procedures performed at different times of the year. But for a small cohort, the time of year of the procedure could be a significant confounder. A period of stable data for 12m pre and 12m post procedure was chosen to minimise such seasonal effects - analysis of a full year of data pre/post for each patient minimises any seasonal effect.

Missing AF burden data due to device programming

CIED records were reviewed to ensure the reliability of atrial sensing. No patient was found to have significant periods of atrial over or undersensing which might significantly affect AT/AF burden.

Covid lockdowns

A proportion of the records included time periods during national Covid lockdowns which could affect physical activity. These periods were not excluded, but were noted, and the proportion of the total 24m period and the proportion of each 12m segment were calculated.

2.4 Sample size: estimated verses actual

As this was a hypothesis generating study with no prior data, the advice of Maas and Hox (2005) was followed to aim for a sample of at least 50 participants. From analysis of the list of catheter ablation (CA) and DCCV procedures (from 2015 onwards), it was estimated that there were 2830 CAs and 1205 DCCVs for an AA at the Trust. Luker et al., (2018) found that 11% of patients undergoing DCCV have a CIED. From this it could be estimated that *133* patients undergoing DCCV during the study period would have a CIED. This estimate proved accurate, since 137 patients with CIEDs who had been treated by DCCV were subsequently identified. Packer et al., (2021) found that 26.3% of patients undergoing AFA have HF, which would suggest that 744 of the CA patients would likely have HF. Noseworthy et al., (2020) found that 25% of HF patients undergoing AF ablation have a CIED. From this it was possible to estimate that 186 patients undergoing CA for AA would have a CIED. However, only 73 patients with CIEDs who had received CA for an AA were subsequently identified.

In total, it was estimated that 319 patients undergoing a procedure for an AA would have a CIED. Of these not all would have D-PA data available via remote monitoring for the period before and after the procedure. It was difficult to accurately determine how many patients would have these data, as rates of patients with remote monitoring have been changing significantly over the last decade. From experience it was estimated that around 90% of ICD patients and 40% of pacemaker patients would be registered on remote monitoring. Approximately 25% of CIED patients have an ICD suggesting that 168 patients would have remote monitoring. If only 1 in 3 patients had 24 months of data surrounding the time of the procedure this would yield a sample of 56 patients. However, due to the lower than expected number of CIED patients undergoing CA, only 210 patients for DCCV or CA were identified. Of these, 124 (59%) were registered on the Carelink or Latitude remote monitoring systems. 30 patients had sufficient data before and after the procedure to be included in the study.

2.5 Comparison of the sample population with the unselected CIED population

The age of the cohort was about 10 years younger than the median age of the total CIED population previously established from a service evaluation (Wright, 2020). This is likely to be because the proportion of ICD patients in the current study was higher than the proportion in the overall population, and because some elderly patients may be considered too frail to undergo therapeutic procedures – particularly AFA which may require general anaesthesia.

Patients with ICDs tend to be younger than pacemaker patients (Elming et al., 2017). The median age of the patients who had a pacemaker (dual chamber or CRT-P) was 76 years compared to a median of 65 years for ICD patients (dual chamber ICD or CRT-D). As well as being younger, ICD patients may be preferentially selected for CA because of inappropriate shocks triggered by AA.

2.6 Identifying the 24m time period for each patient

The date of the procedure was identified. This date was assigned the number 366, and days were numbered backwards from 366 to day 1 and forwards from 366 until day 730. This segment of 730 days (24m) was isolated for further analysis. Each day had an associated date and a variety of daily measurements. Three continuous variables were analysed: D-PA, daily TI and daily AF burden. For both Medtronic and Boston Scientific CIEDs the TI measurements were in Ohms (Ω). For Medtronic CIEDs both D-PA and daily AF burden measurements were recorded in minutes/day. For Boston CIEDs both D-PA and daily AF burden measurements were recorded in milliseconds/day. AF burden was converted to hours/day for all analyses. D-PA was converted to hours/day when presented graphically alongside AF burden, but for statistical analyses minutes/day were utilised.

2.7 Clinical Procedures: DCCV and AFA

The procedures were clinically indicated and were performed as standard care according to local protocols.

DCCV procedures

All patients having DCCV were in PsAF at the time of the procedure. Procedures were performed under general anaesthesia; some in an operating theatre whilst others were carried out in a cardiac catheter laboratory. Electrodes were placed in an anterior-posterior orientation and a synchronised direct-current shock was applied to terminate the arrhythmia. All procedures were acutely successful in terminating the AF.

AF ablation (AFA) procedures

Some patients having AFA were in PsAF at the time of the procedure, but others were in sinus rhythm. Procedures were performed in a cardiac catheter laboratory and all except one were under general anaesthesia (GA). The exception was one cryoablation procedure which was performed under conscious sedation. Pulmonary vein isolation (PVI) was confirmed in all patients. If a patient remained in AF at the end of the procedure, DCCV was performed to achieve sinus rhythm.

Transseptal puncture was performed under trans-oesophageal echo (TOE) guidance in patients under GA or using intra-cardiac echo (ICE) guidance for patients under conscious sedation. For patients having cryoablation (n=4), a 14-F deflectable sheath (FlexCath, Medtronic, Minneapolis, MN, USA) was advanced through the trans-septal puncture and cryoablation was delivered using a 28 mm balloon (second-generation Arctic Front Advance, Medtronic). The balloon was advanced to the ostium of each pulmonary vein (PV) and ablation of the PV antra was performed. Continuous monitoring of the phrenic nerve during ablation of the right PVs was systematically performed by pacing the right phrenic nerve with a deflectable catheter in the superior vena cava (Rordorf et al., 2021). Patients having radio-frequency ablation (RFA) had wide area circumferential ablation to achieve PV isolation, guided by the CARTO 3D electro-anatomic mapping system.

2.8 Ablation of atrial flutter and atrial tachycardia

All patients with atrial flutter (AFL) or atrial tachycardia (AT) were in persistent arrhythmia at the time of the procedure. Ablation of the cavo-tricuspid isthmus (CTI) for the treatment of typical AFL was performed under local anaesthetic using RFA. AFL was terminated by RFA delivery and bidirectional block was confirmed. Ablation of non-CTI dependent atrial tachycardia (AT) was performed, guided by the CARTO 3D electro-anatomic mapping system.

2.9 Statistical analysis

The study was a within-subjects design with repeated measures. Outcome measures were D-PA (minutes per day) and TI (Ω). These are objective, and collected continuously without the need for patient involvement. Furthermore, they have been shown in multiple studies to be associated with prognosis, and to be highly predictive of hospital admission and death. Data from a 24 month period (12m pre, 12m post procedure) were used to account for seasonal variability.

Measurements of D-PA and TI data for the two periods were summarised. The change in these variables before and after the procedure was calculated. Year to year comparisons were performed using a repeated measures approach. If the variable was normally distributed, a T test for dependant means was used to compare mean values across two summary observations in the same patient (mean for 12 months pre and 12 months post procedure). If the distribution of the variable could not be assumed to be normal, a non-parametric test for two dependent means – the Wilcoxon Signed-Rank Test, was used. Normality was checked utilising the Shapiro-Wilk Test (α=0.05).

The two-sample t-test (independent samples t-test) was used for the comparison of mean values between independent groups of patients if the variable was normally distributed. Effect size was calculated using Glass's delta. Glass's delta was used where groups had a different standard deviation. The non-parametric Mann–Whitney U test was used if the distribution of

the variable could not be assumed to be normal. Categorical variables were compare using t-test for proportions.

Pearson correlation coefficient (r) was used to quantify the effect size of the correlation between continuous variables that followed a normal distribution. This was used to quantify the correlation between AF burden and D-PA, and between AF burden and TI. It was also applied to quantify correlation between D-PA and TI.

The slope of D-PA and TI measures over the year pre and post procedure was calculated. The t-test was used to compare the slopes of the regression lines of both D-PA and TI over the two periods.

Time series can be analysed using an interrupted time series methodology. This involves comparing the actual slope post intervention with the counterfactual (forecast) derived from the pre intervention trend. However, when the 12m pre and post procedure slopes for D-PA and TI were examined, they were not statistically different (except in for D-PA slopes in one patient). It was therefore considered inappropriate to employ this type of time series analysis in the context of this study.

Analysis was performed using R version 4.3.0. Two-sided P-values <0.05 were considered statistically significant.

CHAPTER 3:

IMPACT OF RHYTHM CONTROL PROCEDURES ON DIGITAL BIOMARKERS: CHANGE IN ARRHYTHMIA BURDEN CORRELATES WITH CHANGE IN TI BUT NOT D-PA

3.0 Introduction

Atrial fibrillation (AF) is an important public health concern with growing prevalence. It is associated with increased morbidity and mortality, and presents an escalating cost to healthcare systems (Buja et al., 2024). Management is complicated by the chronic, progressive nature of AF, and the complex relationship between disease substrate and coincident comorbid conditions.

There are two broad approaches to the treatment of AF and other AAs; rhythm control and rate control. The aim of rhythm control is to return a patient to a normal heart rhythm - known as sinus rhythm (SR). This can be achieved by medication, by delivering an electric shock to the chest (DCCV) or by catheter ablation (CA). Often, a combination of all 3 approaches is

needed, particularly in patients with HF and other comorbidities. DCCV is often used as a 'trial of sinus rhythm' – to establish if a particular patient derives symptomatic improvement in SR.

A rhythm-control strategy accepts that restoring and/or maintaining SR is not achievable, and instead focuses on preventing symptoms that result from the excessively fast heart rhythm (tachycardia) which can result from AAs. Rate control with medication is the first-line approach, but if this fails, the electrical connection between the atria and the ventricles (the AV node) can be permanently destroyed by applying heat energy in a procedure called AV node (AVN) ablation.This renders the patient more dependent on their pacemaker, but it prevents the rapid atrial impulses from causing symptoms.

The evidence base for rhythm verses rate control strategies in atrial AF remain contentious (Olanisa et al., 2023). There is little data regarding which procedures are most successful in which CIED patients, and which CIED patients derive most benefit from being in normal SR. Despite continued improvements in mapping and ablation technology and the growing experience of specialist teams performing the procedures, the results of CA of AF (AFA) continue to be suboptimal in some people (Boersma et al., 2023). Poor outcomes following AFA may lead to an increase in healthcare utilisation and reduce patient satisfaction (Schwennesen et al., 2023). Outcomes are impacted by a number of demographic and clinical variables, including female sex and the presence of diabetes (Uemura et al., 2023)

Early referral after the onset of AF has been identified as a barrier to improving patient outcomes - shorter diagnosis-to-ablation time consistently improves outcomes from AFA (Chew et al., 2020). Care of CIED patients has traditionally been focused on ensuring optimal performance and longevity of the implanted device and leads; historical workflows have not been designed to provide timely evaluation and escalating treatment strategies for CIED patients who develop AAs. Patients with CIEDs represent a very heterogeneous population, with a wide range of demographic and clinical characteristics, and the optimal functioning of different categories of device is impacted differently by AAs. Dedicated clinics for managing AF have been demonstrated to improve mortality and reduce cost compared to standard care, and broaden access to subspecialty care (Robinson et al., 2022). However, such clinics do not form part of standard care for patients with CIEDs, despite the high incidence of AAs in this population.

3.1 Aims

1. To characterise a cohort of CIED patients referred for DCCV or CA of atrial arrhythmia.
2. To compare referral pathways and patient characteristics of patients undergoing DCCV and AFA procedures

3. To evaluate the success of rhythm control procedures in reducing AF burden, and to investigate if digital biomarkers collected by CIEDs correlated with change in AF burden.

This study was a retrospective, single-centre, observational study of patients undergoing ablation for paroxysmal (PAF), persistent (PsAF) atrial fibrillation, atrial flutter (AFL) or atrial tachycardia (AT).

3.2 Methods

Patients were identified using the institution's electrophysiology lab procedure list, and the operating theatre DCCV list for the period from January 1, 2016, to May 31, 2023.

Inclusion criteria

Patients were included in the study if they were older than 18 years of age and had a CIED *in situ* at the time of undergoing a CA or DCCV procedure to treat an atrial arrhythmia. Patients were not excluded if they had had a prior CA, DCCV, or both.

Exclusion criteria

Patients were excluded if they did not have a device manufactured by Medtronic or Boston Scientific, if they were not enrolled on remote monitoring, or if their CIED was followed-up at another institution. Patients were excluded if they had their current CIED implanted less than 12 months before the DCCV or CA or if it was removed less than 12 months after the procedure.

Arrhythmia recurrence was evaluated at 6 months and 12 months following rhythm control procedures. Data from implantable cardiac monitors and electrocardiograms in the electronic health record (EHR) were also reviewed, when available, and recurrence was defined as 30 seconds of sustained AF, AFL, or AT.

Covariates

Patients' age, sex, and comorbidities were obtained from the EHR. Valvular heart disease (VHD) was defined as at least moderate valvular stenosis and/or the presence of prosthetic heart valves. Comorbidities that were diagnosed after the 24-month study period were not counted.

3.3 Analysis of D-PA and TI data

The mean daily D-PA and mean daily TI were calculated for two 12-month periods; the 12m leading up to the procedure (pre) and the 12m after the procedure (post). For three patients with missing data, this was calculated for the period with available data.

The change in mean D-PA and mean TI from 12m pre to 12m post procedure, and the slope for each measure for each period was calculated, and the pre and post slopes were compared to determine if there was a significant change.

For patients undergoing rhythm procedures the proportion of the year spent in an AA was calculated as a percentage for both the 12m pre and 12m post procedure, as well as the change in burden between the two periods. A graph of change in AF burden was plotted against change in mean D-PA and mean TI. Where TI measures were available, patients were divided into 3 tertiles based on the change in AF burden. The change in TI for each of the 3 subgroups was determined.

3.4 Results (entire cohort)

3.5 Patient characteristics (entire cohort)

A total of 30 patients were identified (Table 1). Average age was 65.7 ±13.8 years. The youngest patient was 36, and the oldest was 88 years. The majority of patients (n=21) were male (70%). Female patients tended to be older (median age 75 vs 66 years for males), had better preserved LV function (median EF 46 vs 35%) and lower BMI (24.5 vs 29.4 kg/m^2). These differences between males and females were not statistically significant. The majority of patients were white (77%). Two patients (7%) were of Asian British- Indian background, one patient was of mixed white and black Caribbean ethnicity and one patient was recorded as 'Asian – any other Asian' background. For one patient, ethnicity was recorded as 'other-not stated'.

The mean BMI for all patients was 28.5 kg/m^2 ± 4.7 (overweight). 7 patients (23%) had a BMI in the normal range, 12 patients (40%) were overweight, 11 patients (37%) were obese, and one patient had a BMI of 42.3 kg/m^2 (morbidly obese).

The LVEF at time of the procedure was 40.1% ± 13.8, which represents moderate LV impairment. The minimum LVEF was 11% and the maximum was 65%. Only 6 patients (20%) had a normal LVEF (EF >55%). Patients could be grouped into tertiles by LV function; 10 patients had a LVEF <35%, 10 patients 35-44% and 10 patients >45%.

Six patients (20%) had VHD, 5 with prior valve replacement (surgical or TAVI). Eleven patients (37%) had chronic kidney disease (CKD) with two patients on dialysis, and 10 (33%) had pulmonary disease. Other comorbidities included 7 patients (23%) with rheumatologic disease, 6 (20%) with peripheral vascular disease and 5 (17%) with Type 2 diabetes mellitus. One patient had localised malignancy, one had epilepsy and one had an inherited clotting disorder. Lastly, 3 patients had admissions for non-cardiac surgery during the study period – a total hip arthroplasty, a hernia repair, and a toe amputation. One patient was on ITU with sepsis at the start of the 24 m period.

Table 1. Description of the study population (n=30).

Mean age (years)	65.7 ± 13.6	Range	36 - 88
Mean BMI	28.5 ± 4.7	Range	19.4 - 42.3
LVEF (%)	40.1 ± 13.8	Range	11 - 65
Creatinine (n=26)	Median 101.5	Range	47 – 696
Haemoglobin (n=28)	135 ± 22.8	Range	72 – 170
BNP (n=12)	Median 1080	Range	15 - 12,557
Free thyroxine T4 (n=18)	13.7 ± 2.1	Range	10.3 - 18.4

BMI = body mass index LVEF – Left ventricular ejection fraction

BNP = B-type natriuretic peptide

3.6 CIED System configurations

Twenty-two patients (73%) had a device with defibrillator function. All the ICD patients in the study had structural heart disease as the aetiology of their sudden death risk. Half of the patients (n=15) had a system capable of delivering physiological pacing either via a left ventricular (LV) lead or conduction system pacing (CSP) lead. Patients had CIEDs from one of two manufacturers: Medtronic (n = 21 [70%]) or Boston Scientific (n = 9 [30%]). The majority of patients had a Medtronic CIED (reflective of the overall market share for our institution).

3.7 Covid lockdowns

For 11 of the patients (37%), the 24m monitoring period included time during one or more of the three national UK Covid lockdowns (2020 and 2021). The percentage of the 24m period spent in lockdown was 17.3% ± 7.6%. Covid lockdowns affected a higher percentage of the pre-procedure year (27.8%) than the year following the procedure (18.6%). Covid lockdowns have been shown to reduce physical activity in some populations with CIEDs (Huttelmaier et al., 2022) and therefore might impact the results.

3.8 Missing data due to timing of device implant

In the initial selection, potential patients were excluded if the CIED was implanted < 12m prior to the date of their procedure. However, after numerical data was retrieved from the manufacturer and validated, the date of procedure was found to be incorrect in three patients, meaning that they had their implant <12m prior to the date of their procedure. It is known that physical activity and TI change after implantation. TI is measured by a current that passes from the lead of the device to the pulse generator ('can'). After implantation there is a drop in TI due to inflammation and fluid around the pulse generator from the healing process. After this, their TI gradually increases over a number of days to a more stable value as a capsule forms around the device. Patients are requested to limit physical activity immediately after the procedure for a period of 14 days. Figure 3.1 shows data from these three patients after removal of data from the period immediately post implantation. It was decided to exclude patient 14 from evaluation of the change in D-PA and TI from pre to post procedure - because more than 25% of the pre-procedure year was excluded due to recent CIED implantation.

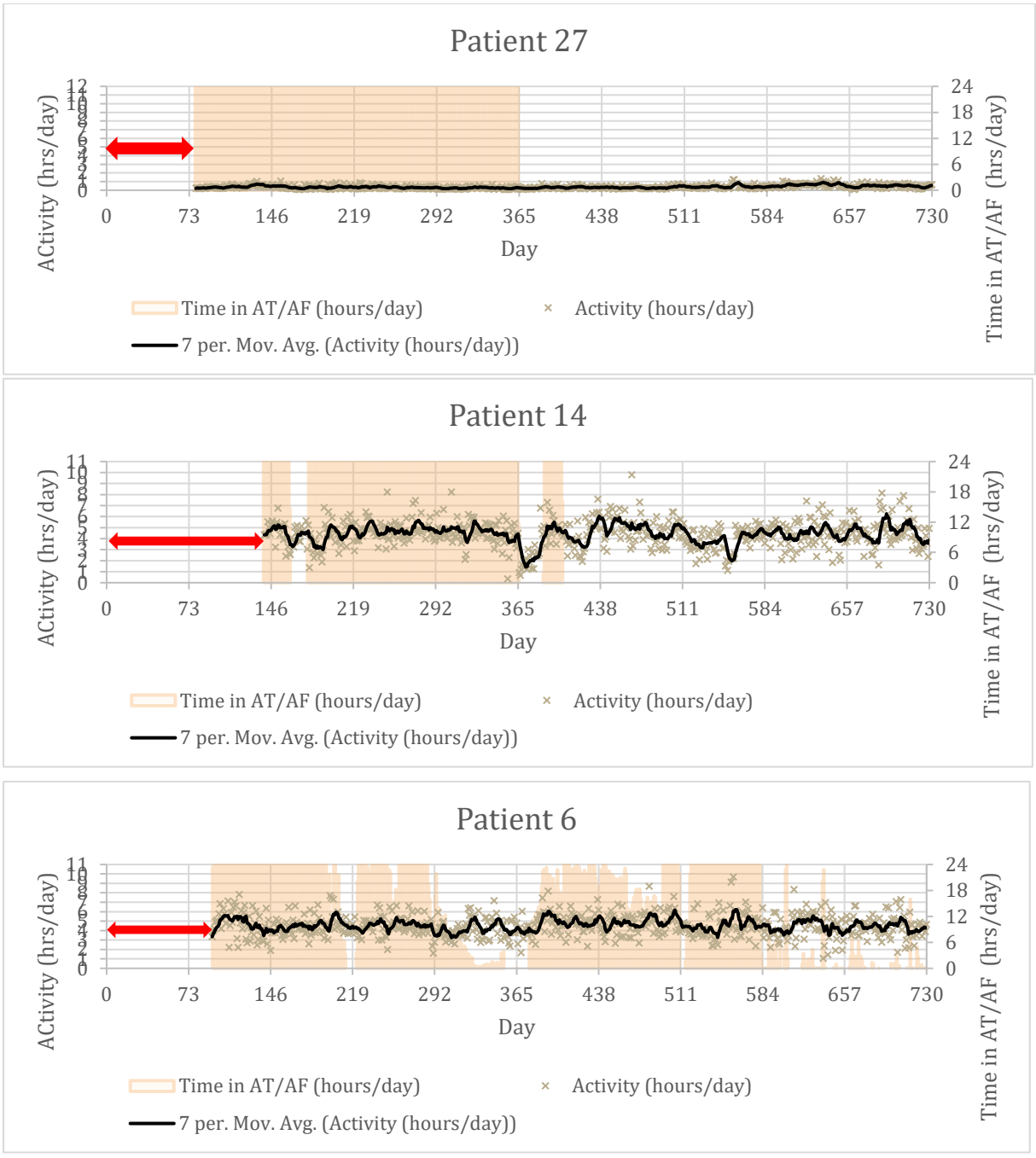


Figure 3.1. Patient activity and time in AT/AF plotted over time. Missing data pre-procedure indicated by red arrows. The black line is a 7 day moving average for D-PA. Grey crosses are daily values for D-PA. The shaded area is the number of hours spent in an atrial arrhythmia per day.

3.9 Rhythm control procedures

26 patients (87%) had a rhythm control procedure. The remaining 4 patients (13%) had an AVN ablation - a rhythm control procedure that enables the heart-rate to be fully controlled by the pacemaker function of the CIED. 14 of the 26 patients (54%) who were treated by a rhythm control procedure had a CA, with the remaining 12 (46%) having a DCCV. Patients having a DCCV tended to be older (69 vs 60.7 years), but this difference was not statistically significant. Of the ablation procedures, the majority (80%) were AFA (n =12). Two were CA for AFL and one was CA for AT.

3.91 Atrial arrhythmia burden

The atria arrhythmia (AA) burden was calculated for each patient for the year preceding the procedure and for the year afterwards; by dividing the number of hours in a year (8760) by the number of hours spent in AF. In patients with missing days at the start of the study period, the number of hours in the number of available days of recording was divided by the number of hours spent in AF. The change in AA burden was then calculated by subtracting the AA burden in year 1 (pre) from the burden in year 2 (post). If a patient had 100% AF before treatment and 0% AF afterwards, this would represent a change in AA burden of minus 100% (or a 100% reduction in AA.

There was a statistically significant reduction in AA burden from pre to post procedure for patients undergoing rhythm control ($p<0.01$). Median AA burden was 56.9% before and 3.4% after the procedure. Twelve patients (46%) were free from persistent AA for the 12m period post procedure. Of these, 9 (75%) had had a high AA burden (>50%) for the 12m leading up to the procedure, and therefore had seen a large reduction in arrhythmia (>50%) after the intervention.

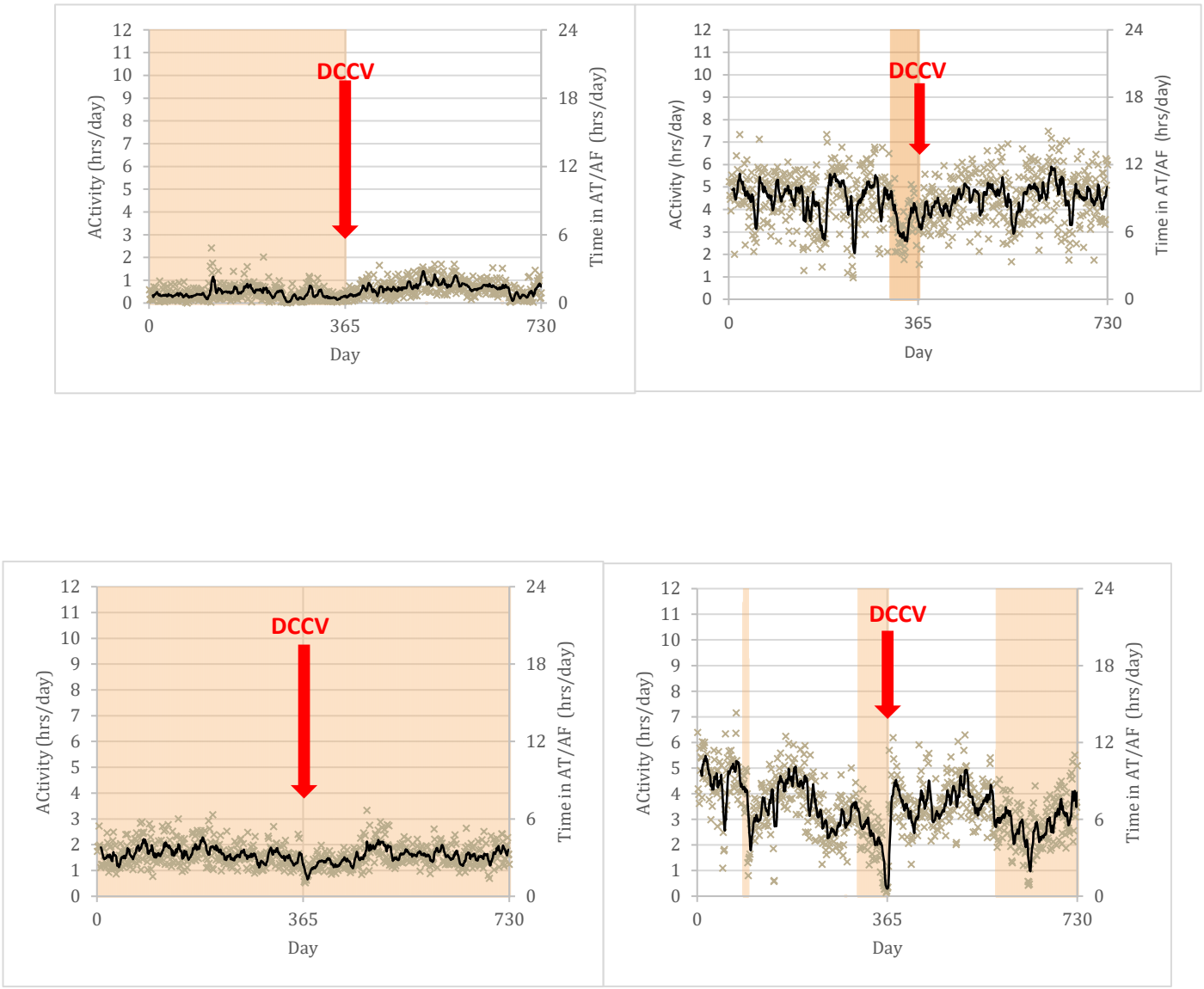


Figure 3.2. Representative graphs showing the different changes in AA burden that were observed after DCCV. The black line is a 7 day moving average for D-PA. Crosses are the daily values for D-PA. The shaded area is the number of hours spent in an atrial arrhythmia per day. Clockwise from top left: 100% reduction, small reduction, increase in burden no change.

3.92 Comparison of AF ablation and DCCV

For the 26 patients who received a rhythm control procedure, the two most common procedures were AFA and DCCV. Twelve patients underwent a DCCV procedure (46%) and 10 (39%) had AFA. The remaining 4 patients (15%) received a CA for either AT or AFL.

3.93 Patient characteristics

Patients undergoing DCCV showed a trend towards being older than those referred for AFA (68.3 ± 13.2 years verses 61.4 ± 12.9 years). There were more females in the AFA cohort (4/10 vs 1/12)). There was a lower prevalence of ischaemic heart disease (IHD) in this cohort compared to those referred for DCCV. There were no significant differences by ethnicity, BMI or NYHA class. There was a similar proportion of Medtronic and Boston CIEDs, and of ICDs and pacemakers.

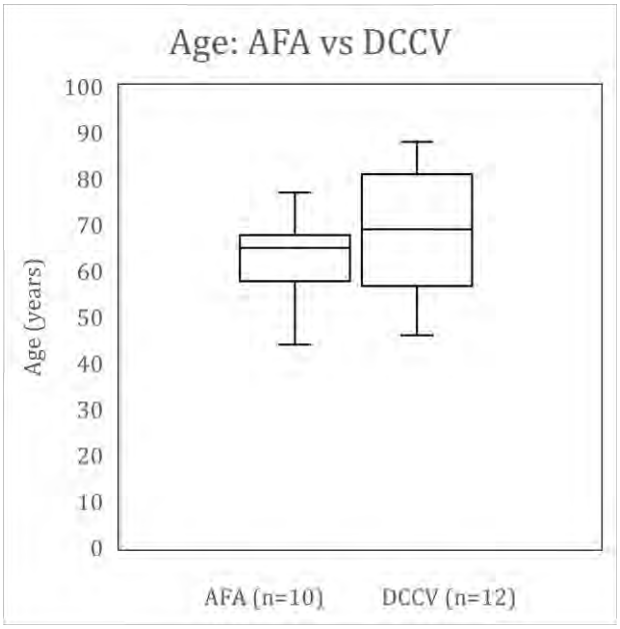


Figure 3.3. Age of patients in this cohort undergoing either AF ablation (AFA) or direct current cardioversion (DCCV). There was a trend towards patients having DCCV being older, but this difference was not statistically significant.

The box is drawn from the first quartile (Q1) to the third quartile (Q3) with a horizontal line to denote the median. The upper whisker boundary is the largest data value that is within 1.5 IQR above the third quartile. The lower whisker boundary is the smallest data value that is within 1.5 IQR below the first quartile. All box plots in this thesis follow this format.

Heart disease

The DCCV cohort contained a higher proportion of patients with ischaemic heart disease and prior MI (8/12 vs 2/10). There was a trend towards worse LV function in those having DCCV,

with EF 34.7% ± 15.7 vs 46% ±14.3 for patients referred for AFA (Figure 3.4), with no apparent difference in the NYHA class.

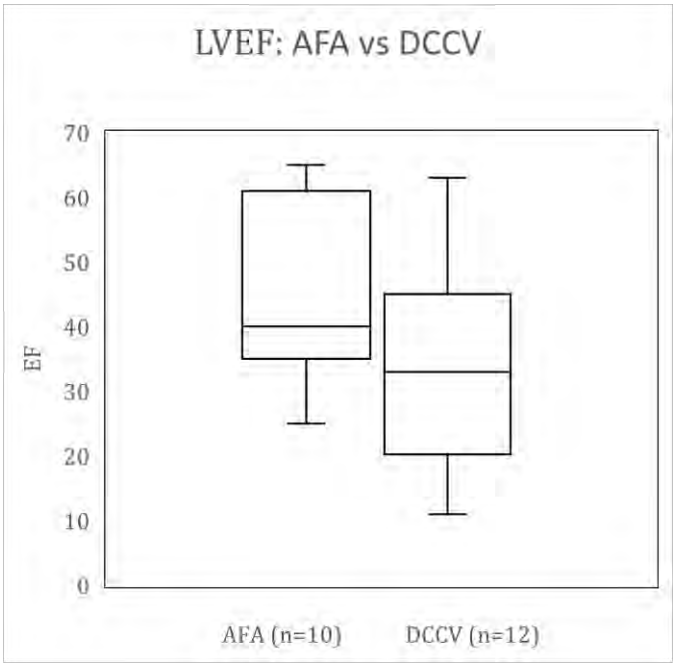


Figure 3.4. Left ventricular ejection fraction (LVEF) size for patients who underwent AF ablation (AFA) verses direct current cardioversion (DCCV). There was a trend towards a higher LVEF in those referred for AFA, but this difference did not meet statistical significance.

However, DCCV patients were significantly more likely to have been admitted to hospital for HF decompensation during the 24m monitoring period (6/12 vs 1/10). In addition, more of the patients referred for DCCV were taking a loop diuretic compared to those having AFA, and for those taking furosemide, the dose was higher (30mg per day higher). The number of diuretic agents used per patient was also higher in the DCCV cohort (2.5 vs 1.4) in keeping with more significant LV dysfunction.

LA size

LA size is an important determinant in the likely success of attempts at rhythm control. There were no significant differences between DCCV and AFA patients, but there was a trend towards a more dilated LA in those referred for DCCV (Figure 3.5). LA dimension was 5.4 ± 1.2 cm vs 4.7 ± 0.7cm, and the LA volume was median 98.1 vs 82.4ml.

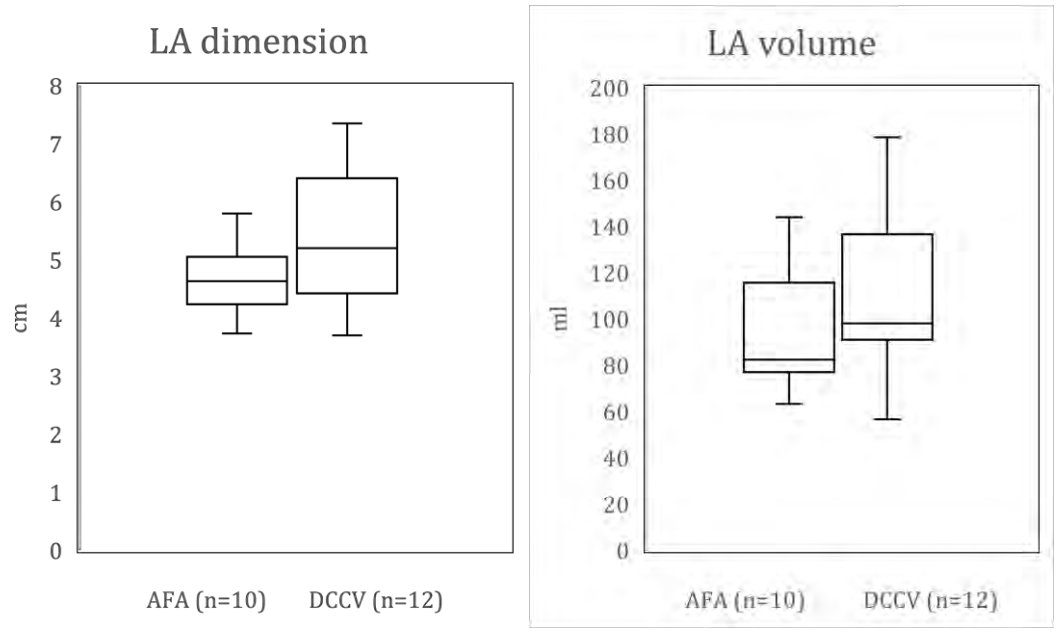


Figure 3.5. Left atrial (LA) size for patients who underwent AF ablation (AFA) and direct current cardioversion (DCCV). There was a trend towards a more dilated LA in those referred for DCCV but this did not meet statistical significance

Anti-arrhythmic medication

There were no significant differences in the use of amiodarone or beta blockers.

