UNIVERSITY OF HULL

Thesis of

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CAN THE MEASUREMENT OF TRANS-VENTRICULAR INTRACARDIAC IMPEDANCE RELIABLY DIFFERENTIATE HAEMODYNAMICALLY STABLE FROM UNSTABLE ARRHYTHMIAS?

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ABSTRACT

Faculty of Medicine – Cardiology

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CAN THE MEASUREMENT OF TRANS-VENTRICULAR INTRACARDIAC IMPEDANCE RELIABLY DIFFERENTIATE HAEMODYNAMICALLY STABLE FROM UNSTABLE ARRHYTHMIAS?

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Introduction: Implantable defibrillators (ICD's) are currently unable to assess the haemodynamic stability of arrhythmias and can occasionally deliver intracardiac shocks when patients are conscious. We investigated the use of trans-ventricular impedance (across the left ventricle {LV}) as a haemodynamic sensor during arrhythmias in man.

Methodology: Trans-ventricular LV impedance and systemic blood pressure (BP) were continuously monitored during clinical VT stimulation studies. LV impedance was measured by injecting a biphasic rectangular current pulse of 600μA amplitude at a sampling rate of 128 Hz between the distal poles of a standard quadripolar pacing/recording electrode positioned at the right ventricular (RV) apex, and the proximal poles of a decapolar catheter positioned within the coronary sinus (CS). Current was injected using an external pacemaker (INOS, Biotronik) connected to the poles of the RV & CS catheters. Haemodynamically unstable arrhythmias were defined as those needing urgent DC cardioversion for loss of consciousness.

Results: 28 patients were studied. Unstable VT: 5 (18%), Stable VT: 5 (18%), SVT: 2 (7%). During haemodynamically unstable VT, the stroke impedance (SZ) – the difference between the end systolic and end diastolic impedance values – dropped to 22% of its original sinus rhythm value (standard deviation = 15 – 32%), which was associated with a simultaneous drop in mean arterial BP down to 13% of its original sinus rhythm value (standard deviation = 3 – 36%), $p < 0.001$. During haemodynamically stable VT, SZ dropped to 58% of its original sinus rhythm value (standard deviation = 33 – 88%), which was associated with a simultaneous drop in mean arterial BP down to 55% of its original sinus rhythm value (standard deviation = 24 – 77%), $p = 0.008$.

Conclusion: Trans-ventricular impedance was able to assess the pumping efficacy of the heart during sinus rhythm, ventricular pacing and ventricular arrhythmias, and correlated well with changes in blood pressure, but was still unable to discriminate between haemodynamically stable and unstable arrhythmias. Further studies are needed to determine the long-term stability of trans-ventricular impedance measurement as a reliable haemodynamic sensor.

CONTENTS

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ABBREVIATIONS USED

AC	Alternating Current
AF	Atrial Fibrillation
ARVD	Arrhyhtmogenic Right Ventricular Dysplasia
ATP	Anti-tachycardia pacing
AV	Atrio-Ventricular
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CW	Continuous Wave Doppler
DC	Direct Current
DCM	Dilated Cardiomyopathy
DDD-ICD	Dual chamber Implantable Cardioverter Defibrillator
DDDR	Rate-responsive Dual Chamber Pacemaker
HCM	Hypertrophic Cardiomypathy
HSVT	Haemodynamically Stable Ventricular Tachycardia
HUVT	Haemodynamically Unstable Ventricular Tachycardia
Hz	Hertz
ICD	Implantable Cardioverter Defibrillator
IHD	Ischaemic Heart Disease
IVS	Inter-Ventricular Septum
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVF	Left Ventricular Failure
MI	Myocardial Infarction
ms	Milliseconds
PVAB	Post-Ventricular Atrial Blanking
PVARP	Post-Ventricular Atrial Refractory Period
RBBB	Right Bundle Branch Block
RF	Radio-frequency

ABBREVIATIONS USED (Continued)

RV	Right Ventricle
RVOT	Right Ventricular Outflow Tract
SADS	Sudden Arrhythmic Death Syndrome
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SD	Standard Deviation
SSS	Sick Sinus Syndrome
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VVI-ICD	single Chamber Ventricluar Implantable Cardioverter Defibrillator
TR	Tricuspid Regurgitation
TVI	Trans-Valvular Impedance

CHAPTER 1

CHAPTER 1

INTRODUCTION

1.0 Sudden cardiac death

1.0.1 ***Definition:***

Sudden Cardiac Death (SCD) is defined as: an unexpected death due to cardiac causes occurring in a short time period (generally within 1 hour of symptoms onset) in a person with or without known cardiac disease in whom there is no apparent previously diagnosed fatal non-cardiac condition [1] [2]. It continues to represent a major challenge for the whole of the medical profession in general, and particularly for those interested in cardiology and arrhythmia management. For the families of affected individuals, SCD comes as a devastating and shocking experience as it often claims the lives of young seemingly previously fit adults. Preventing SCD requires identifying people at risk, to which sound understanding of the underlying pathologies is crucial.

1.0.2 ***Brief historical background:***

Understanding the mechanism of death and appreciating the central role that the heart plays in blood circulation have hugely occupied the thoughts and works of many ancient philosophers. Huang Ti, the Yellow Emperor of China (2698–2598 BC), wrote in Nei Ching (Canon of Medicine): *"The blood current flows continuously in a circle without a beginning or end and never stops"* and *"all the blood is under control of the heart"* [3]. Hippocrates (470–410 BC) provided a concise, but historically compelling, description of SCD in his Aphorisms II, 41:

"Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly" [4]. In the second century, Claudius Galen (131–201), the Graeco-Roman physician clearly mentioned that sudden death is caused by major heart lesions, which he referred to as *"Dycrasias"* [5]. He also suggested that blood diffuses through invisible pores in the IVS from the RV to the LV [6], which remained the belief until Ibn al-Nafis (1210–1288) made the first accurate description of the pulmonary and coronary circulation a thousand years later in his book *"The Perfect Man"* [7]. Avicenna of Persia (Ibn Sina 980–1037) mentioned, also very clearly, that: *"Fast heart beats cause palpitations, faster heart beats cause fainting, and extremely fast heart beats result in sudden death"*. Furthermore, he made a distinction between cardiac (arrhythmic) and gastric (vaso-vagal) syncope stating that: *"Gastric fainting tends to be associated with nausea and dizziness, but recurrent and severe fainting without obvious cause is cardiac and leads to sudden death"* [8]. However, the cornerstone for detailed understanding of the blood circulation was not laid until, in 1628, William Harvey (1578 –1657) – based on work of anatomists such as Leonardo da Vinci (1452–1519) and Andreas Vesalius (1514 –1564) – published his then new theory that the heart acts as a muscular pump in circulating blood around the body [6]. In 1775 Peter Christian Abildgaard (1740 – 1801), a Danish veterinarian and physician, performed the first successful defibrillation through conducting experiments on electrical counter-shock on animals. Using direct current derived from a Leyden

jar he succeeded in first rendering fowl lifeless by an electric shock and then reviving them by a counter-shock applied to the chest [9]. In 1791, Luigi Galvani (1737 – 1798) conducted a series of experiments on severed frogs' legs and discovered that when nerve and muscle touch two dissimilar metals in contact with each other, a contraction of the muscle takes place [10]. This led to the publication of his theory of "animal electricity". Although initially strongly supported the theory was later disputed in 1793 by Alessandro Volta (1745 – 1827), who suggested that the electricity came from the contact of the two metals rather than from animals [11]. The scientific debate continued even after Volta – to prove his theory – invented the Voltaic pile in 1800 [12] [13]. Galvani's nephew and assistant, Giovanni Aldini (1762 – 1834), then led the defence of his uncle's concept against the incessant attacks of Volta. Using Volta's very bimetallic pile he applied electric current to decapitated bodies of animals and humans (executed criminals) in public, successfully stimulating muscular tremor & contractions for an average time of an hour following decapitation. Aldini also treated patients with personality disorders and reported complete rehabilitation following trans-cranial administration of electric current [14]. In 1820, Richard Reece (MD) – in a vision echoing the researches of Aldini – described in his published family medical guide the *"Re-Animation Chair of Doctor De Sanctis"* [15], which recommended cardiac electro-stimulation via oesophageal and precordial electrodes as a means of getting a stopped heart to start beating again. This is similar in concept to defibrillation and external pacing of modern medicine. In 1841, Carlo

Matteucci (1811 – 1868) demonstrated that an electric current accompanies each heartbeat. He used a preparation known as a 'rheoscopic frog' in which the cut nerve of a frog's leg was used as the electrical sensor and twitching of the muscle was used as the visual sign of electrical activity [16]. In 1850, Carl Ludwig (1816-1895) and his student M Hoffa demonstrated that a single electrical pulse could induce bizarre unregulated actions of the ventricles (later called ventricular fibrillation) during experiments involving the application of strong electrical currents across the hearts of dogs and cats [17]. In 1875, Gabriel Lippmann (1845 – 1921) – a researcher in piezoelectricity and seismology – invented the mercury capillary electrometer (Figure 1.0), which measured small differences in voltage [18]. The apparatus was then used successfully by Augustus Desiré Waller (1856 – 1922) in 1887 to make the first ever recording of the electric activity of the human heart, the electrocardiogram (ECG) [19] (Figure 1.1). In 1899, Jean-Louis Prevost, Professor of Biochemistry, and Frederic Batelli, Professor of Physiology, both working at the University of Geneva, discovered that they could defibrillate a dog's heart to sinus rhythm by applying an appropriately high current counter-shock directly to the surface of the myocardium [20]. At the beginning of the twentieth century (1901), William Einthoven invented a new galvanometer for producing ECGs using a fine quartz string coated in silver [21]. For that, he later won the Nobel Prize in 1924. In 1930 Wolff, Parkinson and White reported the ECG syndrome of short PR interval, wide QRS and paroxysmal tachycardias [22]. In 1931 Dr Albert Hyman invented the first "artificial cardiac pacemaker", which

stimulated the heart by using a transthoracic needle [23]. In 1932 Kouwenhoven, an electrical engineer, contributed three major landmarks. He confirmed the earlier work of Prevost and Batelli that an electric shock could indeed reverse ventricular fibrillation. He developed some of the earliest defibrillation devices initially using 60 Hz AC and subsequently DC shocks to defibrillate. He was also involved in the introduction of early methods of external cardiac massage [24].

Figure 1.0:

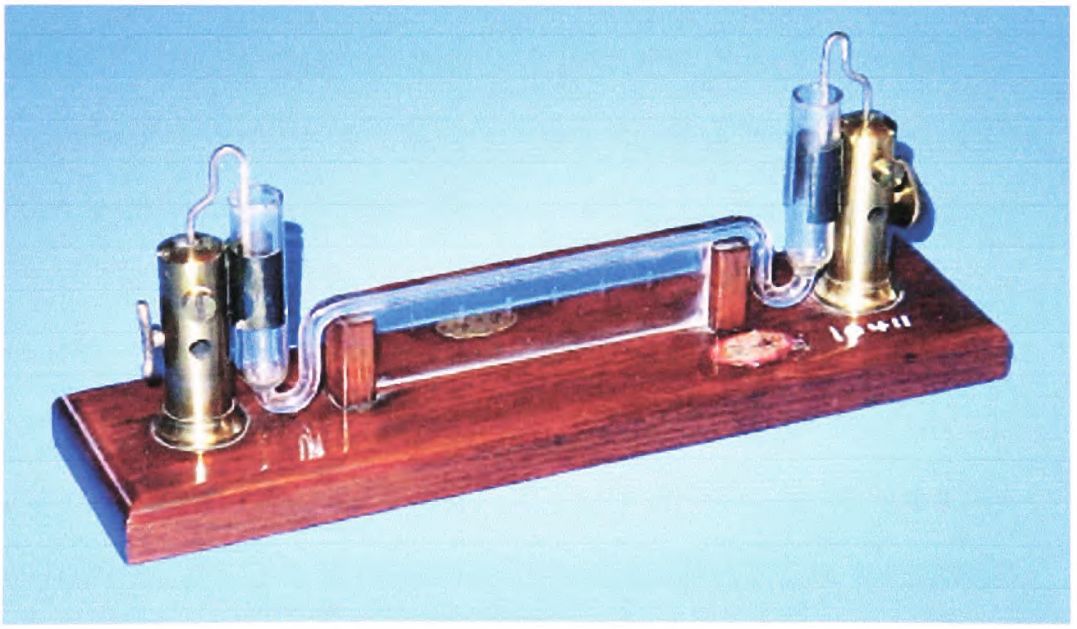


Figure 1.0: The mercury Capillary Electrometer, invented by Gabriel Lippmann in 1875 *(Downloaded with permission from: http://chem.ch.huji.ac.il/~eugeniik/history/lippmann.html)*

Figure 1.1:

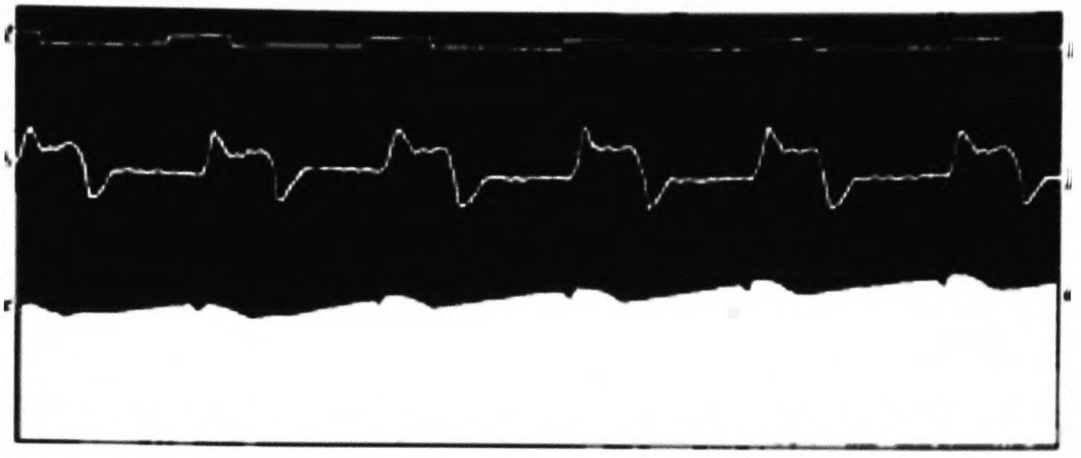


Figure 1.1:

The first human ECG, recorded by A D Waller in 1887.