Comorbidities

A higher proportion of patients having DCCV had renal disease, including one patient on dialysis (6/12 vs 1/10). There was a corresponding significant difference in creatinine levels (DCCV 174.30mg/l vs AFA: 83.75mg/l; $p<0.05$). A higher proportion of patients having DCCV also had rheumatic diseases and peripheral vascular disease. However, there were no observed differences between the groups for hypertension, diabetes, chronic pulmonary disease, liver disease, malignancy or anaemia.

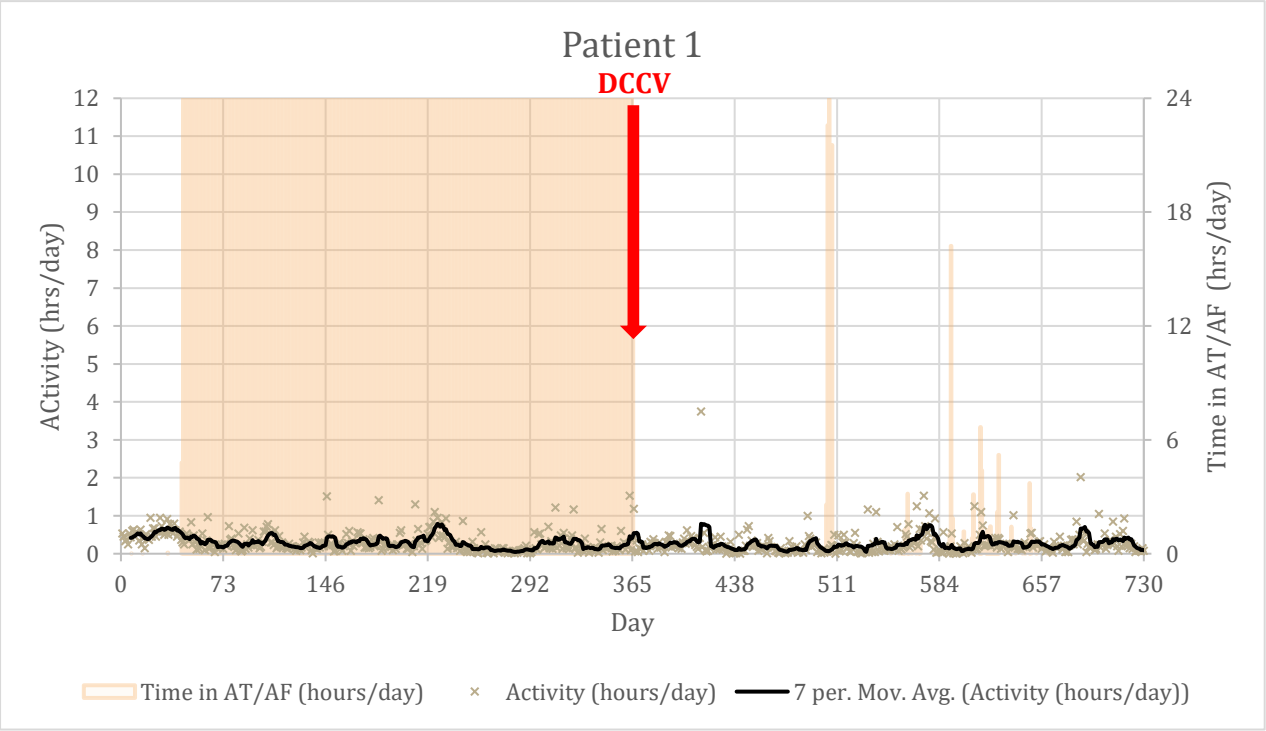
3.94 Procedural outcomes: DCCV vs AF ablation

DCCV

All patients were in PsAF at the time of the DCCV. Median AF burden for the year leading up to the procedure was 72.2% (range 7.9 - 99.8%). Half of the patients (n=6) had an AF burden >80% before DCCV, and 2 (17%) had been in AF for at least 12m. However, 6 patients (50%) had been in sustained PsAF for <3m at the time of DCCV.

DCCV was acutely successful in all 12 patients, with no reported complications. One patient however, reverted to AF after only a few hours in normal rhythm, despite being on amiodarone and a beta-blocker. This patient had the largest LA volume of all the patients in the study (LA dimension 7.11cm LA volume 178.46 ml). LA size is a well-recognised factor in determining likelihood of maintaining sinus rhythm (Raniga et al., 2024).

9/12 (75%) of patients remained in SR at 6m post DCCV, and 8 patients (67%) remained in SR at 12m. However, in two patients an additional procedure was required to achieve SR after a recurrence of PsAF. 3 patients (35%) were back in in PsAF at 12m, and one patient (8%) was in pAF. Five patients (42%) remained free from any episodes of persistent AF for the 12m post DCCV and the median AF burden post-DCCV was only 2%. Interestingly, some patients with a successful outcome had a very low functional status (Figure 3.6), and D-PA did not appear to be correlated with procedural success or change in AF burden.



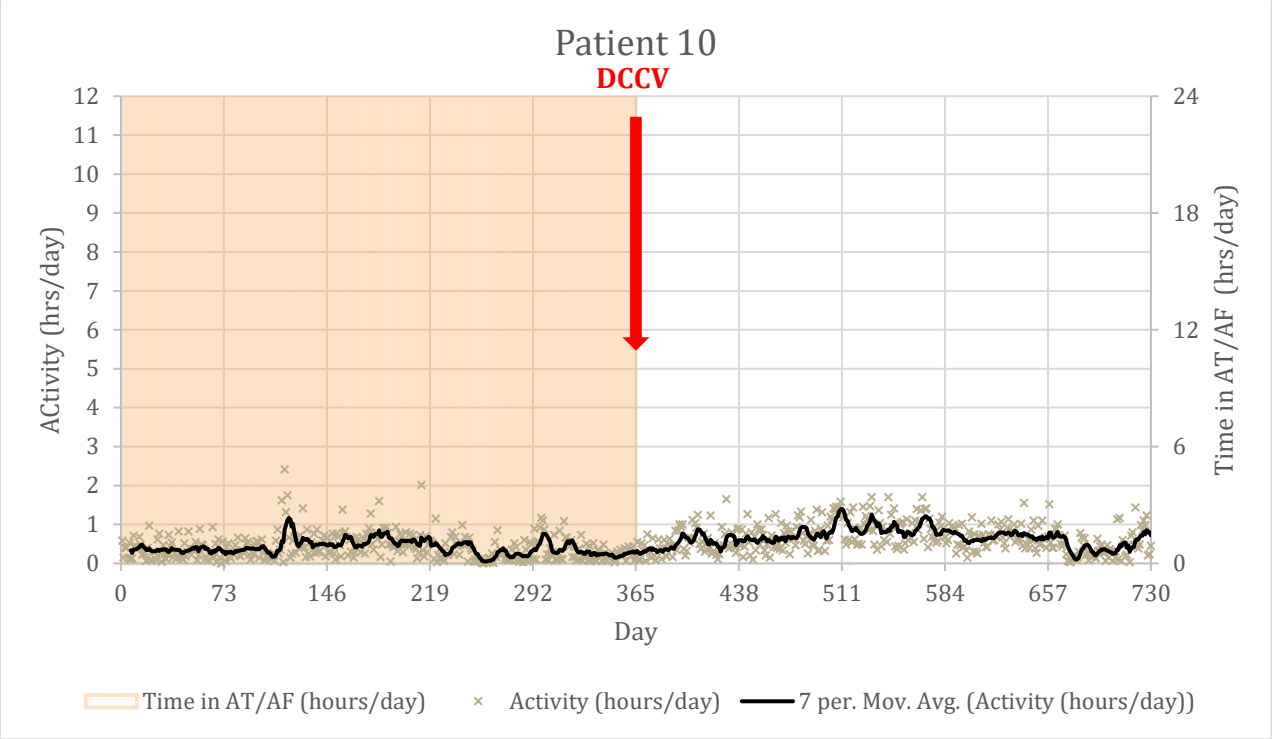


Figure 3.6. Successful outcome in two patients with very low baseline physical activity as defined by D-PA. The black line is a 7 day moving average for D-PA. Grey crosses are daily values for D-PA. The shaded area is the number of hours spent in an atrial arrhythmia per day. Both patients had a high atrial arrhythmia burden pre DCCV and very low burden afterwards. Both have an average D-PA <1 hour a day, which suggests a low functional status.

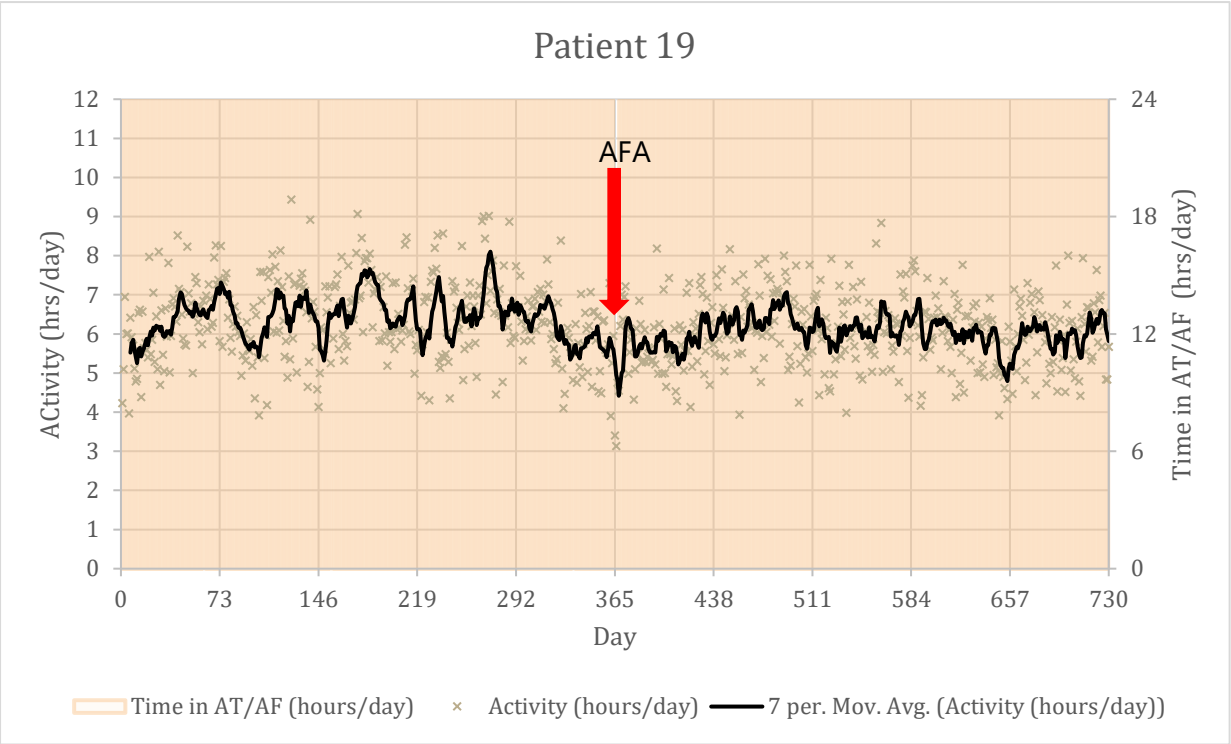
AF ablation

The majority (60%) of patients receiving AFA had undergone radiofrequency (RF) ablation, with the remainder receiving cryoablation. Two patients had a left atrial appendage occlusion device (LAAO) implanted at the same procedure. Half of the patients were in PsAF at the time of the AFA, with the other half being in SR. Median AF burden for the year leading up to the procedure was 25.7% (range 0.0 - 99.0%). 4 patients (40%) had an AF burden >80% before

AFA, and 2 (20%) had been in AF for at least 12m. All four pulmonary veins were acutely isolated in 9/10 patients (90%). There were two complications reported (20%); one stroke and one case of vocal cord damage (from intubation during general anaesthesia).

6/10 (60%) of patients remained in SR at 6m post AFA, and 5 patients (50%) remained in SR at 12m. Two patients with long-standing PsAF remained in the arrhythmia for the vast majority of the 24m monitoring period (Figure 3.7) One of these patients (patient 19) reverted to AF after only three days in normal rhythm - this patient had hypertension, obesity (BMI 34.6) and dilated cardiomyopathy with EF 35%, all known risk factors for AF recurrence after ablation (Darby et al., 2016). They were not on amiodarone but did not have a severely dilated left atrium (LA) – LA dimension was 4.67cm, LA volume 83.93ml. Soon after the procedure they were seen in CIED clinic - where it was recognised that they had reverted to AF, but unfortunately it does not appear that this observation was escalated: they were not subsequently reviewed in cardiology clinic or complex device clinic and they had no further interventions within the year. The second patient (patient 23) had an AFA at the same time as having a LAAO device. Patients implanted with LAAO devices are brought back for DCCV after a period of weeks to allow for endothelialisation of the closure device. If pre-procedural transoesophageal echocardiography shows good device position, absence of device-related thrombus, and a peri-device leak of ≤5 mm (Sharma et al., 2019) then the patient can be cardioverted. In this case, the patient had a DCCV a few weeks post AFA/LAAO. It appears that either they subsequently reverted to AF after a very short time or the DDCV was not effective, (but this was not appreciated at the time). This patient was not on amiodarone, the LA was not

severely dilated (LA dimension 4.80 cm LA volume 144.00 ml), and there were unfortunately no subsequent attempts at DCCV.



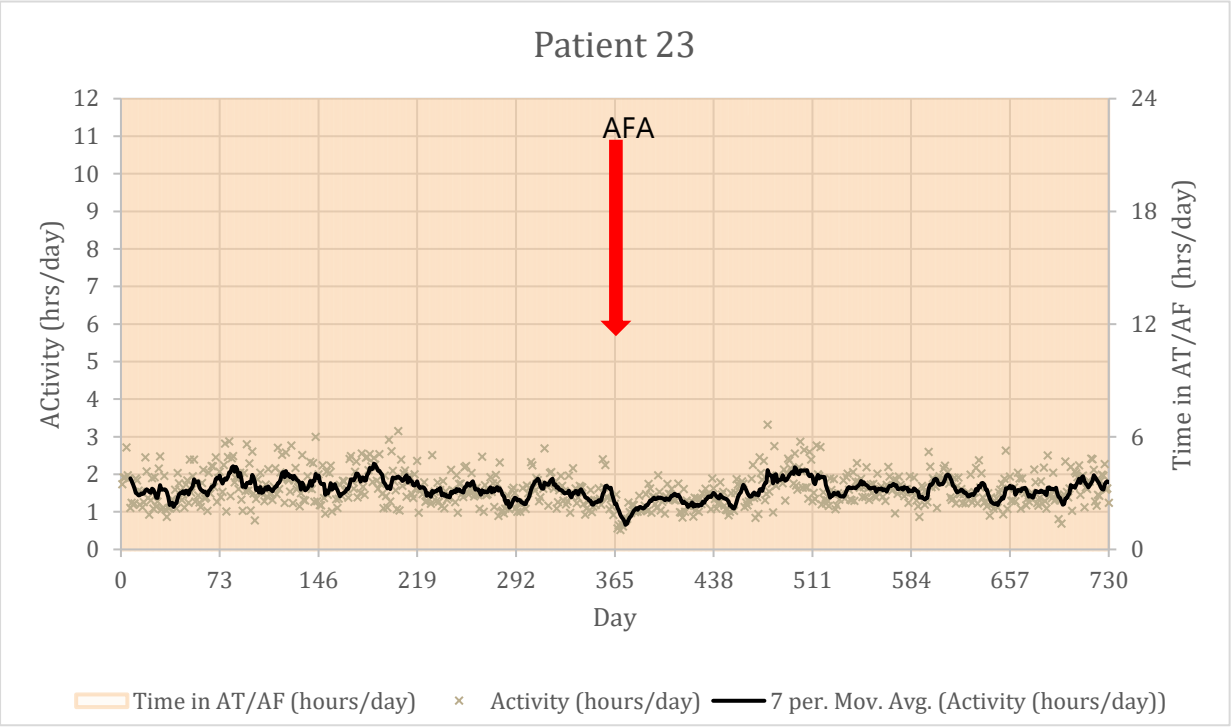
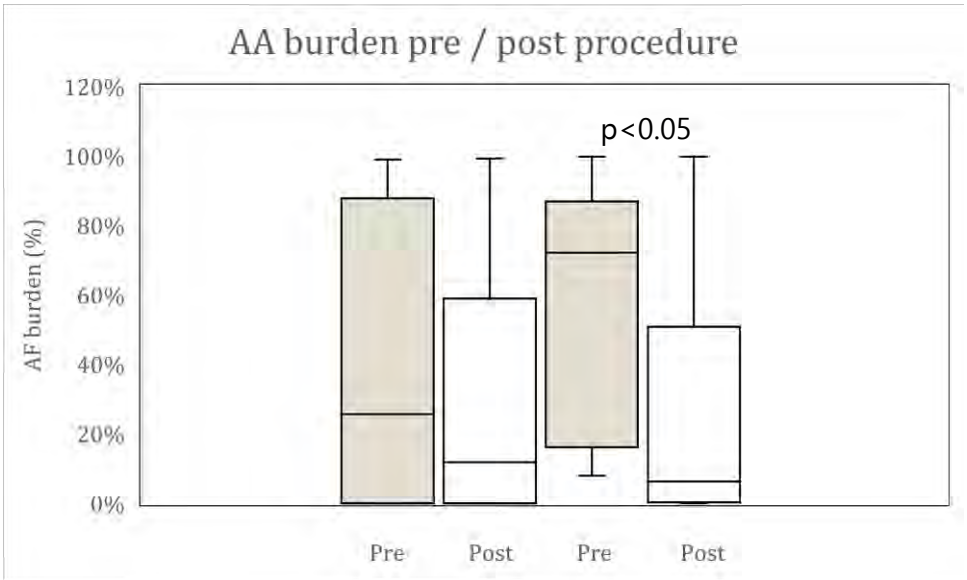


Figure 3.7. Two patients with long-standing PsAF who remained in the arrhythmia for virtually all of the 24m monitoring period despite AFA, resulting in no change in AF burden. The black line is a 7 day moving average for D-PA. Grey crosses are daily values for D-PA. The shaded area is the number of hours spent in an atrial arrhythmia per day.

3.95 AA burden

There was a statistically significant decrease in AA burden for the cohort undergoing DCCV, from a median of 72.2% in year 1 96% CI [15, 98] to median 6.3% in year 2, 96% CI 0.24, 50.89] (Wilcoxon Signed-Rank Test for dependent means $p<0.05$; Figure 3.8). There was a decrease in AA burden for patients having AFA, but this reduction did not meet statistical significance.



AFA (n=10) DCCV (n=12)

Figure 3.8. Statistically significant decrease in AA burden for the cohort undergoing direct current cardioversion (DCCV). The 2 groups were compared separately. (AFA = AF ablation)

There was considerable heterogeneity in the response to treatment in both groups, which can be seen in the change in AA burden by patient (Figure 3.10). Some patients had a reduction in AA burden of minus 100% - i.e. persistent AA for 12m pre-procedure followed by complete freedom from it for the 12m afterwards. Some had no change in burden; for example, some

patients had 100% AA burden pre procedure and 100% post-treatment. Some patients showed an increase in burden (positive percentage value). For those undergoing AFA, those experiencing an increase in AF were balanced by those with a decrease in burden - the median change was 0.0%. For those undergoing DCCV, the median change was -14.3% (a reduction in AF burden).

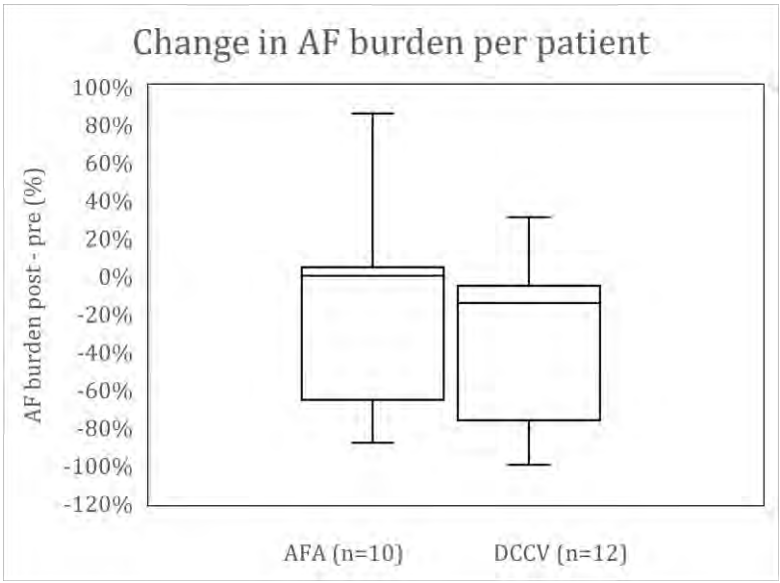


Figure 3.9. Change in AF burden (per patient) after AF ablation (AFA) and direct current cardioversion (DCCV). Any difference between groups was not significant.

3.96 D-PA and TI

There was a trend towards a higher D-PA in the AFA cohort (195 vs 142 mins) consistent with a younger population with less comorbidity (Figure 3.10). However, this difference was not statistically significant. TI was also lower (69.1 vs 62.7Ω) in the DCCV group, but this difference was not statistically significant (Figure 3.12). Lower TI measurements have been associated with older age and worse outcomes (Zile et al., 2016).

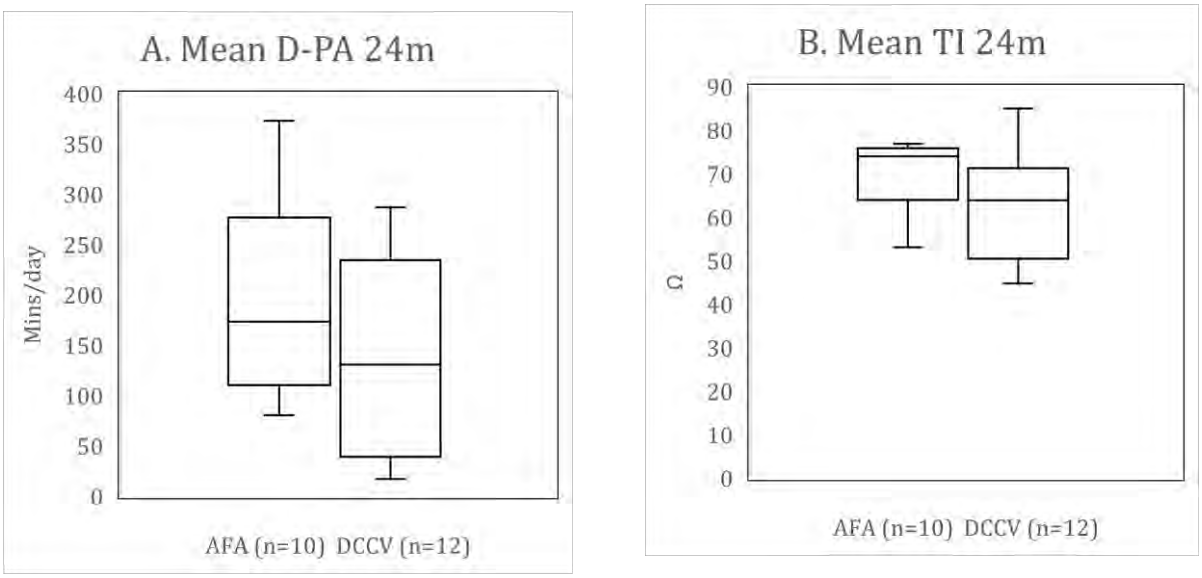


Figure 3.10. Mean device-measured physical activity (D-PA) [Panel A] and thoracic impedance (TI) [Panel B] for patients undergoing AF ablation (AFA) and direct current cardioversion (DCCV). No significant difference between groups. There was no significant change in D-PA or TI after AFA or DCCV (Figure 3.11). Of note, two patients had excellent outcomes from DCCV despite having very low functional status (activity <1 hour/day).

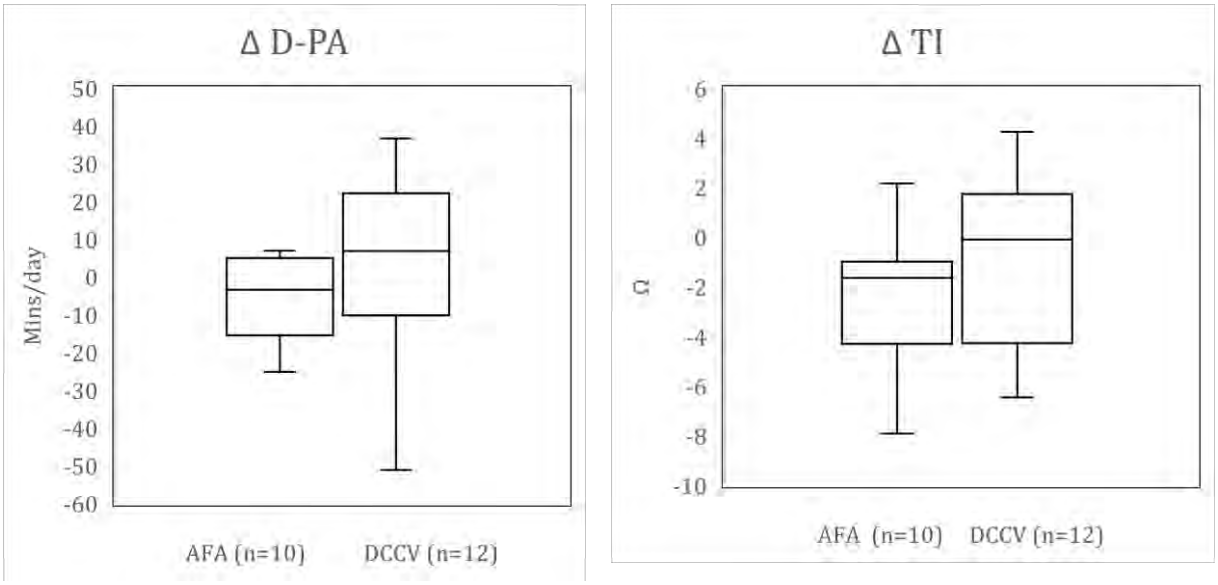


Figure 3.11. Change in device-measured physical activity (Δ D-PA) and change in thoracic impedance Δ TI for patients undergoing AF ablation (AFA) and direct current cardioversion (DCCV). No significant difference between groups

3.97 Referral for AFA and DCCV

DCCV

8 patients (67%) had an elective DCCV where the waiting time was 60 ±12 days. 7 patients (58%) were referred from a cardiology out-patient clinic (two of these patients were subsequently admitted to hospital). Three patients (25%) were referred by a consultant cardiologist from a specialist complex device clinic after having first been triaged by a cardiac physiologist, and two patients (17%) were referred from HF clinics.

There is little published data around waiting times for DCCV, but one study determined that, once a decision for rhythm control was made, patients waited 114 days (range 57–376) for the procedure (Abdullah et al., 2024). In our cohort, two patients (17%) were referred for urgent DCCV directly from an out-patient setting (one from cardiology out-patient clinic, the other from a consultant HF nurse clinic); both patients had the procedure the next day, without being admitted to hospital. Two patients (17%) were admitted to hospital after experiencing worsening HF whilst on the waiting list for an elective DCCV. Their procedure was performed whilst they were in-patients; 3 days after admission in one case, and 4 days in the other.

AFA

9 patients (90%) were referred from a cardiology out-patient clinic (one of these patients was subsequently admitted to hospital) and one patient (10%) was referred from a specialist complex device clinic after being triaged by a cardiac physiologist. Nine patients (90%) had a routine elective AFA for which the waiting time was 276.6 ± 138 days. The non-urgent wait for AFA was significantly longer than for DCCV (276.6 days verses 60.1 days; $p<0.01$; Figure 3.12).

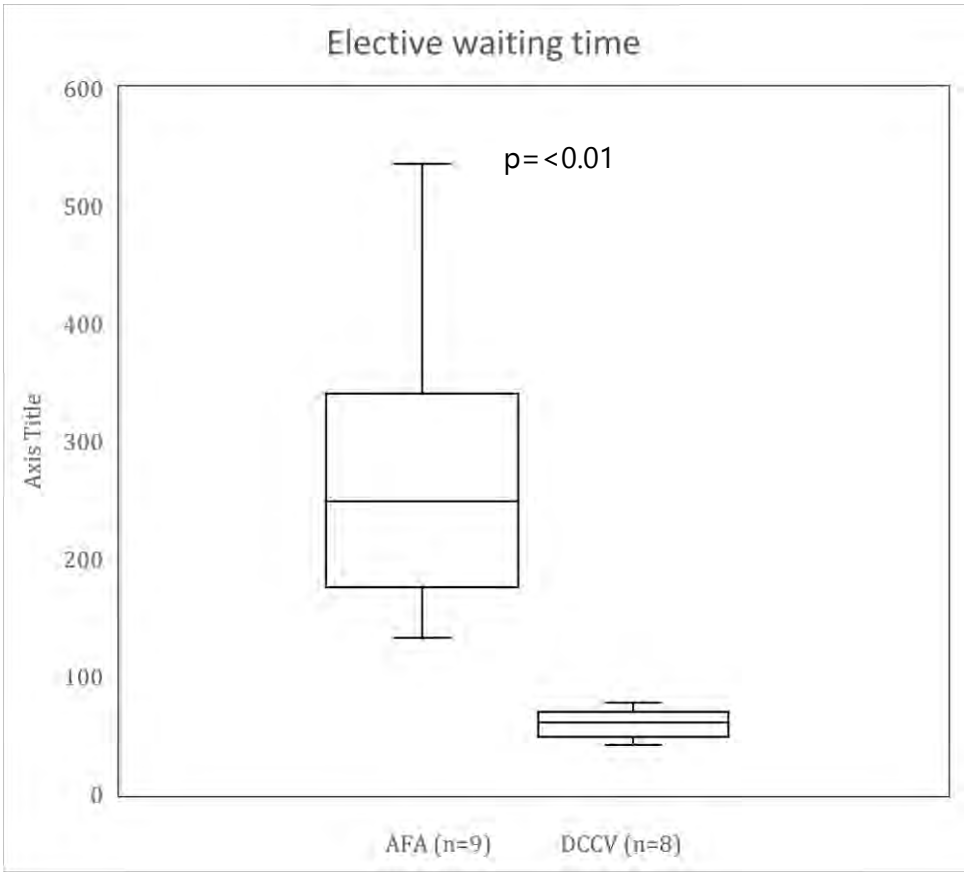


Figure 3.12. Elective waiting time for patients undergoing AF ablation (AFA) and direct current cardioversion (DCCV). The difference is statistically significant. This would be expected for procedures with very different requirements in terms of facilities and personnel.

3.98 Discussion

CIED patients undergoing DCCV tended to be older and sicker than those having AFA. DCCV is a relatively short, non-invasive, safe procedure with good acute success rate; clinicians are more likely to consider it in older people with more comorbidity. Patients having DCCV were more likely to have IHD, and although not statically significant, there was a trend towards worse LV function in those having DCCV. NYHA scores are wide, relatively subjective, and not often updated in the electronic record despite changes in clinical condition. Despite there being no difference in the recorded NYHA scores, patients having DCCV were more likely to be taking diuretics, and at higher doses than those having AFA – perhaps suggesting more highly symptomatic HF despite the similar reported NYHA scores. Diuretic use might be a better way of assessing the degree of HF in real world cohorts.

There is a lack of data on outcomes from DCCV in the CIED population. In the study cohort, DCCV appeared to be highly successful in patients with CIEDs despite a high burden of co-morbidities, even in patients with very low baseline physical activity. Outcomes in our cohort compare favourably to published studies of DCCV in the general population. For example, Carpenter et al., (2019) analysed the outcomes of 550 DCCV cases in non-CIED patients but with broadly similar characteristics to our cohort (median age of 67, 30% obese). They found that 94% were acutely successful, but only 37% of patients were free from AF at 6 months, dropping to 24% at 12m. This could potentially be explained by the fact that a higher proportion of patients been in AF for more than 12m (37% vs 17% in our study cohort) and

only 19% were on anti-arrhythmic medication (flecainide, sotalol or amiodarone) compared with 67% (amiodarone) in our CIED cohort. Anti-arrhythmic medication can cause a slow heart rhythm (bradycardia) which can restrict their use in patients without a CIED (which can pace the heart to prevent bradycardia). Amiodarone has significant side effects, but in patients with defibrillators, it has the additional benefit of preventing ventricular tachycardia (VT) which can cause the device to deliver painful shocks, increasing the likelihood that patients will be prescribed it. If patients are already on amiodarone, this speeds up the referral pathway, as loading takes approximately 3 weeks to reach therapeutic levels, which extends the minimum time before DCCV can conceivably take place. Atrial pacing has been shown to reduce the incidence of AF and this may be another reason why patients with CIEDs might remain in SR after DCCV. In addition, patients with CIEDs are intensively monitored; their AF burden is measured automatically and can be reviewed remotely, leading to prompt referral which may improve outcomes. In addition, the fact that CIED patients are reviewed by cardiac physiologists who have a good working relationship with cardiac electrophysiology consultants means that these patients are afforded excellent access to an expert opinion that would take longer if they did not have an implanted device. Few patients in the cohort had been in continuous AF for 12m at the time of the procedure, and they were very well-optimised in terms of anti-arrhythmic medication. In addition, the waiting time for an elective DCCV procedure was relatively short at 60 days, due to a dedicated arrhythmia nurse-led cardioversion service. However, the fact that two patients were admitted whilst waiting for a procedure emphasis the need for a streamlined referral pathway. AF is common in the CIED population, and it is likely that more patients with CIEDs might benefit from DCCV than currently receive it. The excellent results from DCCV observed in our study emphasise the need

to develop a structured AF pathway within the CIED service to standardise the triaging and referral of CIED patients. This might be able to reduce the diagnosis to DCCV time still further, which has been shown to be associated with improved outcomes.

Despite a trend to larger LA size, patients having DCCV had a greater reduction in AA burden from pre to post procedure. This was driven mainly by a higher burden pre procedure in patients having DCCV. A number of patients having AFA had a surprisingly low burden of AF in the year prior to the procedure. This appears to be because the referral was triggered by a small number of AF episodes that caused inappropriate shock therapy from their ICD. ICD therapy is painful and causes anxiety, and so it is a powerful driver for clinicians who want to prevent future AF episodes. The elective waiting time for DCCV was significantly shorter than for AFA. This is due to the length of AFA procedures and the specialist teams and equipment needed to perform them.

3.99 Conclusion:

CIED patients referred for DCCV are older and have more comorbidity than those referred for AFA. DCCV resulted in significant reduction in AF burden despite older age, multiple comorbidity and low physical activity. Advanced age should not in itself be a barrier to considering treatment of CIED patients with AA by DCCV; cardiac physiologists should refer CIED patients with new or untreated PsAF for clinical evaluation of the risks and benefits of DCCV, regardless of age.

3.99.2 Methods

The electronic health record for each patient was reviewed for demographic and clinical data. Since the study was retrospective and the recording periods were historic, clinical data was selected that was relevant to the study period. For echocardiographic data, where available, examinations were selected that were performed during the study period, with those closest to the time of the procedure prioritised. For the biochemistry test data, it was not always possible to go back far enough in time to the study period. In that case, measurements were selected that were closest in time to the study period for that individual.

Data distributions for individual patients were analysed graphically for daily D-PA and TI measurements. Measures of spread and central tendency for each patient were then calculated from approximately 730 individual daily measurements. The distribution of this two year mean for all patients was then analysed graphically and tested for normality using the Shapiro-Wilk test.

A T-Test for two independent means was used to compare the means for Medtronic versus Boston Scientific devices. Measures of data spread were also aggregated for all patients and compared by manufacturer.

Slope of D-PA and TI

Time series can be analysed by evaluating changes in slope resulting from an intervention. The slope of D-PA and TI measurements for the year before the intervention were determined and compared to the year after the procedure for all 30 patients. Although there was a change in slope in many cases, this change in slope was not statistically significant, except for one patient who had a significant change in slope for D-PA (Figure 3.13). This patient had a negative slope for the year preceding an AFA of -0.19 and a positive slope over the year after the procedure of 0.29. The change in slope was significant ($p<0.05$). This patient enrolled in a gym rehabilitation program at a similar time to the procedure and it seems reasonable to conclude that this was at least in part responsible for the significant change in daily physical activity. Interestingly, this patient did not demonstrate a significant increase in TI which might suggest that the increase in activity was not associated with a decrease in pulmonary congestion.

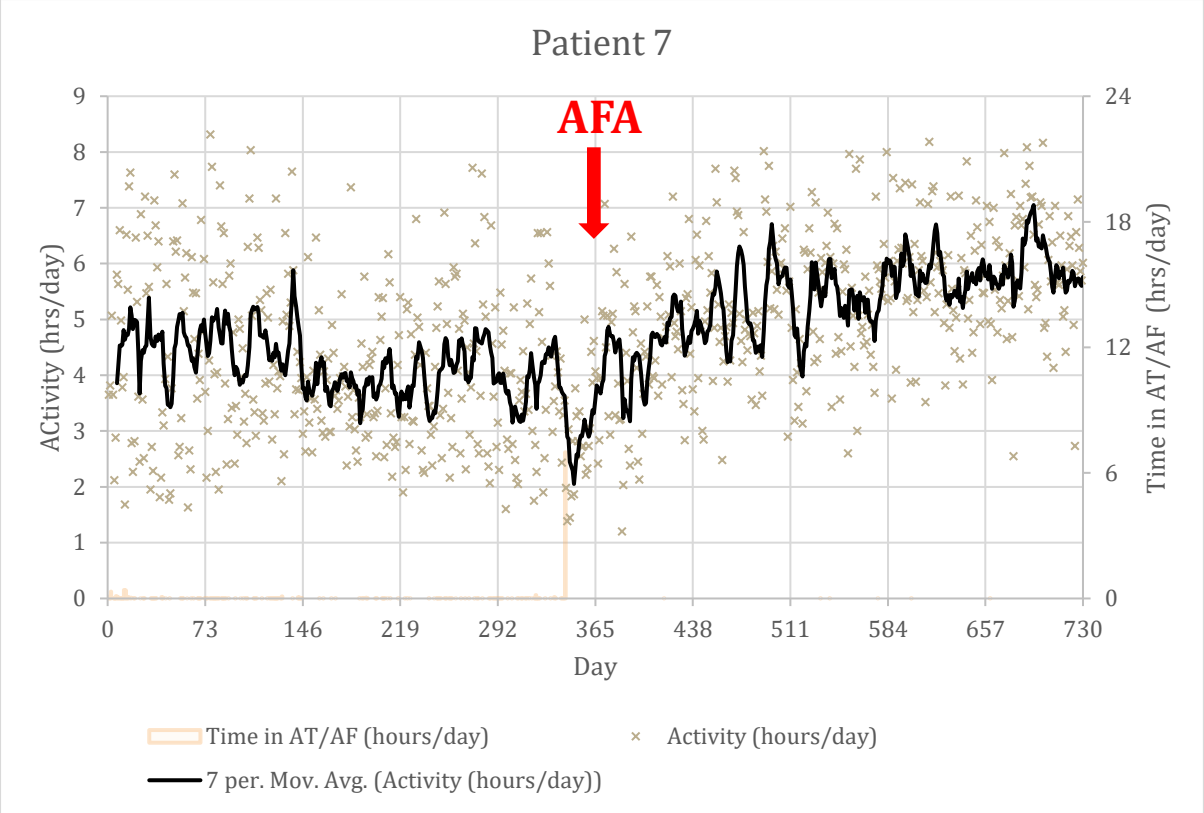


Figure 3.13. The only patient with a significant change in slope between the year pre and post procedure. The black line is a 7 day moving average for D-PA. Grey crosses are daily values for D-PA. The brown shaded area is the number of hours spent in an atrial arrhythmia per day.

3.99.3 Correlation between reduction in AA burden and change in D-PA and TI

D-PA

For the 26 patients undergoing rhythm control procedures there was a change in D-PA of 4.3 ±26.4 minutes in the year after the procedure. There was a weak (non-significant) negative correlation between reduction in AF and change in activity, with a Pearson's r value of 0.17;

95% CI [-0.50, 0.20]. There was therefore a trend towards increasing activity with a larger reduction in AF burden, but this was a very weak association (Figure 3.14).

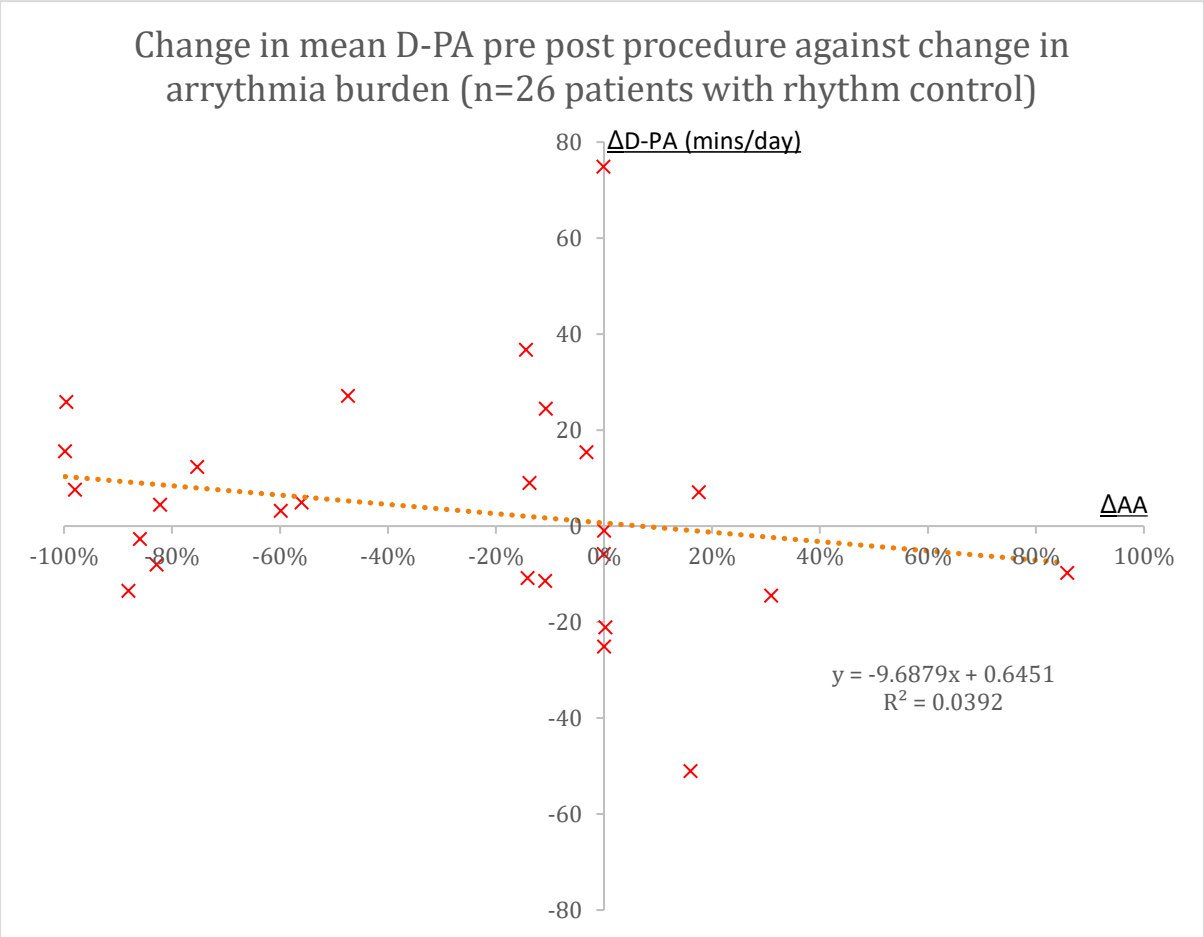


Figure 3.14 Correlation between change in device measured physical activity (Δ D-PA) and change in atrial arrhythmia burden (Δ AA) for all 26 patients who underwent a rhythm control procedure. Red dotted line is linear regression trend line (R2 value given). Y axis is change in D-PA (mins/day) and the x axis is change in AA burden in %.

Thoracic Impedance (TI)

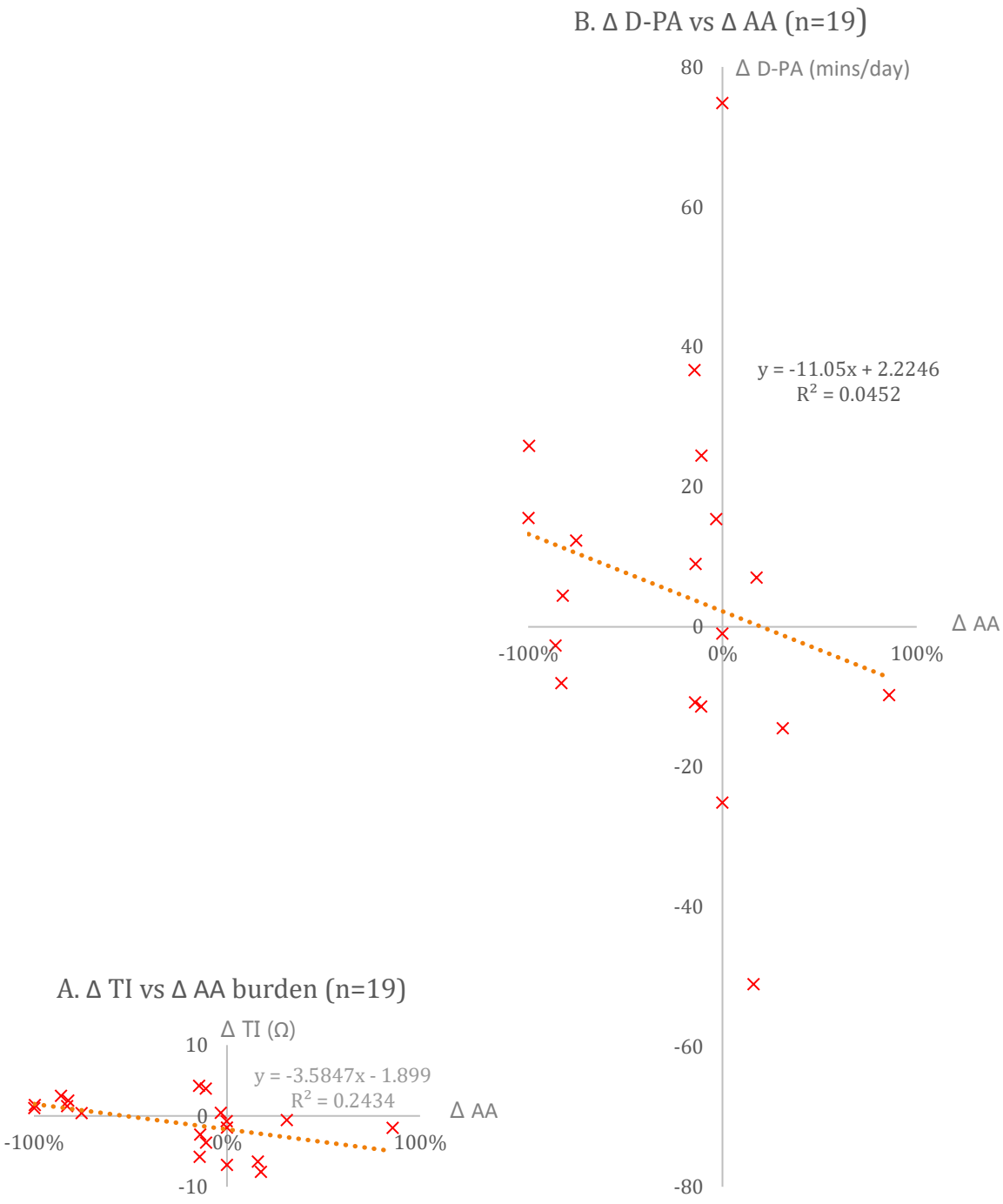


Figure 3.15. Panel A. ΔTI against Δ AA burden. Red dotted line is the linear regression line. Pearson's correlation coefficient (r) was -0.49, 95% CI [-0.77, -0.05].

Panel B: Physical activity (D-PA) and arrhythmia burden for the same 19 patients

We found that in contrast to D-PA, there was a significant correlation between Δ TI and Δ AA burden ($p<0.05$) (figure 3.15]. The effect size as determined by Pearson's correlation coefficient (r) was -0.49, 95% CI [-0.77, -0.05] p-value (r; H0: $r \geq 0$) 0.02. This demonstrated that the greater the reduction in AA, the greater the increase in mean TI. Clinically, this suggests that a reduction in the AA burden was associated with a reduction in pulmonary congestion.

This was a significant finding, and so patients with TI measurements available were further analysed as below.

Introduction

A decrease in thoracic impedance (TI) represents an increase in thoracic fluid and pulmonary congestion. Conversely, an increase suggests a reduction in congestion. Successful rhythm control should have a beneficial effect on cardiovascular performance. Improved cardiovascular performance might be expected to translate into better clinical outcomes. This is currently difficult to quantify without large-scale clinical trials.

Aims:

1. Quantify the intra-subject variation in thoracic impedance over time
2. Quantify the effect of rhythm control procedures on thoracic impedance
3. Examine the relationship between arrhythmia burden and thoracic impedance

Inclusion: Patients age >18 years with a Medtronic or Boston Scientific CIED in situ at the time of CA or DCCV for an atrial arrhythmia.

Exclusion: Remote monitoring data covering <90% of the 2 year period centred on the procedure (i.e. 12m pre, 12m post).

Population

19 patients were included in the analysis. 20 patients who had received a rhythm control procedure had TI data available, but one patient was excluded because they had data for less than 90% of the 2 year study period.

3.99.5 Method

19 patients were divided into tertiles by the percentage change in atrial arrhythmia (AA) burden:

- Group 1 (n=6): Large reduction in AA burden (>75%)
- Group 2 (n=6): Modest reduction (<15%)
- Group 3 (n=7): No change or an increase in burden

Mean daily TI for the year before and the year after the rhythm control procedure was calculated for each patient. Change in mean daily TI (Δ TI) from pre to post procedure was calculated. Finally, Δ TI was compared between the three groups

3.99.6 Results

3.99.7 Patient characteristics

19 patients were included in the analysis. Their mean age was 66 (±13) years. 15 (79%) were male. Mean BMI was 25 (± 4). The patients were predominantly white (14 [74%]). Of the non-white patients, two were coded in the EHR as 'Asian' or 'Asian British Indian', one was recorded as 'Asian - any other Asian background', and one as 'black - any other black background'. For one patient ethnicity was not recorded. Patient baseline characteristics can be seen in table 2 below.

Table 2. Baseline characteristics of patients with TI data (n=19)

	n	% / range
Ischaemic cardiomyopathy	9	45
Dilated cardiomyopathy	6	32
Hypertrophic cardiomyopathy	3	16
Valvular heart disease	3	16
NYHA class	Median II	Range II-III
Ejection Fraction	38 ± 14	
Congestive cardiac failure	17	89
Admission for HF (24m)	9	47
Device measured activity	153 ± 94 min	
Left atrial size (median)	5.4cm	range 3.7-7.4

Left atrial volume (median)	96.8ml	range 56.6 – 117.7
AF burden pre procedure (median)	19.90%	range 0-99.6

Medications

Diuretic	18	95
Beta blocker	15	79
Amiodarone	13	68

Peripheral vascular disease	4	21
Cerebrovascular disease	3	16
Renal disease	8	42
Chronic pulmonary disease	6	32
Rheumatologic disease	5	26
Malignancy (localized)	1	5

NYHA = New York Heart Association HF = heart failure AF = atrial fibrillation

CIEDs

17 of the patients had ICDs (89%). 10 of these were dual chamber ICDs, 7 CRT-D. 4 of the CRT-Ds utilised a conduction system lead. Two patients (11%) had a dual chamber pacemaker (both with conduction system leads). The majority (n=15 [79%]) of the CIEDs were Medtronic.

3.99.8 Procedures

10 patients (53%) had received DCCVs, and 9 (47%) had undergone ablation procedures. Of the ablation procedures the majority (n=7) were AFA, one was an ablation for AT, and one

patient had a CTI ablation for typical flutter. 16 (84%) of the procedures were acutely successful.

3.99.9 Change in arrhythmia burden

Percentage time in AT/AF for the year pre-ablation or DCCV was median 19.9% (93.6% CI [7.9, 82.3]; range 0-99.6%). Post procedure, the median burden was 0.4% (93.6% CI [0.1, 12.2%]; range 0-85.8%). The median change in burden between the two periods was -10.9%. (93.6% CI [-75.3, 0.0%]; range -99.8 to 85.8%) (Figure 3.16).

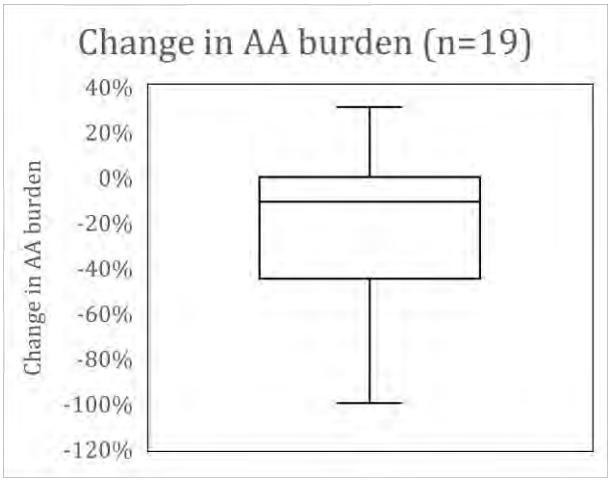


Figure 3.16: Change in AA burden from pre to post procedure

The data for atrial arrhythmia (AA) burden pre and post procedure was not normally distributed, so a non-parametric test for two dependent means (Wilcoxon Signed-Rank Test)

was applied to the repeated measures of AA burden pre and AA burden post procedure. No significant differences were detected. Change in AA burden was also not normally distributed (Shapiro-Wilk p-value 0.04).

3.99.91 Change in TI

Mean TI values for all patients from pre to post procedure can be found in Appendix A.

Δ TI was 1.1 ± 3.7Ω (range -7.9 to 4.2Ω). For the entire cohort of patients with available TI measurements (n=19), the change in TI from pre to post procedure was not significant. For some patients the mean daily TI value was on average higher after DCCV or CA, whilst for others it was lower.

The change (Δ) in TI for each individual patient was calculated and is presented in Figure 3.17.

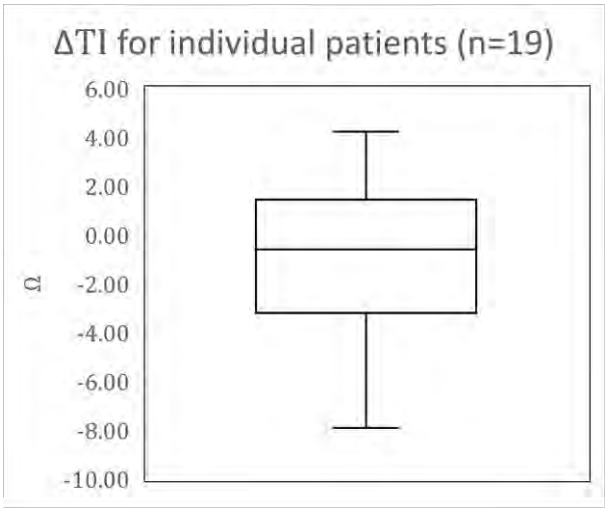


Figure 3.17: Change in thoracic impedance (ΔTI). ΔTI was normally distributed (Shapiro-Wilk p-value 0.30) therefore, a paired T test was applied.

There was a significant correlation between Δ TI and Δ AA burden ($p<0.05$). The greater the reduction in arrhythmia burden, the greater the increase in mean TI. No patient demonstrated both an increase in arrhythmia and a reduction in congestion.

3.99.92 Sub-group analysis by change in arrhythmia burden

Due to the large inter-subject differences in the change in AA burden, it seemed possible that there would be a corresponding heterogeneity in the changes in TI. To investigate this, the patients were divided into tertiles according to the amount of change in AA burden from pre to post procedure. This resulted in the creation of 3 groups, with 6 patients in two (groups 1 and 2), and 7 patients in the third group (group 3) [see tables 3.and 4].

Table 3. Atrial arrythmia burden pre and post procedure for each patient in the 3 groups.

GROUP 1		GROUP 2		GROUP 3	
burden		burden		burden	
12m pre	12m post	12m pre	12m post	12m pre	12m post
99.8%	0.0%	14.8%	0.4%	0.1%	0.0%
99.6%	0.0%	80.4%	66.3%	0.0%	0.0%
87.9%	2.0%	14.0%	0.2%	0.0%	0.0%
82.9%	0.1%	11.3%	0.4%	83.8%	99.8%
82.3%	0.1%	23.0%	12.2%	1.3%	18.9%
75.8%	0.4%	7.9%	4.7%	19.9%	50.9%
				0.0%	85.8%

Table 4. Change in AA burden (to the nearest whole percentage point) for each of the patients in the three groups. A negative value represents a reduction in AF burden, a positive value an increase in burden.

Group 1	Group 2	Group 3
-100%	-14%	0%
-100%	-14%	0%
-86%	-14%	0%
-83%	-11%	16%
-82%	-11%	18%
-75%	-3%	31%
		86%

Patients in group 1 had a large reduction in AA burden of ≥75% after their rhythm control procedure. Patients in group 2 all had a much more modest reduction - of <15%, and patients in group 3 demonstrated no change in AA burden (or an increase). The change in AA burden was significantly different between each of these subgroups ($p<0.01$) [Figure 3.18].

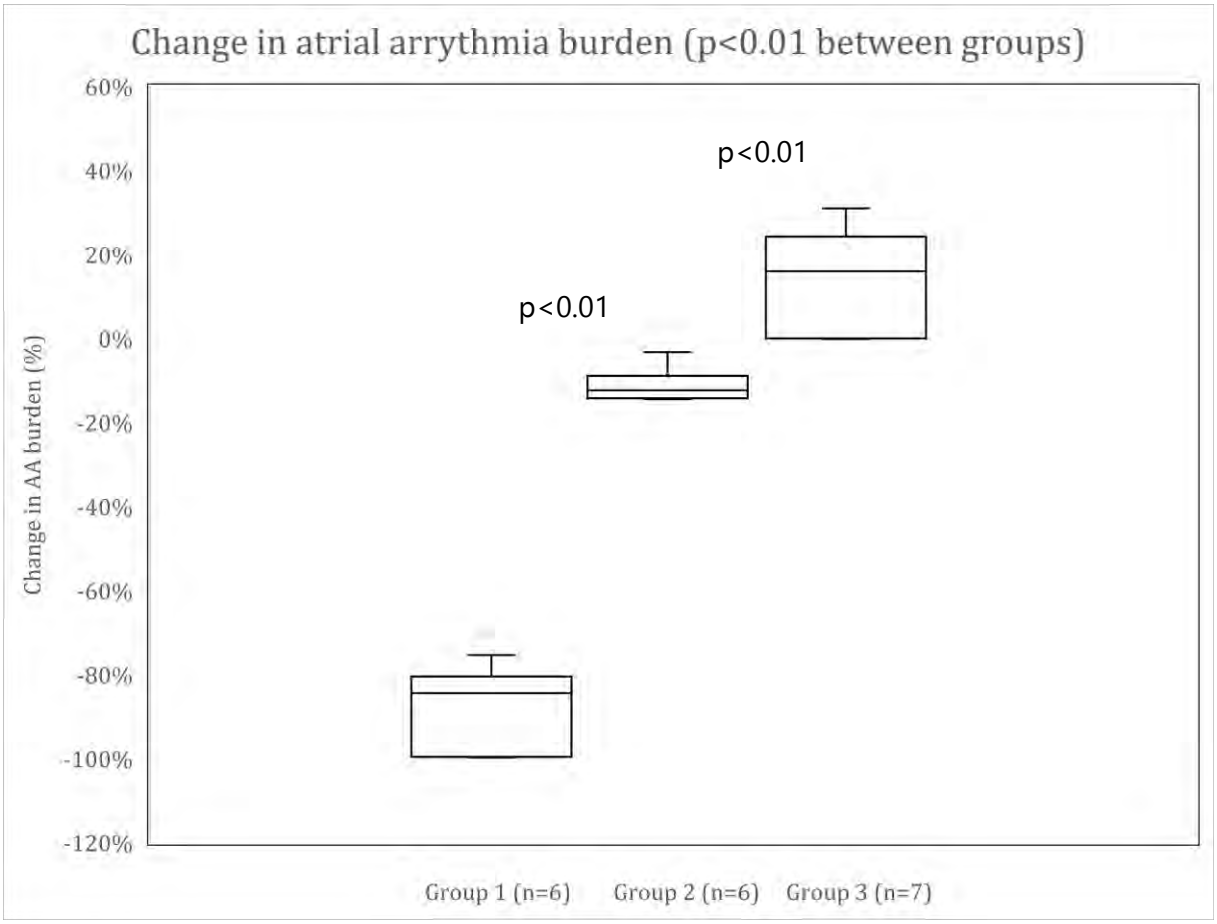


Figure 3.18: Change in atrial arrhythmia burden for three subgroups

The patients in the 3 groups were identified on the correlation graph and are highlighted in Figure 3.19. Δ TI for each patient in each group can be seen in Appendix B. Patients in group 1 all demonstrated an increase in mean TI from pre to post procedure (Figure 3.20). Interestingly, no patient who had an increase in AA burden had an increase in mean TI, which is in-keeping with the expectation that AA has a negative impact on cardiovascular function.

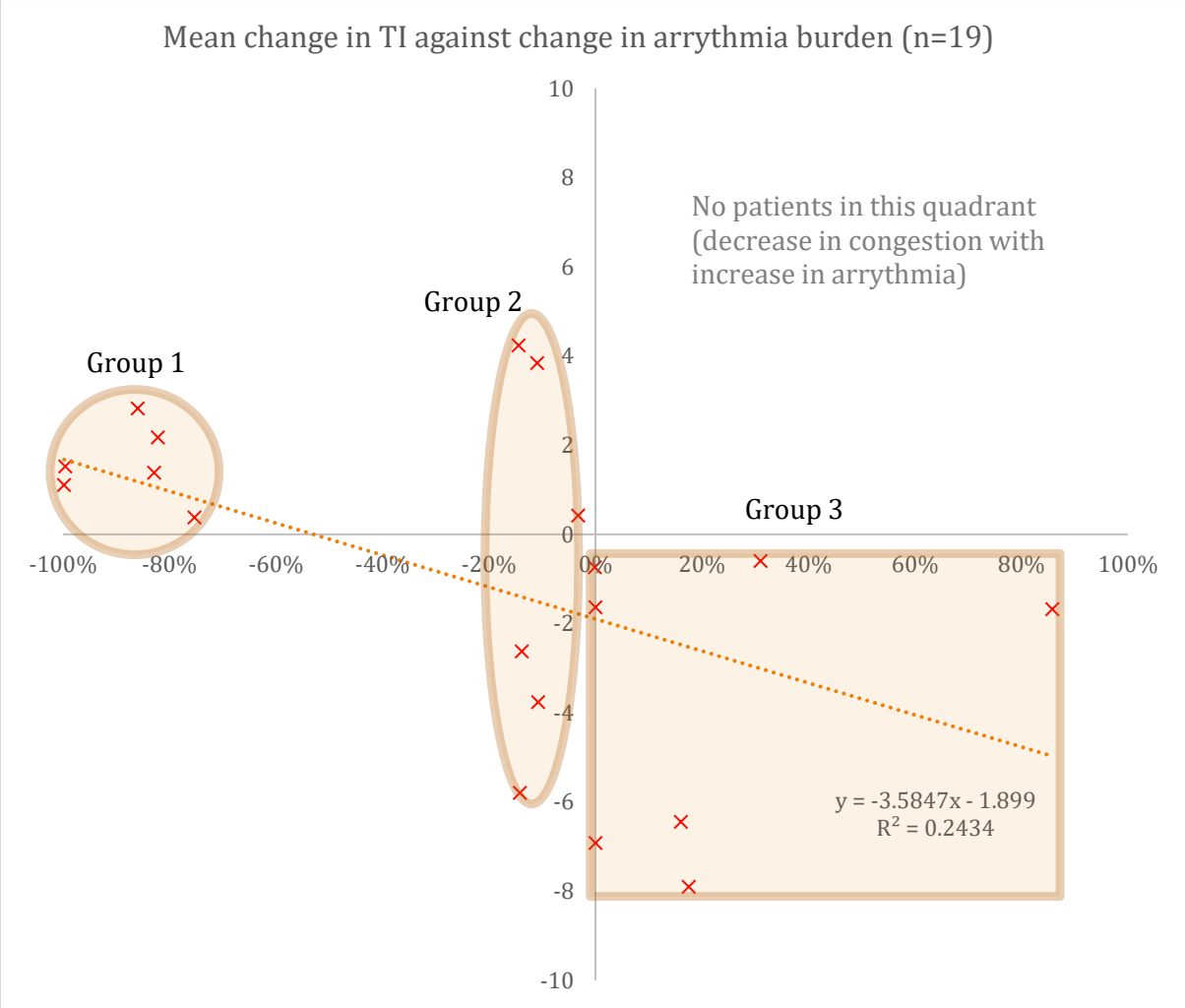


Figure 3.19. Correlation between change in thoracic impedance (ΔTI) and change in atrial arrhythmia burden (Δ AA). No patient had both an increase in AA burden and an increase in TI. Red dotted line is linear regression trend line. Y axis is change in thoracic impedance (Ohms) and the x axis is change in AA burden in %.

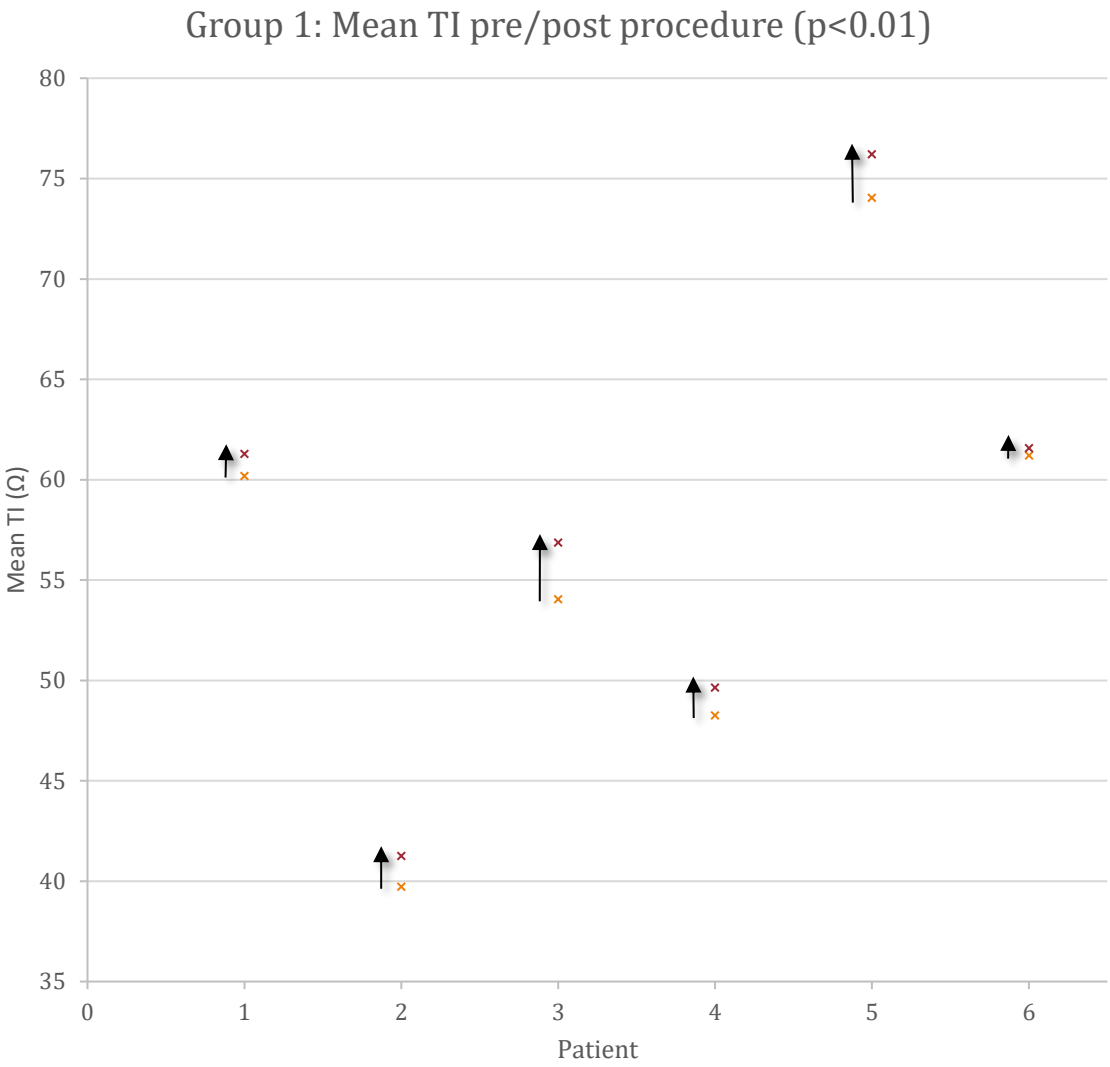


Figure 3.20, Daily thoracic impedance (TI) averaged for the year for pre procedure (orange crosses) and the year post procedure (red crosses). The difference was statistically significant (T-test for dependent means). Black arrows indicate direction of change after the procedure.