In 1946 two Russian workers, Gurvich and Yuniev reported the successful restoration of regular rhythm in the fibrillating mammalian heart with capacitor charges applied externally across the closed chest [25]. In 1947 Claude Beck *et al* reported the first case of successful defibrillation of the human heart during cardiac surgery with full recovery. The patient was a 14-year-old boy [26]. Two years later Norman Jeff Holter, the Montana physician, developed a 75-pound backpack that could record the ECG of the wearer and transmit the signal. The system, the Holter Monitor, was later greatly reduced in size and combined with digital recording for convenient ambulatory ECG monitoring [27]. In 1956 Paul Zoll – a cardiologist – managed to perform closed-chest defibrillation in a human using a more powerful defibrillator [28]. The "R-on-T" phenomenon was first described by Smirk and Palmer in 1960 [29].

They also accurately described its role in SCD causation by initiating ventricular fibrillation. In 1966 François Dessertenne of Paris publishes the first case of 'Torsade de pointes' polymorphic Ventricular Tachycardia [30]. Recently, in 1992, Pedro & Josep Brugada of Barcelona published a series of 8 cases of sudden death, RBBB pattern and ST elevation in V1 – V3 in apparently healthy individuals. This Brugada Syndrome is now known to be the commonest cause of SCD in individuals aged under 50 years in South Asia [31].

1.0.3 ***Epidemiology:***

SCD is one of the major causes of adult mortality in the developed world. It accounts for an annual incidence of 3,000,000 deaths worldwide. Of those, 400,000 deaths occur in Western Europe and 340,000 occur in the United States [2]. In UK alone, SCD is responsible for 75,000 to 100,000 deaths each year [32]. The majority of those patients have either underlying poor left ventricular function (LVEF < 35%) with or without coronary disease, or inherited cardiac conditions with tendency to generate malignant ventricular arrhythmias [33]. In a national epidemiological survey undertaken by the SADS – Sudden Arrhythmic Death Syndrome – study investigators, the incidence of *unexplained* sudden cardiac deaths in England, UK, in healthy people aged between 16 – 64 years was estimated at 11 per 100,000 (3500 deaths per year). This constitutes about 4.1% of the total UK SCD annual incidence [34]. Worldwide, less than 1% of those who experience sudden cardiac arrest manage to survive [2]. The greatest incidence

occurs in cohorts with identifiable risk factors but most events – in absolute numbers – occur in individuals *without* prior known risk factors (Fig: 1.2) [35]. In one study, around 12% of all natural deaths were classified as sudden, of which 88% were caused by cardiac disease [36]. Furthermore, SCD is the commonest – and often the first – manifestation of coronary heart disease and accounts for approximately 50% of cardiovascular disease mortality in the developed world. In developing countries, SCD rates are lower. Several population-based studies have documented a 15% to 19% decline in the incidence of SCD caused by coronary heart disease since 1980s. However, the increasing incidence of congestive cardiac failure may adversely affect this decline in the future [37].

Figure: 1.2

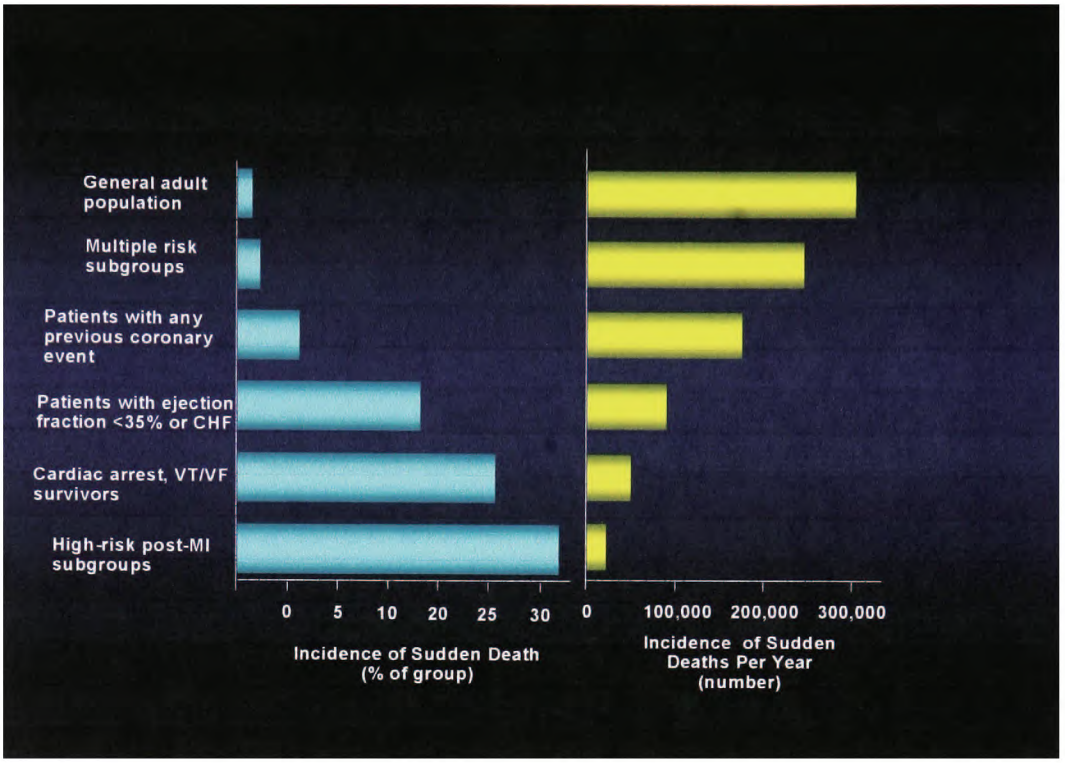


Figure 1.2: Percentage incidence of SCD in specific populations (left) and annual SCD absolute numbers (right)
(Adapted with permission from: Myerburg RJ. Sudden Cardiac Death: Exploring the Limits of Our Knowledge. J Cardiovasc Electrophysiol Vol. 12, pp. 369-381, March 2001.)

1.0.4 ***Risk Factors:***

Multiple epidemiological studies have shown that the conventional risk factors for IHD are also predictive of SCD [38] [39] [40] [41]. In a study that looked into independent risk factors for SCD in 24 British towns [42], elevated heart rate, heavy drinking, and arrhythmia emerged as factors that appear to be specific to SCD. Those three factors along with age and blood cholesterol level have been found to be associated with an increased risk of SCD in men both with and without pre-existing IHD. Reduced physical activity, elevated systolic blood pressure, and current smoking were associated with SCD only in men *without* pre-existing IHD whereas HDL cholesterol level and haematocrit have been found to be strong predictors of SCD only in men with pre-existing IHD. Diabetes, forced expiratory volume in 1 second, body mass index, white blood cell count, and antihypertensive drugs have been found *not* to be associated with SCD. Malignant ventricular arrhythmias – VF & haemodynamically unstable VT (HUVT) – are the principal and direct cause of SCD. Underlying pre-existing structural, genetic or electrical cardiac pathology commonly predisposes to such arrhythmias.

1.1 Aetiology &mechanism of ventricular arrhythmias

1.1.1 ***Definition:***

Ventricular fibrillation is described as a *"turbulent, disorganised electrical activity of the heart in such a way that the recorded electrocardiographic deflections continuously change in shape, magnitude and direction"* [43]. Ventricular tachycardia is defined as a succession of three or more

beats of ventricular origin at a rate greater than 100 beats per minute [44]. Depending on the QRS morphology of the arrhythmia ECG, VT can be classified as either monomorphic (QRS complexes of similar morphology) or polymorphic (QRS complexes of variable morphologies, axes, and amplitudes). VF is uncommon as a primary arrhythmia and tends to be preceded by VT in approximately 80% of cases.

1.1.2 ***Aetiology:***

Ventricular arrhythmias can be induced or precipitated by a number of cardiac, and sometimes non-cardiac, disorders. If untreated, sustained VT often degenerates into VF and then Asystole [45]. Apart from fascicular & RVOT – right ventricular outflow tract – tachycardias, monomorphic VT tends to affect damaged myocardium. Causes of monomorphic VT include:

- Acute myocardial infarction or ischaemia.
- Previous MI (Scar-related VT).
- Cardiomyopathies (HCM, DCM).
- Myocarditis.
- Arrhythmogenic Right Ventricular Dysplasia (ARVD)
- Valvular heart disease (e.g. mitral valve prolapse).
- Post-cardiac surgery (e.g. repair of tetralogy of Fallot).
- Severe LV dysfunction (from any cause).

On the other hand, Polymorphic VT tends to result from genetic, electrical or even non-cardiac disorders in otherwise structurally normal hearts. Causes of polymorphic VT include:

- Bradycardia due to Sick Sinus Syndrome or Atrio-Ventricular block.
- Congenital Long QT syndrome.
- Brugada Syndrome.
- Catecholaminergic Polymorphic VT (CPVT)
- Electrolyte imbalance (e.g. Hypokalaemia or hypomagnesaemia).
- Most anti-arrhythmic drugs (e.g. Quinidine, Sotalol, Amiodarone, Flecainide).
- Other non-cardiac drugs (e.g. Tricyclic antidepressants, Erythromycin, Tetrafenadine).
- Anorexia Nervosa.

1.1.3 ***Mechanism:***

Due to the practical problems involved with mapping large areas of the heart simultaneously and the inappropriateness of sustaining VF, researchers have confined their interest and work to its induction and termination. Therefore, much of the current data on the dynamic electrophysiological changes during cardiac arrhythmias comes either from computer modeling, electrode studies or the use of high resolution optical mapping and Mathematical models. Mechanisms of arrhythmia genesis can be divided into disorders of impulse conduction, disorders of impulse formation or both [46].

Disorders of impulse conduction (Re-entry – figure 1.2A):

This has been first demonstrated separately by Mines and Garrey (1913 -14) [47] . For re-entry to occur there needs to be an area of non-excitable myocardium – ischaemic or scar tissue – surrounded by a ring of

excitable tissue that has a short refractory period and a sufficient length of ring circumference with different conduction velocities of the two ring arms. This allows antegrade conduction through one arm of the ring before retrograde propagation of the depolarisation wavelet proceeds through the other ring arm, thereby resulting in self-sustaining circus movement phenomenon. A slow propagation velocity promotes re-entry. Therefore, transient or permanent conduction block forms a substrate for VF / VT through re-entry phenomenon.

Figure 1.2A

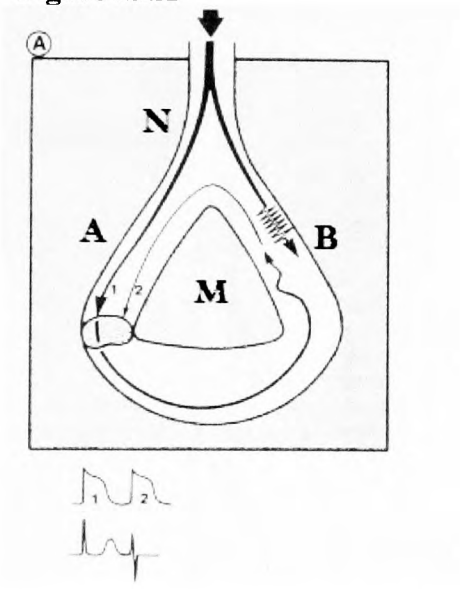


Figure 1.2A: **Mechanism of re-entry tachycardia**

For re-entry to occur there needs to be an area of non-excitable myocardium (M) such as ischaemic or scar tissue, surrounded by a ring of excitable tissue that has a short refractory period and a sufficient length of ring circumference with different conduction velocities of the two ring arms. As a cardiac impulse travels through conduction tissue (N) onto area (M), the ring arm (A) conducts the impulse at a much faster speed compared to ring arm (B) and it therefore transmits the impulse around area (M) first. That impulse then travels up via ring arm (B) but meets the initial depolarisation wave halfway through and can't therofore be transmitted up any further through the already depolarised part of ring arm (B). The impulse then finds that ring arm (A) is no longer refractory and therefore uses it to travel downwards and completes the circuit around area (M), and the cycle continues creating a re-entrant tachycardia.

Disorders of impulse formation (Increased automaticity – figure 1.2B):

Automaticity is a measure of the propensity of an area of tissue to initiate an impulse spontaneously. Factors, such as hypoxia, poromote automaticity by causing a net gain in the intracellular positive charge during diastole. This occurs due to a raised external concentration of K+, a decreased intracellular concentration of K+, increased permeability to Na+ or a decreased permeability to K+. Therefore, the maximum diastolic potential becomes less negative and lies closer to the threshold potential.

Figure 1.2B

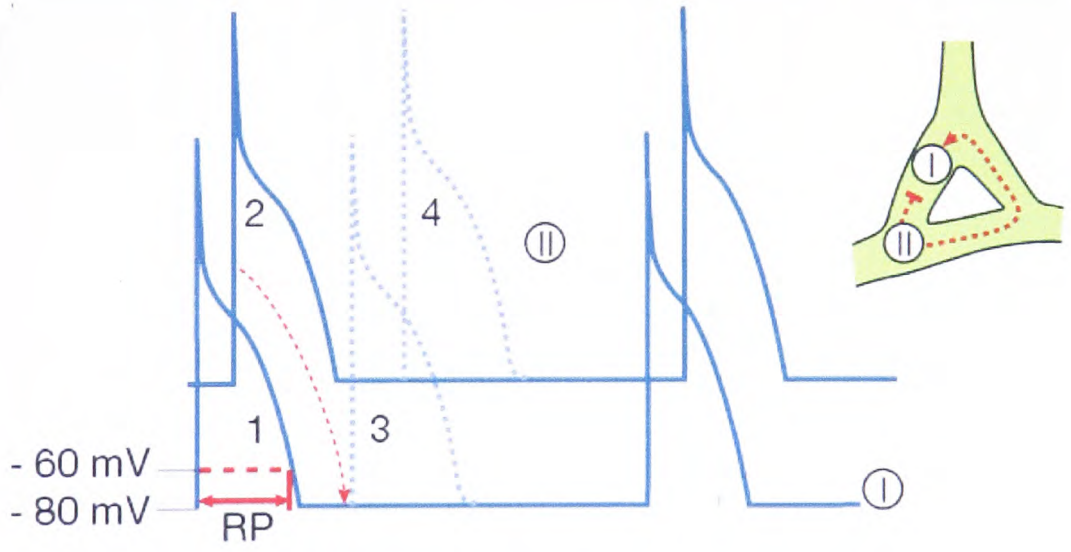


Figure 1.2B: Increased automaticity

In cases of increased automaticity as the mechanism of arrhythmogenesis, the maximum diastolic potential – due to factors such as hypoxia – becomes less negative and lies closer to the threshold potential. The numbers 1, 2, 3 & 4 in the figure represent the different stages of the myocardial cell action potentional. RP stands for "Resting Potential".