There were no significant differences between the three groups in terms of demographic or clinical variables, device type/manufacturer, or procedure type. Patients in group 3 waited significantly longer for their procedure than patients in group 1 (248 vs 74 days) $p<0.05$.

The change in mean daily TI (pre to post procedure) for the three AF burden groups is shown in figure 3.21. Only group 1 (with a reduction in AF burden of ≥ 75%) had an increase in mean TI, whereas group 2 and group 3 had a fall in mean daily TI. The difference between group 1 and 3 was statistically significant ($p<0.01$).

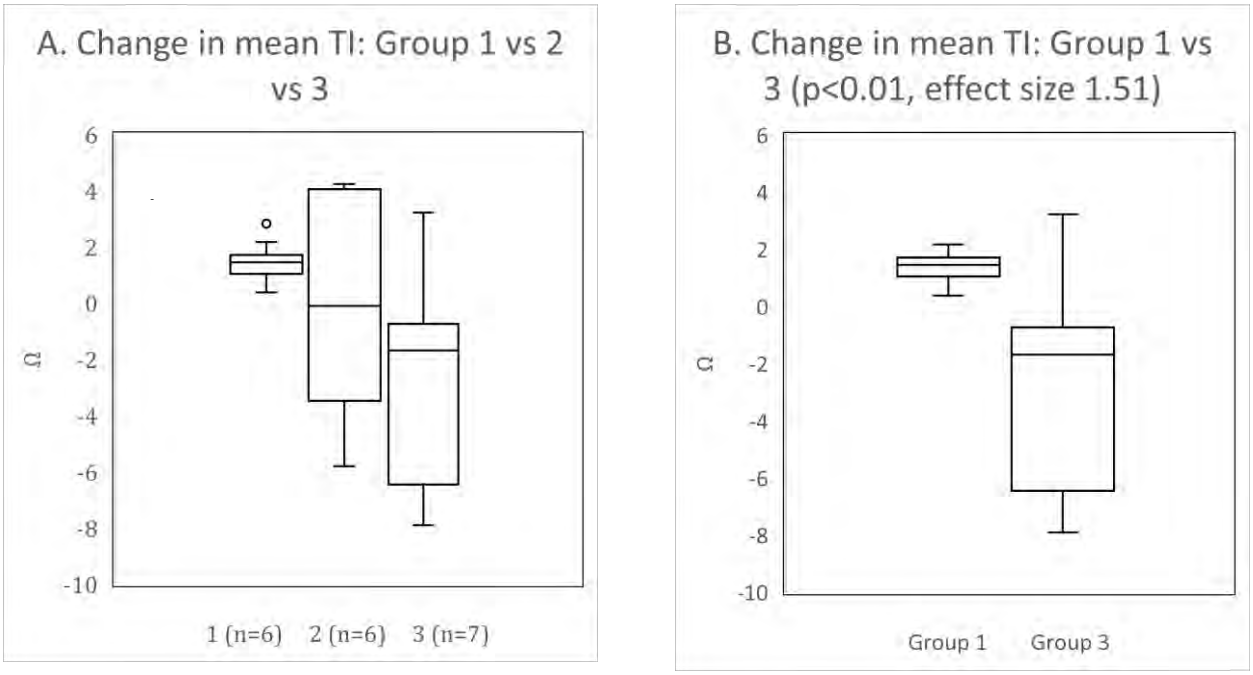


Figure 3.21. Change in mean TI for the year after the procedure compared to the baseline pre-procedure year. Panel A: All three tertile groups. Panel B comparison between patients with the largest reduction in AA burden (group 1) compared with those with no change or an increase in burden (group 3).

The change (Δ) in mean TI was positive for all patients in group 1 (+1.57 ± 0.85Ω), indicating that TI increased and that their pulmonary congestion was less during the year after the procedure. Δ in mean TI was negative for all patients in group 3 (-3.70 ± 3.22Ω), showing that TI reduced, and their pulmonary congestion increased in the year after the procedure. Patients in group 2 had a variable response but overall demonstrated a small decrease in AF burden and a small decrease in mean TI (-0.61 ± 4.13Ω).

The difference between ΔTI for group 1 verses ΔTI for group 3 was 5.27Ω which was significant ($p<0.1$) with a very large effect size of 1.51 (Glass's delta). A Glass's Delta of 0.8 or higher is generally considered a large effect size. Glass's delta was used as each group has a different standard deviation. Group 3 was treated as the control group. The value of TI varied very little for each patient, with the mean standard deviation for TI for all patients over 24m being only approximately 4Ω (Figure 3.22). Therefore, this difference of more than 5Ω associated with successful rhythm control is more than one SD and is significant. This value is also 6.1% of the mean TI over 24m (65.3Ω).

In contrast, for the same 19 patients, the standard deviation of D-PA over 24m is 55.3 mins, corresponding to 36.6% of the mean D-PA over 24m (153.1 mins).

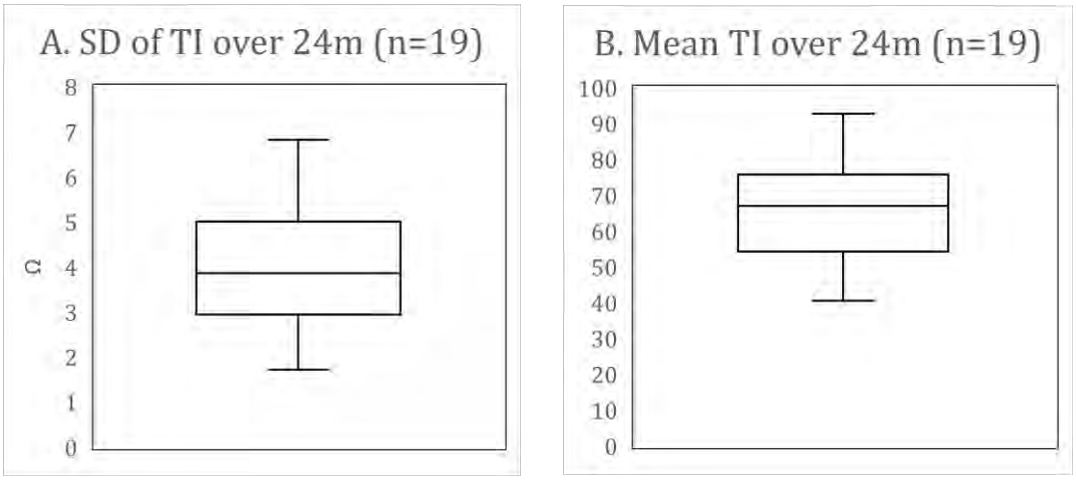


Figure: 3.22. Panel A. Standard deviation of TI for all patients with thoracic impedance (TI) data. This represents 6.1% of the mean TI (Panel B).

There were no significant differences between Groups 1, 2, and 3 in terms of demographic or clinical variables, device type/manufacturer, or procedure type. However, patients in group 3 waited significantly longer for the procedure than patients in group 1 (248 vs 74 days) $p<0.05$.

3.99.93 Discussion

TI exhibits less intra subject variation than D-PA, meaning that relatively small changes may still be significant. Change in mean daily TI after a rhythm control procedure correlated with the change in AA burden. This association has not previously been reported, but is in keeping with successful rhythm control having a beneficial effect on cardiovascular performance. This is biologically plausible, and it seems reasonable to assume that the reduction in congestion was caused by greater time spent in normal rhythm - with associated improvement in cardiovascular status. There was a significant difference in the change in TI in patients with

high AA burden pre-procedure and a low burden afterwards, compared with patients whose burden stayed the same or increased. Patients with a large reduction in AA burden all showed an increase in TI, whilst TI reduced in all those whose burden stayed the same or increased - suggesting that successful rhythm control results in reduced pulmonary congestion. This association has not previously been demonstrated.

A reduction in pulmonary congestion (without need for diuretic therapy) might be expected to be associated with outcome benefits such as reduced symptoms, improved survival and decreased hospitalisation. The fact that patients with no reduction or an increase in AF burden all demonstrated a decrease in TI (more congestion) illustrates the negative impact of sustained AAs on cardiovascular performance. Further studies are warranted to confirm this association and investigate correlation with clinical outcomes

3.99.94 Conclusion

Successful rhythm control reduces pulmonary congestion. This association has not previously been demonstrated using an objective measure. TI is a promising digital biomarker for assessing the impact of changes in cardiac rhythm on cardiovascular performance, and objectively evaluating the effect of treatments. This could be helpful in identifying those patients who benefit most from being in normal rhythm, for whom repeat procedures may be warranted.

CHAPTER 4:

COMPARISON OF DEVICE-MEASURED PHYSICAL ACTIVITY AND THORACIC IMPEDANCE MEASURES FROM TWO LEADING CARDIAC IMPLANTABLE ELECTRONIC DEVICE MANUFACTURERS

4.0 Introduction

This chapter focuses on the measurement of D-PA and TI by Medtronic and Boston Scientific CIEDs. D-PA and TI measures are increasingly utilised in the remote monitoring and management of patients with CIEDs, where they may be employed in the evaluation of conditions such as heart failure (HF) and frailty (Rossman et al., 2018: Kramer et al., 2017). The raw data is processed before being presenting in a modified form for clinicians to view. Unprocessed daily values over extended periods of time (months/years) are not made readily available to clinicians in routine practice, but can be requested for research purposes. These measures also have potential utility as outcome biomarkers in clinical trials. It is commonly assumed that data from single manufacturer studies can be generalised to all CIED patients,

but this assumption may not be valid, as manufacturers employ propriety sensors and algorithms to derive these data and head-to-head comparisons are lacking. Almost all studies involving CIEDs focus on devices from one manufacturer. Therefore, the aim was to compare these CIED measures in a real-world cohort.

For both manufacturers, D-PA is continuously recorded by a single axis accelerometer and interpreted with a proprietary algorithm that calculates the total number of active minutes per day based on a pre-set threshold. Both manufacturers report activity as "minutes active per day" but the threshold for logging a minute as "active" differs. The proprietary nature of the algorithms do not facilitate easy comparisons between D-PA measured by devices from different manufacturers.

CIEs have a set threshold when considering an acceleration input as either active or sedentary. There is no universal method to convert accelerometer-assessed activity units into standard intensity levels for direct clinical interpretation (Butler et al., 2024). Although accelerometer units are usually converted into time active, these are sensitive to activity thresholds. Precise information about how the proprietary sensors function that would enable better comparisons are not in the public domain. (Butler et al., 2024).

Medtronic

Medtronic thresholds are known to be based on accelerometer deflections equivalent to ***steps per minute*** (Puppala et al., 2020). In Medtronic devices, patient acceleration that is equivalent

to a walking rate of approximately 70 steps per minute is considered an active minute (ibid). A summary score for total activity in minutes per day is automatically calculated and stored in device memory for up to 14 months. Since a stepping rate equal to 100 steps/minute is considered moderate-intensity physical activity, (Bae et al., 2024) D-PA measured by Medtronic CIEDs appears to fall between light and moderate-intensity activity (e.g., walking at a slow pace) (Taylor 2023).

Boston Scientific

Boston Scientific process the accelerometer data in terms of crossing a walking speed threshold. When patient acceleration exceeds a pre-set threshold of 25 milligravities, equivalent to an approximate walking speed of 2 miles per hour or energy expenditure of 2.8 metabolic equivalent of task (METs), an "active minute" is recorded (Taylor 2023). Based on established MET level categories (activity ≤ 2.99 METs = light intensity), 1 D-PA measured by these devices could be considered light-intensity activity. (Rosman et al., 2018)

Thoracic impedance measurements

There is little data describing thoracic impedance measurements from different manufacturers. The value of TI will be determined both by unchanging (or at least minimally changing) factors affecting the resistance to current through the path of the electric current, as well as dynamic factors such as changing fluid constitution. Electrical aspects of the discrete signal waveform used during the measurement may also vary between manufacturers, and might affect measurements.

4.2 Results

CIED Systems and Manufacturer

All the CIEDs were either dual chamber or CRT systems, with well-functioning atrial leads (required for monitoring atrial arrhythmia burden). The majority of the devices (n=22 patients, 73%) were ICDs or CRT-Ds. Half the patients (n=15) had a system capable of delivering physiological pacing (via an LV lead or CSP lead).

The majority of the CIED systems were Medtronic (Med.) n = 21 (70%). 9 patients (30%) had a Boston Scientific (BSc.) device. The Trust remotely follows-up about 4000 patients with CIEDs from these two manufacturers. The sample of 30 patients represents a small fraction (just under 0.75%) of this total population. The Trust monitors approx. 3000 patients with Med. CIEDs and around 1000 with BSc. (approximately a 3:1 ratio). The proportion in the sample was 2.67 Med. to 1 BSc. - which appears in line with the proportion in the overall population.

The mean values for LVEF for patients with the two manufacturers were very similar (Medtronic, 39.7%; Boston Scientific 40.9%). However, a higher proportion of patients with Medtronic devices were taking a loop diuretic (90% vs 66.7%) which might indicate more severe HF in the Medtronic Group. This difference did not quite meet statistical significance ($p = 0.06$).

1368 days of measurement (6%) were recorded during UK Covid lockdowns, which may have affected patient activity (although this effect is unlikely to have affected the overall statistics). Patients were in an atrial arrhythmia for 41% of the total 2 year period.

Data were analysed for 21,588 days of measurements. Activity `was available for all 30 patients, giving over 600,000 daily D-PA measures. The mean daily activity for all patients over the 2 years was 2 hours 37 minutes per day.

TI data was available for 22 (73%) of the patients, yielding over 400,000 daily measurements. Although the patient sample is relatively small, the number of repeated measurements yielded very precise estimates of the 2 year mean values (see appendix B).

The D-PA and TI data for 2 years for each patient were summarised and found to follow a normal distribution regardless of manufacturer. Example distributions for 4 patients are presented in Figure 4.0.

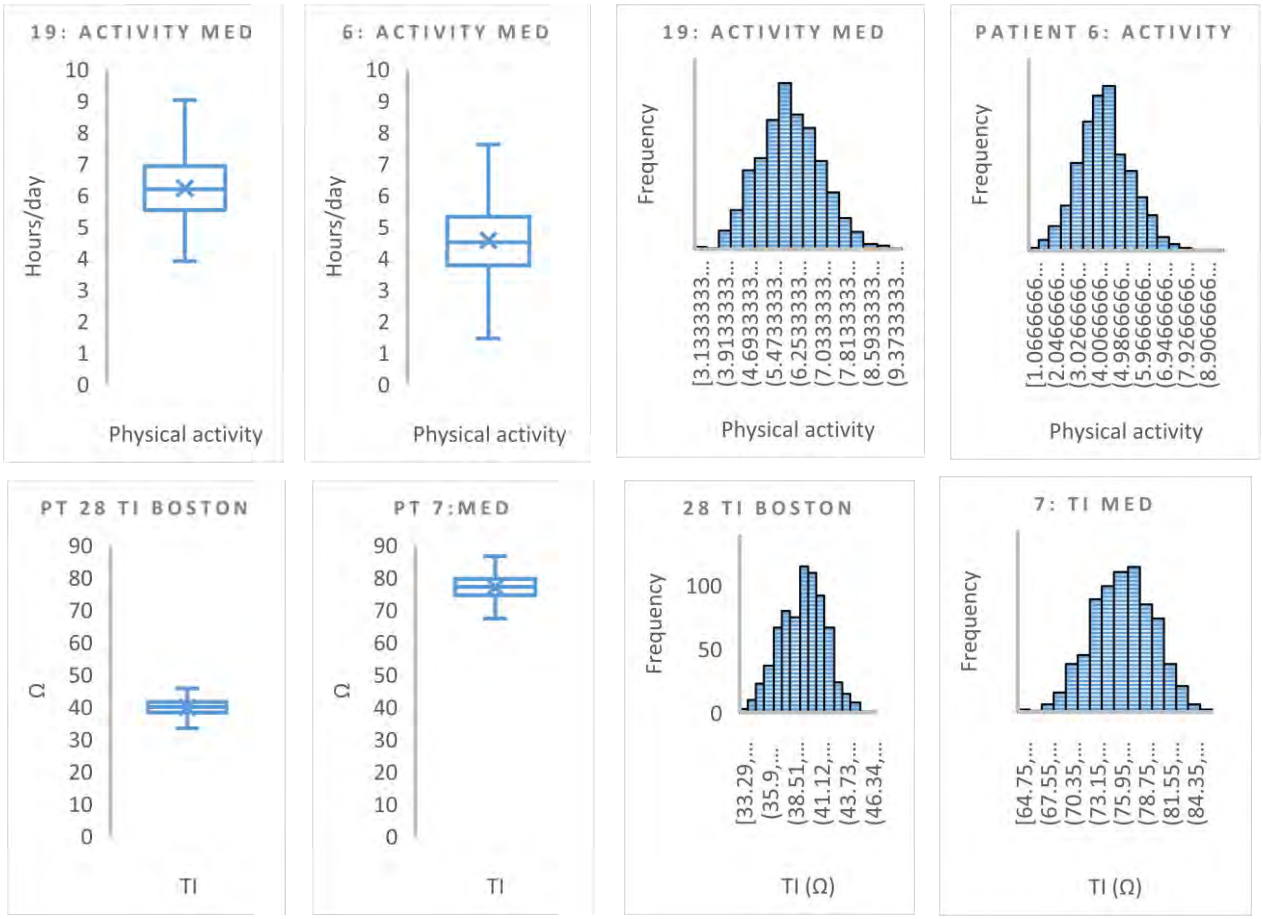


Figure 4.0. Example distributions for 4 patients. Variables followed a normal distribution

Med = Medtronic, Boston = Boston Scientific

4.3 Differences between manufacturers

Table 5. Summary statistics for physical activity (D-PA) and thoracic impedance (TI) for all patients, patients with Medtronic devices, and patients with Boston Scientific (BSc) deviation

D-PA (mins)

	Number	Mean	SD	Min	Max	Range
All patients	30	156.9	92.8	17.1	372.8	355.7
Medtronic	21	180.3	91.9	17.1	372.8	355.7
BSc	9	102.4	68.9	23.4	267.1	243.6
		* p <0.05	* p <0.05			

TI (Ω)

	Number	Mean	SD	Min	Max	Range
All patients	22	66.3	13.3	40.6	92.7	52.1
Medtronic	18	69.8	11.2	51	92.7	41.7
BSc	9	50.9	11	40.6	69.1	28.5
		* p <0.05				

D-PA = device determined physical activity TI =thoracic impedance

SD =standard deviation BSc = Boston Scientific

Patients with Medtronic devices demonstrated significantly higher D-PA measurements, with higher variation (Figure 4.1). Both the lowest and highest D-PA values across all patients were recorded by Medtronic devices.

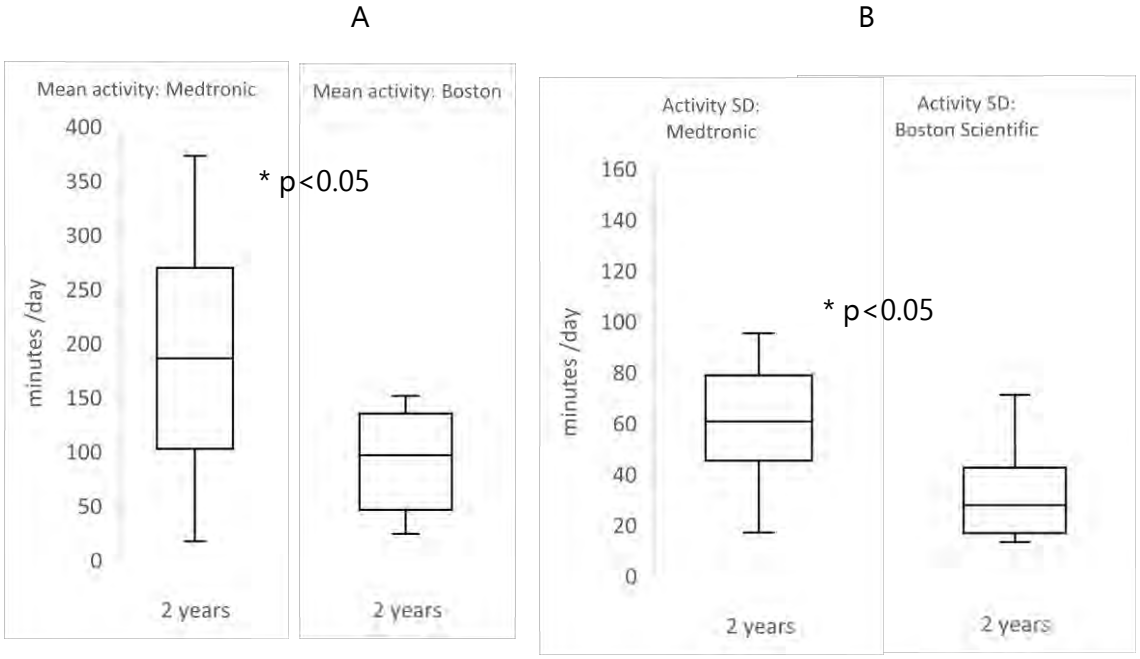


Figure 4.1. Mean device-measured physical activity (D-PA) - panel A, and standard deviation of D-PA (panel B) for Medtronic and Boston Scientific CIEDs.

Absolute values for TI also appeared to differ between Med. and BSc. CIED devices (figure 4.2).

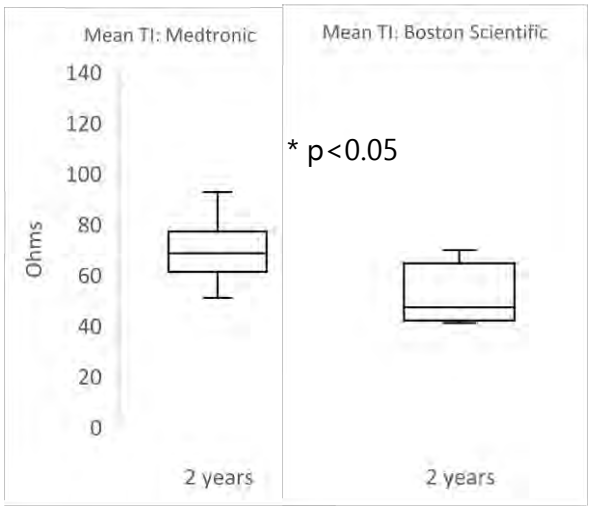


Figure 4.2 Mean thoracic impedance (TI) for Medtronic and Boston Scientific CIEDs

4.4 Discussion

Remarkably, there are no studies that directly compare activity data from these two leading manufacturers of CIED. There is, however, a consistent trend in single manufacturer studies of reporting higher activity levels with Medtronic CIEDs compared to Boston (e.g Conraads et al., 2014 (Powell et al., 2013). The patient populations in these studies appear broadly comparable to our cohort, but the lack of detailed reporting of clinical variables makes it difficult to draw comparisons. However, in the current study, the levels of activity for the two manufacturers were similar to that reported in the literature (see table 6).

Table 6. Present study compared to large cohort studies reported in the literature.

Study	Manufacturer	n	Age	Analysis period	Activity
Conraads et al.	Med.	836	65	30-days	199 ± 106
This thesis	Med.	21	65.2	2 years	180.3 ± 91.9
Altitude study	BSc.	98,437	67.7	2.2 years	111.0 ± 66.1
This thesis	BSc.	9	66.9	2 years	102.4 ± 73.1

Conraads *et al.*, (2014) reported a mean activity of 199 minutes per day (±106), as recorded by Medtronic CRT-D and ICD devices over a 30-day period in 836 patients in the SENSE-HF and DOT-HF studies. The mean age was 65 years, 85% were male, 80% had a CRT device and 46% of participants had NYHA class III/IV HF symptoms. Both the SENSE-HF and DOT-HF studies excluded people with COPD, which might explain the higher activity reported in these studies.

The ALTITUDE study (Powell et al., 2013) was a very large single manufacturer Boston Scientific sponsored study which included an analysis of D-PA data from ICD and CRT-D patients. For the combined cohort (CRT-D plus ICD), mean activity was 111.0 ± 66.1 minutes per day over the entire 2.2-year follow-up (for 98,437 patients with a mean age 67.7 ± 13.1 years) [Powell

et al., 2013]. Very limited demographic and medical details for participants were available, limiting comparative analysis with the current study. Taylor (2023) speculated that the observed lower range of physical activity in Boston Scientific cohorts might be due to manufacturer-specific activity processing. However, since comparison of cohort demographics was not possible, the author could not confirm this insight. The ALTITUDE study also reported intra-individual variation in daily activity - as an average SD of 79.2 minutes from their mean daily activity across the 2.2 year follow-up period. This is broadly similar to the value of 68.9 minutes for Boston devices in our study.

Absolute D-PA measurements, and the degree to which D-PA varied, differed for Medtronic and Boston Scientific CIEDs. These differences could not be explained by differences in the characteristics of those in whom the devices were implanted. The differences are clinically significant – questioning the ability to generalise from single manufacturer studies, and in setting common thresholds for triggering clinical interventions. Absolute values for TI also differ between Medtronic and Boston Scientific devices, but in contrast to D-PA, variation in TI is similar for both companies. Change in TI, rather than its overall magnitude, is the clinically important aspect - suggesting that it may be reasonable to generalise between the two manufacturers with regard to changes in TI in individual patients.

Mean BMI tended to be higher for patients with Medtronic devices (Med 29.1 kg/m^2 vs Boston Scientific 26.8 kg/m^2), but this difference did not meet statistical significance. Previous studies

have suggested that patients with a higher BMI have a higher activity. This difference alone does not appear to be sufficient to explain the result (Shoemaker et al., 2019)

The original and primary use of accelerometer data in CIEDs was to vary the rate of pacing in accordance with physiological demand (rate responsive pacing). For Medtronic devices the accelerometer is the only sensor that can be used for varying the pacing rate, which means that it is critical that this data is sufficiently sensitive and optimised for this particular use - it must be able to reflect the activities of daily living in a wide range of patients, some of whom will be elderly or frail. Therefore, the sensor must be able to detect, and reflect changes in, relatively low levels of physical activity.

For Boston Scientific devices, the primary sensor used to determine physiologic demand is minute ventilation (MV); a sensor that reflects the rate of respiration rather than activity. MV utilises small oscillations in TI measurements caused by changes in lung volume that accompany breathing movements. This sensor is separate from the TI measurement employed for HF monitoring by both Boston Scientific and Medtronic. Accelerometer data can be used (either instead of, or as well as MV) but the default sensor is MV. This could perhaps explain the different sensitivity of the two manufacturers revealed by this study.

4.5 Clinical implications

For the Medtronic Triage HF ™ algorithm, physical activity is considered 'low' if patients are active for less than 1 hour/day over a one-week period (non-overlapping), or there is a sustained downward trend over the previous fourteen days (Virani et al., 2018). This figure is easy to remember and is 'flagged' in Medtronic device reports when it occurs. This threshold has become a known standard for identifying low physical activity in CIED patients, which may be interpreted as indicating HF decompensation or frailty, with the potential to influence patient management. Although restricted to Medtronic devices, the figure of 1 hour has been widely generalised to other manufacturers. The results from our current study indicate that this may not be appropriate. Since the number of patients in our study was small, larger studies should be conducted to evaluate D-PA levels in CIEDs from different manufacturers.

4.6 Limitations

The current study population was small (n=30), with only 9 Boston Scientific devices represented. Since not all devices were capable of being programmed to record TI measurements, the sub-group with TI data consisted of 22 patients, with only 4 Boston Scientific devices. However, despite these small numbers, the large number of repeated measures for each variable (typically 730) resulted in precise estimated for mean and variation. (Schober and Vetter, 2018).

CHAPTER 5:

SEASONAL EFFECTS ON DEVICE-DETERMINED PHYSICAL ACTIVITY AND TRANSTHORACIC IMPEDANCE

5.0 Introduction

Levels of physical activity vary with the seasons and various explanations have been proposed to explain this finding. For example, poor weather can be a barrier for participation in physical activity, especially outdoor activity, and weather can influence motivation (Brustio et al., 2018). The effect of season is not limited to activity conducted outside, however. In a retrospective study in older, functionally impaired people, Sumandas *et al* (2008) correlated daily activity measured using an external accelerometer (in Scotland in the UK) with local weather data, and found that day length, sunshine duration and maximum temperature profoundly affect physical activity levels. The mean daily activity counts showed striking seasonal variation, with maximum activity in June and minimum in February (Klompstra, et al., 2019). Also using step counts objectively measured by an accelerometer, Izawa *et al* (2014) found similar seasonal

changes in the PA of older cardiac patients with chronic HF. Symptom severity dictated by the physiological effects of seasonal changes likely play a role. In one study conducted in Valencia, Spain with 87 patients with HF, increased symptom severity during the winter was associated with lower activity levels and decreased PA, and did not appear to be related to motivation (Klompstra et al., 2019). There has not been any previous investigation of a possible seasonal effect on TI measurements.

Seasonal effects need to be better understood, so they can be accounted for when interpreting clinical data, monitoring disease progression, and designing and analysing the results of future clinical trials to investigate interventions.

5.1 Seasonality in physical activity measured by CIEDs

Shoemaker *et al.*, (2020) confirmed that daily D-PA measurements in patients with HF show seasonal effects by analysing 168 CIED patients over one whole year (figure 5.1). The daily D-PA seasonal difference between winter and summer months was 0.4 hours per day; the same magnitude as the minimum clinically important difference (MICD) that signifies a clinically meaningful functional decline (Shoemaker et al., 2012). This finding highlights that seasonal variation must be accounted for when designing and interpreting results of clinical trials using

D-PA to investigate interventions (Shoemaker et al., 2020). People with fewer comorbidities and higher overall activity levels showed a disproportionate seasonal effect (ibid).

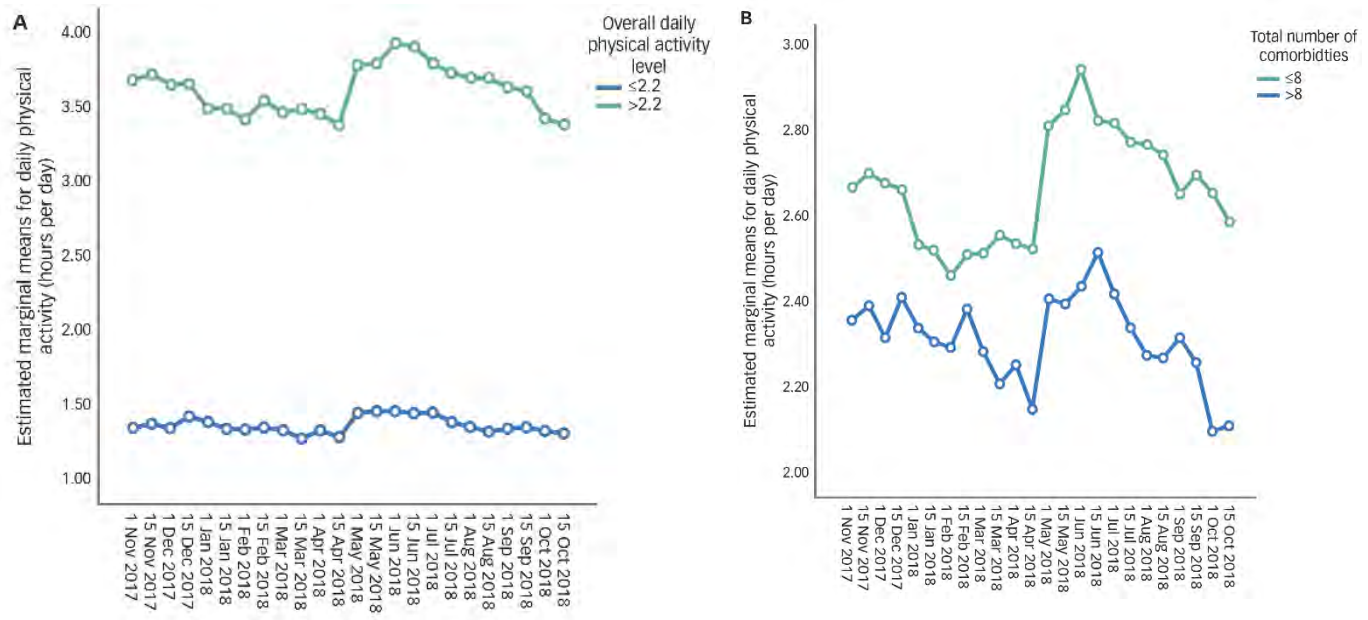


Figure 5.1. Estimated marginal means based on overall daily physical activity level (A) and total number of comorbidities (B) From Shoemaker *et al.*, 2020

However, the effect of season on daily PA is heterogeneous, where both sinusoidal seasonal variation and overall declining patterns have been observed. Those who are more active (greater than 2.2 h per day), and have fewer comorbidities (8 or less), demonstrate a greater seasonal difference (42 min per day) vs those who are inactive and have a greater number of comorbidities (6 min per day). Those who showed the greatest seasonal variation were male,

with low comorbidity/NYHA, a high BMI, but were not hospitalized. Downward trajectories (40–80 mins) throughout the year were associated with female patients and hospitalization (Shoemaker et al., 2021).

5.2 Other factors affecting physical activity

Daily activity is affected by factors other than cardiac function. As well as requiring adequate cardiopulmonary function, daily physical activities such as walking, running and climbing stairs require proper coordination between the nervous system and the musculoskeletal system. Therefore, any abnormalities in the functioning of these systems may potentially affect the natural patterns of these activities (Majumder & Deen, 2019). Viral infections cause sudden, profound but short-term changes in PA recorded by accelerometers in consumer devices and have been used to track the progress of viral epidemics (Samson et al., 2019).

During physical activity, HF patients often report symptoms such as shortness of breath and fatigue that can limit activity; these symptoms may cause feelings of fear, anxiety, and powerlessness and can decrease confidence in the ability to perform physical activity (Klompstra, et al., 2019). HF patients may also lack the motivation to exercise, or knowledge of the importance of physical activity (ibid).

5.3 Thoracic Impedance (TI)

There have been no investigations into the effect of season on TI. There is a well-documented association between meteorological variables, hospital admissions and mortality from HF (Goggins et al., 2017), with an increase in admissions and cardiovascular mortality during winter in the northern hemisphere. The precise cause of this effect is unknown. It seems likely that pulmonary congestion might be worse during the winter than summer months, and this might be detectable in TI measurements (D'Amato et al., 2018). Changes in TI reflect the fluid status of the lungs and have shown the potential to reveal changes in heart failure status early in the clinical course of HF decompensation. Outside of severe HF decompensation events, variation in TI measures have not been studied. It is possible that sub-clinical seasonal variation exists.

5.4 Methods

A 6th order polynomial spline was found visually to be the best fit model for both D-PA over the 24 month period for each patient. For one patient, the D-PA data and local temperature data (Met Office 2024) data were compared graphically (Figure 5.2). There was a visual fit between temperature variation and the D-PA data, suggesting that the 6^{th} order polynomial approximated the sinusoidal variation in D-PA.

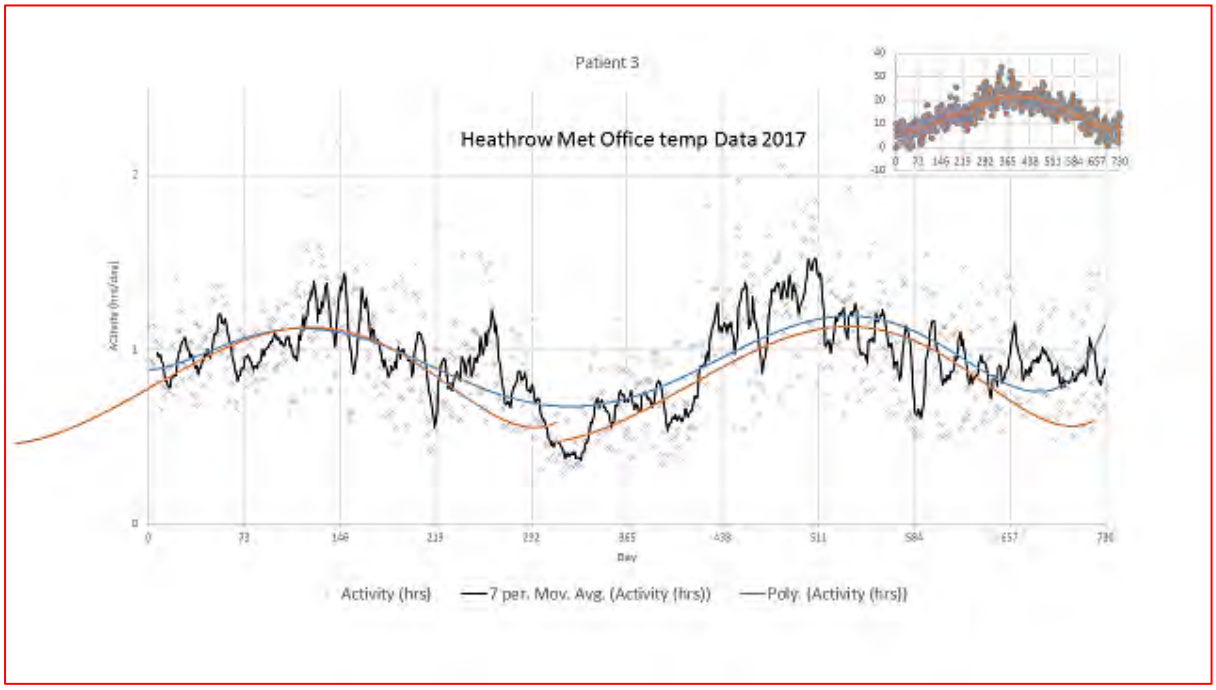


Figure 5.2 Polynomial spline fitted to the D-PA data for one patient is shown. The blue line is a 6th order polynomial trendline of D-PA (y = 2E-15x6 - 3E-12x5 + 2E-09x4 - 7E-07x3 + 6E-05x2 + 0.0006x + 0.8829 [R^2 = 0.25] . Red line is a 6th order polynomial trend line fitted to Met Office daily local temperature data (raw data shown in insert) for the most recent available year (2017) (y = 1E-15x6 - 1E-12x5 + 5E-10x4 - 5E-07x3 + 0.0003x2 + 0.0125x + 5.4819 [R^2 = 0.7061] https://www.metoffice.gov.uk/research/climate/maps-and-data/historic-station-data

The 6^{th} order polynomial trend was applied to all 30 patients and the results were analysed graphically to identify patients exhibiting a summer to winter sinusoidal pattern. The presence of identifiable peaks coinciding with each season of warmer months (April – October) and nadirs with each occurrence of the cooler months (November – March) were assessed. 10 patients (33%) who demonstrated this association were identified (Figure 5.3).

5.5 Results

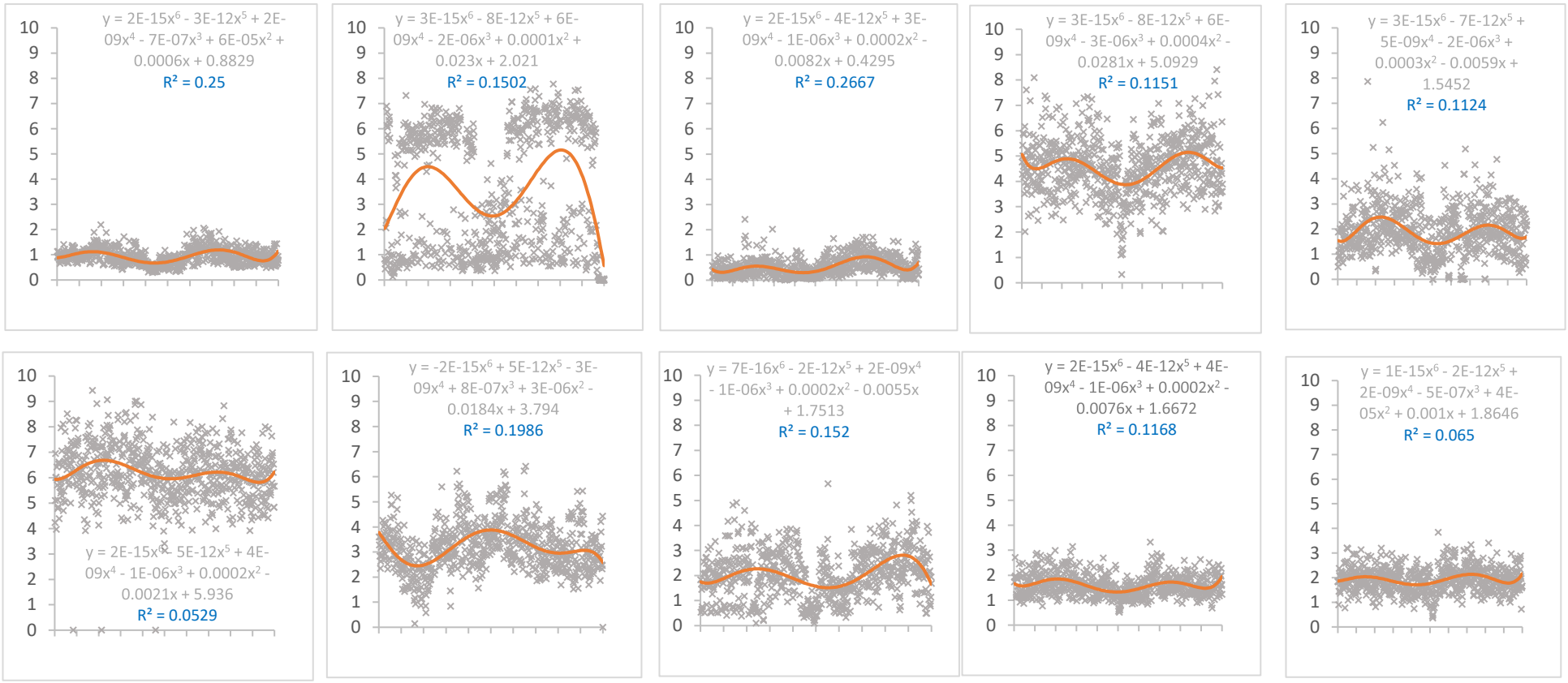


Figure 5.3: Patients (n=10) with sinusoidal seasonal variation over 2 years. The y axis is hours of activity per day (D-PA data). D-PA is modelled with a 6th order polynomial trend line. Peaks occur each spring/summer and nadirs each autumn/winter. R2 values for the 6th order polynomial trend lines are shown.

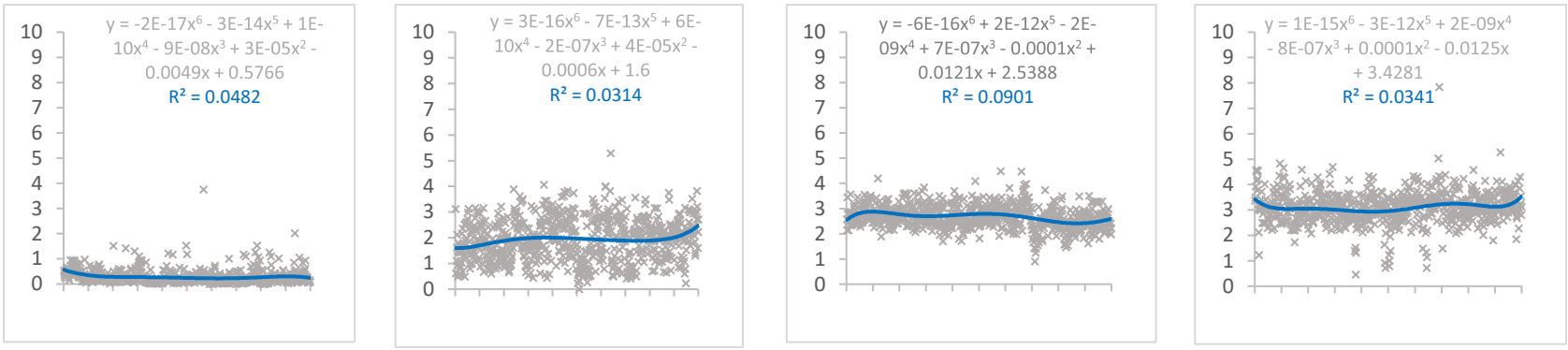


Figure 5.4: Examples of four patients where no clear sinusoidal tend could be identified by visual inspection. The y axis is hours of activity per day (D-PA data). D-PA is modelled with a 6th order polynomial trend line. A sinusoidal trend could not be identified in n=20 (66.7%) of patients. R2 values for the 6th order polynomial trend lines are shown.

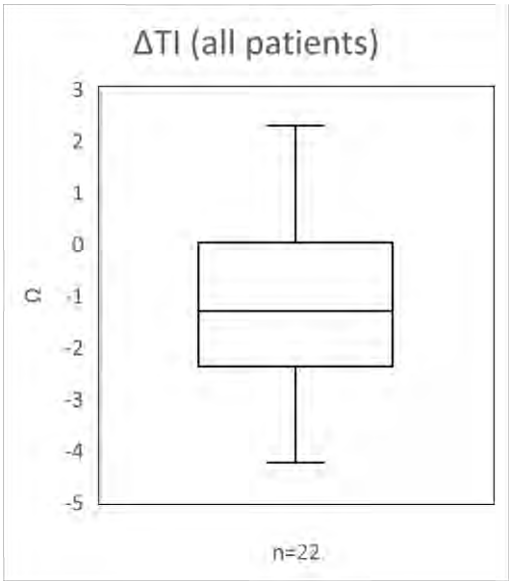
Patients with a seasonal trend that could be identified visually tended to have a higher R2 value for the 6th order polynomial trend line. There were no significant differences in demographic, clinical or other variables, between the seasonal and non-seasonal groups. There was a trend towards a lower number of comorbidities (4.60 vs 5.45) in patients with a seasonal trend, but this difference was not significant. There was only one patient (10%) with NYHA 3 HF in the seasonal group, compared to 7 (35%) in the non-seasonal group, although this difference also did not

meet statistical significance (p= 0.08). This may suggest that patients with less severe cardiac dysfunction are able to increase their activity in response to more favourable conditions in summer.

Individual seasonal patient data can be seen in appendix D. For all 30 patients, the mean D-PA for the warmer months was 161.5 minutes/day compared to 145.4 for the cooler months; a difference of 16.1 minutes/day. This was not statistically significant. In the 21 (70%) who demonstrated a decrease in average activity winter compared with summer, the difference was 26.5 minutes (174.6 vs 148.1). This was also not statistically significant. 9 patients (30%) actually demonstrated an increase in activity in winter.

In 15 of the 22 patients (68%) where TI measurements were available, there was a decrease in average TI over winter compared with summer. The difference between seasons was in the same direction as the change in activity in 12 of the 15 (80%).

In the 14 patients who demonstrated a reduction in TI in winter the difference was 2 Ω (mean 1.9 SD 2.1) [Figure 5.5]. Standard deviation in TI was 4Ω overall, so in this group it appears that perhaps as much as half of the variation in TI may be seasonal. However, this difference in TI did not meet statistical significance in our relatively small sample size. In all cases, the 10 patients identified with sinusoidal seasonal pattern demonstrated a decrease in D-PA during the 'winter', with 9 of the 10 patients also showing a reduction in TI



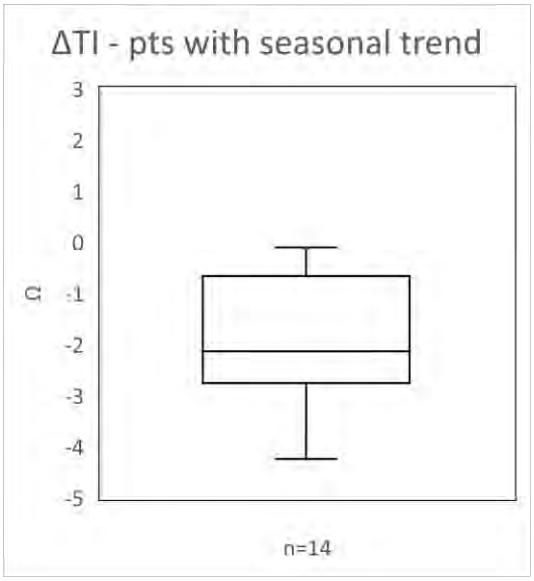


Figure 5.5 Change in TI (ΔTI) – all patients on the left, and only those with a possible seasonal trend (lower TI in winter, higher in summer) on the right. Differences were not statistically significant.

One patient appeared to be an outlier with regard to D-PA. (Figure 5.6). On further investigation, this patient was found to have been hospitalised for sepsis during the winter months and also had a very active physical job. This set of circumstances generated an extreme change in activity between summer and winter. For this reason, it was decided to exclude this patient from further analysis. Excluding this patient resulted in a normal distribution of change in activity by season (Figure 5.6).

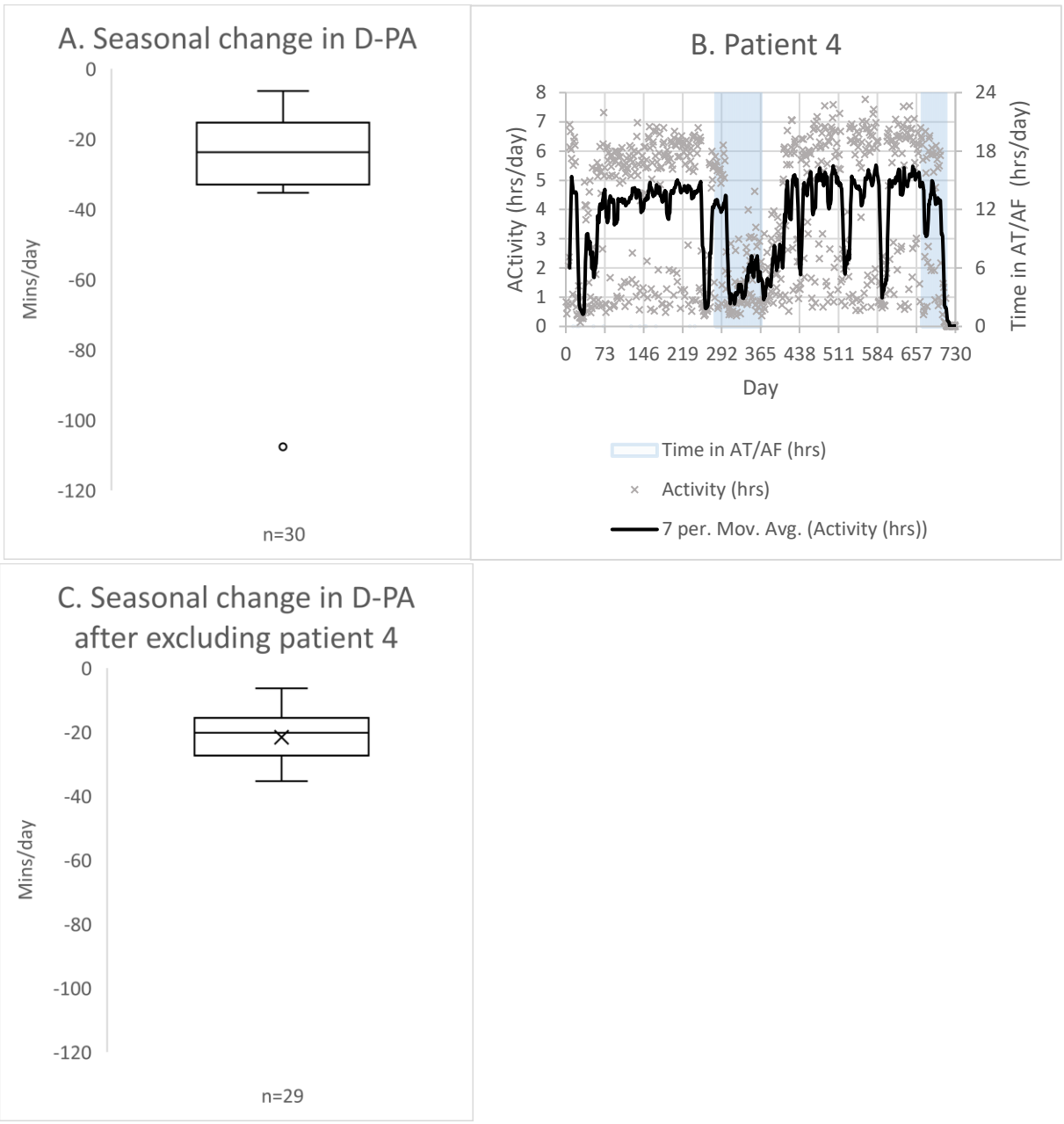


Figure 5.6 Seasonal change in D-PA. Panel A shows the spread of change for all patients. Patient 4 can be seen as an extreme outlier. This was due to acute admission for sepsis in winter. When this patient was removed the distribution followed a normal distribution.

Patient 10 demonstrated a clear seasonal trend in activity, and also had a 'perfect' result from DCCV (100% AF burden to zero). In addition, there were no confounding factors affecting activity such as Covid lockdowns, physical injury or surgery. This patient demonstrated an increase in the summer peak in activity after return to sinus rhythm. This increase of 23 mins represented an increase of 69%, due to the low level of baseline activity for this individual (<1 hr /day). This patient experienced significant symptomatic improvement from DCCV.

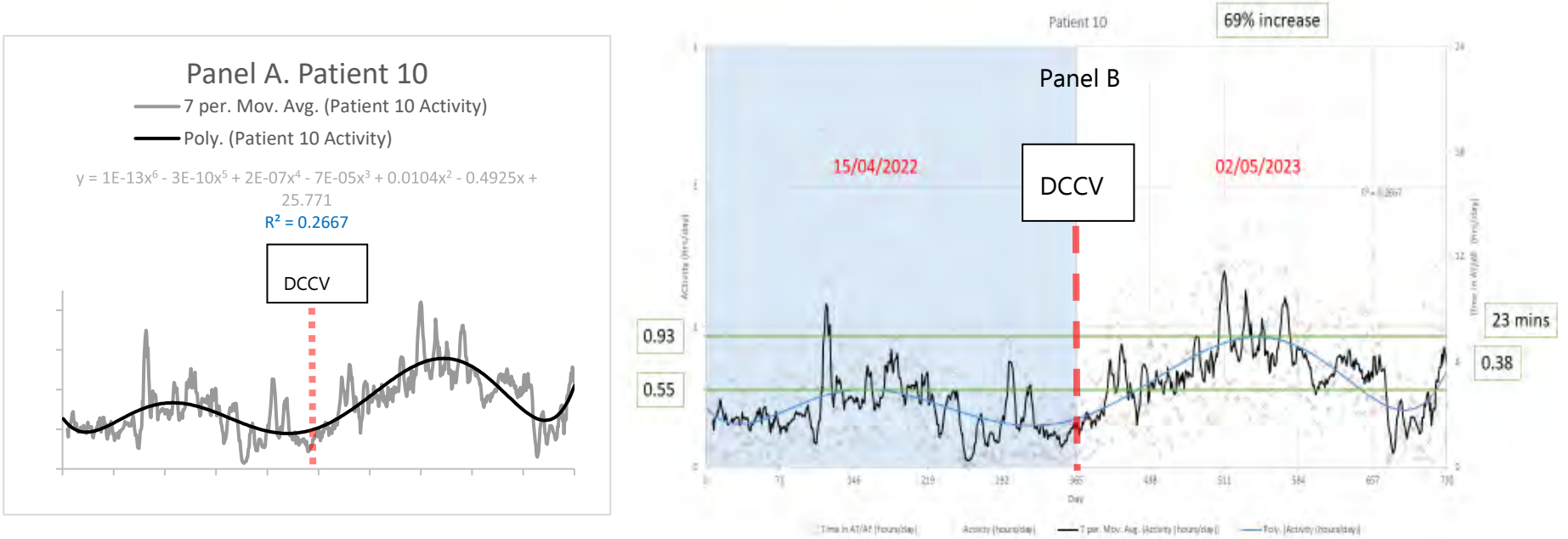
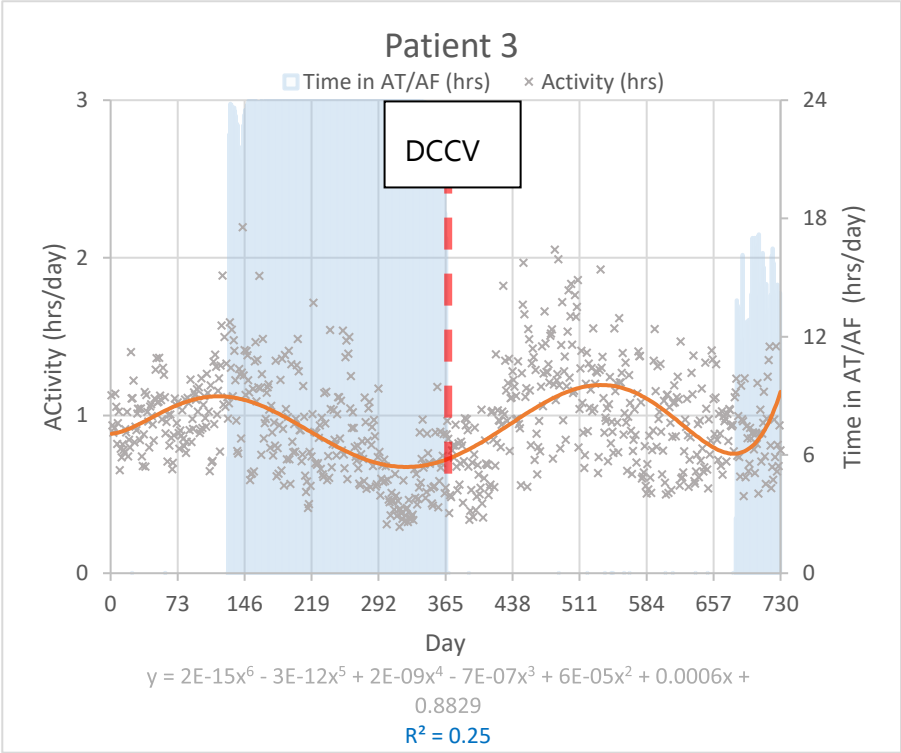


Figure 5.7: Example of a patient with an increase in the summer maximum after successful treatment. Panel A. shows a 6th order polynomial curve fitted to the D-PA data. Panel B illustrates the apparent increase in summer maximum of 69% after successful rhythm control by DCCV

Time of year as a confounder



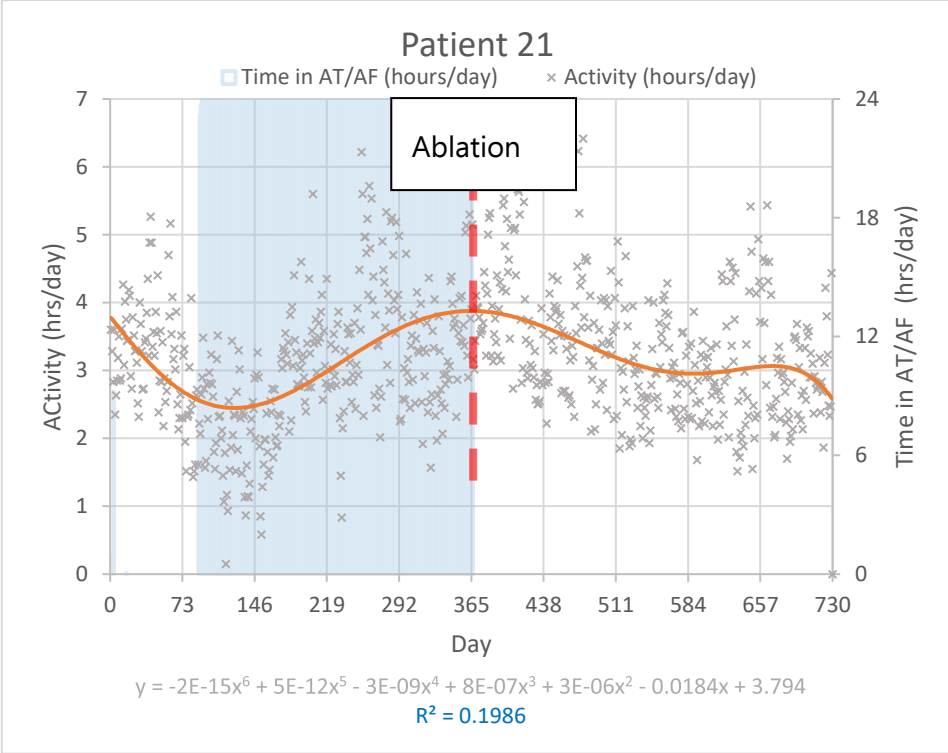
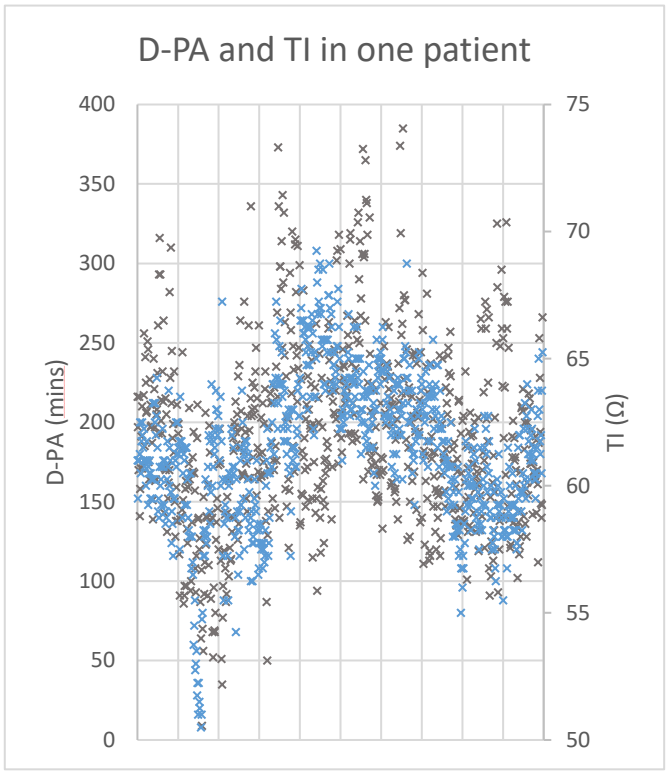
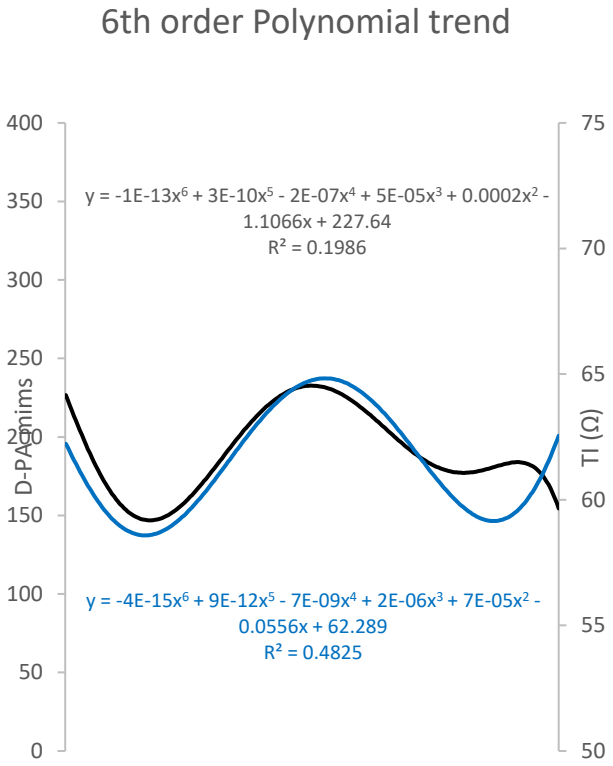


Figure 5.8: Time of year as a confounder. Patient 3 was referred by a cardiac physiologist for consideration of DCCV largely on the observation of decreasing activity coincident with the onset of AF. However, this is likely due to initiation of AF occurring at the peak of the summer maximum. Conversely, for patient 21, sinus rhythm appears to cause a worsening of their capacity for physical activity, R2 values for the 6th order polynomial trend lines are shown.

The increase in activity following successful DCCV seen in patient 3 could be miss-interpreted as evidence of benefit from the procedure. However, the increasing trend in activity actually begins before the procedure itself, and the increase is more likely to be seasonal. This patient reported no symptomatic benefit from the procedure. If patient 21 was part of a clinical trial using D-PA as an outcome marker, there might appear to be a decline resulting from the intervention, because the ablation procedure occurred simultaneous with the summer peak in activity. Seasonal variation needs to be considered when interpreting activity data for use in clinical research

In 2 (20%) of the 10 patients with seasonal variation we observed that there was a similar trend in TI with very similar phase (see figure). The seasonal variation in D-PA was less that the variation in D-PA (by a factor of about 8). This reflects the fact that TI varies my much less overall than D-PA.





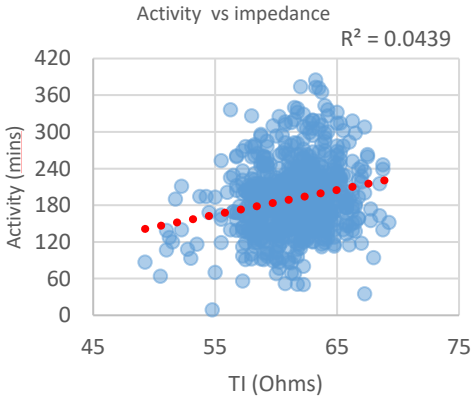


Figure 5.9: Striking correlation between the time series for D-PA (black) and TI (blue). Right hand pane shows a 6th order polynomial trend line fitted to points. Inset left shows linear correlation between TI and D-PA. Equations and R2 values for the 6th order polynomial trend lines are shown.

Pearson's r Correlation Coefficient was calculated for the patient shown in figure 5.9 and found to be positive: r = 0.21 95% CI [0.14 , 0.28]. Correlation coefficients were calculated for all 22 patients with TI data and will be presented in the next chapter.

5.6 Discussion

This is the first study to investigate seasonal changes in individual patients in conjunction with procedures to treat atrial arrhythmias, and raises some important questions with regard to interpreting the effect of arrhythmias, and treatments based on D-PA measurements. Although studies have been reported documenting the seasonal trend in D-PA measurements (Shoemaker et al., 2019), this phenomenon is not widely recognised by clinical staff monitoring these patients. The seasonal effect has potential implications for interpreting changes in activity in a clinical and research setting (Figure 5.8). At least one example of a likely seasonal trend being misinterpreted as resulting from the onset of an arrhythmia was revealed.

It may be possible to identify an increase in the summer maximum after treatment in a larger cohort (free from confounding effects on activity) which could represent a marker for cardiovascular improvement. Although the most common peak of the sinusoidal trend was in July, it was observed that it can occur in late spring (and early autumn) in a number of patients. It may be that impaired cardiac function curtails the normal increase in activity that occurs seasonally, or that that higher temperatures in summer disproportionately affect people with HF.

These data are in line with those presented by Shoemaker et al 2021; namely that a subgroup of patients demonstrate a sinusoidal seasonal trend in D-PA whilst others do not. Patient factors that may explain this difference were not identified. This trend needs to be born in

mind when interpreting data for clinical or research purposes. Of note, a matching sinusoidal trend in TI in a subgroup of patients exhibiting a trend in D-PA was identified. To our knowledge, such as trend in TI has not previously been described. A trend to higher TI values in summer and lower in winter in the population as a whole was detected, but this difference did not meet statistical significance.

A seasonal effect on TI has not previously been described in the literature. The trend towards a possible seasonal effect should be investigated in a larger sample. A seasonal difference in pulmonary congestion would be an interesting finding - because of the well-described seasonal variation in cardiac and pulmonary disease. The sinusoidal variation in TI demonstrated in at least one patient, matches closely the pattern seen in physical activity, suggesting that there may be a unifying physiological mechanism driving the fluctuation in both D-PA and TI.

There is a clear relationship between death rates and the outside temperature, with more deaths in colder months (ONS 2023). However, hypothermia-related deaths are rare in the EU – probably around 1% of the total number of winter deaths are attributable directly to cold in mild EU countries. Winter mortality is not solely a reflection of temperature, but of other factors as well. These include respiratory diseases and pressure on services (ONS 2023). Cardiovascular deaths rise in winter - the composition of blood changes in the cold; the red cell count, plasma cholesterol and plasma fibrinogen all increase and are factors known to contribute to thrombosis (Fares et al., 2013). Respiratory and other viral and bacterial infections, which

mostly occur in winter, can trigger coronary heart disease or stroke, because they affect blood coagulation factors, can cause damage to vessel walls and may promote atherosclerotic plaque development. A seasonal fluctuation in TI (and potentially therefore in subclinical pulmonary oedema) might have implications for understanding or predicting seasonal mortality.