Triggered activity (Figure 1.2C):

Depolarising oscillations in the membrane voltage are induced by preceding action potentials and are called "afterdepolarisations". All afterdepolarisations may not reach threshold potential but if they do they can trigger another afterdepolarisation and thus self perpetuate resulting in VT / VF.

Figure 1.2C

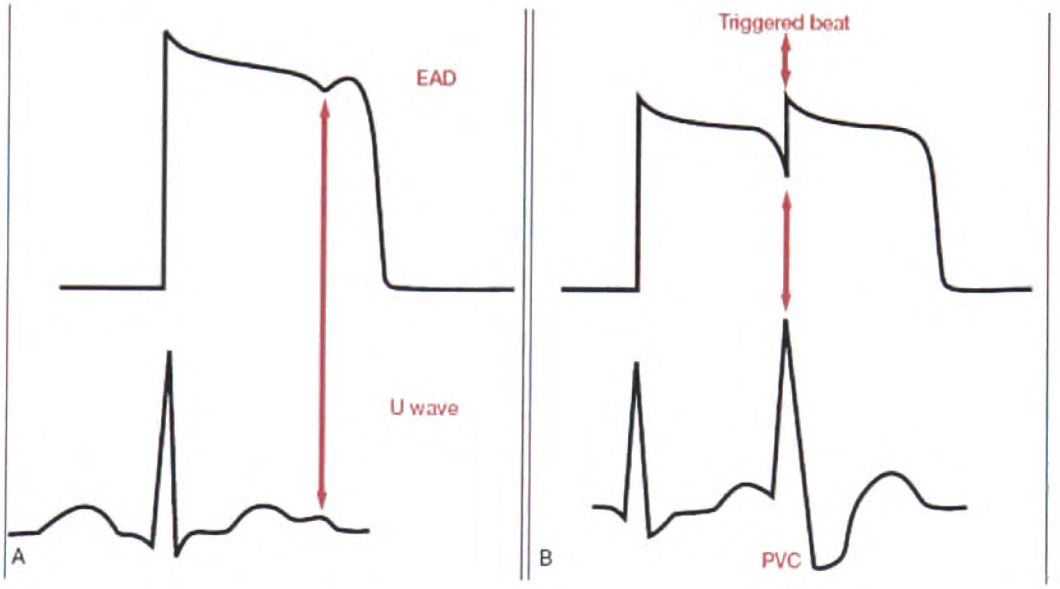


Figure 1.2C: Triggered Activity

Figure A on the left shows an early afterdepolarisation (EAD) that has not reached the threshold potential, thus resulting only in a U wave appearing on the surface ECG. Figure B on the right demonstrates an EAD that has reached the threshold potential, thereby generating a premature ventricular complex (PCV).

1.2 Management of ventricular arrhythmias

Termination of an arrhythmia and prevention of its recurrence is the mainstay of treatment. Termination can be achieved by DC cardioversion, transvenous overdrive pacing, or intravenous administration of anti-arrhythmic therapy. Prophylactic therapy includes oral anti-arrhythmic drugs, radio-frequency ablation, surgery, and implantable cardioverter defibrillators (ICDs). An acute episode of VF or HUVT is often easily treatable with DC cardioversion; this should however be delivered extremely urgently if fatal outcome is to be avoided. The chance of a successful resuscitation declines by about 7–10% each minute [48]. In the setting of recurrent or persistent haemodynamically stable VT (HSVT), intravenous anti-arrhythmic drug therapy may be preferred over DC Cardioversion as the latter is neither then urgently required nor is it likely to help prevent arrhythmia recurrence.

1.2.1 Anti-arrhythmic drugs:

Although anti-arrhythmics are useful in terminating and lowering the recurrence rate of arrhythmias, there is little evidence to suggest that they alter the outcome. A number of randomised controlled clinical trials have evaluated whether acute or chronic anti-arrhythmic drug therapy can reduce mortality in post-MI patients. Of those, only the use of acute intravenous and long-term beta-blockers, independently and in combination, had been shown to reduce mortality.

The Cardiac Arrhythmia Suppression Trial (CAST) studied placebo Versus Encainide, Flecainide, or Moricizine. It was stopped early due to

excess deaths in the anti arrhythmic arms [49]. Both of the European Myocardial Infarct Amiodarone Trial (EMIAT) & Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) showed that Amiodarone reduced arrhythmic but not overall mortality [50]. Two further trials studied Amiodarone in heart failure patients: Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiac en Argentina (GESICA) & Amiodarone in Patients With Congestive Heart Failure and Asymptomatic Ventricular Arrhythmia (CHF-STAT). Amiodarone has been associated with a neutral overall survival and a statistically non-significant trend towards improved survival in non-ischemic cardiomyopathy patients in CHF/STAT and improved survival in GESICA [51] [52]. Conventional Versus Amiodarone Drug Evaluation (CASCADE) study demonstrated that Amiodarone reduced arrhythmia recurrence rates compared to other anti-arrhythmic agents (Mexiletine, Procainamide, Propafenone, Quinidine & Sotalol) – guided by serial Holter or electrophysiologic studies – but nevertheless arrhythmic death rates were still high in both treatment arms of the study [53]. On the other hand, beta-blocker therapy has been shown in a number of large randomised trials to significantly reduce the incidence of SCD as well as all-cause mortality in post-MI patients and in patients with heart failure. Carvedilol was studied by the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial [54] and has been shown to significantly reduce all cause mortality (11.9% versus 15.3% placebo, $p = 0.031$) but had little effect on sudden arrhythmic death. Propranolol was associated with 26% ($p = 0.005$) and 28% ($p = 0.05$) relative reduction in all cause

mortality and sudden death respectively in BHAT (Beta-blocker Heart Attack Trial) [55]. Timolol provided 39% (p = 0.0001) and 45% (p = 0.0005) relative reduction in all cause mortality and sudden death respectively in the Norwegian Multi-centre Study group [56]. In the post-MI ICD trials, AVID (Antiarrhythmic Versus Implantable Defibrillator) and MUSTT (Multicenter Unsustained Tachycardia Trial), beta-blocker therapy – with the exception of those treated with ICDs – was associated with improved overall 5-year survival (34% mortality) compared to the non-beta blocker arm (50% mortality) adjusted *p* = 0.0001 [57]. Extended-release Metoprolol reduced all-cause mortality and sudden death by 34% (p = 0.00009) and 41% (p = 0.0002) respectively in MERIT-HF (Metoprolol controlled-release/Extended-Release randomized Intervention Trial in Heart Failure) [58]. Bisoprolol was associated with a 32% reduction in overall mortality (p = 0.0001) and 42% reduction in sudden death (p = 0.0011) in CIBIS-II (Cardiac Insufficiency Bisoprolol Study II). Furthermore, carvedilol was associated with a 35% mortality reduction in the COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival) trial (*p* = 0.00014) [59]. Intravenous atenolol given early in acute MI has been shown to reduce chest pain, enzyme release and incidence of arrhythmias. Data published before the first report of the ISIS-1 group (International Studies of Infarct Survival) showed a 12% decrease in the probability of death using intravenous beta blockade albeit with large confidence limits [60]. Table 1.0 below summarises six of the main beta-blocker clinical trials data and outcomes.

Table 1.0:

Study	BHAT	Norwegian	CAPRICORN	CIBIS II	MERIT-HF	COPERNICUS
Number of patients	3837	1884	1,959	2647	3991	2289
Mean age (Years)	55	70	63	61	64	63
Study arms	Propranolol versus Placebo	Timolol versus Placebo	Carvedilol versus Placebo	Bisoprolol versus Placebo	Metoprolol versus Placebo	Carvedilol versus Placebo
Patient group	5-21 days post MI	7-28 days post MI	3-12 days Post MI LVEF < 40% On ACE inhibitors	NYHA class III-IV LVEF ≤ 35%	NYHA class II-IV LVEF ≤ 40%	NYHA class IV LVEF ≤ 25%
Mean follow up	24 months	17 months	15 months	1.3 years	1 year	10.4 months
Mortality Placebo (%)	9.8 Total 4.6 SD	17.5 Total 13.9 SD	15.3 Total 7.0 SD	17.3 Total 6.0 Total	11.0 Total 6.6 SD	16.8 Total
Mortality treatment (%)	7.2 Total 3.3 SD	10.6 Total 7.7 SD	11.9 Total 5.0 SD	11.8 Total 4.0 SD	7.2 Total 3.9 SD	11.2 Total
RRR (%)	26 Total 28 SD	39 Total 45 SD	23 Total 28 SD	32 Total 42 SD	34 Total 41 SD	35 Total
P value	0.005 Total 0.05 SD	0.005 Total 0.0001 SD	0.031 Total 0.098 SD (NS)	0.0001 Total 0.0011 SD	0.00009 Total 0.0002 SD	0.00014 Total

Table 1.0:

Summary of the six of the main beta-blocker trials data and outcomes; BHAT: Beta-blocker Heart Attack Trial, CIBIS II: Cardiac Insufficiency Bisoprolol Study II, MERIT-HF: Metoprolol controlled-release/Extended-Release randomized Intervention Trial in Heart Failure, COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival trial, MI: myocardial infarction, NYHA: New York Heart Association, LVEF: left ventricular ejection fraction, RRR: relative risk reduction, SD: Sudden Death.

Besides the poor efficacy of anti-arrhythmic drugs, their use is further limited by a multitude of serious side effects and contraindications. Nearly all class-1 anti-arrhythmic agents *can* cause polymorphic VT as a side effect, particularly in patients with underlying LV dysfunction or structural heart disease. Amiodarone can cause – or worsen existing – liver and thyroid dysfunction besides causing long QT & *torsades de pointes*, lung fibrosis, corneal deposits and skin photosensitivity. Beta-blockers are contra-indicated in asthma and severe peripheral vascular disease. Class-4 anti-arrhythmics are negatively inotropic and are therefore contra-indicated in patients with LV dysfunction. Recently, non-pharmacological forms of therapy were sought in order to overcome some of the limitations of anti-arrhythmic drugs.

1.2.2 ***Interventional treatment:***

Various radio-frequency (RF) catheter ablation techniques have been developed in the last two decades. They have been shown in some small studies to significantly reduce arrhythmia recurrence rate [61]. Initial techniques adopted a focal approach based on ECG morphology and activation sequence mapping [62]. As the complex nature of VT – particularly in scar-related ischaemic re-entrant forms – became better understood, more refined techniques were later developed such as entrainment mapping (pacing during induced tachycardia) and substrate-based mapping (characterisation of the re-entry substrate during stable sinus rhythm) [63]. Other forms of RF ablation techniques using cooled catheter tips (to prevent overheating of the catheter-tissue

interface) and epicardial mapping & ablation devices were further developed aiming to ablate deeply-sited foci that are normally difficult to reach by conventional endocardial ablation techniques [64]. The epicardial technique requires the insertion of a sheath into the pericardial space using a needle and guidewire under fluoroscopic control [65].

Further advances in catheter ablation techniques are still underway which will result in further improvements in procedural success rates. Despite such advances, technical challenges, complications – 3% mortality was observed in a study of 69 patients who underwent cooled RF ablation [66] – and arrhythmia recurrence remain a major problem. At present, procedures are offered at experienced centres only, with an estimated success rate of 80% when substrate-based mapping method is used [67]. Recurrence rates have been quoted in some studies to be as high 40-50% after 3 years follow-up [68].

1.2.3 ***Surgical treatment:***

Many surgically based techniques for VT treatment were developed in recent years. This was in response to the increasing complexity of endocardial mapping systems, which are generally time consuming and require specialised equipment and expertise. Furthermore, the current outcome data on RF ablation success and recurrence rates although promising are far from being satisfactory. All surgical ablation techniques involve destruction of tissue at the border-zone between scar and viable muscle. Some techniques such as encircling ventriculotomy have largely been abandoned because of their harmful effects on LV function. Other techniques such as endocardial excision of visible scar

tissue and cryoablation were frequently used in the late 1980s, [69 70 71 72] but the latter has been found to cause extensive damage if applied under cold cardioplegic conditions. Other surgical ablation techniques include direct shock ablation [71], laser photoablation, or radio-frequency ablation [73]. Left ventricular reconstruction is performed following the ablation / resection procedures as a complementary part to aid restore LV size and geometry towards normality [71]. Surgical ablation results achieved with respect to operative mortality, control of VT, and long-term survival were variable depending on many factors including patient selection, use of mapping data, and type and extent of ablation technique employed. Reported series generally included high-risk patients with poor LV function (mean EF of 25-30%) [68 69 71] and severe underlying coronary disease. Success rates have been quoted in some studies to be as high as 90%, with 10-20% recurrence rates for the first year, with an overall 5-years survival of only 70% [68 69 71]. Post-operative mortality remains high at 5-10% [69 71]. Besides these statistical limitations, surgical ablation for VT has poor results in patients without anterior LV infarcts and aneurysms [74].

1.3 Implantable Cardioverter Defibrillators (ICDs)

1.3.1 ***Background:***

ICDs now constitute the cornerstone in the management of ventricular arrhythmias. All patients who survive sudden cardiac arrest – not occurring within the context of acute MI and without an identifiable reversible precipitant – and those who are at a significantly increased

risk of ventricular arrhythmias due to underlying structural, genetic or electrical cardiac disorders should be considered for ICD implantation, in addition to standard pharmacological therapy +/- interventional or surgical ablation whenever appropriate [75]. In the early 1980s, ICD devices implantation involved major surgery, general anaesthesia and long hospital stays with peri-operative mortality approaching 10% [76]. Devices were implanted abdominally and connected to the heart via epicardial leads; delivered therapy was in the form of high-energy shocks only. Programming facilities were not available and the average device half-life was only 1.5 years [77]. At present, devices are much smaller in size and are easily implantable using a simple procedure with local anaesthesia and transvenous positioning of endocardial leads. Peri-operative mortality has dropped down to < 1% [78]. Device longevity has improved (average of 7 years), and individually tailored fine-tuning of an extensive range of programmable features has become widely available.

1.3.2 ***Evidence base:***

Implantation of ICDs has been shown in – six out of eight – primary prevention randomised controlled ICD trials to be consistently superior to pharmacological therapy alone in reducing mortality by preventing ventricular arrhythmias and SCD (Table: 1.1).

Two trials: the Coronary Artery Bypass Graft (CABG) Patch Trial [79] – 1998 – and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) [80] – 2004 – have found that the prophylactic implantation of an ICD did not reduce the risk of death in patients undergoing CABG

and in those who had sustained acute MI within 40 days respectively; it is therefore now accepted that, in these two cohorts of patients, ICD implantation is both more expensive and less effective than control therapy.