CHAPTER 6:

CORRELATION OF DEVICE-DETERMINED PHYSICAL ACTIVITY AND TRANSTHORACIC IMPEDANCE

6.0 Introduction

Activity and thoracic impedance both fall rapidly with the onset on worsening HF (Assa et al., 2023). The fall in impedance is due to the increased pulmonary congestion that accompanies reduced left ventricular performance (ibid). The combination of reduced cardiac output and impaired oxygen uptake by the lungs lead inevitably to a reduced oxygen availability in the muscles, and a fall in physical activity. In chapter 5, a close relationship between D-PA and TI was identified in a subset of patients with a sinusoidal seasonal trend in D-PA. This is interesting - because it suggests that activity in these patients may be limited primarily by physiological rather than behavioural factors. The long-term sub-clinical relationship between D-PA and TI has not been investigated. Therefore, the aim of this chapter is to explore this possible subclinical relationship in the cohort of patients with both D-PA and TI data available.

6.1 Methods

Twenty-two patients with both D-PA and TI data were identified. Pearson's correlation coefficient for D-PA and TI was calculated for each patient and categorised as positive, negative or equivocal/indeterminate (making use of the 95% confidence interval) [see figure 6.1]. The characteristics of patients with positive and negative correlation coefficients were compared, and the relationship between the two variables examined graphically by plotting them together for each patient. The relationship was further characterised by calculating the Pearson correlation co-efficient for D-PA and TI against time, and the 95% CI was utilised to determine if the slope of each was positive, negative or indeterminate. Next the polarity of the slope for D-PA and TI for each patient was compared to determine whether they were either both positive or both negative (i.e. concordant), or if one was positive and the other negative (discordant). If one of the correlations had indeterminate slope then the relationship was characterised as equivocal. This allowed an assessment of the direction of change in the two variables over 24 months; i.e. did D-PA and TI both increase, both decrease, or did they change in opposite directions?

6.2 Results

For all 22 patients with TI trends, there was a mean correlation coefficient between the two parameters of +0.08 with a normal distribution of values. Twelve patients (55%) showed a positive correlation, 6 (27%) a negative correlation, and the remaining 4 patients (18%) could not be assigned a polarity (Table 7). There were no statistically significant differences in patient characteristics between those with negative and positive correlation, although there was a non-significant trend towards higher BMI in patients with negative correlation (mean BMI 32.4 vs 28.5; $p<0.081$).

Table 7. Correlation coefficients of D-PA and TI (n=20). The correlation was categorised as positive, negative or neutral

Patient	Pearson r	95% CI	Polarity
1	-0.258	[-0.3242 , -0.1887]	Negative
6	-0.079	[-0.1552 , -0.0008]	Negative
7	-0.131	[-0.2021 , -0.0594]	Negative
9	-0.131	[-0.2021 , -0.0594]	Negative
22	-0.245	[-0.3119 , -0.1754]	Negative
28	-0.089	[-0.1601 , -0.0161]	Negative
2	0.295	[0.2266 , 0.3597]	Positive
4	0.117	[0.0450 , 0.1881]	Positive
12	0.360	[0.3057 , +1]	Positive
13	0.170	[0.0984 , 0.2393]	Positive
14	0.157	[0.0771 , 0.2344]	Positive
16	0.260	[0.1914 , 0.3267]	Positive
17	0.153	[0.0812 , 0.2230]	Positive
18	0.384	[0.3208 , 0.4446]	Positive
21	0.210	[0.1390 , 0.2780]	Positive
27	0.078	[0.0011 , 0.1538]	Positive
29	0.396	[0.3326 , 0.4551]	Positive
30	0.097	[0.0246 , 0.1684]	Positive
10	0.007	[-0.0653 , 0.0799]	Equivocal
11	0.024	[-0.0484 , 0.0967]	Equivocal
15	0.0322	[-0.1045 , 0.0405]	Equivocal
20	-0.024	[-0.0967 , 0.0485]	Equivocal

CI = confidence interval

The relationship was further explored graphically by plotting D-PA and TI together for each patient. Changes in TI are smaller than changes in D-PA, so the starting point of the axis for TI was adjusted so that the changes in TI were of a similar size to the variation in D-PA. For the n=6 patients (26%) with a positive correlation >0.2, a visible association was observed (Figure 6.2). The highest correlation was 0.396.

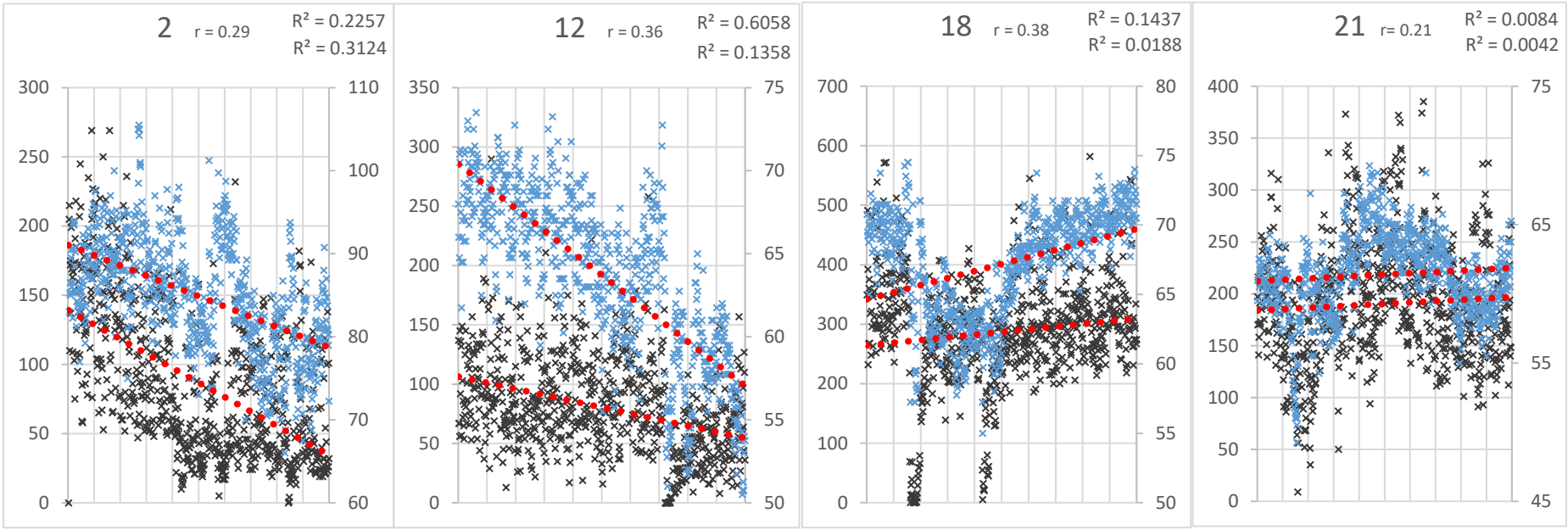


Figure 6.2: Examples of patients with positive Pearson's correlation coefficient between D-PA and TI. Left hand y axis is D-PA in minutes/day, right hand axis is TI in Ohms. Blue crosses are daily data points for thoracic impedance (TI), Black crosses are daily data points for device-measured physical activity (D-PA). The linear regression line for the two measures is also shown as a red dotted line showing the same polarity of slope for both measures. R2 values for the linear regression trend lines are shown (blue = TI, black = D-PA).

In 4 patients (18%) there was an increasing trend seen in both TI and D-PA. An example can be seen in Figure 6.3.

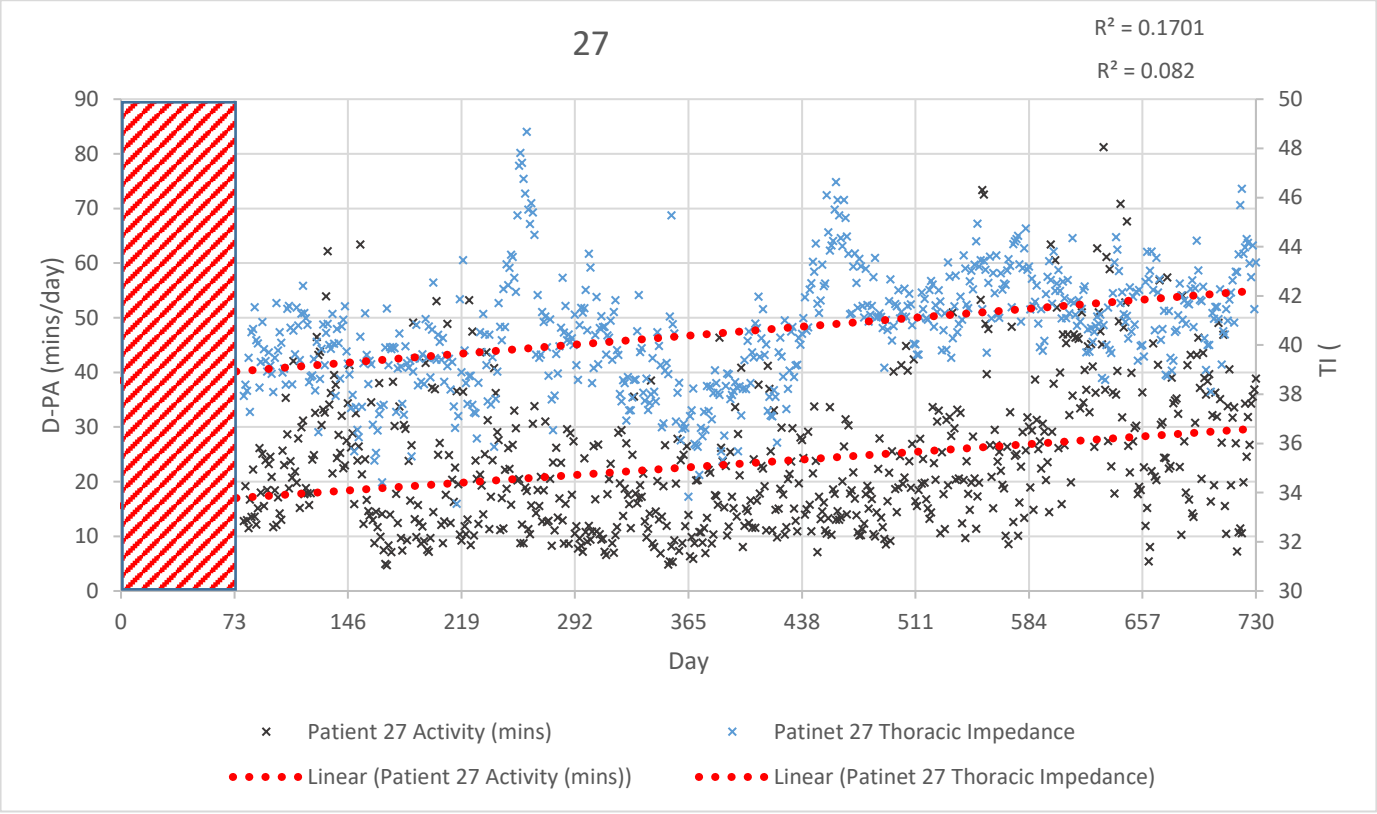


Figure 6.3. Concordant positive trends in D-PA and TI in a patient with a large reduction in AF burden after catheter ablation of atrial flutter. Blue crosses are daily data points for thoracic impedance (TI), Black crosses are daily data points for device-measured physical activity (D-PA). Hashed area is missing or deleted data due to recent device implantation. R2 values for the linear regression trend lines are shown (blue = TI, black = D-PA).

6.3 Correlation and trend polarity

Correlation coefficients of D-PA and TI values against time were calculated along with 95 % confidence intervals which allowed an assessment of the significance of the correlation (see appendix E).

Patients were divided into three sub-groups based on the polarity of the correlation of daily D-PA and TI (Table 8). Half of the patients with a positive correlation between D-PA and TI also displayed a concordant 24m linear trend between the two measures. That is to say, the long-term trend in activity and TI was in the same direction, either both increasing or both decreasing over time.

Table 8. Summary data for the relationship between slope of D-PA and slope of TI

		Relationship of the slope for D-PA and TI		
Correlation group	n	Discordant	Concordant	Equivocal/Indeterminate
Negative	6	4	1	1
Positive	12	1	6	5
Equivocal/indeterminate	4	2	1	1
Total	22	7	8	7

D-PA = device determined physical activity TI = thoracic impedanc

6.4 Time series Cross Correlation

In time series cross correlation, if TI and activity are most highly correlated when activity is shifted backward in time, this means that there is a delay between changes in impedance and changes in activity (and vice versa). This finding may suggest (but not prove) possible causality; if one measure changes before the other. In patients with a positive lag, there is no clear lag pattern, suggesting that changes in D-PA and TI are likely caused by another factor. A Granger Causality test is another way that this could be investigated.

Cross-correlation plots for TI and D-PA were performed (Figure 6.4). Negative cross correlations mean that the two-time series move in opposite directions. The cross-correlation outcome in general agrees with the Pearson result.

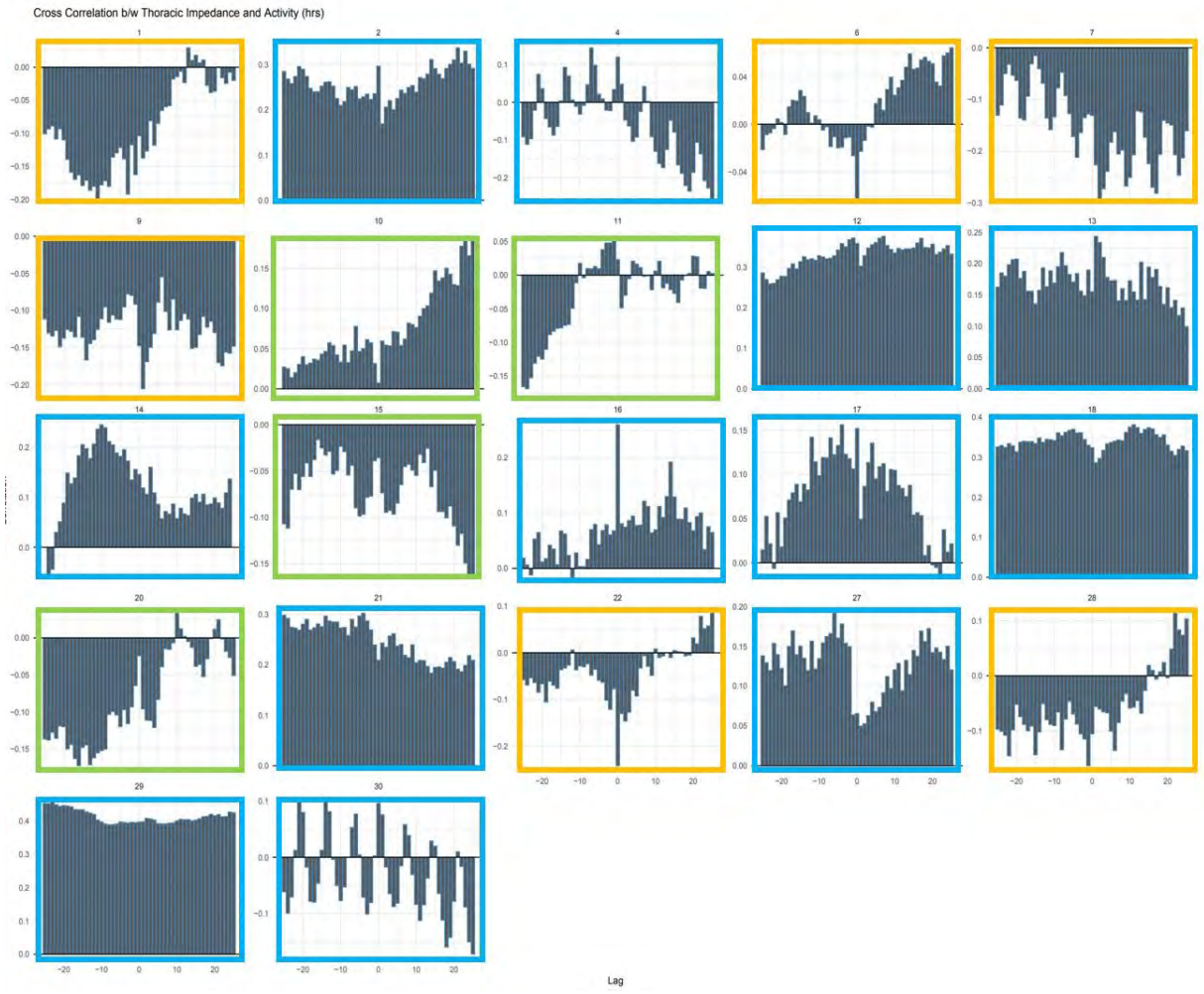


Figure 6.4 Cross-correlation plots for TI and D-PA. Negative cross correlations mean that the two-time series move in opposite directions. Blue boxes show patients identified with a positive Pearson correlation, orange for a negative correlation. Green boxes identify patients with indeterminate Person correlation.

The cross correlation result in a small number of patients was affected by failure to de-trend the time series prior to cross correlation. The cross correlation shows a reversal in the

correlation at a lag of 7 days in some patients, particularly those of working age This reflects the fact that TI remains stable whilst D-PA changes between week days and weekends – altering the relationship between the two variables. This is evidence that changes in one does not cause changes in the other. This artefact could be removed by de-trending the time series prior to cross correlation by using the decomposition of additive time series function in R.

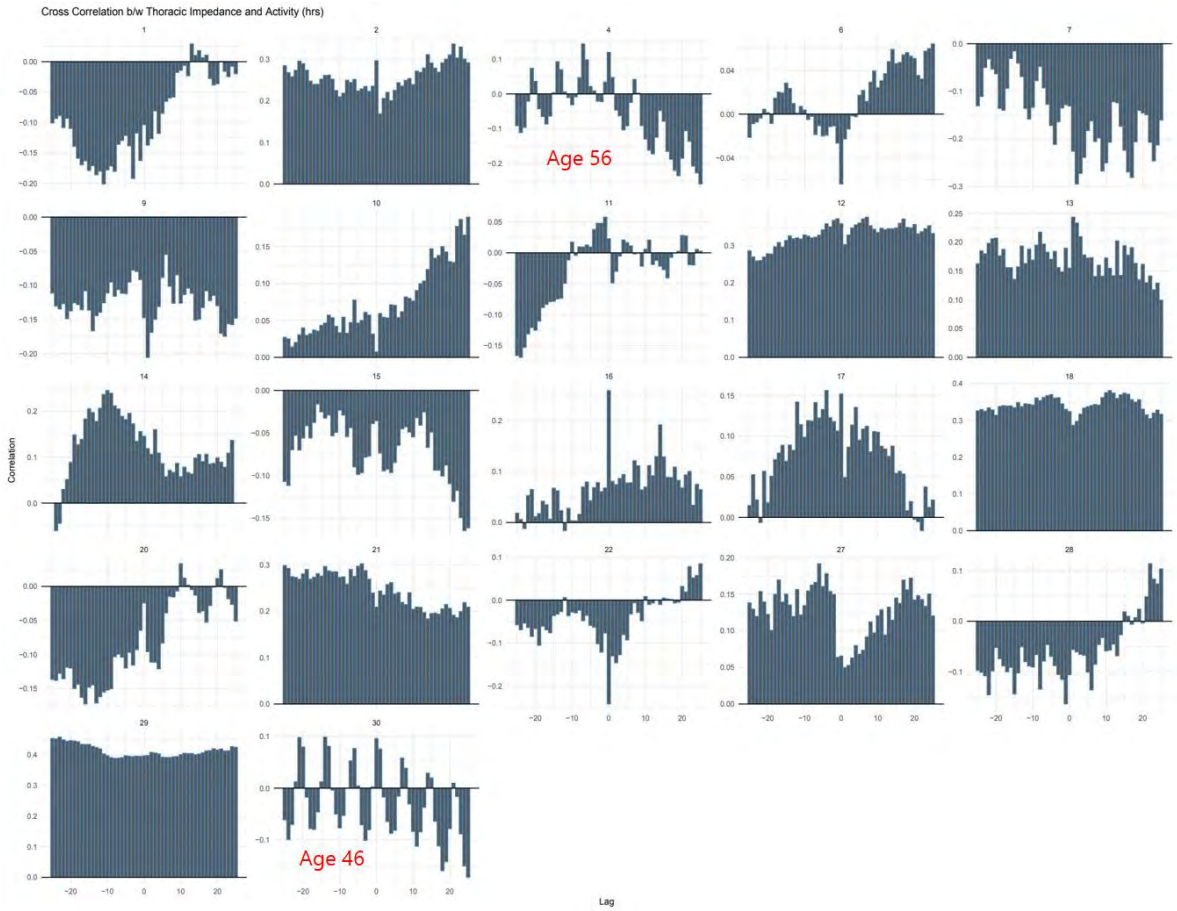


Figure 6.5. The effect of the working week/weekend on cross correlation results

Discordance between Activity and TI in younger patients likely to be still working

Where changes in activity or TI result from factors other than cardiovascular performance, this may result in deviation from the positive correlation. Extrinsic or 'extra-ordinary' factors may impact both activity and TI, or may affect one and not the other. Changes in activity level independent of cardiac performance might decrease activity but not increase pulmonary congestion. One case was observed that appeared to show such a scenario with regard to D-PA – patient 7 started a cardiac rehabilitation exercise class immediately following their ablation procedure and started going to the gym daily. This may explain the observed increase in D-PA without a matching trend in TI (figure 6.6).

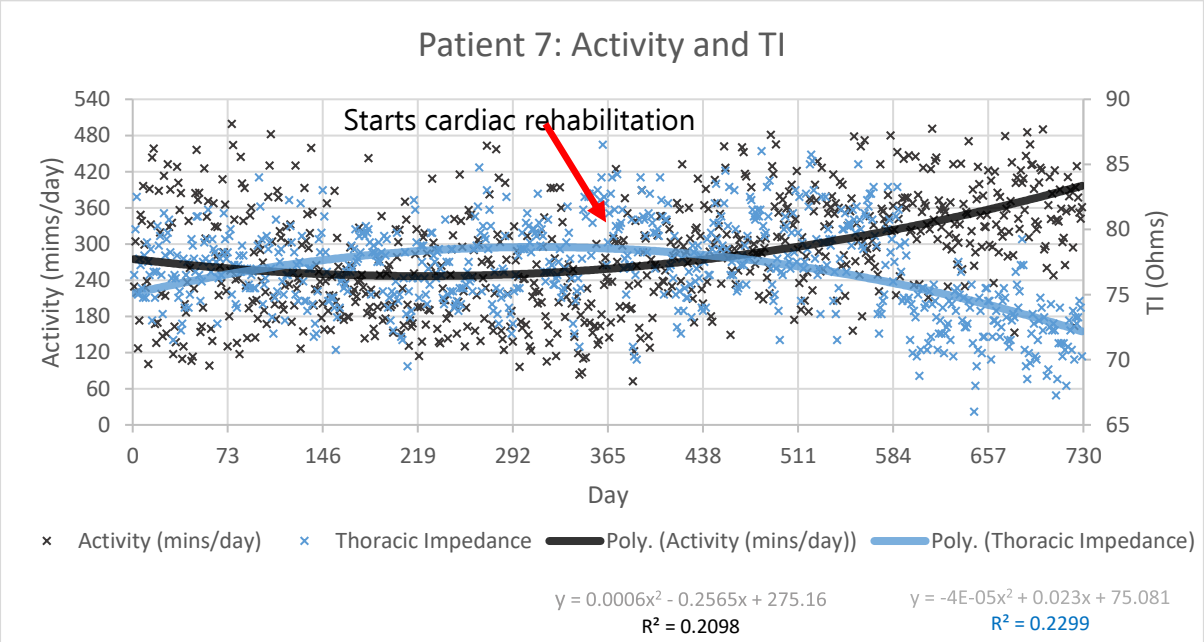


Figure 6.6. D-PA and TI time series for patient 7 who started cardiac rehabilitation following their ablation procedure and started going to the gym daily. (blue = TI, black D-PA).This may explain the increase in D-PA without a similar trend in TI. R2 values for the 2th order polynomial trend lines are shown.

6.5 Administration of diuretics

In patients with a high degree of correlation between D-PA and TI there were some time periods when the two trends unexpectedly diverged. This could be traced to the initiation of a loop diuretic medication, or an increase in the dose. Diuretic medication has previously been documented to increase TI when used intra-venously to treat HF decompensation (Yu et al., 2005). This effect has not previously been described for oral diuretic use. An example in one patient can be seen in Figure 6.7.

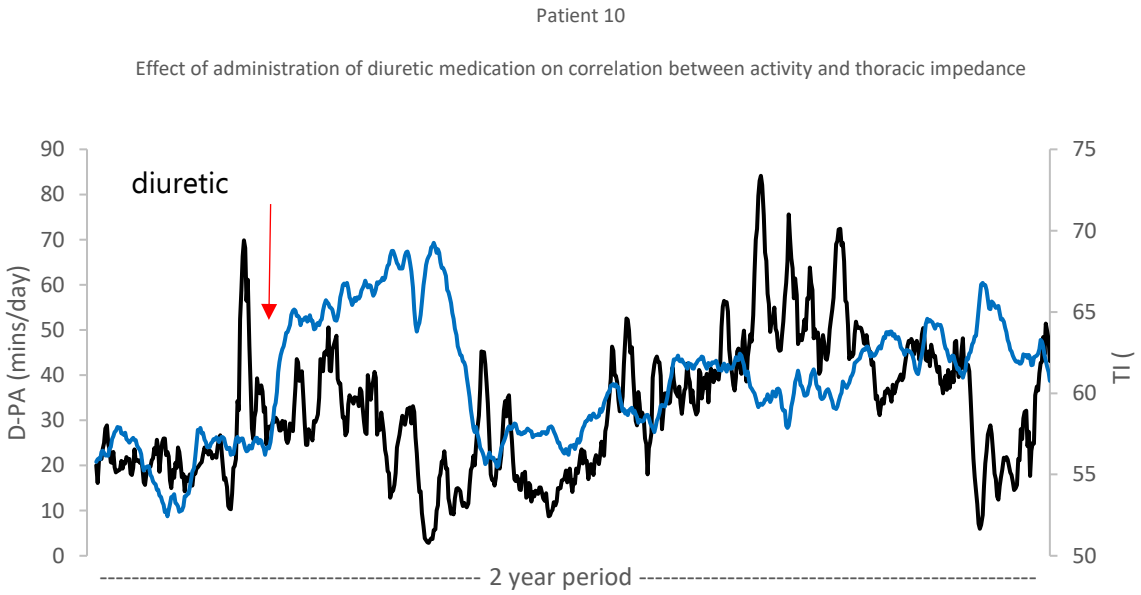


Figure 6.7. Divergence in otherwise closely correlated 7 day moving average trend lines for TI (blue line) and D-PA (black line) that could be traced to the administration of an oral loop diuretic (furosemide).

In the same patient, a subsequent reduction in dose of the diuretic was documented - and the effect on the TI level could be clearly seen (Figure 6.8)

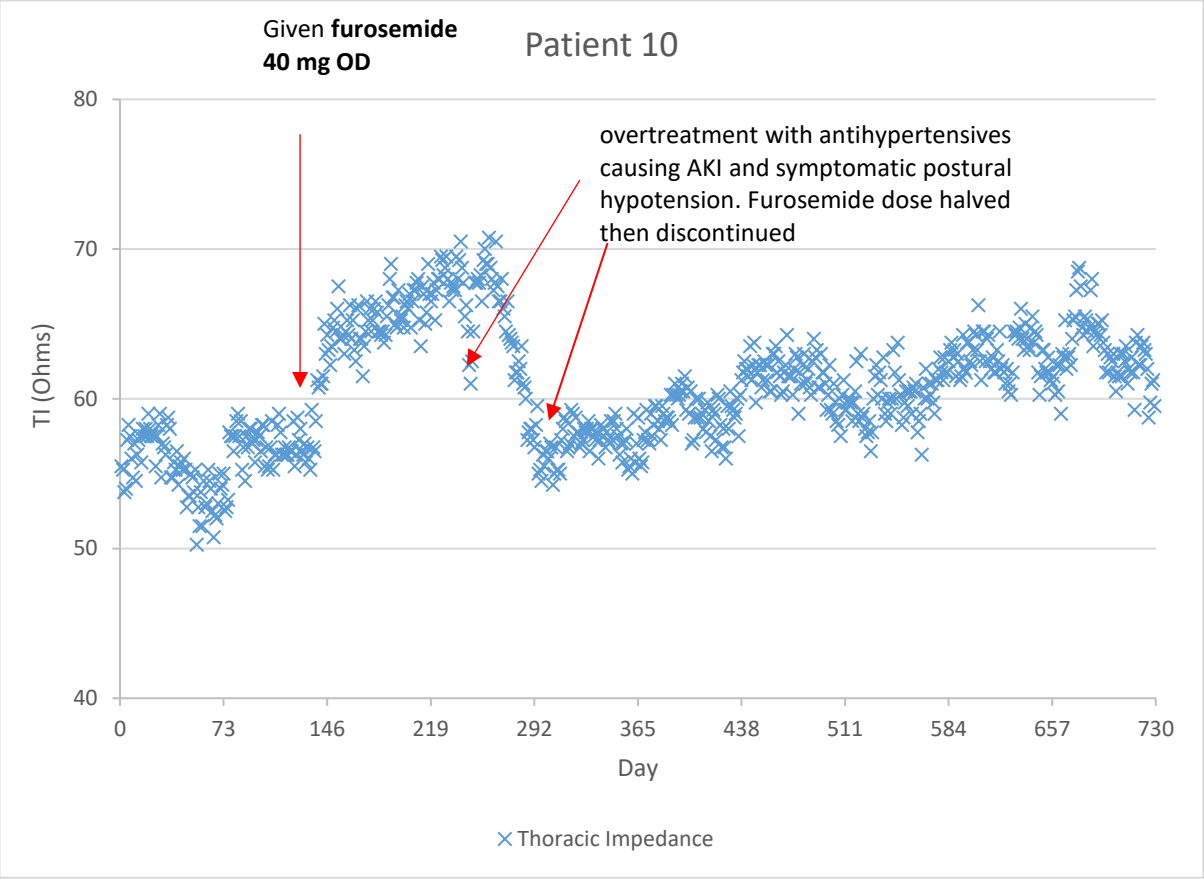


Figure 6.8. Effect of changes in diuretic therapy on thoracic impedance (TI) in one patient

Administration of diuretics often coincides with a point in time when HF is worsening and therefore activity is decreasing. The paradoxical increase in TI stimulated by diuretics therefore causes a complete reversal of the previously observed positive correlation between D-PA and TI. Examples of two other patients where the effect of changes in diuretic therapy can be seen are shown in Figure 6.9.

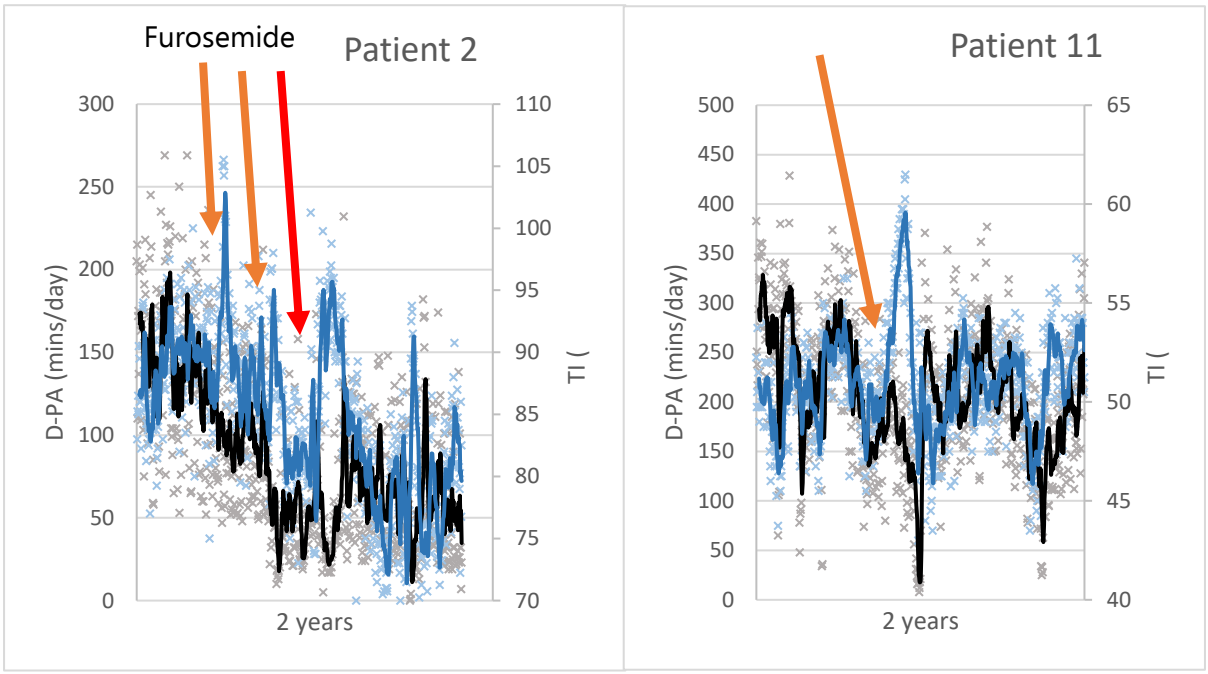


Figure 6.9 Deviation in TI (blue) away from concordance with the trend in D-PA (black) due to administration of diuretics. Orange arrows - administration of oral diuretic, red arrow - IV furosemide.

A similar effect on TI trend was seen with the second most commonly used loop diuretic - bumetanide (Figure 6.10)

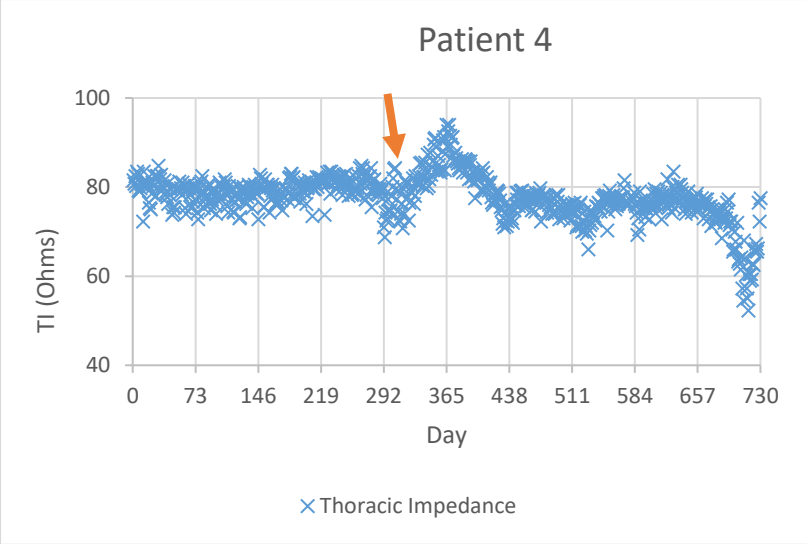


Figure 6.10 Thoracic impedance data from one patient given an increased dose on the loop diuretic bumetanide

6.6 Discussion

This is the first study to identify a possible long-term sub-clinical correlation between D-PA and TI (outside of acute HF decompensation events). A positive correlation between D-PA and TI is biologically plausible; if pulmonary congestion decreases (TI goes up) as activity likely increases and *vice versa*. One factor does not appear to *cause* the other; there is no consistent lag on cross-correlation and the association is more likely to reflect changes in the underlying state of the cardiovascular system. It can be hypothesised that this 'baseline' relationship may be disturbed by factors which disproportionately affect either pulmonary congestion or activity independently. For example, non-cardiovascular diseases, physical injury or surgery may limit physical activity without necessarily affecting pulmonary congestion. Pulmonary congestion may improve due to treatment for cardiovascular disease in a patient who cannot increase

their activity due to mobility limitations (e.g. resulting from musculo-skeletal disease). Or, a patient may undertake a program of exercise that increases their activity, but does not improve their left ventricular function and associated pulmonary congestion. TI is clearly affected independently of D-PA by the administration of diuretic medication (particularly loop diuretics) which change the short term correlation between D-PA and TI (but probably not long term trends).

Long-term changes in activity have been the subject of previous studies in the literature, and decreasing activity has been associated with worse outcomes (Anderson et al., 2019). The long-term implications of decreasing or increasing trends in TI over time are currently unknown, although there are some studies that correlate low or decreasing TI with increased mortality (Zile et al., 2016). The current study was limited in terms of patient numbers and the sophistication of the time series analysis. However, a possible correlation between D-PA and TI raises fundamental questions around the underlying physiology that determines thess variables that should be investigated further. TI data also appears to be a sensitive marker for diuretic use, and this could be used to monitor compliance and optimal dosing.

CHAPTER 7:

A TALE OF TWO CARDIOVERSIONS: UTILITY OF THORACIC IMPEDANCE AS A MARKER FOR CARDIOVASCULAR IMPROVEMENT IN INDIVIDUAL PATIENTS

7.0 Introduction: Thoracic impedance

Historically, the primary focus of biomarkers has been in the diagnosis of disease and the monitoring of disease progression (DePrimo 2007); however, biomarkers can also be utilised to quantify the effect of a therapeutic intervention or response to specific treatment (DePrimo 2007). When paired with analytical tools, biomarkers can be used to track trends and patterns for both populations and individuals (Motahari-Nezhad et al., 2022).

Clinical trial endpoints, such as morbidity and mortality, often require extended timeframes and may be difficult to evaluate. In a typical trial or clinical setting, there is almost no visibility about the patients' status for the majority of the time outside the clinic but digital biomarkers

can be recorded continuously, providing objective endpoints that give insights into the temporal effects of treatment (Motahari-Nezhad et al., 2022)

Modern CIEDs measure and store a number of digital biomarkers, the most important of which are device-determined physical activity (D-PA) measured by an on-board accelerometer, and thoracic impedance (TI), estimated by passing current from the lead of the device to the implanted generator (the 'can'). These measurements are increasingly being utilised to monitor clinical status over time in chronically ill patients as an ancillary functionality of the CIED. D-PA provides an estimate of functional capacity, and TI is an indicator of pulmonary congestion. Functional capacity and pulmonary congestion are both important measures in the assessment of patients with heart failure (HF).

Thoracic impedance

Thoracic impedance can detect pulmonary fluid retention at a pre-clinical stage in ambulatory patients, with the potential to reveal changes in heart failure status early enough to enable the initiation of appropriate therapeutic interventions to prevent further progression to overt cardiac decompensation. (Yu et al., 2005). The purpose of implanted device–based TTI measurement is to monitor clinical status over time in chronically ill patients as an ancillary functionality of the implanted device (Tang and Tong 2011) But, as well as indicating HF decompensation events, the measurement of TI facilitates the detection of impedance trends over time in a particular individual. These 'sub-clinical' trends have not been extensively studied. The focus of TI measurement is usually on sudden lowering of this value as this

indicates clinical deterioration. However, in a previous chapter it has been demonstrated that the effect of successful treatment for AA is reflected in changes in TI measurements. This raises the question as to whether TI can be used as an outcome biomarker and correctly identify patients deriving cardiovascular improvement after treatments, including ablation and DCCV. Measuring more subtle changes in a physiologic surrogate such as impedance may identify subclinical vulnerabilities that often lead to alterations in clinical status.

7.1 Methods

The time series of TI measurements and AF burden and were graphically analysed for two patients (A and B) with very similar clinical characteristics who underwent DCCV procedures for persistent AF but with different medium-term procedural outcomes. Changes in TI were compared with the clinical course in considerable detail. TI was plotted together with AF burden for each patient and the procedural result was assessed. The TI time series for both patients were compared graphically and the time points of deflections in the time series correlated against the course of clinical events. Summary statistics for AF burden, TI and D-PA were calculated for the whole 24 months, and for the year preceding DCCV and the year afterwards. Spearman rank correlation was used to assess the correlation between AF burden and TI.

7.2 Results

The two patients had similar clinical characteristics which can be seen in table 9.

Table 9. Baseline clinical characteristics of two patients undergoing DCCV

	Patient A	Patient B
Age at procedure (years)	72	81
Sex	M	F
Ethnicity	White - British	Asian British - Indian
BMI (kg/m^2)	31.4	22.7
CIED type	CRT-D	Dual chamber ICD
ICD indication	Primary prevention	Primary prevention
Manufacturer	Boston Scientific	Boston Scientific
Ischaemic heart disease	Yes	Yes
Prior Myocardial infarction	Yes	Yes
Ischaemic cardiomyopathy	Yes	Yes
Hypertension	Yes	Yes
Diabetes (controlled)	No	Yes
Ejection fraction at time of procedure	30-35%	30-35%
Congestive heart failure	Yes	Yes
New York heart association class at procedure	II/III	II/III
Chronic pulmonary disease	Yes	Yes
Rheumatologic disease	Yes	Yes
Haemoglobin g/L	148	120
Creatinine	131	73
B-type naturitic peptide	1363	NA
Free T4 (thyroxine)	11.6	13.5
Left Atrial dimension (cm)	7.35	3.7
Left Atrial volume (ml)	141.44	56.6
Relevent medication (daily dose)		
Furosemide (mg)	60	50
Epleronone (mg)	50	25
Furosemide (mg)	60	50
Beta Blocker (Bisoprolol; mg)	10	1.25
Amiodarone (mg)	200	200

BMI =body mass index CIED = Cardiac implantable electronic device ICD =implantable cardiac defibrillator

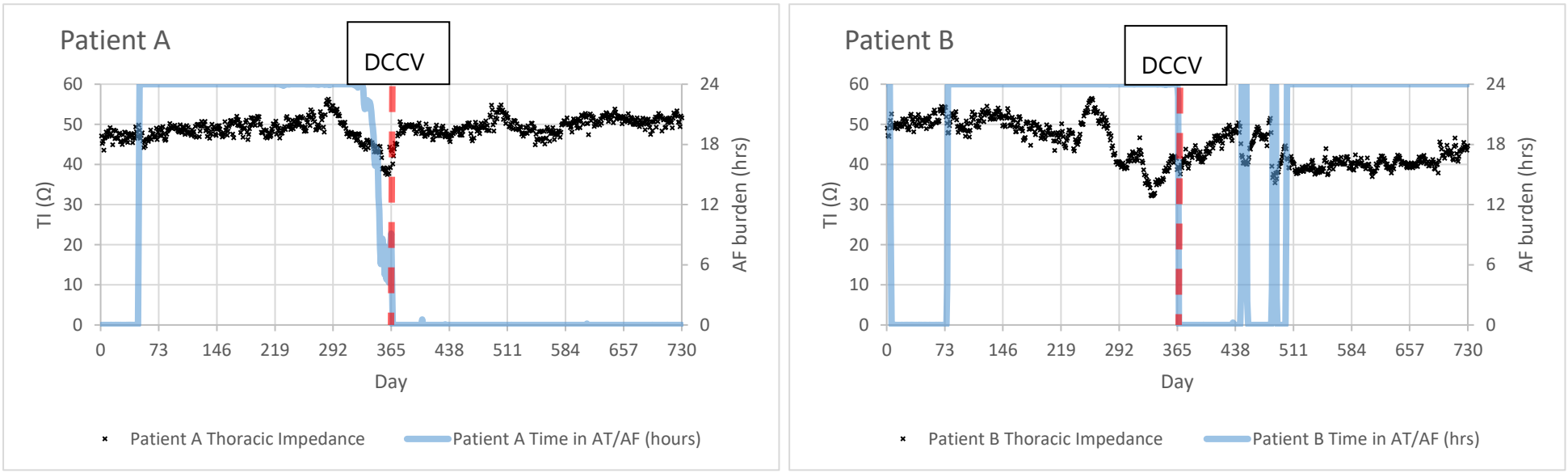


Figure 7.1: Thoracic impedance (TI) and AF burden over two years for two patients A and B undergoing DCCV on day 366. Patient B experiences recurrence of the arrythmia which becomes persistent

Both patients were in sinus rhythm at the outset, but both transitioned into persistent AF (PsAF) by day 73 (Figure 7.1). The cardioversion was acutely successful in both patients. Patient A remained in normal rhythm for the entire year following the treatment, whereas Patient B started to have recurrences of AF shortly after day 438, and the arrhythmia became persistent shortly before day 511 (just under 5 months post DCCV). Patient B remained in AF for the remainder of the year. A similar pattern of changes in TI measurements was observed in both patients in the 3-4 months leading up to DCCV, with an initial rise then fall in TI.

TI measurements for both patients were overlayed to highlight any similarities (Figure 7.2).

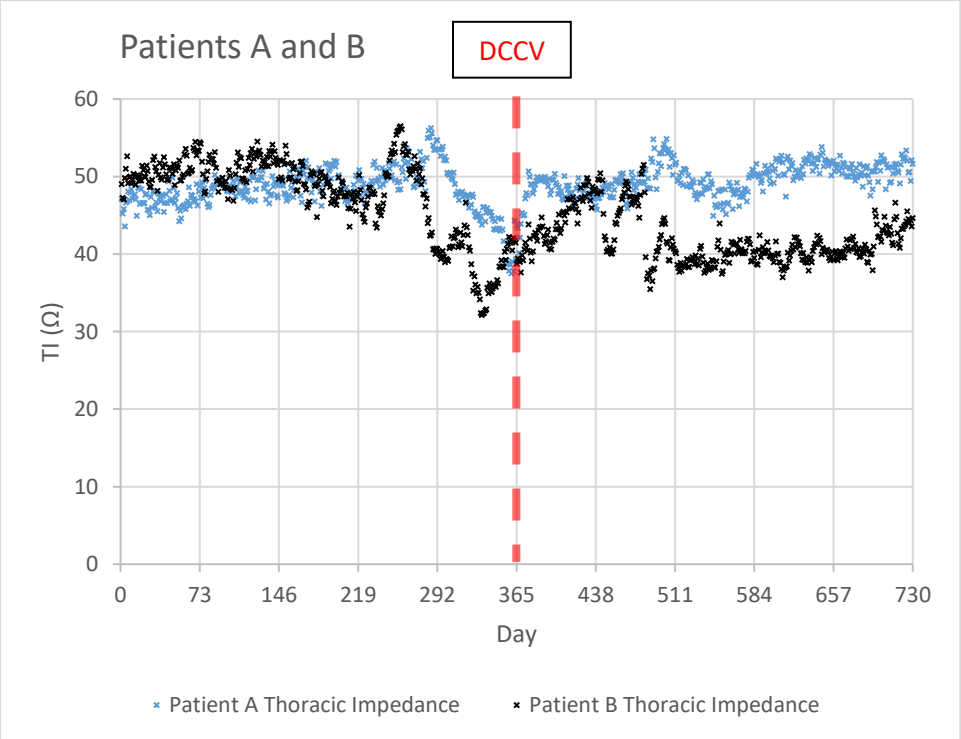


Figure 7.2: Overlay of TI measurements for Patient A and B. Dotted red line denotes the time of the DCCV procedure.

Initialy the traces follow a similar pattern for both patients (at around 50 Ω) until aroung day 219. After that point, there is a similar, initial rise to a peak of around 56 Ω followed by a fall over the course of about 10-11 weeks observed for both patients. The initial rise for patient B follows documentation of the initiation of furosemide (40 mg OD) treatment. Patient A was also taking furosemide (40 mg OD) at some point (undocumented) but was advised to stop. Although not documented, it seems likelty that patient B also stopped taking furosemide due to the subsequent fall in impedance. The initiation of furosemide at this point would seem to indicate a worsening clinical picture in both pateints. Yu et al., (2015) reported that intravenous diuretic therapy over 3.2±1.8 days resulted in a significant 17.1±9.4% increase in intrathoracic impedance. There are no data for changes in TI induced by oral diuretics. The increase seen here is in the order of about 12-13Ω or a 25% increase but over approx 20-25 days.

This pertubation of the time series occurs first for patient B, and the fall in TI is more rapid and to a lower level (32 vs 38 Ω). The overal shape of the change is remarkably similar. From a nadir, the impedance increases in both patients, eventually returning to the baseline (e.g. 50 Ω) at day 430,or 9 weeks after the DCCV. Moreover, the recovery in impedance starts before the DCCV (Figure 7.2), corresponding to the re-introduction of diuretic therapy. Interestingly, patient A (blue trace) continues at the same level for the remainder of the year, even increasing a little further. In contrast, the TI measurements for patient B decrease rapidly to a much lower level, at around 40 Ω (figure 7.3). It is clear from the AF burden data that this regression coincides with a relapse into persistent AF.

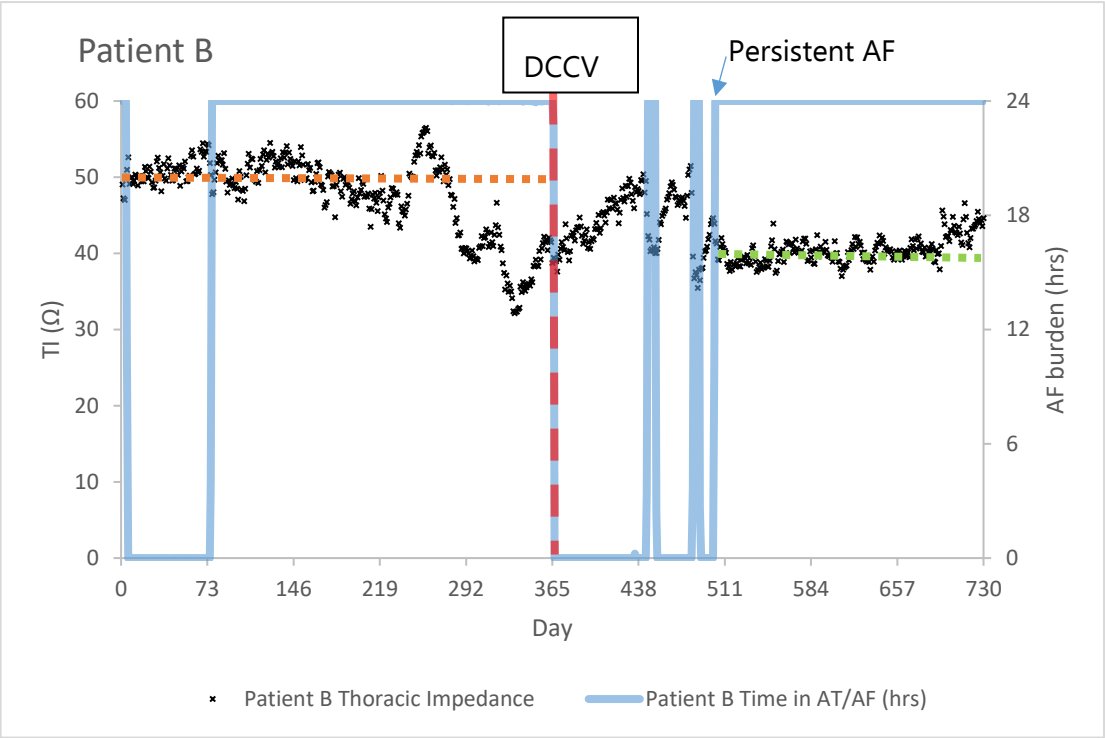


Figure 7.3. Change in TI level after DCCV for patient B, The initial TI level at 50Ω is highlighted with an orange dotted line to the left, and the new equilibrium at around 40Ω is highlighted by the green dotted line to the right.

A 10Ω drop in TI is clinically significant. Yu et al., (2015) reported that thoracic impedance decreased before acute admission for fluid overload on each admission by an average of 12.3±5.3%. 10Ω represents a change of 20% from a baseline of 50Ω. This change occurred over a much longer time frame but may indicate significant pulmonary congestion. The change in average TI for patient B over the preceding year to DCCV treatment to the year post-DCCV was 13.9%.

Another way to visualise the change in TI after treatment is to plot values for the pre and post treatment years on the same X axis (Figure 7.4). The trends for patient A are very similar for both years (they are suoperisimposed), the only difference being the drop in impedance corresponding to increase in HF at the end of year 1. For patient B the TI approached the pre DCCV level after return of sinus ryhtm but then the trends diverge after bouts of AF and then return of persistent AF.

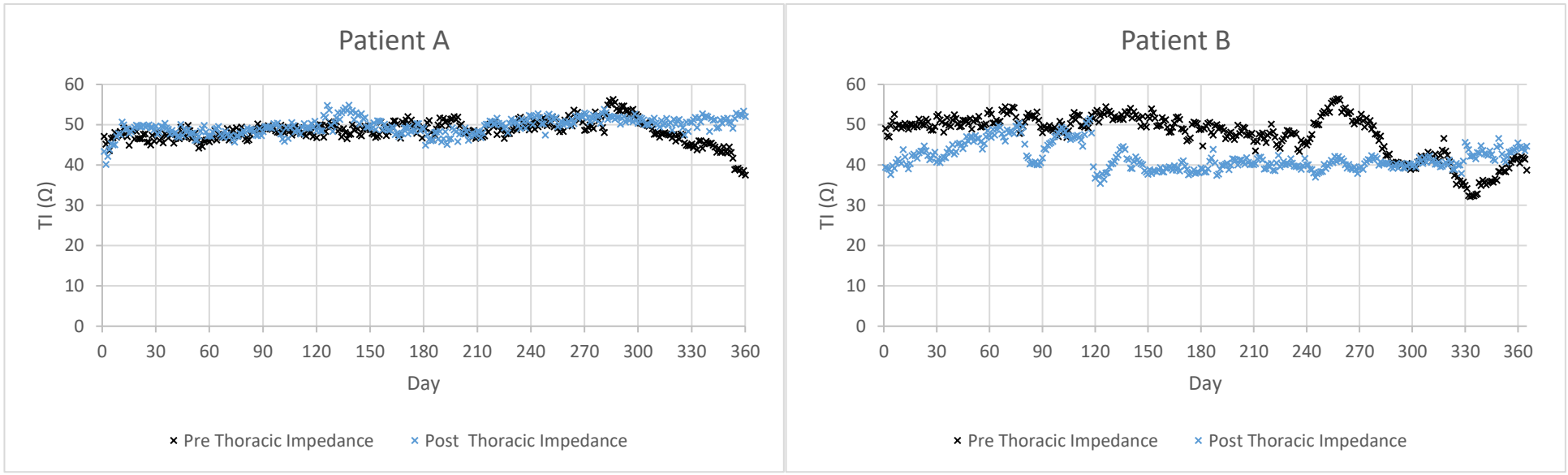


Figure 7.4 Differences in the thoracic impedance (TI) trend pre and post DCCV for patients A and B (post treatment year superimposed onto baseline year). The black crosses are TI measurements for the year pre DCCV and the blue are the equivalent for the year after the treatment.

7.3 Clinical course: Patient A

Following a prior DCCV, AF had returned, and it was noted that the patient felt better when in sinus rhythm. Their LV function had improved, which was thought to be due to the prolonged period of normal rhythm. They were restarted on amiodarone (a powerful anti-arrhythmic medication) and a repeat DCCV was planned. Whilst waiting for the DCCV they developed hip pain and were admitted for orthopaedic surgery (Figure 7.5).

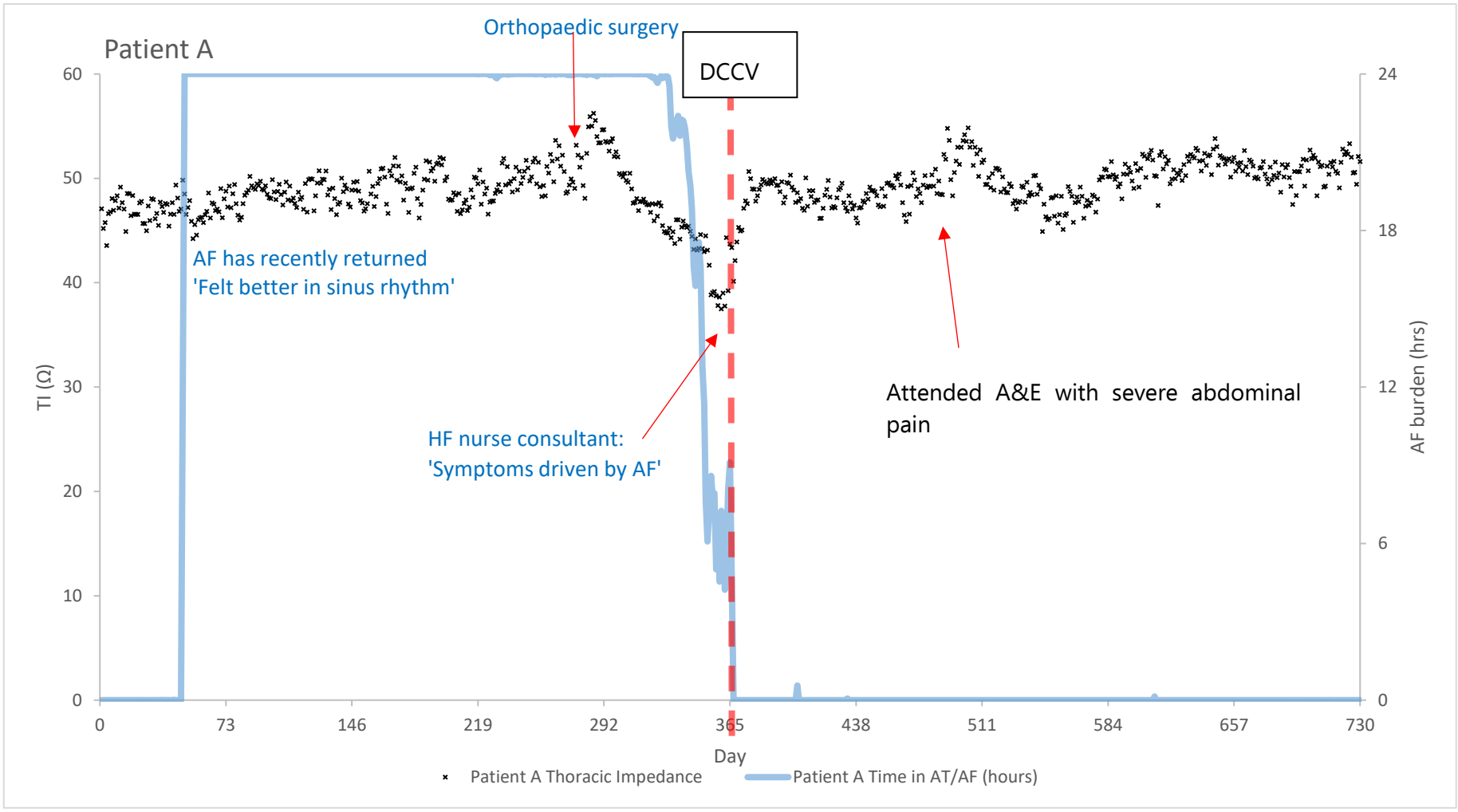


Figure 7.5: The clinical course of patient A aligned with TI data.

The patient had been well post operatively but after discharge they complained of increasing shortness of breath and reduced exercise tolerance and was seen by the HF nurse consultant. He had stopped taking his diuretics some time ago following medical advice. On examination he had significant bilateral pitting oedema to below the knees and abdominal bloating. His lungs were clear on auscultation but he described orthopnoea, consequently he was sleeping in a recliner chair at night as unable to lie flat in bed. He had gained 10kg in weight with AF and had gone from his usual condition of NYHA score 1 to NYHA 3.

This decline is reflected in a drop in TI from a peak of 56 to 38 Ω over a period of about 10 weeks (a reduction of 18 Ω) leading up to the DCCV. This drop mirrors the clinical course which suggests worsening pulmonary congestion. The HF nurse consultant liaised with a cardiologist specialising in the treatment of arrhythmias and they both felt that his symptoms were driven by his AF and arranged for him to attend the following day for an urgent DCCV and increased his furosemide to 40mg twice a day.

7.4 Clinical course: Patient B

In the year leading up to the DCCV, patient B reported variation in her weight due to heart failure and she was started on furosemide 40 mg once daily. This treatment caused a rapid increase in TI (Figure 7.6). An echocardiogram whilst in AF showed an LV EF of 35-40% indicating significant LV impairment.

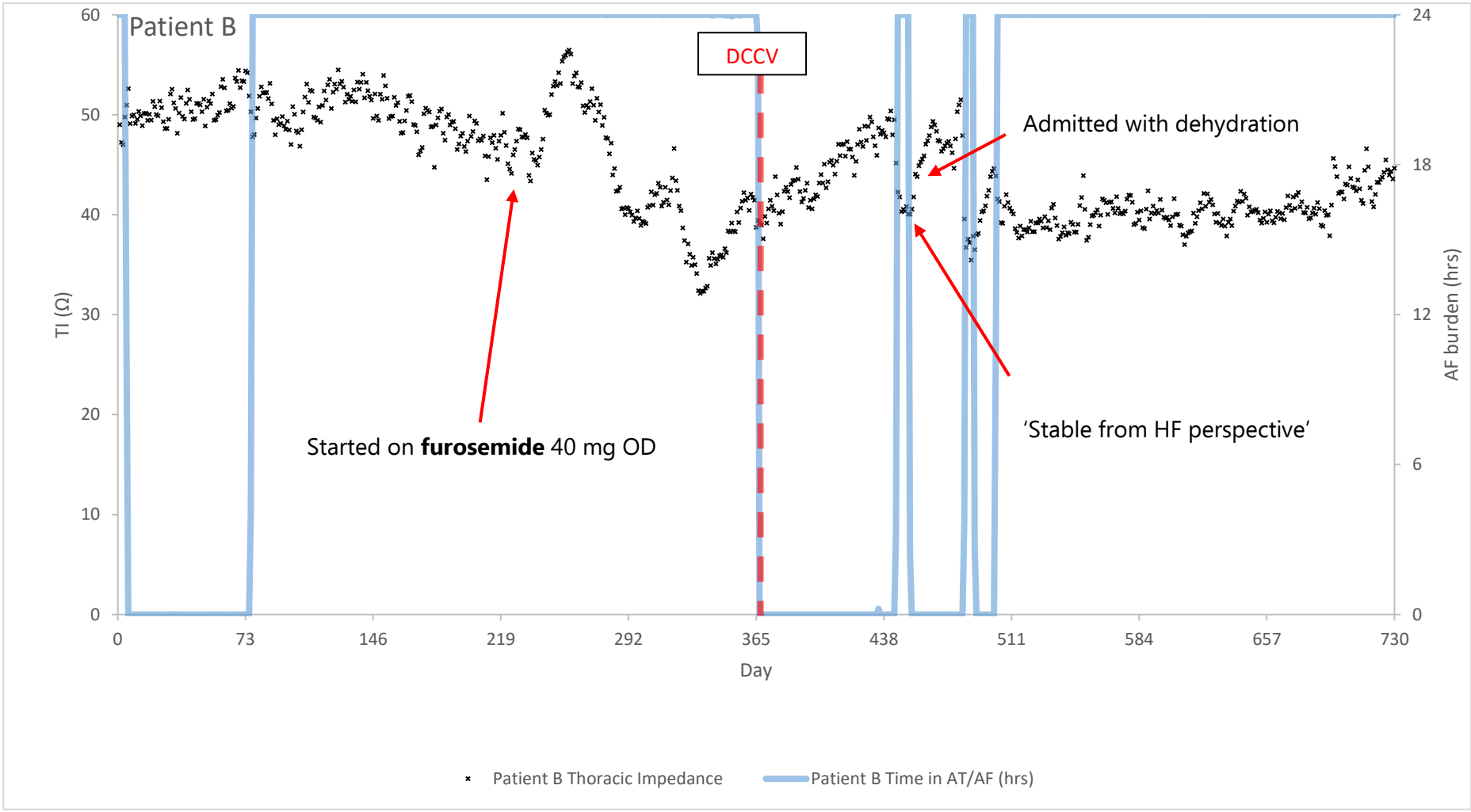


Figure 7.6: The clinical course of patient B aligned with TI data.

Due to the emergence of persistent AF, the patient was referred by one of the cardiac physiologist team to the Complex Device Clinic, a hybrid consultation with a physiologist and a cardiologist. The patient reported worsening of her symptoms, being more tired, shorter of breath, and unable to walk as much as when she was in normal sinus rhythm. The patient was started on amiodarone and booked for a DCCV. A few weeks after the DCCV she was admitted to hospital with syncopal episodes (fainting) and blurry vision. She was found to have low blood pressure secondary to dehydration. An echocardiogram performed at this time showed that the LV function had completely normalised in sinus rhythm (LVEF 60-65%) and the left atrial size had reduced to within normal limits.

The patient was seen in the cardiology outpatient department of a neighbouring hospital after reverting to persistent AF. A further echocardiogram was ordered, which showed that her LV function had reduced (LVEF: 52%) from the level seen in sinus rhythm. She described symptoms of minimal leg swelling, no shortness of breath when lying down and she did not complain of being woken by breathlessness. There was a language barrier in the consultation, with a relative acting as translator. There is no mention of further attempts at rhythm control, and she was prescribed a beta blocker for heart rate control.

Patient B demonstrated declining slope in TI during periods of AF – highlighting the impact of the arrhythmia on cardiovascular performance and pulmonary congestion in this patient (Figure 7.7). The drops are particularly steep during the initial episodes of re-initiation of AF post DCCV.

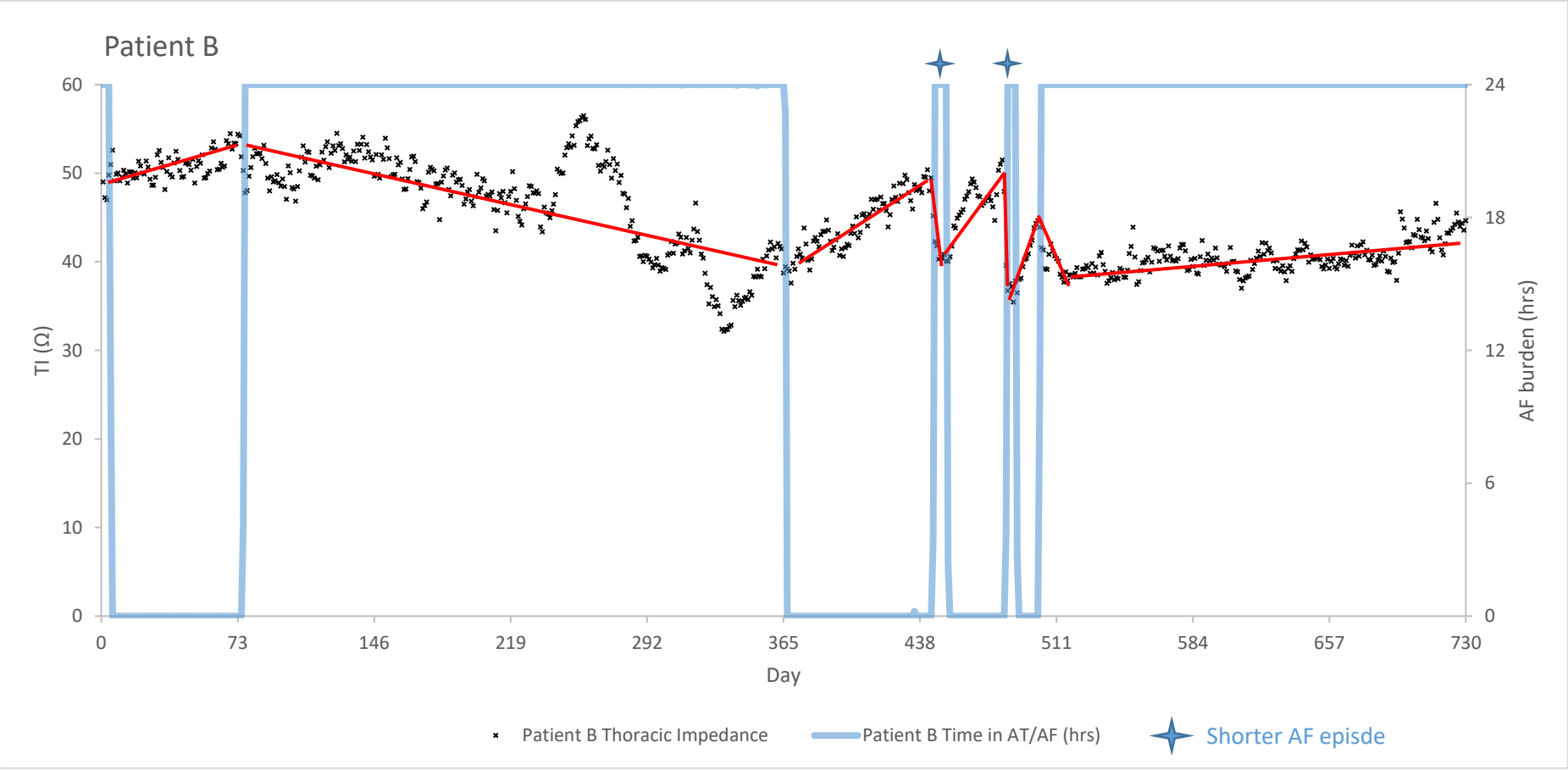


Figure 7.7 Declining TI during periods of AF for patient B – highlighting the impact of the arrhythmia on cardiovascular performance and pulmonary congestion in this patient.