The other six primary prevention trials – the Multi-centre Automatic Defibrillator Implantation Trial (MADIT I – 1996) [81], MADIT II – 2001 [82], the Multi-centre Unsustained Tachycardia Trial (MUSTT – 1997) [83], the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE – 2003) [84], the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial (COMPANION – 2004) [85], and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT – 2005) [86] – have all demonstrated unequivocal superiority of ICDs over optimal pharmacological therapy in reducing overall cardiovascular mortality and arrhythmic death in cohorts of heart failure patients whose EF ≤ 35% with or without underlying coronary disease.

Table 1.1

Study	*Patient population*	*Entry Criteria*	*Treatment Arms*	*Results*	*Conclusions*
CABG PATCH ***N=900*** ***NEJM*** ***337:1569, 1997***	CAD (83% post MI)	EF <35% + abnormal signal averaged ECG. Follow up from post op CABG	ICD versus conventional therapy	No difference in all cause mortality	EF <35% with abnormal signal averaged ECG undergoing CABG do not benefit from prophylactic ICD
MADIT-I ***N=196*** ***NEJM*** ***335:1933, 1996***	> 3 weeks post MI	EF <35% + NSVT or Inducible non suppressible VT	ICD versus conventional medical therapy	Mortality: 15.7% ICD versus 38.6% medical therapy	Terminated prematurely because of large ICD benefit. RRR 46%
MUSTT ***N=704*** ***NEJM*** ***341:1882, 1999***	95% post MI	EF <40% + NSVT & inducible VT/VF	EP guided therapy (46% ICD) versus conventional treatment	5 year mortality: 42% EP guided ICD versus 48% conventional therapy	Only in EP guided therapy (chosen to be an ICD), mortality reduction occurs
MADIT-II ***N=1232*** ***NEJM*** ***346: 877, 2002***	>1 month post MI, > 3 months CABG	EF < 30%	ICD versus conventional therapy	Mortality: 19.8% conventional therapy versus 14.2% ICD	Prophylactic ICD decreases mortality by 31% post-Mi in pts with poor LV function
COMPANION ***N=1604*** ***ACC 2003*** ***www.uchsc.edu/cvi***	CHF 45% DCM 55% CAD	CHF Hosp in yr before entry EF < 35% QRSD > 130 ms PR > 150 ms	Conv therapy Vs ICD + CRT	35%↓ in Hospitalisation for HF in both. 40% ↓mortality CRT +ICD, 20%↓ mortality ICD only	Terminated prematurely for primary endpoint total mortality + all cause Hospitalisation
SCD-HeFT ***N=2521*** ***NEJM*** ***352: 225, 2005***	NYHA Class >2 EF <35% 50% DCM	Up to 2 yr post onset CHF, 50% DCM	Amiodarone/ Placebo versus ICD	Mortality: 29% Placebo, 28% Amiodarone, 22% ICD	ICD reduced overall mortality by 23%, whereas Amiodarone had no effect.
DINAMIT ***N=674*** ***NEJM*** ***351: 2481, 2004***	Within 30 days post MI	EF <35%, depressed HRV or mean 24 h heart rate >80/min	ICD versus medical therapy	Arrhythmic death: ICD 12, Control 29, p =0.009. Non arrhythmic death: ICD 62, Control 58, p =0.66	ICD reduced arrhythmic death but was associated with higher non-arrhythmic deaths. No effect on overall mortality.
DEFINITE ***N=458*** ***NEJM*** ***350: 2151, 2004***	DCM patients with no CAD	EF <36%, Premature VE's or NSVT	Standard medical therapy alone versus standard medical therapy + ICD	2 yr arrhythmic death: Control 14, ICD 3, p =0.006	ICDs significantly reduced arrhythmic death in study patients

Table 1.1:

Summary of the eight main primary prevention ICD trials; CAD: Coronary artery disease, MI: myocardial infarction, EF: ejection fraction, CABG: coronary artery bypass grafting, RRR: relative risk reduction, NSVT: non-sustained VT, DCM: dilated cardiomyopathy, QRDS: QRD duration, CRT: cardiac resynchronisation therapy, HRV: heart rate variability.

The more recent observational study (ALTITUDE study – May 2009) [87], which followed 85,000 patients with primary-prevention ICDs for up to five years, has suggested that survival at three years was 96%. The study also found that shocks from ICD devices are common, confirmed that many of them are inappropriate (shocks delivered in the absence of a life-threatening ventricular arrhythmia), and suggested that any kind of shock can point to patients with an increased risk of dying. It also suggested that supraventricular arrhythmias, including atrial fibrillation, might be the trigger for >80% of such inappropriate shocks.

Furthermore, several secondary prevention trials (Table 1.2), including the Antiarrhythmics Versus Implantable Defibrillators Study (AVID), the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH), have demonstrated the superiority of ICD therapy compared to empirical amiodarone in improving overall survival [88] in cohorts of patients who survived episodes of ventricular arrhythmias that neither occurred within the context of acute MI, nor had clear identified reversible causes.

Table 1.2:

Clinical trial	AVID	CASH	CIDS
Dates of conducting study	1993-97	1986-97	1990-97
Medical treatment	Amiodarone / sotalol	Amiodarone	Amiodarone
Eligibility	CA, VF, VT	CA, VF	CA, VF, VT, syncope
Mean follow up (years)	1.51	4.48	2.96
Number of patients (Amiodarone)	509	92	331
Number of patients (ICD)	507	99	328
All Amiodarone deaths (rate)	122 (16.5%)	35 (9.4%)	98 (10.2%)
All ICD deaths (rate)	80 (10.0%)	37 (7.7%)	83 (8.3%)
Amiodarone arrhythmic deaths (rate)	55 (7.4%)	19 (5.1%)	43 (4.5%)
ICD arrhythmic deaths (rate)	24 (3.0%)	7 (1.5%)	30 (3.0%)

Table 1.2:

Summary of the three main ICD secondary prevention trials; CA: cardiac arrest, VF: ventricular fibrillation, VT: symptomatic sustained ventricular tachycardia.

1.3.3 ***Cost-effectiveness of prophylactic ICD implantation:***

In recent years, the number of patients eligible for prophylactic ICD implantation has significantly increased. Meeting this increased demand on devices presents a huge financial challenge for health authorities. Researchers from the Duke Clinical Research Institute (DCRI) – Stanford University and the VA Palo Alto Health Care System, California, USA – have analysed the above eight secondary prevention trials to determine cost-effectiveness of prophylactic ICD therapy. For their analysis, the team used a model that accounts for a wide range of variables, including patient characteristics, ICD box changes, clinical outcomes, actual and potential medical costs, and quality of life variables. They concluded that, although ICDs are expensive, in appropriate patients they provide value for money. The use of an ICD has been calculated to add between 1.01 and 2.99 quality-adjusted life-years (QALY) and between $ 68,300 - $101,500 in cost. Using base-case assumptions, they found that the cost-effectiveness of the ICD as compared with control therapy in the six trial populations that benefited from device implantation was between $34,000 and $70,200 per QALY gained. Further analyses showed that this cost-effectiveness ratio would continue to remain below $100,000 per QALY providing that the ICD reduces mortality for ≥7 years [89].

1.3.4 ***Limitations of ICD therapy:***

Although they are better than conventional medical therapy in reducing both arrhythmic and non-arrhythmic cardiovascular mortality, ICDs still

have major limitations. Complications (risk <1%) [90] may occur at times of device implantation and subsequent box changes; these include system infection, pneumothorax, subcutaneous haematoma, haemothorax, early lead displacement or late lead fracture / insulation damage, in addition to peri-operative complications such as death and stroke. Other problems related to device programming can occur, the commonest of which is inappropriate shock delivery affecting approximately 12 - 25% of patients [91]; this is mainly triggered when ICDs sense atrial arrhythmias – commonly AF or sinus tachycardia – and interpret them as VT and consequently deliver DC-cardioversion while patients are fully awake and haemodynamically stable. Other causes of inappropriate shocks include over-sensing of T waves, noise from electronic devices, and lead damage [92 93 94 95 96 97]. If it becomes recurrent, inappropriate shocking can lead to patients adopting major lifestyle restrictions and, in some cases, can result in severe psychological disturbances [98]. The problem persists even with fourth generation ICDs [99]. The addition of anti-arrhythmic drugs to decrease the incidence of inappropriate shocks has only helped slightly, but the bulk of the problem remains yet to be solved.

1.4 ICD arrhythmia detection mechanisms

1.4.1 ***Sensing and detection:***

Sensing is the first step in recognising tachyarrhythmia. It involves measurement of the intracardiac electrogram signal from two implanted lead electrodes or a bipolar sensing lead [100]. A bipolar sensing lead is

an electrode catheter that has two different sensing electrical poles located in close proximity to each other, close to the catheter tip (Figure 1.2D). The two poles sense any intrinsic cardiac depolarisation activity – occurring within the chamber where the bipolar electrode catheter is positioned – and the sensed signal is then transmitted to the device for processing. Sensing systems primarily define the time between successive R waves produced by ventricular depolarisation, or the time between successive P waves produced by atrial depolarisation. In other words, it is what the device "sees" using its atrial or ventricular lead sensing poles. Over-sensing results in P and T waves being sensed as R waves, thereby causing devices to misinterpret sinus rhythm as an arrhythmia. External interferences from skeletal muscle myo-potentials or electromagnetic interference can also be over-sensed and subsequently wrongly interpreted by devices as cardiac depolarisation signals. On the other hand, under-sensing can lead to under-detection of low-amplitude fragmented R waves that occur during ventricular fibrillation, and can also cause inappropriate pacing in the presence of intrinsic myocardial activity, which may generate arrhythmias (e.g. VF from R on T, AF, ...etc). Modern devices have features such as automatic gain control or auto-adjusting threshold, which have considerably reduced the occurrence of sensing problems.

Figure 1.2D:

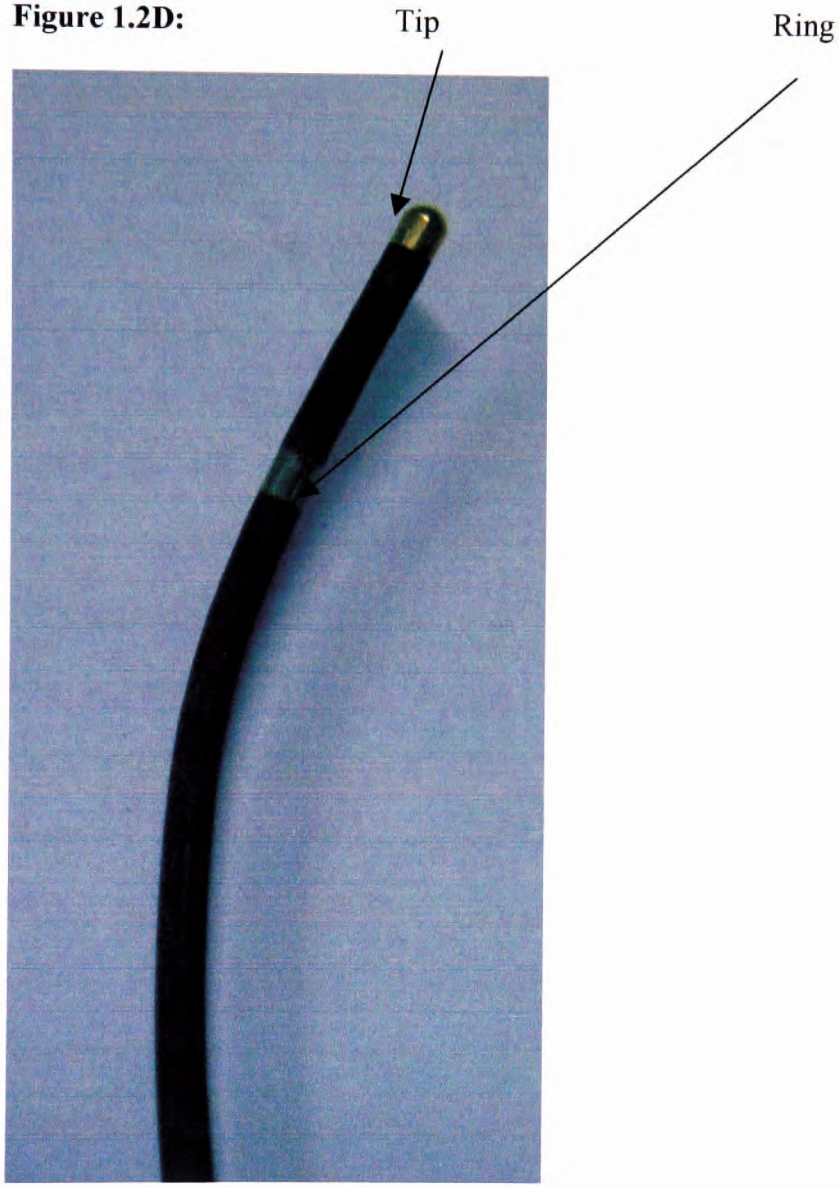


Figure 1.2D:

A bipolar sensing lead. The distal pole is called the tip and the proximal one is called the ring. Through these two poles, an ICD senses intrinsic cardiac activity of the chamber in which the sensing lead is positioned, most commonly, the right ventricle.

Detection involves analysis of R-wave cycle length [99]. Ideally, detection algorithms should discriminate between sinus rhythm, VT (stable or unstable) and VF in order for appropriate therapy to be prescribed and delivered. A series of ICD detection and correction measures are used to diagnose and treat ventricular arrhythmias occurring in various circumstances.

1.4.2 ***ICD rhythm recognition algorithms:***

Single chamber ICD devices can detect and treat ventricular tachy-arrhythmias besides permitting ventricular pacing and monitoring of ventricular rhythm. In these systems, ventricular rhythm detection is primarily based on identifying an increase in the ventricular rate by the RV electrode through sensing a series of short R-R intervals [101] [102]. As this technique does not use any form of atrial sensing, it can't discriminate between sinus, atrial or ventricular arrhythmias and therefore does not protect against inappropriate shock delivery. Other rhythm detection algorithms - mainly based on detailed analysis of the sensed ventricular electrogram - were later introduced. Features such as arrhythmia rate of onset and regularity, QRS morphology, and patterns of electrogram interval changes have now been incorporated into ICDs rhythm recognition algorithms with some success. QRS morphology is analysed using template-matching technique, which involves comparison of electrogram configuration during arrhythmias with a standard template derived during sinus rhythm. This is achieved using various analysis methods such as correlation waveform analysis

[103], the bin area method [104], area of difference analysis [105], and gradient pattern detection [106].

1.4.3 ***Programming an ICD:***

Modern ICDs have three programmable zones for the detection and management of ventricular arrhythmias. The sensed heart rate is the principal variables that determines which treatment zone the detected arrhythmia falls into, while the other rhythm recognition algorithms mentioned above aid in discriminating ventricular from supra-ventricular arrhythmias. Often the three zones are programmed to detect and treat "slow" VT, "fast" monomorphic VT, and VF [107]. The slowest zone is intended for haemodynamically stable or non-syncopal rhythms; these often respond to tiered therapy (anti-tachycardia pacing - ATP), which is effctive in up to 80% of cases [108]. The second zone is intended for faster VT, which often causes haemodynamic instability resulting in symptoms such as pre-syncope; for this, early cardioversion with a rapid charge time and a lower energy shock – 5-joule biphasic shock – is successful in about 80% of cases [106]. VF causes syncope in all patients due to loss of cardiac output and requires a higher-energy DC shock to restore sinus rhythm, which is the function of the third programmed zone. When prophylaxis from VF alone is all that is needed, as in patients with long QT syndrome or CPVT, a single zone programming of the device is performed (zone-3) and the two other zones are deactivated. In general, a minimum of two-zone programming is usually needed for discrimination of monomorphic VT from VF; but often devices are programmed to have all three zones activated [106].

1.4.4 ***Inappropriate defibrillation prevention algorithms:***

Currently available dual chamber ICDs can provide atrial pacing, rate-responsive pacing, and atrial ATP & defibrillation. New algorithms provide better but limited discrimination of supraventricular and ventricular tachy-arrhythmias. In DDD-ICDs, tachycardia discrimination uses rate-based detection algorithms overlaid with pattern analysis of atrial and ventricular electrogram relationships, thereby reducing the risk of inappropriate delivery of DC shocks. However, the consequences of inappropriate shocks remain far less significant than those of under-detection of ventricular arrhythmias. Algorithms designed to allow ICDs to continue to identify malignant ventricular tachyarrhythmias but at the same time protect patients from inappropriate therapy have been increasingly adopted in recent years, albeit with limited success. Currently used algorithms include:

- *Electrogram width criterion* (the wider the QRS the more likely the arrhythmia is of ventricular origin).
- *Probability density function* detects the percentage of the intracardiac electrogram isoelectric signal; VT has a weaker isoelectric signal compared to sinus rhythm and supra-ventricular arrhythmias.
- *The onset criterion* only discriminates between sinus tachycardia, which has a gradual onset, and all other forms of arrhythmia, which generally tend to have an abrupt onset.
- *Rate stability criteria* discriminate an irregular rapid ventricular rate, such as atrial fibrillation, from more stable rapid VT.

- The *sustained-rate duration* algorithm allows delivery of therapy if an arrhythmia has exceeded a programmed elapsed time, regardless of sudden onset or the stability criteria. In addition, when an arrhythmia occurs at an "extended high rate" interval, the device can be programmed to provide shock therapy regardless of other rhythm recognition criteria.

Devices can also be programmed with the function of "non-committed therapy" which merely allows devices to detect treatable arrhythmias and to start charging for shock therapy. Further rhythm analysis is performed upon completion of charging to confirm the persistence of the initial arrhythmia before shocking is finally delivered. Therapy is aborted if re-detection reveals that the tachycardia no longer meets the initial detection criteria, thereby avoiding shocking of non-sustained VT.

Difficulties still remain when AV relationships are fixed and the rates are identical. Clinical studies using dual chamber ICDs showed specificity values as high as 80-90% combined with 100% sensitivity [109] [110] [111]. Nevertheless, inappropriate detection and therapy may still happen. In spite of some differences due to the algorithms themselves, typical and atypical junctional tachycardia, orthodromic atrio-ventricular tachycardia and 1:1 atrial flutter represent the most challenging patterns [112]. A randomised study compared the incidence of inappropriate shock therapies in patients treated with VVI-ICDs versus DDD-ICDs and not only concluded that the two systems were equally safe and effective to treat life-threatening ventricular arrhythmias, but also declared that although DDD-ICDs theoretically allow better rhythm classification, the

applied detection algorithms did not offer any additional benefits in avoiding inappropriate therapies during supraventricular tachyarrhythmias [113]. In this series, 75% of inappropriate therapies in the DDD-ICD group were due to atrial sensing problems, either over-sensing or under-sensing. A possible explanation for such frequent problems may be the special filter settings in the atrial sensing channels of DDD-ICD, which differs substantially from those of DDD pacemakers. In fact, most detection algorithms in DDD-ICDs require continuous and accurate atrial sensing with only short PVAB / PVARP or even no blanking times. This may be difficult when taking into account low voltage atrial electrogram during atrial fibrillation and large ventricular far fields during ventricular pacing. Multi-sensor ICDs are currently being developed to try and enhance devices capacity to differentiate between supra-ventricular and ventricular arrhythmias.

1.5 The need for a haemodynamic sensor

Despite the huge established – and further expected – advances in ICDs arrhythmia detection and recognition algorithms, devices are still devoid of a direct and reliable sensor capable of assessing patients' haemodynamic stability during various types of arrhythmias. The benefit of having such a haemodynamic sensor is that future generation ICDs can then use tiered therapy (ATP) to treat haemodynamically stable arrhythmias, whereas DC cardioversion and high-energy shocks are reserved only for arrhythmias that result in haemodynamic instability. If developed and applied successfully, such ICDs with haemodynamic

sensors will understandably avoid the major problem of delivering inappropriate shock therapy.

What type of sensor?

The ideal haemodynamic sensor should reliably and closely correlate with a haemodynamic variable (BP or cardiac output); it should also be highly sensitive for malignant ventricular arrhythmias (pulseless VT and VF) but still capable of reliably discriminating haemodynamically stable from unstable rhythms. The sensitivity and specificity of such a haemodynamic sensor should remain unaltered during various physiological and metabolic conditions, and should also prove to have long-term stability.

A few haemodynamic variables have been identified as potential substrates for use as ICD haemodynamic sensors, and their correlation with changes in blood pressure during arrhythmias has been extensively investigated over the past two decades.

1.5.1 ***Maximal systolic right ventricular contractility (dP/dt):***

The variable dP/dt is commonly used as an index of cardiac contractility and can be estimated echocardiographically by using a time interval between 1 and 2 meters per second on the TR velocity CW spectrum (on echocardiography) during isovolumetric contraction [114]. It represents the change in right ventricular pressure as a function of time and is determined from the slope of the waveform during systole. Maximum dP/dt (dP/dt*max*) is used as an index of the initial velocity of myocardial contraction. The maximal positive and negative systolic right ventricular dP/dt (RV + dP/dt*max*, RV - dP/dt*max*) have been investigated by

Kapadia *et al* [115] as to the feasibility of their inclusion as haemodynamic sensors into the detection algorithms of future implantable defibrillators. They studied frequency band limited positive and negative RV dP/dt*max* prior to, during, and after 13 episodes of VT lasting at least 40 beats in duration in a total of 9 male patients. RV + dP/dt*max* correlated poorly with mean arterial pressure, systolic BP and VT cycle length. On the other hand, RV - dP/dt*max* had an expected opposite waveform pattern to that of RV + dP/dt*max* but nevertheless exhibited similar poor correlation with BP and arrhythmia cycle lengths.

1.5.2 ***Mixed venous oxygen saturation (MVO_2):***

MVO_2 measures the saturation of oxygen remaining in the blood after passing through the systemic capillary bed. Using reflective oximetry technique and a flow-directed thermo-dilution fibre-optic pulmonary artery catheter, Cohen *et al* [116] investigated the use of mixed venous blood oxygen saturation as a haemodynamic sensor for differentiating stable from unstable, paced and induced tachycardias. They demonstrated that mixed venous oxygen saturation decreased as cycle length shortened with rapid RV pacing. Furthermore, for any given cycle length, rapid ventricular pacing has been shown to result in greater mixed venous oxygen de-saturation compared with atrial pacing. Similarly, mixed venous oxygen saturation decreased during induced haemodynamically stable ventricular tachycardias (cycle lengths > 230 ms) but remained unaltered during haemodynamically unstable VT (cycle lengths ≤ 230) ms and with ventricular fibrillation. This is because the increased use of peripheral oxygen during unstable

tachyarrhythmias results in greater desaturation, whereas pulseless VT and VF resulted in complete circulatory arrest and no admixture in the central veins. On the basis of these findings, they then developed a mixed venous oxygen saturation-tiered therapy algorithm and tested it retrospectively in 113 paced and induced tachyarrhythmias in 10 patients. The mixed venous oxygen algorithm had 93% sensitivity and 96% specificity compared with rate-only detection of 93% sensitivity and 71% specificity.

However, following the onset of an arrhythmia, changes in MVO_2 were rather slow to take place (up to 30 seconds to become apparent) and were similarly slow to return back to normal following restoration of sinus rhythm. This is a shortcoming that may lead to inappropriate shock delivery and can possibly limit the potential of using MVO_2 as a haemodynamic sensor for VT stability recognition.

1.5.3 ***Right ventricular and right atrial pressures:***

Right ventricular (RV) pulse pressure has been shown to possess acceptable characteristics as a sensor for incorporation in ICDs. The sensing subsystem of the first experimental models of the automatic implantable defibrillator was based on monitoring the pulsatile RV pressure (Mirowski et al [117]), a sudden drop in which triggered the capacitor charging cycle as it indicated the onset of a life-threatening arrhythmia. However, for reasons of convenience, such sensing systems have been replaced by algorithms based on electrical variables. In 1990, Ellenbogen *et al* [118] and Sharma *et al* [119] have shown that changes in RV pulse pressure correlate with and predict well the

drop in mean and systolic pressure during VT. The decrease in RV pulse pressure during episodes of VT at two different times during a single electrophysiology study has been found to be highly reproducible, suggesting that RV pulse pressure may be a reliable sensor over time. However, Wood et al [120] have measured the values of RV pulse pressure (RVPP) and maximal systolic right ventricular dP/dt before, during and after 91 episodes of HSVT, HUVT, SVT and sinus tachycardia (ST) induced in 49 male patients. They concluded that the mean percent changes in RVPP (% delta RVPP) from baseline was significantly different between groups of patients during all arrhythmias indicating good sensitivity but with a large degree of overlap suggesting limited overall specificity and therefore poor reliability in separating different arrhythmias. Cohen and Liem [121] investigated the responses of right atrial (mean) and right ventricular pressures (mean, systolic, diastolic, and pulse) to 64 induced and paced supraventricular and ventricular tachyarrhythmias studied in 10 patients with the aim of developing an algorithm capable of differentiating stable from unstable rhythms. A combined detection algorithm has been developed that identified a haemodynamically unstable rhythm at a cycle length of 400 ms or less, a mean right atrial pressure increase of 4 mm Hg or more and right ventricular systolic pressure drop of 5 mm Hg or more during 15 seconds. The rate-only detection algorithm had 100% sensitivity but only 68% specificity for detection of unstable tachyarrhythmias, whereas the combined rate-mean right atrial pressure-right ventricular systolic pressure detection algorithm was claimed to have sensitivity and

specificity of 100%. However, the rate of change in right atrial pressure at the onset and termination of tachyarrhythmias was too slow – taking an average of 15 to 30 seconds to initially rise and then to return to baseline after tachycardia termination – to be practically incorporated into ICDs' arrhythmia detection algorithms

1.5.4 ***Coronary sinus blood temperature:***

In an experiment on anaesthetised dog, Hiles et al [122] demonstrated the occurrence of small, cyclic, thermal variations in the coronary venous system as the baseline component of venous blood temperature rose during periods of ventricular tachycardia and fibrillation. Although this study has substantiated the concept of measuring metabolic activity to assess ventricular function and arrhythmia recognition, further studies in this field are needed to quantify the safety, specificity, reliability and applicability of such metabolic variables in humans before incorporating them into ICDs' arrhythmia detection algorithms.

1.6 Intracardiac Impedance

1.6.1 ***Definition of impedance:***

Impedance (Z) is generally defined as the total opposition a device or circuit offers to the flow of an alternating current (AC) at a given frequency, and is represented as a complex quantity, which can be graphically illustrated on a vector plane (Figure: 1.3) [123] [124] [125]. It is like resistance, but it also takes into account the effects of capacitance and inductance, which in turn vary with the frequency of the current passing through the circuit. Impedance is measured in ohms, (symbol Ω) and is

of the energy source and be received at its positive terminal in the circuit. It is normally measured in volts.

Direct current (DC): Is an electric current of fixed magnitude and polarity in a circuit where – as a result of a fixed voltage – electrons move in one direction only. Various types of devices such as electrochemical and photovoltaic cells and batteries produce DC (Figures 1.4 & 1.5).

Alternating current (AC): Is an electric current that continuously and periodically changes its magnitude and polarity as a result of a continuously changing voltage in a circuit where, as a consequence, electrons change their direction of movement at regular intervals. It is the type of electric current used in buildings, including homes (Figures 1.4 & 1.5).

Figure: 1.4

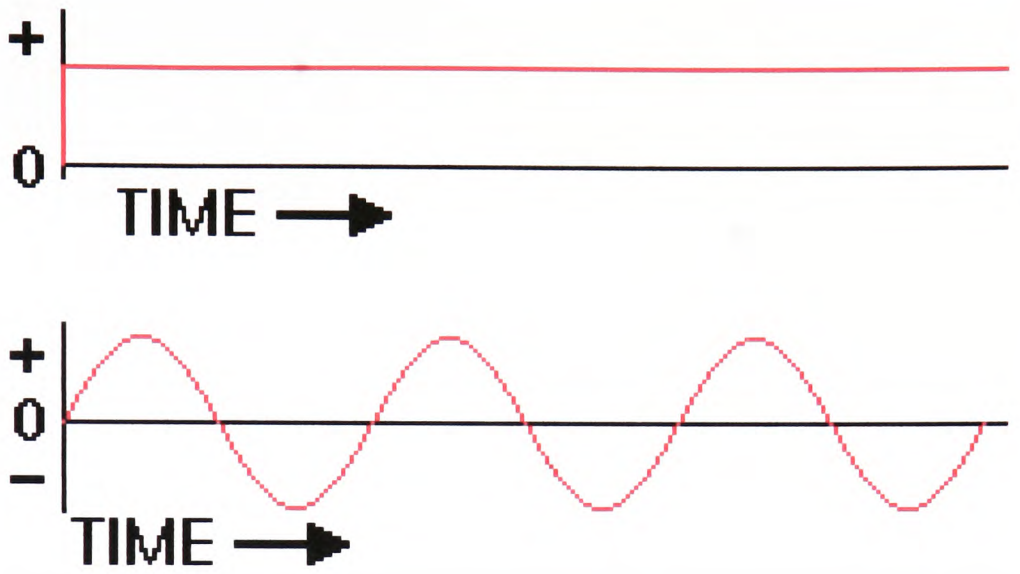


Figure 1.4:

Top: In circuits with direct current (DC), the voltage remains constant throughout (red horizontal line)

Bottom: In circuits with alternating current (AC), the voltage changes regularly and periodically (wavy red line) resulting in a continuously changing current in both magnitude and polarity.