Changes in metrics from the baseline pre-DCCV year to the post DCCV year are summarised in Table 10. Applying Spearman's correlation coefficient to AF burden and TI (because the two measures do not follow a similar distribution) demonstrates a statistically significant negative correlation of -0.18 for patient B. That is the TI tends to be lower when the AF burden is higher. Patient A demonstrated a similar but somewhat smaller negative correlation (-0.14).

Table 10. Change in metrics between year 1 and year 2 for patient A and B. Both patients had near identical burden of persistent AF pre-procedure. Patient B had a 39% reduction in activity post DCCV and a 13.9% reduction in TI. TI for patient A actually increase by 2.8% following successful rhythm control.

Patient	A	B
AA burden pre DCCV	82.94%	80.44%
AA burden post DCCV	0.06%	66.27%
Reduction in AA year 2 vs year 1	82.87%	14.17%
Mean activity pre DCCV	98.1	38.5
Mean activity post DCCV	90.0	27.7
Reduction in activity	8.1	10.8
% Reduction in activity	8.9%	39.0%
mean TI pre DCCV	48.3	47.6
mean TI post DCCV	49.6	41.8
Change in TI pre/post	1.4 increase	5.8 decrease
Percentage Change in TI	2.8 % increase	13.9 % decrease

AA =atrial arrhythmia DCCV = direct current electrical cardioversion

TI = thoracic impedence

7.5 Discussion

Ablation and DCCV can be effective but carry risks and consume healthcare resources. Recurrence of arrhythmia after ablation or DCCV is common, and a clinical decision has to be made whether to persevere with a rhythm control strategy. This decision is usually informed by the presence or absence of symptomatic improvement in normal rhythm following termination of arrhythmia. However, symptoms may be difficult to interpret, particularly if there is reversion to AF after only a short period of time, although there are no studies that have looked at this. Assessment of symptoms may also be affected by barriers to communication such as cultural or language differences (Al Shamsi., et al 2020). An objective marker for cardiovascular improvement after restoration of normal rhythm could augment clinical evaluation and improve the identification of responders, helping to select those standing to benefit most from repeat intervention.

These two cases demonstrate the cardiovascular benefit of being in sinus rhythm. In both cases, changes in the level of long-term TI measures closely match the progression of HF symptoms, diuretic use and measures of left ventricular function. The difference of around 10Ω in TI and the end of the second year is likely to represent a clinically significant difference in pulmonary congestion between a patient with long-term freedom from AF and one with reversion to persistent arrhythmia.

The case of patient B illustrates the possible use of thoracic impedance measurements to assist clinical decision-making. The left atrium was not particularly dilated in patient B suggesting that further attempts at rhythm control might be successful, although the older age of the patients might be considered a barrier to an ablation procedure. The patient appears to have a degree of tachycardia-induced cardiomyopathy – the LV function is very sensitive to changes in rhythm. This is evidenced by the LVEF but also by the downward trajectory of TI measurements during AF. The drop in TI for this patient of 13.9% is likely to represent clinically important pulmonary congestion. The data presented here could have been invaluable in deciding on a future treatment strategy in addition to conventional in-clinic patient follow-up.

This is the first detailed study of long-term TI measurements in similar individuals with different outcomes from rhythm control of AF. Clearly there is a limitation in the fact that this is a very small case series of only two patients. However, the comparison in terms of TI data is striking. Future appropriately powered studies should be untaken to explore the use of TI data as an objective treatment outcome biomarker to supplement standard clinical assessment. This may be particularly useful where there are barriers to communication. AI could be useful for real-time analysis of the times series data. Currently the only biomarker that is used routinely to monitor HF alongside patient-reported symptoms is b-type natriuretic peptide (BNP) but this requires a blood test and is not measured continuously, only very sporadically. TI data is monitored continuously and remotely, and has the potential to provide rapid assessment of the impact of a return of the arrhythmia.

CHAPTER 8:

CONCLUSIONS

8.0 Introduction

Patients with CIEDs represent a discrete sub-population of referrals for CA and DCCV. AAs in these patients are common, and are likely to be first identified by cardiac physiologists - from data stored in the CIED memory. Many patients with CIEDs have HF, and AAs may exacerbate this condition, sometimes precipitating hospital admission. AAs can prevent or reduce the delivery of cardiac resynchronisation pacing therapy, limiting the dramatic improvement in symptoms and outcomes that this therapy has the potential to deliver for some patients with HF. People with ICDs can experience painful inappropriate shocks as a result of rapidly conducted AF – a unique consequence of AAs in this population. Cardiac physiologists play a central role in monitoring CIED patients, and increasingly this monitoring is remote, via data transmission over the mobile internet. The British Heart Rhythm Society (2020) defines the objective of a CIED follow-up service as "To improve and extend the lives of people with CIED therapy" which may be achieved by "personalised evidence-based programming, vigilance in identifying and addressing complications and system failures, responsive remote monitoring and disease surveillance, appropriate and timely referral to other specialities and services, provision of education, counselling and support services" (British Heart Rhythm Society 2020 p. 5).

Consequently, DBs such as D-PA and TI that reflect individual cardiac status are becoming increasingly important in informing decision-making at a distance. In individuals with HF, D-PA has been associated with many important clinical endpoints; including actual and predicted mortality risk, aerobic capacity, health-related quality of life, sympathetic nervous system activity and hospitalization. Improving D-PA is therefore an important clinical outcome, but interventions that objectively improve physical activity are elusive. TI has been studied less intensively than D-PA but has also been associated with mortality and HF hospitalisation. The role of cardiac physiologists in the triaging and onward referral of CIED patients with AAs, the outcome of CA and DCCV procedures in this sub-population, and the use of DBs in assessing response to treatment has not been extensively studied.

For this retrospective, observational cohort study, a population of patients with CIEDs who had received CA or DCCV to treat AA were identified. Patients with extensive remote monitoring data pre and post procedure were selected for analysis. The use of a 12m baseline and post procedure period was chosen to minimise seasonal effects, which have been shown to affect physical activity to a significant degree. Raw D-PA and TI data from 30 patients with Medtronic or Boston Scientific CIEDs who underwent procedures for AAs were obtained. Twenty-four months of daily measures were analysed for each patient and summarised, yielding precise estimates for the mean and variation of these variables. The CIED population identified had significant LV impairment and HF, but was younger than the unselected CIED population,

reflecting the higher proportion of ICD patients in the sample, but also suggesting a referral bias, particularly for AFA.

8.1 Summary of main findings

1. Change in mean TI correlated with change in AA burden after rhythm control procedures. Patients with a large reduction in AA burden (≥75%) showed a statistically significant increase in TI ($p<0.05$). Patients with no change in AA burden, or an increase in burden showed a decrease in TI.

2. The magnitude of D-PA and TI measurements were significantly different between the two leading manufacturers of CIEDs ($p<0.05$). The variation in D-PA values (assesses by standard deviation) was also significantly different between manufacturers. However TI varied by a similar amount regardless of manufacturer.

3. 10 patients (33.3%) exhibited a 'classic' sinusoidal seasonal variation in D-PA (high in summer, low in winter). Two of these patients also demonstrated a remarkably similar sinusoidal seasonal variation in TI (high in summer, low in winter). In the entire cohort there was a trend towards higher TI values in summer and lower in winter.

4. 12 of the 22 patients with TI measurements (55%) demonstrated a positive correlation between D-PA and TI over two years. In half of these (6 patients) the correlation between the two variables had an r value >0.2. Patients with a positive correlation

between D-PA and TI were more likely to demonstrate concordance in the polarity of the long-term trends in D-PA and TI measurements over 2 years.

Time series correlation did not suggest a specific causal relationship between the two measures. 'Extra-ordinary factors' affecting only one of the two measures (such as administration of diuretics, admission to hospital or starting an exercise class) were found to distort the observed correlation between D-PA and TI in particular individuals.

5. Changes in TI very closely matched the clinical course of two patients after DCCV. This observation (of an increase in TI, and therefore a reduction in pulmonary congestion with a return to sinus rhythm), might have been useful for informing decision-making for these patients (for example whether to pursue further attempts at a rhythm control.

8.2 Summary of chapter 3:

Change in arrhythmia burden correlates with change in TI but not change in D-PA

Chapter 3 includes a description of an investigation into the effect of CA and DCCV for rhythm control on D-PA and TI measurements in 26 patients (19 of whom had TI data). It had been the intention to conduct an interrupted time series analysis for this data. However, there was no statistically significant change in slope between the pre and post treatment phases, so this analysis was not pursued. Instead, D-PA and TI daily measurements were summarised for the

pre and post treatment periods, and the change from pre to post was analysed for individual patients.

There was a correlation between ΔD-PA and ΔAA burden, but this was not significant. No statistically significant change in D-PA pre versus post treatment was identified. However, for the 19 patients with TI data, there was a statistically significant correlation between ΔTI and ΔAA burden correlation can be seen in Figure 3.18.

There was significant heterogeneity in the change in AA burden in these patients from the pre to post intervention periods; from a reduction of 100% to an increase of 86%. Patients were then grouped into three tertiles according to AA burden, in order to examine the effect of change in burden on TI; group 1 were those patients with large reduction in burden (≥75% reduction), group 2 had a much more modest reduction (reduction up to 15%), and those with no change in burden or an increase in AA formed group 3. The change in AA burden between groups was significantly different (Figure 3.17).

No statistically significant change in TI pre/post treatment was found for the whole cohort. But a statistically significant change after treatment was identified for the subgroup of patients (group 1) with a reduction in AA burden of ≥75% reduction ($p<0.01$). The magnitude of the difference between the averages for the two years was small (1.56Ω) but it should be born in mind that overall, variation in TI measurements is also small, so this increase is still likely to be clinically significant. SD in TI was a mean of 4Ω (over 2 years), so an increase in 1.56Ω represents

39% of one SD. ΔTI for group 1 was also found to be significantly different to ΔTI for group 3, patients with no reduction or an increase in burden (see figure 3.20).

8.3 Summary of chapter 4:

Comparison of D-PA and TI measures from two leading CIED manufacturers

It is commonly assumed that data from single manufacturer studies can be generalised to all CIED patients, but manufacturers employ propriety sensors and algorithms, and head-to-head comparisons have been lacking. This chapter describes a comparison of D-PA and TI measurements in patients with CIEDs from two leading manufacturers; Medtronic and Boston Scientific. Mean D-PA recorded by Medtronic devices was significantly greater than for Boston Scientific (180.3 vs 102.4 minutes/day, $p<0.05$).

Mean TI recorded by Medtronic devices was also significantly greater than for Boston Scientific (69.8 vs 50.9 Ω, $p<0.05$). Variance measures (SD, min, max and range) for each patient were also compared by manufacturer. For D-PA, the SD, max and range were all greater for Medtronic than Boston Scientific ($p<0.05$). These differences could not be explained by differences in patient characteristics. These results have implications for the generalisability of findings from single manufacture studies. For TI, the differences in measures of variation were not significant. Comparison between manufacturers is summarized graphically in Figures 4.1 and 4.2.

Change in a digital biomarker in an individual over time is clinically important and we also compared variation in the measures for each patient. There was a statically significant difference in the variation (measured by standard deviation) of D-PA measurements over 2 years ($p<0.05$) but not for TI measurements. The magnitude of D-PA is clinically significant, as it has been used to identify patients with conditions such as frailty and dementia. This suggests that findings regarding both magnitude of D-PA and the size of changes in D-PA from single manufacturer studies should not be generalised to other manufactures. Absolute magnitude of TI is not particularly clinically relevant; change in TI is of much greater interest. These findings suggest that the magnitude of change in TI due to variation in the clinical situation may be comparable between manufactures, and that findings regarding changes in TI from single manufacturer studies might be able to be generalised to other manufactures.

8.4 Summary of chapter 5:

Seasonal effects on D-PA and TI

The pattern of seasonal variation in D-PA and TI was explored graphically by fitting a 6^{th} order polynomial trend line to the data. The result for D-PA was broadly similar to those published by Shoemaker et al in large cohorts of CIED patients, namely that a proportion of patients (33.3%) exhibited a sinusoidal seasonal variation in D-PA; higher in summer, lower in winter (figure 5.3).

Shoemaker et al were interested in exploring seasonality in the context of assessing exercise rehabilitation programs in patients with HF and did not utilise TI measurements in their analysis. It was a surprise to find that two individuals showed a visually similar seasonal variation in TI (higher in summer, lower in winter) that closely matched their D-PA variation (Figure 5.8). In the cohort as a whole, there was a trend towards higher TI values in summer and lower in winter but this did not meet statistical significance.

8.5 Summary of chapter 6:

Correlation of D-PA and TI with each other

12 out of the 22 patients with TI measurements demonstrated a positive correlation between D-PA and TI over two years. Half of these (6 patients) had a correlation coefficient (r) >0.2.

Patients with a positive correlation between D-PA and TI also demonstrated concordance in the polarity of the slope in D-PA and TI measurements over 2 years. An example of concordant slopes is shown in Figure 6.2. Concordance in slope suggests that long-term changes in both D-PA and TI may reflect changes in the same systemic factors over time.

Time series correlation did not suggest a specific causal relationship between the two measures. 'Extra-ordinary factors' that affect only one measure can distort the usual correlation in a particular individual, including administration of diuretics, admission to hospital or starting an exercise class (Figure 6.9). These factors may explain the reduced or negative correlation seen in a minority of patients.

8.6 Summary of chapter 7:

A Tale of two Cardioversions

Ablation and DCCV can be effective but carry risks and consume healthcare resources. Recurrence of arrhythmia is common, and a clinical decision has to be made whether to persevere with a rhythm control strategy. The time series of TI measurements were analysed from two patients with similar clinical characteristics but different outcomes from DCCV procedures for persistent AF, and any changes in TI were compared with their clinical course. TI measurements increased rapidly in both patients after restoration of sinus rhythm, returning to a level in line with the pre-decompensation baseline (Figure 7.2). TI for patient A remained stable at or above their baseline but TI for patient B degenerated back to a lower level on reversion to AF, and despite a small improvement, remained well below the level of patient A for the majority of the post cardioversion year.

8.7 Clinical implications

HF is a life-limiting condition affecting millions of people worldwide (Maraey et al., 2024). It is associated with significant morbidity and mortality, and the prevalence of HF has been rising inexorably in recent years. Hospitalisations related to HF decompensation contribute significantly to increased healthcare expenditure (ibid). AAs can cause or worsen HF, and their onset frequently triggers hospital admission in vulnerable patients. Procedures can be used to treat AAs but they carry risks, are expensive, and often require repeat procedures. Assessment of symptoms is the mainstay of the clinical evaluation of patients with HF and AAs, but patients with HF present with a variety of symptoms, most of which are non-specific; and clinical features alone are often an inadequate indicator of severity, particularly in women, the elderly, or obese patients (Watson et al 2000). In recent years, digital biomarkers (DBs) have emerged as a promising new approach to aid the diagnosis, monitoring, and treatment of various health conditions. CIEDs continuously collect and store variables which have shown potential as DBs. More understanding of the factors affecting these measures, and their relation to disease progression and recovery after treatment, is critical if this 'free' source of data is to be better utilised to improve patient care.

Assessing the impact of complex medical interventions is of critical importance in healthcare. This is especially the case where the intervention has significant risks or associated high cost. Although patient symptoms are the primary outcome of interventions for AAs, there has been a general feeling amongst cardiologists that the predicted improvement in cardiac function

brought about by a return to normal rhythm ought to translate into improvements in outcomes such as hospitalisation and mortality. However, this has proved difficult to demonstrate in the general population undergoing rhythm control procedures, although there is increasing evidence that this is the case for patients with pre-existing HF.

8.8 Which parameter has more potential as an outcome biomarker – D-PA or TI?

The initial focus of this thesis was D-PA, as this marker has received the most attention with regard to correlation with cardiac events; in particular, short-term reductions in activity have been associated with HF deterioration. There are, however, a number of problems with this metric as a potential biomarker to assess outcomes from treatment.. For example, a treatment might significantly improve cardiac function, but if activity is ultimately limited by non-cardiac, or non-physiological constraints then this may not translate into an increase in physical activity. Although cardiovascular physiology influences the ability to undertake PA, activity is also moderated by psychological, behavioural, social and cultural influences. Interestingly the only patient who demonstrated a statistically significant change in the slope of PA after treatment had joined a gym rehab program at the same time, highlighting the role of motivation and behavioural factors that have a significant impact. An individual with a sedentary lifestyle may remain sedentary - despite significant improvement in cardiac function,

either because this is their preferred lifestyle, or due to time constraints, lack of motivation, or financial limitations. In addition, activity may be primarily limited by non-cardiac health conditions, for example arthritis, or neurological conditions including Parkinson's disease or dementia.

In contrast, TI is a physiologically-determined variable with no obvious psychological or behavioural input. It is closely linked to disease pathology; pulmonary congestion is primarily influenced by cardiac function, rather than non-cardiovascular co-morbidities. Pulmonary congestion in patients with HF is increased when heart function worsens, and heart function is negatively affected by AAs. Increased intrathoracic fluid accumulation is believed to be the inciting factor of acute HF decompensation (Maraey et al., 2024). A decrease in TI represents an increase in thoracic fluid, and in most cases this reflects an increase in pulmonary congestion. Conversely, an increase in TI suggests a reduction in congestion.

During the course of the investigation it became apparent that PA shows a higher degree of intra-subject variation over time (large SD) compared with TI - in a small cohort, only a large change in D-PA following treatment could be detected. The only study to date to assess the effect of AFA on D-PA showed no difference before and after treatment - even though this was a relatively large trial. In contrast TI demonstrated a small intra-subject variation over time (small SD). In addition, although the absolute value of TI appears to be affected by device manufacturer, the intra-subject variation is similar for both the manufacturers studied. This is in contrast to D-PA; where both the absolute value, and the variation of the measure over time,

are significantly different for different manufacturer's devices. This suggests that a similar magnitude of changes in TI recorded in patients with devices from different manufacturers (at least for Medtronic and Boston Scientific) may reflect similar changes in clinical status. TI appears to be a potentially more sensitive and specific marker for cardiovascular improvement after cardiac procedures than D-PA. This needs to be explored in larger studies.

The finding of an increase in mean daily TI in patients experiencing a large decrease in AF burden is clinically significant. The results point to a sustained reduction in pulmonary congestion ('high is dry') in patients with high AA burden pre-procedure and low burden afterwards. An increase in mean daily TI achieved without alteration in diuretic therapy might be expected to be associated with outcome benefits such as reduced symptoms, improved survival and decreased hospitalisation. The fact that patients with no change in AF burden, or an increased burden, had a decrease in TI (more congestion) demonstrates the negative impact of AAs on cardiovascular performance. TI appears to be a more useful marker for the impact of cardiac rhythm on cardiovascular performance than D-PA. Further studies are warranted to confirm this association and investigate correlation with clinical outcomes.

The finding of a statistically significant difference between D-PA for Medtronic and Boston Scientific CIEDs is clinically significant. Differences between manufacturers have not been intensively investigated and are not appreciated by the clinicians and physiologists

interpreting D-PA data. A low level of activity has been associated with frailty and dementia (Kramer et al., 2017; Goto et al., 2020). With patients increasingly being monitored remotely these data are being integrated alongside demographics and clinical history into forming a clinical picture of the individual. In the case of patients with ICDs, this may trigger referral for discussions around end of life care and potential deactivation of the shock function of the ICD. Shocks from ICDs in patients who are dying from comorbid conditions may not be desired by them or their loved ones. Data on the association between D-PA and frailty and dementia has come from single manufacturer studies (mostly Medtronic CIEDs) but there has been a tendency to generalise to other manufactures. The current study suggests that such generalisation may not be appropriate, and that patients with a similar activity measure from different manufacturers may not have the same functional status.

The observation of a possible seasonal variation in TI is novel and clinically significant. An increase in pulmonary congestion in winter might be caused by winter respiratory viral and bacterial infections. However, it may be related to seasonal changes in cardiac performance. Increased congestion could be a cause of chest infections, as well as being caused by them, leading to increased susceptibility to infection.

In many patients there appears to be correlation between physical activity and pulmonary congestion. In general, it appears that when physical activity is high pulmonary congestion is low and vice versa. However, there was no evidence of a causal relationship between the two variables. It seems likely that they both vary in response to other physiological phenomena

but understanding this is beyond the scope of this study. One possibility is the duration of sleep which is known to demonstrate seasonal variation (Mattingly et al., 2021). People sleep for longer in the winter when the hours of darkness are longer. This reduces the available waking hours for activity to occur. In addition, lying flat when sleeping causes increased fluid accumulation and congestion in the lungs due to gravitational influences on movement of fluid (McGee 2018). Many patients with HF cannot lie completely flat without getting short of breath because of this effect of posture on pulmonary congestion. Indeed, TI has been demonstrated to exhibit circadian variation, with lowest values (highest congestion) in the early morning and increasing during waking hours. Longer time spent sleeping in winter may lead to lower values of daily TI.

8.9 Long-term trends in TI values: a new area for research

Widespread use of CIED TI monitoring to guide the pre-emptive management of HF has been hampered by the considerable number of false-positive alerts triggered by device-based algorithms such as Optivol, which may lead to increased healthcare utilization without corresponding clinical benefit (Maraey et al., 2024). The changes in TI that trigger supposed false alerts do clearly reflect a change in the patient's thoracic fluid, but are deemed to be either due to sub-clinical fluctuation in HF status (in the short-term), or due to non-cardiac conditions such as respiratory infections, or due to postural changes and the systemic effects of medical treatment associated with non-cardiac hospital admission (e.g. for general surgery).

This has reduced interest in exploring the possibilities of this parameter in providing useful, clinically relevant data. However, these investigations have focussed on short-term changes in TI - i.e. days and weeks rather than months and years. The findings of the current project suggest a re-examination of how to utilise TI as a biomarker - that long-term trends in TI may yet contain clinically important and significant information, and should be investigated further in larger studies.

Larger studies will be required to confirm and clarify the results from this investigation, but the results suggest that TI shows promise as a DB to monitor the effect of interventions to treat AAs on cardiac performance. These data could be used to inform selection criteria for randomised trials/experiments. More work will be needed to allow studies to be designed with the right number and length of alternations to give precision in separating a true change in TI from background noise. TI has potential to be used as an outcome measure to evaluate treatment effects, and possibly as a surrogate for hard outcomes as it is associated with mortality. Such a tool would allow clinicians to monitor the effect of treatments and might enable better and more personalised treatment decisions. The use of TI as a DB could lead to increased understanding of individual treatment effects of rhythm control that might be useful for individualized care, enhancing therapeutic precision and improving patient outcomes.

8.91 Managing people with advanced HF who develop significant peripheral fluid overload

The best way to manage people with advanced HF who develop significant peripheral fluid overload is currently unknown. Such patients are likely to have multiple hospital admissions and experience reduced quality of life. Managing such patients in the community would optimal - avoiding costly and disruptive hospital admissions and maximising quality of life. However, whilst oral diuretic formulations can be self-administered, intravenous and subcutaneous diuretics usually need to be administered by nursing or other healthcare staff, usually in a hospital setting. Knowledge of the most clinically and cost-effective routes of administration for diuretic therapy has been highlighted by NICE as an important area for study, as this will dictate the level of resource needed to provide services. NICE have highlighted the need for research to inform practice of how best to manage people with advanced heart failure in the community if they develop significant peripheral fluid overload. The observation from this project that effect of diuretic administration can be readily observed in TI data suggests a novel approach to investigating this question. As a continuous and objective marker of pulmonary congestion, analysis of TI time series may offer new insights into the impact of different diuretic administration strategies, and objective data relating to effectiveness and compliance. Patients with CIEDs and HF could be assigned to alternative diuretic treatments/routes of administration and the effect of TI compared along with conventional end-points, either with a within-patient design or as a randomised trial.

8.92 Pace-and-ablate therapy or aggressive attempts at rhythm control?

The current approach to determine eligibility for pace-and-ablate therapy is rooted in physician experience and opinion rather than evidence. No formal criteria exist beyond 'AF ablation non-eligible' (Joza et al., 2024). However, it is crucial to account for patient-specific characteristics, and it has been highlighted that there is a need for future research that focuses on patient selection and patient outcomes, particularly in those with less clear indications (Joza et al., 2024). Analysis of objective TI data may provide additional information to aid in addressing these questions. TI data may reveal those patients whose cardiovascular system benefits most from being in normal rhythm, who would be candidates for AFA (or repeat AFA) rather than rate control by AV node ablation.

8.93 Ongoing and planned clinical trials

It had been intended to incorporate D-PA measurements as an outcome variable in a number of on-going prospective interventional studies in patients with CIEDs. The results of the current study however, suggest that, TI may be a superior digital biomarker for this purpose, particularly in studies with a repeated measures design. TI data is included along with D-PA in the suite of measures provided in data exports from the device manufacturer, and so is available to be analysed alongside D-PA.

Studies should be conducted to compare D-PA measurements between manufactures as they appear to be significantly different. One approach could be to attach external CIED generators from two manufacturers to the surface of the skin of a number of individuals (e.g. with strong adhesive tape) in approximately the usual sub-clavicular implant location, and record D-PA data via remote monitoring. By comparing values from the same person, demographic and clinic variables would be controlled for. The data would be from the same patient at the same time doing the same activity. Re-sterilised explanted devices could be utilised to reduce costs.

The observed temporal association between D-PA and TI, and between TI and the seasons, could be assessed in a larger retrospective sample of patients with CIEDs – few exclusions would be necessary as there would be no intervention limit the time-period for analysis.

This investigation has highlighted TI as a potentially powerful digital biomarker that may be useful as an indicator of ongoing cardiovascular status outside of acute decompensation episodes. More research will be needed to determine if analysis of impedance data can inform clinical decision-making and the impact the quality and cost-effectiveness of care provided to CIED patients.

8.94 D-PA data from different manufacturers

D-PA data is increasingly being used to assess functional capacity in patients with CIEDs. The current study has highlighted that the values from two leading manufacturers appears

substantially different. This requires further exploration. There are currently no 'head to head' comparisons of D-PA data from different manufacturers because patients only have one device implanted. Direct comparison could be achieved by using explanted devices from different manufactures taped to the bodies of volunteers (close to the usual implant site but not implanted). The simultaneously acquired D-PA data could then be analysed for the same subject and compared.

8.95 Limitations

A retrospective study design using existing clinical data is an effective way to collect pilot data, which can identify feasibility issues and feed into the design of future prospective studies (Hess, 2004).However, this approach contains inherent threats to both internal and external validity (Tofthagen, 2012). The single-group design employed in this retrospective study limits the ability to determine cause and effect (ibid). The use of repeated, objective and blinded measures reduces some of the limitations. For some patients, the period of the study included the Covid-19 lockdowns which has been documented as affecting physical activity.

There was a small number of patients due to the constraints of the necessary inclusion and exclusion criteria. The final sample of 30 patients was less than the >50 that was forecast from a preliminary investigation into feasibility. This number was reduced further for the analysis of TI, due to not all of the CIEDs collecting this measure, further limiting the statistical power. The

requirement for remote monitoring introduces a degree of selection bias – patients who do not utilise remote monitoring were not represented and may have different characteristics than the individuals in the study. However, the majority of patients now utilise remote monitoring.

Due to the exploratory nature of the study, statistical analysis was largely post hoc. The intended approach for both D-PA and TI was to apply time-series analysis to individual patient-level data. However, a preliminary analysis revealed that there was not a statistically significant change in the gradient of the individual time-series, suggesting that this approach would not have sufficient power. Because of this, and to reduce the complexity of the analysis, the large number of repeated measures were averaged to generate two summary repeated measures (pre and post procedure) each describing an entire 12m period. This approach loses much of the information contained in the time series. The full time series was only utilised (in a descriptive way) to compare the time course of events in two patients for chapter 7.

There are five globally important CIED manufacturers. The present study was restricted to only two manufactures (Medtronic and Boston Scientific) so the findings may not be generalizable to all manufactures. There is a lack of research data on the effect of procedures on TI measurements; the findings of this thesis highlights the need for further research.

8.96 Knowledge gaps and Future directions

There are many unanswered questions regarding the optimal management of patients with AAs and HF, including:

In which patients should a rhythm control strategy be pursued aggressively?

Is there a role for AFA in end-stage HF?

What is the best strategy for very old patients with AF; rate or rhythm control?

Who should be selected for an AV node ablation and pace strategy?

What is the best way to manage people with advanced HF who develop significant peripheral fluid overload?

What is the gold standard for long-term clinical monitoring and objective assessment of HF patients with CIEDs?

The study of DBs from CIEDs may offer new insights to help to answer some of these questions by providing an objective marker for the impact of different procedures and management strategies at the individual level. TI represents a promising DB for tracking cardiac performance in individual patients over time, which could be utilised in a number of contexts. This approach will allow the inclusion of patient groups not usually included in clinical trials, such as the very elderly or those with end stage HF or renal failure.

Mean thoracic impedance (TI) values for all patients from pre to post procedure

Mean TI pre (Ω)	Mean TI post (Ω)	Difference (Ω)
60.18	61.29	1.11
39.73	41.25	1.52
54.04	56.87	2.83
48.26	49.64	1.38
74.04	76.21	2.17
61.20	61.58	0.38
65.07	69.31	4.24
47.64	41.84	-5.80
70.45	67.82	-2.62
90.78	94.62	3.84
79.68	75.92	-3.76
66.82	67.24	0.42
77.27	76.54	-0.73
53.89	52.25	-1.64
67.17	60.25	-6.92
88.18	81.73	-6.45
80.48	72.57	-7.90
51.30	50.71	-0.60
74.84	73.16	-1.68
n=19	Mean difference	-1.06
	SD	3.67

SD = standard deviation

TI = thoracic impedance

Change in thoracic impedance (TI) for each patient in each group

	Group 1	Group 2	Group 3
	Δ TI pre/post	**Δ TI pre/post**	**Δ TI pre/post**
	1.110273973	10.99621021	-0.734931507
	1.522310279	4.240410959	-1.636986301
	-1.221754152	-5.798164384	-6.92034096
	2.826027397	-2.622732124	-6.449724518
	1.381506849	3.841780822	-7.903223318
	2.171232877	-3.761643836	-0.595890411
	0.379893581	0.421900873	-1.680136986
			-2.906164384
Mean	1.167070115	1.045394646	-3.703033429
SD	1.307798078	5.785505639	3.223910728
n	7	7	8

SD = standard deviation

TI = thoracic impedance

Mean values for D-PA and TI for all patients over 2 years, demonstrating very precise estimates of the mean due to the number of repeated measures, particularly for TI.

Patient number	Manufacturer	D-PA (mins/day) mean ± 95% SE	TI (Ω) mean ± 95% SE
1	Med	17.09 ±1.034	55.46 ±0.272
2	Med	86.72 ±3.295	84.96 ±0.415
4	Med	217.98 ±8.983	77.80 ±0.307
5	Med	91.32 ±3.695	NA
6	Med	273.53 ±4.781	84.39 ±0.463
7	Med	284.44 ±5.584	76.91 ±0.215
8	Med	167.50 ±4.954	NA
9	Med	240.17 ±5.099	67.03 ±0.105
10	Med	32.14 ±1.367	60.73 ±0.239
11	Med	205.39 ±4.329	51.01 ±0.173
12	Med	80.41 ±2.477	63.71 ±0.302
13	Med	274.24 ±4.132	75.13 ±0.216
14	Med	265.57 ±5.157	64.27 ±0.217
15	Med	113.82 ±3.481	92.70 ±0.331
16	Med	115.47 ±3.032	53.07 ±0.177
17	Med	160.48 ±1.697	74 ±0.182
18	Med	286.98 ±5.803	67.19 ±0.235
19	Med	372.85 ±3.7	NA
20	Med	185.99 ±2.334	76.53 ±0.374
21	Med	190.35 ±3.494	61.39 ±0.181
22	Med	123.05 ±3.558	69.91 ±0.211

3	BSc	56.57 ±1.176	NA
23	BSc	95.80 ±1.640	NA
24	BSc	115.37 ±1.835	NA
25	BSc	147.16 ±3.115	NA
26	BSc	89.08 ±1.292	NA
27	BSc	23.40 ±0.820	40.58 ±0.147
28	BSc	94.03 ±1.965	48.95 ±0.158
29	BSc	33.11 ±0.760	44.74 ±0.318
30	BSc	267.14 ±4.285	69.13 ±0.246

Med = Medtronic Bsc = Boston Scientific

Change in variables between late spring /summer and winter/early spring

	May,June July		Dec ,Jan, Feb		
Patient	Mean D-PA (mins/day)	Mean TI (Ω)	Mean D-PA (mins/day)	Mean TI (Ω)	Change in D-PA from summer to winter
4	260.40	76.97	152.74	76.26	-107.66
9	278.74	66.63	212.09	66.52	-66.65
11	223.64	49.99	160.67	51.05	-62.97
15	122.72	92.10	87.37	91.58	-35.36
22	133.89	69.00	101.64	69.85	-32.25
6	290.41	83.44	260.96	84.09	-29.45
13	298.95	75.99	271.54	74.46	-27.41
19	380.57	NA	353.36	NA	-27.21
18	325.46	68.61	301.39	66.23	-24.07
21	193.68	62.95	173.43	60.04	-20.25
12	80.17	62.41	62.51	62.44	-17.66
16	130.50	54.29	114.28	52.17	-16.22
3	59.88	NA	43.92	NA	-15.96
24	122.91	NA	107.31	NA	-15.60
23	100.96	NA	86.50	NA	-14.46
5	91.70	NA	78.68	NA	-13.01
25	151.07	NA	140.06	NA	-11.01
26	87.83	NA	80.49	NA	-7.35
10	36.96	64.33	30.63	58.01	-6.33
14	255.98	65.05	249.79	63.75	-6.19
27	40.89	NA	40.50	NA	-0.40
8	172.33	NA	172.69	NA	0.36
20	186.66	77.48	187.51	75.34	0.85
1	14.01	56.89	15.15	54.63	1.14
2	19.43	87.06	23.88	83.51	4.44
28	94.05	47.27	99.42	49.56	5.38

30	253.07	65.81	266.90	70.62	13.82
7	283.00	77.90	297.11	75.19	14.11
17	152.23	73.93	166.93	73.71	14.71
29	4.36	47.73	24.00	43.50	19.64

D-PA = device-determined physical activity TI = thoracic impedance Ω =Ohms

Correlation coefficients of D-PA and TI values against time. 95 % CI were calculated which allows an assessment of the significance of the correlation.

	D-PA vs TI			D-PA vs time (days)					TI vs time (days)						
	Pearson r	95% CI	Polarity	Pearson r	95% CI		squares gradient	Polarity	Pearson r	95% CI		squares gradient	Polarity	Agreement D-PA and TI	

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