Figure: 1.5

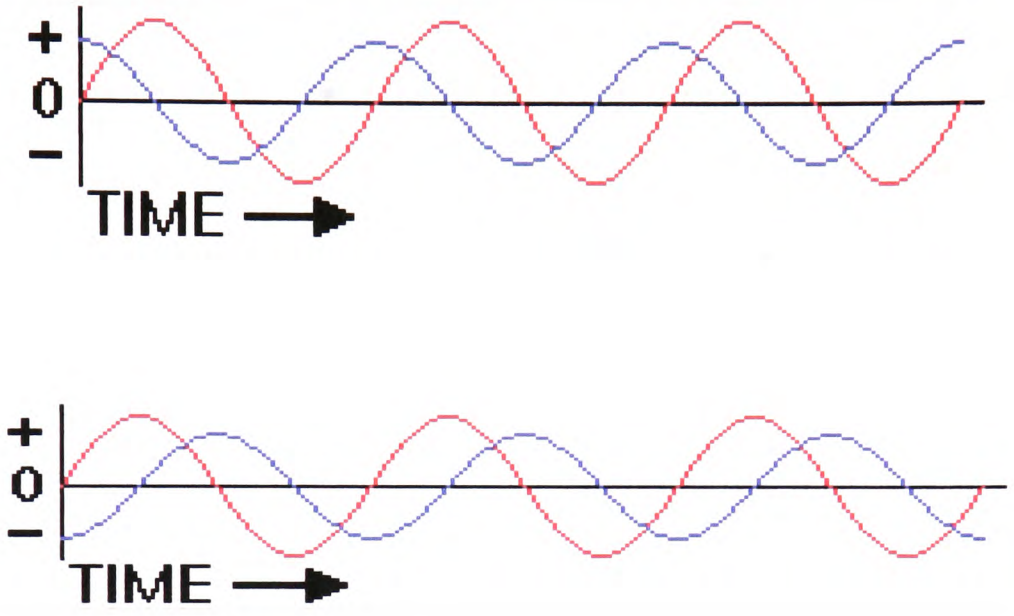


Figure 1.5:

Top: The effect of capacitive reactance results in a phase shift that causes AC (blue line) to lead the applied voltage (red) by 90° (¼ cycle).

Bottom: The effect of inductive reactance results in a phase shift that causes AC (blue line) to lag the applied voltage (red) by 90° (¼ cycle).

Resistance (R): Is the opposition offered by a conductor to the flow of direct current (DC) in an electric circuit.

Inductance (L): Is the property of a circuit or circuit element that opposes a change in alternating current flow, thus causing current changes to lag behind voltage changes.

Capacitance (C): Is a measure of a capacitor's ability to store charge. A large capacitance means that more charge can be stored. Capacitance is measured in farads.

Frequency (f): Of an alternating current (AC) is the number of cycles or completed alternations per second. It is normally measured in Hertz (Hz). For example, in Europe, including the UK, the AC power system operates at a frequency of 50 Hz whereas in North America it operates at a frequency of 60 Hz.

Reactance (X): is a measure of the opposition of capacitance and inductance to current. Reactance varies with the frequency of the electrical signal. Reactance is measured in ohms (symbol Ω).

Conductance: Is the mathematical reciprocal of resistance ($\mathbf{R}$).

Admittance: Is the mathematical reciprocal of impedance ($\mathbf{Z}$).

1.6.3 ***Measurement of impedance:***

Impedance ($\mathbf{Z}$) of a conductor varies directly with its length ($\mathbf{Len}$) and inversely with its cross-sectional area ($\mathbf{A}$). It also depends on the component material of the conductor (resistivity, symbol: σ).

In DC circuits, Ohm's law applies where: $\mathbf{R = V / I}$ (where "**I**" is the electric current).

For a pure AC resistor, $\mathbf{Z = R}$, thus preserving Ohm's law:

$$\mathbf{Z = V / I} \quad \text{---------- (1)}$$

The volume (**Vol**) of a cylindrical AC conductor can therefore be derived as follows:

$$\mathbf{Vol = A \times Len} \quad \text{---------- (2)}$$

$$\mathbf{Z = \sigma\ Len / A} \quad \text{---------- (3)}$$

$$\mathbf{Z = \sigma\ Len^2 / Vol} \quad \text{---------- (4)}$$

$$\mathbf{Vol = \sigma\ Len^2 / Z} \quad \text{---------- (5)}$$

However, more commonly in AC systems, the capacitance (X) and inductance (L) cause a phase shift between the current and voltage (Figure: 1.4.1) which means that the resistance (R) and reactance (X) cannot be simply added up to give impedance. Instead they must be added as vectors with reactance at a right angle to resistance as shown in Figure: 1.3. Therefore, impedance value is derived from the following equation:

$$\mathbf{Z = \sqrt{X^2 + R^2}} \quad \text{---------- (6)}$$

Where **X** is the total reactance, which is the difference between inductive ($\mathbf{X_L}$) and capacitive (**XC**) forms of reactance in AC systems. **XC** and $\mathbf{X_L}$ vary inversely and directly with frequency, respectively. DC systems have zero frequency and therefore infinite **XC** and zero $\mathbf{X_L}$.

Capacitive reactance, (XC) is derived from the equation:

$$XC = 1 / 2\pi fC \quad \text{---------- (7)}$$

Where: XC = reactance in ohms (Ω)
f = frequency in hertz (Hz)
C = capacitance in farads (F)

Inductive reactance, (X_L), is derived from the equation:

$$X_L = 2\pi fL \quad \text{---------- (8)}$$

Where: X_L = reactance in ohms (Ω)
f = frequency in hertz (Hz)
L = inductance in henrys (H)

From equations (6), (7) and (8):

$$Z = \sqrt{(X_L - XC)^2 + R^2} \quad \text{---------- (9)}, \text{ and therefore:}$$

$$Z = \sqrt{(2\pi fL - 1 / 2\pi fC)^2 + R^2} \quad \text{---------- (10)}$$

1.6.4 ***Measurement of intracardiac impedance:***

During physiological measurements, the additional resistance caused by blood resistivity has been found to be negligibly small at the frequencies used to measure physiological activities ($<10^6$ Hz). Therefore blood impedance can be considered practically equal to its ohmic electrical component: $Z = R$ [124] [125].

By introducing an alternating current through the ventricular cavity via two electrode catheters or via a single multi-electrode catheter, the potential difference measured between the electrodes of the two catheters, or between the adjacent poles of the multi-electrode catheter, can be used to assess the intra-ventricular blood volume by measuring intracardiac impedance. Variations in the calculated impedance signal

reflect changes in the ventricular blood pool volume adjacent to the electrodes. The data obtained can be used to construct pressure-volume loops allowing the continuous real-time assessment of myocardial contractility [144]. Using such impedance measurement to calculate the ventricular blood volume assumes a homogeneous blood resistivity (σ), a negligible total blood reactance ($\mathbf{X}$), a uniform cylindrical ventricular volume, and no loss of current by dissipation outside the ventricular cavity into the adjacent tissues [124] [144]. Accounting for those assumptions is vital if accurate calculation of the ventricular volume is to be performed. In 1937, Sigman *et al* studied the effect of motion on the electrical conductivity of the blood and found blood resistivity (σ) to be homogeneous throughout [144]. Total blood reactance ($\mathbf{X}$) has been found to be negligibly small for frequencies < 10^6, as described by Salo *et al* [123] in 1986.

The left ventricular cavity is far from being a uniform cylinder, thereby rendering inaccurate any impedance-based volume measurement that does not account for such a significant discrepancy. Baan *et al* (1981) largely rectified this problem by inventing the stacked-cylinder model. This involves artificially subdividing the left ventricular cavity into multiple cross-sectional cylinder-shaped segments. This is achieved by injecting an alternating current (AC) of a fixed magnitude and frequency between the outer poles of a multi-electrode conductance catheter placed inside and along the longitudinal axis of the left ventricle. The inner electrodes measured voltages generated by the current and the impedance of the blood within the cavity. The boundaries of those segments were defined

by the inner surface of the cardiac wall and by the equi-potential surfaces through the electrodes, thus forming ventricular cylindrical cross-sections perpendicular to the current density lines running between the electrodes [129]. The volume of each segment can then be calculated using equation **(6)**. Summation of those volumes provides a near accurate estimation of the total left ventricular volume.

As the ventricular volume is a time-linked dynamic variable, measurement of the volume at any given time only provides information about its instantaneous value at that particular point of the cardiac cycle. Stroke volume is the value that determines cardiac output and therefore correlates well with haemodynamic stability or otherwise. The volume of each LV volume segment that contributes to the stroke volume can be calculated by the following equation, which merely calculates the volume difference between end diastole and end systole for each segment:

$$\Delta Vol = Len_b^2 / \sigma\, Z\, ed - Len_b^2 / \sigma\, Z\, es \quad \text{---------- (11)}$$

Where ***Z ed*** and ***Z es*** are the impedance measurements in end diastole and end systole respectively. Len_b is the distance between each of the electrodes in the conductance catheter.

Using equation **(11)**, the stroke volume (***SV***) is calculated as the summation of ***ΔVol*** values:

$$SV = \Sigma\, \Delta Vol = \Sigma\, \{Len_b^2\, (Z\, es - Z\, ed) / \sigma\, (Z\, es\ \ Z\, ed)\} \text{--------(12)}$$

The difference between end-systolic and end-diastolic impedance values is the impedance value that correlates with the stroke volume and is referred to as the stroke impedance (***SZ***). Therefore, equation **(12)** can be reformed as:

$$SV = \Sigma\, \{Len_b^2\, SZ / \sigma\, (Z\, es\ \ Z\, ed)\} \text{----------(13)}$$

1.6.5 ***Current clinical uses of intracardiac impedance:***

Background

Rushmer *et al* [126] were the first to describe the relationship between intracardiac impedance and stroke volume over half a century ago. Experimenting in canines, they attached endo-myocardial clip electrodes transmurally to the walls of the right and left ventricles. They demonstrated an increase in the measured impedance – across the intra-ventricular blood – during systole when the electrodes approached each other. As the electrodes were in direct contact with the endocardium, it was assumed that some of the current actually traversed the myocardium via alternative electrical pathways rather than the intra-ventricular blood. This raised doubts about the accuracy of the results, and subsequent experiments at the time could not reproduce similar findings.

The dynamic geometry of the left ventricle has been assessed by Rankin *et al* [127] and Tyson *et al* [128] using ultrasonic dimension transducers in animals and in post-CABG patients respectively; they concluded that directional changes in systolic shortening of the LV diameter measured by ultrasonic transducers correlated well with stroke volume measured by thermo-dilution techniques and could be used as an on-line index of cardiac output. They also concluded that – by using chronically implanted pulse-transit ultrasonic dimension transducers – the exact pattern of left ventricular contraction was mainly a function of the left ventricular volume.

Measurement of stroke volume and cardiac output

Several previous studies have investigated the relationship between intracardiac impedance and stroke volume. In 1981, Baan *et al* [129] demonstrated excellent correlation between the measured intracardiac impedance on the one hand and the LV stroke volume and cardiac output on the other hand both in vitro, using an artificial heart model, and in vivo, by experimenting in 12 dogs. The animal study was performed using a multi-electrode catheter placed along the long axis of the LV. It was concluded that the catheter had great potential for application in man as it fulfilled its primary aim of continuously recording stroke volume and cardiac output. McKay *et al* [130] reproduced similar results in 1984 after conducting a study in humans during cardiac catheterisation using a multi-electrode impedance catheter. They compared stroke volumes determined by electrical impedance with stroke volumes determined by the thermo-dilution technique in 10 patients and revealed excellent correlation (r value of 0.95). Furthermore, they also compared directional changes in impedance recordings throughout the cardiac cycle with volume curves obtained by radionuclide ventriculography, and in all instances the agreement between the two volume recordings was excellent. Similar directional changes in stroke volume were also recorded in both left and right ventricles. Subsequently plotted pressure-volume diagrams showed characteristic isovolumetric contraction and relaxation phases as well as typical ejection and filling periods. In an animal experiment using anaesthetised open-chest dogs and pigs (McKay *et al* [131]), volume

changes as measured by the impedance catheter method closely paralleled simultaneous changes in the ultrasonic crystal-determined segment length, and the impedance end-systolic pressure-volume relation slope was reproducible with repeated load-altering manoeuvres. 1n 1998, Al-Khalidi *et al* [132] examined the validity of the conductance catheter method in vitro under conditions where pump rate, conductance, viscosity, and temperature of the fluid inside the heart chamber are changed as happens in cardiac surgery. They used the conductance catheter to measure the pressure-volume data in a physical model of the human left ventricle. The volume, salinity, viscosity, and temperature of the fluid inside the model were rigorously controlled. The measured pressure-volume data were compared with the actual values to assess the accuracy and dependence of the conductance-measured volumes on salinity, viscosity, temperature, and pump rate. Conductance-measured volumes were not significantly different over a range of heart rates extending from 60 to 100 beats per minute, and they were not significantly different over a salinity range of 0.2 – 2 normal saline, a viscosity range of 2.7 – 3.5 Centipoises, or over a temperature range of 20 – 39 °C. The investigators therefore concluded that there was no dependence of conductance-measured volume on heart rate, viscosity, temperature, or salinity, provided the correct value of fluid resistivity was used.

RV contractility & rate responsive pacemakers

When a unipolar pacing system is implanted, the measured impedance between the pacemaker can and the electrode tip at the RV apex is composed of the electrical impedance of the conductor coil and the trans-thoracic impedance [133]. Since the impedance of the conductor remains constant, changes in the sensed unipolar ventricular impedance are mainly caused by changes of electrical conductance at the bio-interface between the electrode tip and myocardial tissue & intra-ventricular blood [134]. Slow impedance changes are caused by variations in the thoracic air content due to respiration, whereas rapid impedance changes occur within the cardiac cycle and are caused by contraction-related changes in the contents of blood (low impedance) and tissue (high impedance) [135]. Thus, at the end of diastole, there is more blood around the electrode tip resulting in lower overall impedance. On the other hand, during systole, the ejection of blood leads to higher tissue content around the electrode tip resulting in higher overall impedance, which progressively increases further until it reaches its peak in late systole. This impedance increase correlates with RV contractility and, thus, with the inotropic state of the heart [136]. Osswald *et al* [133] analysed the effect of increasing dobutamine challenge on RV contractility and the measured impedance signals in patients undergoing implantation of dual chamber rate responsive (DDDR) pacemakers. A right ventricular pigtail catheter was inserted for continuous measurements of RV-dP/dt*max*, and unipolar RV intra-cardiac impedance signals were simultaneously measured along with RV-dP/dt*max* during intrinsic and ventricular paced

rhythm. A stress test with a stepwise increase of intravenous dobutamine was then performed. There was a highly significant correlation between dP/dtmax and impedance for both ventricular paced (r^2 = 0.93) and intrinsic (r^2 = 0.92) rhythms. It was concluded that for intrinsic and ventricular paced rhythms, sensor signals derived from RV unipolar impedance curves closely correlate with dP/dt*max*, and thus, with a surrogate of RV contractility during dobutamine stress testing.

Further derivations of impedance measurement have been incorporated into permanent pacing systems, allowing effective heart rate modulation. Current commercially available rate-responsive pacing systems use intracardiac impedance, according to the Closed-Loop Stimulation (CLS) principle, to assess the inotropic state of the heart by assessing RV contractility [136].

Non-fluoroscopic radiofrequency (RF) ablation

Based on impedance changes related to catheter movements in trans-thoracic current fields, non-fluoroscopic navigation – using LocaLisa, EnSite or CARTO systems – of intracardiac electrode catheters during radiofrequency ablation of arrhythmias has become possible and is currently applied in day-to-day clinical practice. This significantly reduces fluoroscopy times compared to conventional RF techniques, as demonstrated by Schneider *et al* [137] in a randomised prospective study that compared the efficacy of the LocaLisa system with the conventional mapping/ablation approach for RF ablation of isthmus-dependent atrial flutter. Nsah *et al* [138] studied changes in impedance during RF ablation and concluded that monitoring of the initial impedance and the fall in

impedance during ablation procedures may provide clinically valuable information to assess the efficacy of tissue heating and lesion formation. Furthermore, still based on impedance monitoring during RF ablation, Eick *et al* (2002) [139] developed a safety device capable of detecting sudden changes in position of the ablation electrode and consequently stimulating an electronic switch to interrupt the connection between the ablation electrode and the RF generator, thereby minimising the risk of incidentally damaging non-arrhythmogenic myocardial tissue during RF ablation.

Thoracic bio-impedance

Acute left ventricular failure (LVF) evolves through two phases; the first is a pre-clinical stage during which fluid accumulates in the interstitial lung tissues, the second phase is clinically overt alveolar pulmonary oedema with accompanying typical symptoms and signs of lung congestion. Shochat *et al* [140] developed a new device, based on lung bio-impedance measurement, and used it on patients admitted with acute coronary syndrome – without clinical evidence of acute LV failure – to assess the feasibility and efficacy of detecting pre-clinical LVF. Although their conclusion was that the device was sufficiently sensitive in detecting pre-clinical LVF, further larger studies need to be conducted to ascertain the consistency of such results before any widespread clinical application is undertaken. Baralla *et al* [141] have also shown in a small study that measuring the thoracic bio-impedance aids in optimising the atrio-ventricular interval (AVI) in patients with dual chamber pacemakers programmed to VDD mode.

1.6.6 ***Intracardiac impedance; a suitable haemodynamic sensor?***

Intracardiac impedance correlates closely with RV contractility [134] [135] [136] and has been shown to be a reliable tool for assessment of LV stroke volume and cardiac output during cardiac catheterisation procedures [129] [130] [131] [132]. It has also been demonstrated that cyclical changes in the measured intracardiac impedance correlate reliably with phases of the cardiac cycle [136] (impedance reaches its peak in late systole and decreases to its lowest value in late diastole). Furthermore, the measured intracardiac impedance has been shown to be relatively resistant to changes in other variables such as salinity, viscosity, temperature, and heart rate when tested in vitro [132]. Therefore, an interest has developed as to the feasibility of using intracardiac impedance as a haemodynamic sensor. Two main measurement methods of intracardiac impedance were previously closely examined to assess their suitability of being used as haemodynamic sensors for tachyarrhythmias.

RV unipolar intracardiac impedance

Previous human and animal studies have demonstrated good correlation between impedance-measured RV stroke volume and stroke volume directly measured by pulmonary arterial electromagnetic flowmeter [124] [142]. In 1995, Dickstein *et al* [143] obtained a series of right ventricular pressure-volume loops in open chest pigs during transient vena caval occlusion using a 12-electrode conductance catheter. Relationships of end systolic pressure-volume, stroke work-end diastolic volume, and dP/dt-end diastolic volume were compared at control and

during infusion of dobutamine and esmolol. Right ventricular pressure-volume loops generated with this technique were consistent with previously reported findings by other volume measurement methods. Furthermore, the response to changes in inotropic state has been found to be predictable and appropriate. The feasibility of using RV impedance measurement as a sensor for discriminating haemodynamically stable from unstable arrhythmias was first investigated in humans by Arthur *et al* in 2000 [124] [125] [144]; using an external INOS^2 pacemaker the stroke impedance was measured between the distal electrode of a quadripolar catheter positioned at the RV apex and a cutaneous patch electrode placed between the patient's scapulae. There was a significant positive linear correlation between normalised, mean BP and mean impedance wave amplitude (r=0.594). However, compared to impedance, tachycardia cycle length was still found to provide superior sensitivity and specificity for detection of HUVT.

Transvalvular intracardiac impedance

In 1996, DiGregorio *et al* [145] investigated the use of transvalvular impedance (TVI) in maintaining atrial-synchronised ventricular pacing in VDD pacemakers by means of a tri-polar single pass lead. TVI signal has been found to be a sharp periodic wave, with high signal-to-noise ratio, that was detected exclusively in the presence of cardiac mechanical activity. The minimum and maximum TVI values were measured during atrial systole and at the end of ventricular systole, respectively. Different variables of TVI waveform were affected by changes in the inotropic state of the heart, and could therefore be

proposed as potential signals for new rate responsive pacing algorithms based on the correlation between inotropic and chronotropic regulation. Furthermore, the study investigators also suggested that the signal might be used for pacing and sensing validation in auto-regulating pacemakers and for fibrillation recognition in ICDs. We previously conducted a pilot study to determine the feasibility of using TVI as a haemodynamic sensor for discrimination of stable from unstable arrhythmias in man. 14 patients were studied (10 males, mean age 57 years and mean EF 45%). During ventricular tachycardia stimulation studies, an external INOS^2 pacemaker was used to measure TVI (across the tricuspid valve) between the distal poles of two quadripolar catheters positioned inside the right atrial and right ventricular cavities (Figure 1.6). 10 episodes of VT were induced (8 HUVT and 2 HSVT). Significant correlation has been demonstrated between TVI and arterial blood pressure, with good separation between sinus rhythm, HUVT and HSVT in a way that permits the use of such impedance signal as a potential haemodynamic sensor (Figures 1.7, 1.8, 1.9 & 1.10). However, the TVI waveform morphology was deemed too complex for current ICD technology to accommodate and reliably analyse & interpret. We think that this may be due to the fact that the TVI impedance had a rather complex tri-phasic waveform pattern (TVI waveform consists of atrial, valvular and ventricular components) compared to the much simpler mono-phasic sine curve shaped waveform pattern of RV unipolar impedance. Furthermore, the TVI waveform tends to change its morphology depending on the activation sequence of the cardiac

chambers. Further research into the use of TVI as a haemodynamic sensor was therefore subsequently abandoned. Such research work may resume in the future as ICD technology advances.

Figure: 1.6

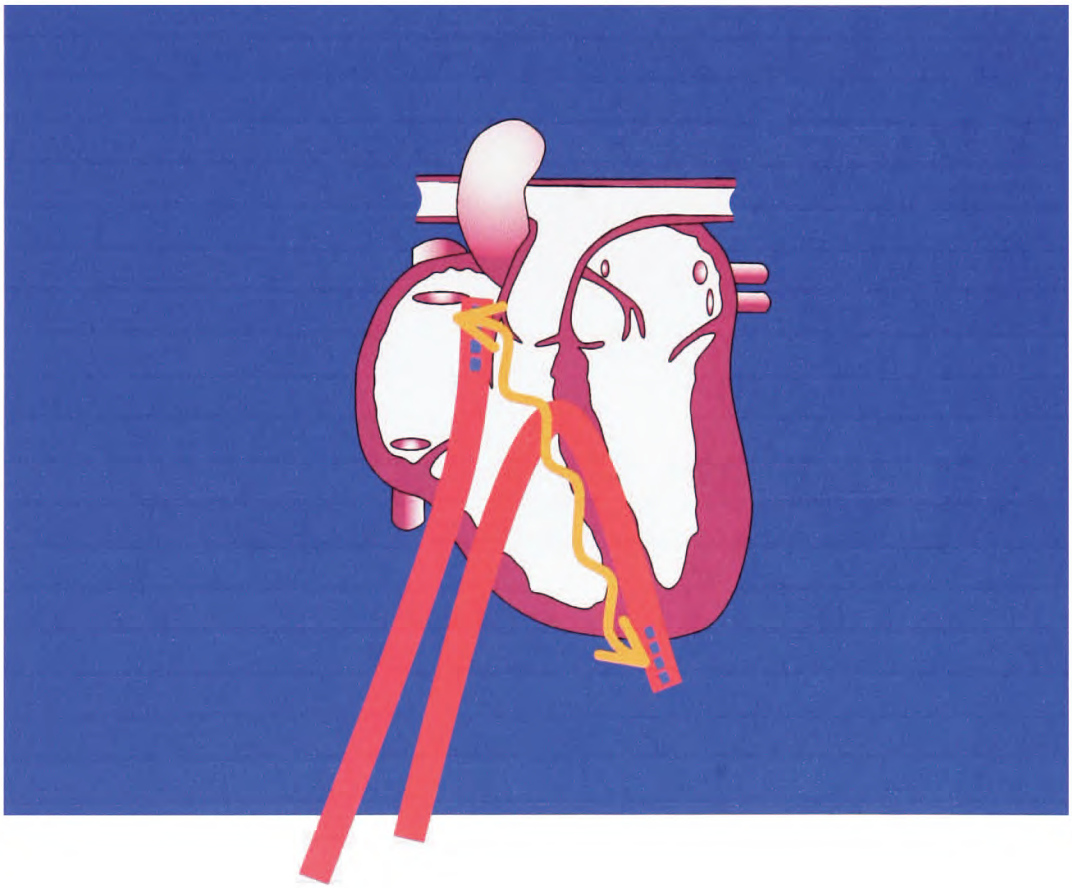


Figure 1.6:

Transvalvular impedance (TVI) was measured across the tricuspid valve using two quadripolar catheters placed inside the right atrial and ventricular cavities.

Figure: 1.7

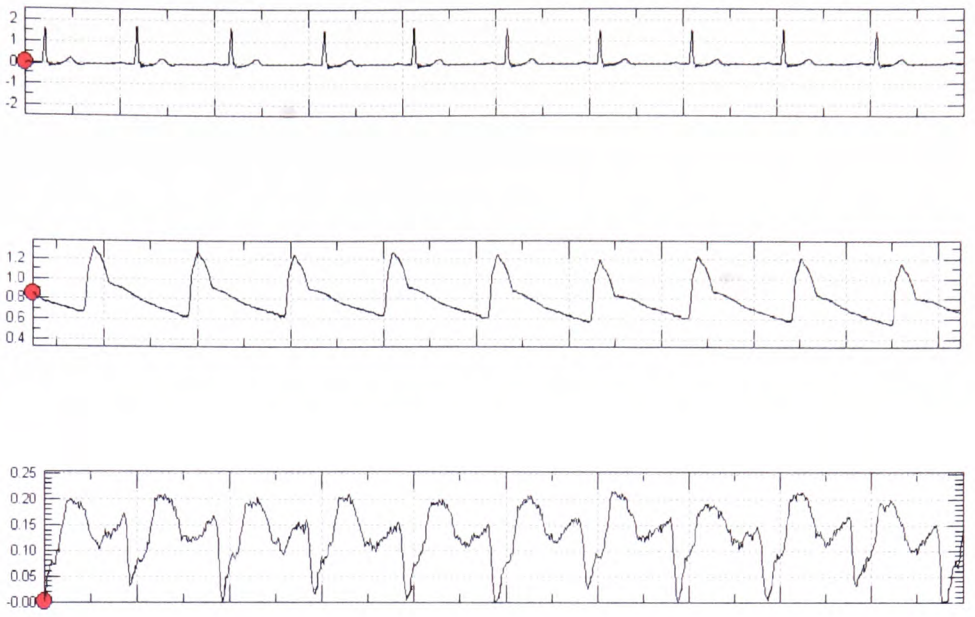


Figure 1.7:

Measurement of transvalvular impedance (TVI) during sinus rhythm; with simultaneous recording of the surface ECG, arterial BP, and transvalvular impedance waveform.

Top:	Surface ECG
Middle:	Invasive arterial BP
Bottom:	Impedance waveform (Z)

Figure: 1.8

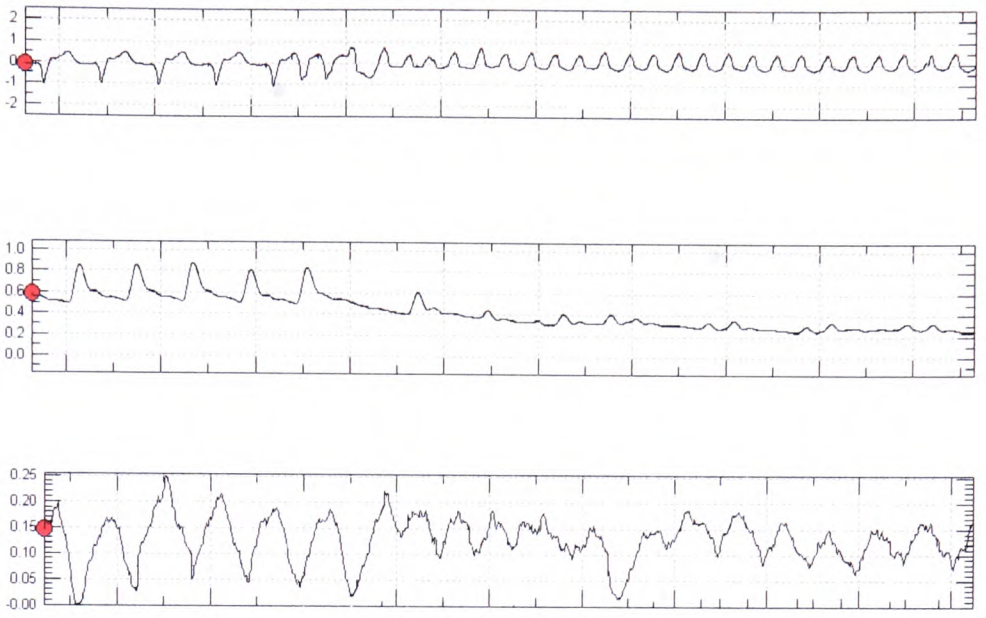


Figure 1.8:

Measurement of transvalvular impedance during haemodynamically stable VT, with simultaneous recording of the surface ECG, arterial BP and transvalvular impedance waveform.

Top:	Surface ECG
Middle:	Invasive arterial BP
Bottom:	Impedance waveform (Z)

Figure: 1.9

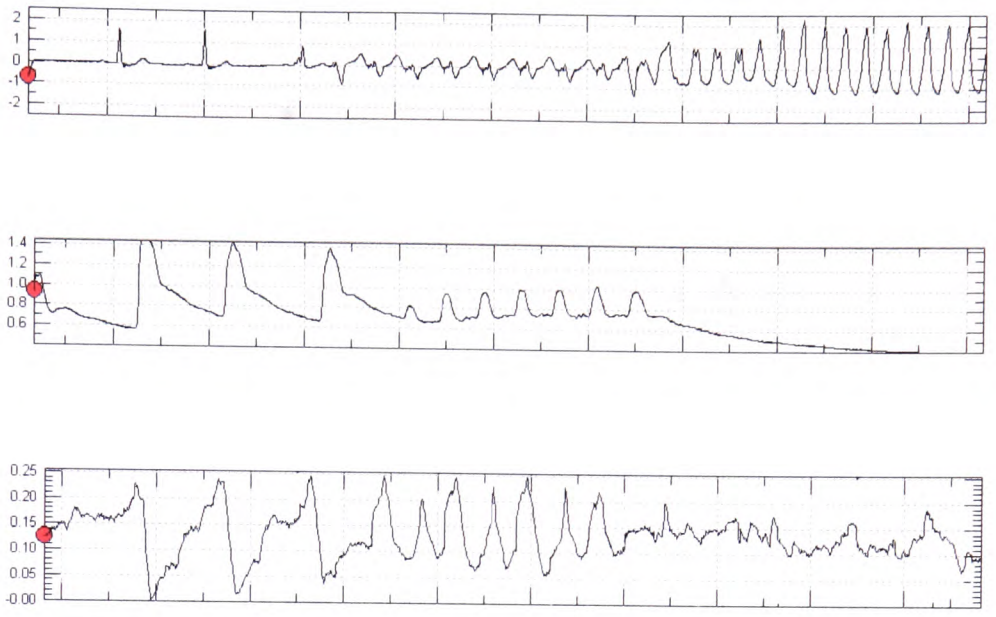


Figure 1.9:

Measurement of transvalvular impedance during haemodynamically unstable VT; with simultaneous recording of the surface ECG, arterial BP and transvalvular impedance waveform.

Top:	Surface ECG
Middle:	Invasive arterial BP
Bottom:	Impedance waveform (Z)

Figure: 1.10

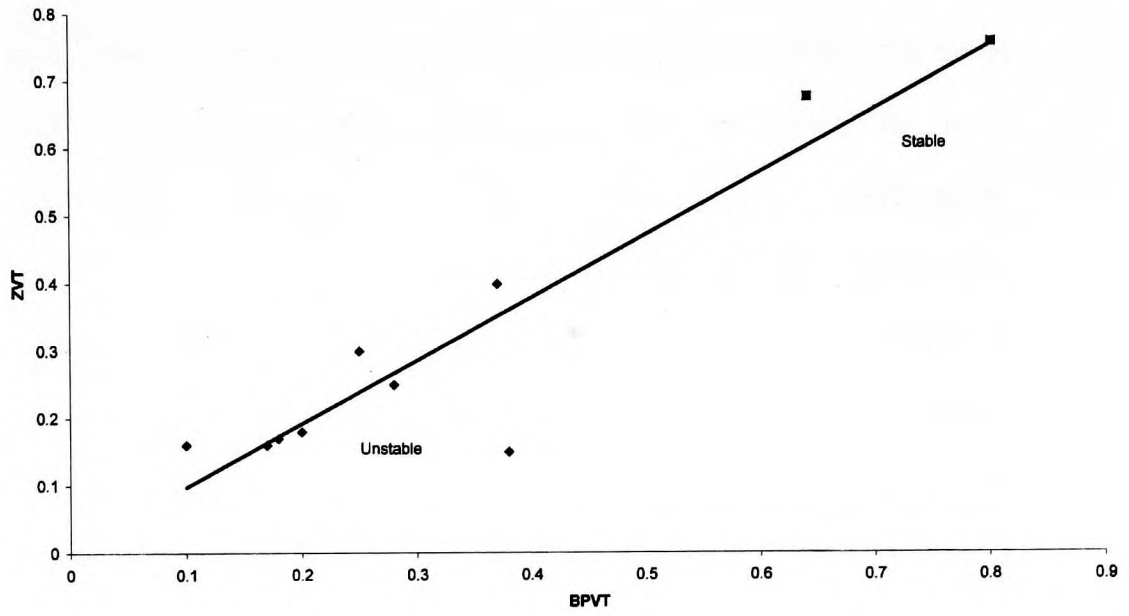


Figure 1.10:

Transvalvular impedance (TVI) versus blood pressure during VT. Note the clear separation between haemodynamically stable (top right) and unstable (bottom left) VT.

ZVT: TVI during VT
BPVT: Invasive arterial pressure during VT

1.6.7 ***Transventricular intracardiac impedance:***

In 1980-82, Arredondo and colleagues [146] [147] investigated the effect of body temperature on transventricular defibrillation threshold. They compared the results of two separate animal studies involving mongrel dogs under conditions of body hypothermia versus normothermia using simple capacitor-discharge defibrillations. They concluded that body hypothermia significantly reduces transventricular defibrillation thresholds, and that current is a better descriptor of what is needed for electrical defibrillation. The measured transventricular impedance remained rather constant. In 1994, Peters *et al* [148] examined various electrical variables while experimenting on canines undergoing internal ventricular defibrillation and concluded that the trans-myocardial impedance during defibrillation was primarily resistive, non-linear, voltage dependent, and declined with successive shocks. Defibrillation success was, however, still not influenced by those phenomena. In 1994 (same year), in an animal study involving anaesthetised closed chest dogs, Geddes *et al* [149] investigated the effect of high intensity transventricular current on cardiac output. The current was injected between an internal LV electrode and a left chest cutaneous one. The investigators mainly concentrated on analysing the data related to the link or otherwise between current intensity and cardiac output. Although cardiac output was measured using both thermo-dilution and pressure-impedance volume loop methods as part of the required study data, no direct comparison results of the data obtained from those two methods were made available.

So far, no human studies have investigated the feasibility of using transventricular impedance as a haemodynamic discriminator between stable and unstable arrhythmias. This thesis examines the role of transventricular impedance measurement as a potential haemodynamic sensor for arrhythmias in humans.

1.7 Summary & Comments

SCD is one of the major causes of death affecting young adults in the developed world. In most cases, SCD is due to malignant ventricular arrhythmias that lead to haemodynamic instability and subsequent loss of cardiac output. Although – in absolute numbers – the majority of those who experience sudden cardiac arrest / death are individuals with no previously known cardiac disease or risk factors for SCD, The greatest incidence occurs in cohorts with identifiable risk factors for SCD (EF < 35% from any cause, and inherited cardiac channelopathies with or without structural heart disease). While anti-arrhythmic drug therapy may be used to terminate or reduce the risk of recurrence of stable arrhythmias, haemodynamically unstable arrhythmias require emergency treatment with DC cardioversion via an external (or implantable) defibrillator. Successful restoration of sinus rhythm depends crucially on the speed with which shock therapy is delivered. All patients with clear identifiable risk(s) of SCD should be considered for ICD therapy whenever appropriate. ICDs have been shown in many randomised clinical trials to be superior to drug therapy in preventing SCD. Since the invention of the first ICD in 1980, huge advances have

been made in ICD technology. Compared to their first generation predecessors, current fourth generation ICDs are much smaller in size (<30 cm^3), have better longevity with an average half-life of 7 years, use transvenous (as opposed to epicardial) leads which greatly facilitated and simplified the device implantation process, and are non-invasively programmable with many additional features for individual fine-tuning, including anti-tachycardia pacing (ATP).

ICDs rely principally on the sensed ventricular rate for arrhythmia recognition and therefore have 100% sensitivity for detection and treatment of life threatening arrhythmias such as VF or HUVT. Their specificity, however, is still nowhere near as good. In consequence, occasional shock therapy is sometimes delivered inappropriately to treat fast but otherwise stable supraventricular and ventricular arrhythmias. Such inappropriate shocks are unpleasant and frightening, and if they were to become recurrent may lead to significant life style restrictions and not uncommonly cause major psychological disturbances. The advent of dual chamber ICDs together with the addition of electrogram rhythm recognition criteria such as arrhythmia rate of onset, QRS morphology, width, and regularity has partially reduced but not fully abolished the occurrence of inappropriate shocks. Many haemodynamic variables – such as unipolar RV impedance, maximum RV contractility (RV dP/dt-*max*), and mixed oxygen venous saturation – have been extensively investigated for their possible use by ICDs as haemodynamic sensors. Many studies demonstrated good correlation between the tested haemodynamic variable and arterial blood pressure

(as a measure of haemodynamic stability), albeit with significant limitations that would preclude practical implementation, e.g. RV unipolar impedance measurement revealed significant correlation with arterial BP during all rhythms but has been found to be inferior to electrogram cycle length in both sensitivity and specificity. Although data from our pilot study of the transvalvular impedance measurement revealed highly significant correlation with arterial BP during all rhythms, practical implementation of TVI as a haemodynamic sensor was deemed inappropriate, as the impedance waveform was too complex for current ICD technology to properly analyse and interpret. For the foreseeable future, researchers will continue to work in this field until a suitable haemodynamic sensor for arrhythmias is identified and successfully incorporated into ICDs arrhythmia recognition algorithms. This thesis examines the feasibility of using intracardiac impedance with transventricular configuration as a haemodynamic sensor for cardiac arrhythmias in man.

CHAPTER 2

CHAPTER 2

METHODOLOGY

2.0 Introduction

2.0.1 ***Background:***

Intracardiac impedance was first investigated as a means of assessing the contractile capacity of the heart more than half a century ago. In 1953 Rushmer *et al* [150] demonstrated that changes in impedance related predictably to various phases of the cardiac cycle. The strong relationship between changes in stroke volume and changes in intracardiac impedance is well recognised [133] [151]. Currently, implantable cardioverter defibrillators (ICDs) identify arrhythmias mainly on the basis of changes in the heart rate with no direct assessment of the haemodynamic situation. Occasionally, inappropriate shock delivery can occur for otherwise haemodynamically stable arrhythmias, which can be both painful and frightening for the patient. A device capable of monitoring the haemodynamic stability of arrhythmias can potentially reduce the frequency of inappropriate intracardiac shocks. Also, such a form of haemodynamic monitoring could help in assessing the optimal pacing mode of bi-ventricular pacing systems.

Many haemodynamic sensors have been used with variable success in the past. The ideal might include a lead based pressure sensor in the right ventricle and current technology is such that long term pressure sensing may now be feasible [152]. In a previous study by Khoury *et al* [153], impedance amplitude was measured using a multipolar catheter within the right ventricle with simultaneous right ventricular pulse pressure

during stable and unstable arrhythmias. Impedance fell significantly during unstable arrhythmias and the study showed 100% specificity at detecting haemodynamic instability. This clearly suggested that intracardiac impedance could be used as a haemodynamic sensor. However, current commercial systems use unipolar impedance, measuring changes in impedance between the tip of the pacing lead and the generator can. This reflects alterations in RV contractility. (Ions, Protos and Cylos – Biotronik GmbH) [154].

Using temporary pacing leads we have previously investigated the role of unipolar intracardiac impedance in discriminating haemodynamically stable from unstable arrhythmias [144] but have been unable to reproduce the result shown by Khoury using a multipolar catheter. Thus far a reliable change in impedance during arrhythmias has proven elusive.

These investigations have raised the question of "what is the optimal impedance configuration capable of acting as a reliable haemodynamic sensor?" Unipolar impedance would tend to reflect right ventricular dynamics and may not give an accurate reflection of left ventricular changes. The effect of predominantly left ventricular function might require measuring impedance across the left ventricle (transventricular impedance).

2.0.2 ***Objective:***

The primary aim of this study was to assess the feasibility of using intracardiac trans-ventricular impedance measurement – across the left ventricle – as a sensor for haemodynamic stability during rapid cardiac pacing and arrhythmias. We arbitrarily defined haemodynamic instability

as a drop in BP that causes loss of consciousness and effective cardiac output, necessitating emergency intervention with external DC cardioversion. The study also enabled us to directly compare between the accuracy & reliability of continuous non-invasive BP monitoring (Finger Plethysmography) to that of standard methods of invasive intra-arterial BP monitoring.

Approvals of the study protocol (complied with the Declaration of Helsinki) from both the local research and ethics committee (LREC) and the trust's research and development department (R&D) were obtained prior to patients' inclusion in the study. The protocol was thoroughly explained to all patients, and written explanatory information sheets were made available to them. All patients then signed an informed consent form upon enrolment into the study. All procedures were performed electively in the cardiac catheter & electrophysiology (EP) laboratory at room temperature between 15 - 20 °C.

2.0.3 ***Patients:***

A total of 37 patients were initially included. 9 were later excluded due to difficulty placing the coronary sinus electrodes. 28 patients had their data analysed. We included all patients undergoing routine, clinically indicated, intracardiac electrophysiological studies (EPS) for the induction and assessment of ventricular arrhythmias. Patients < 18 years of age and pregnant women were not included in the study. Baseline characteristics are detailed in table 2.1 below:

Table 2.1

Patients N = 28	*Males N = 25 (89%)*	*Females N = 3 (11%)*
Age in years (mean ± 2SD)	60 ± 9	67 ± 6
Diabetes Mellitus	5 (18%)	0 (0%)
Hypertension	6 (21%)	1 (3.5%)
Dyslipidaemia (TC >5.0 mmol/l on statin)	17 (61%)	3 (11%)
Smoking (current or within 1 year)	19 (68%)	2 (7%)
IHD (Previous MI, PCI or CABG)	20 (71%)	3 (11%)
DCM	2 (7%)	0 (0%)
HCM	0 (0%)	0 (0%)
Resting HR <100 bpm	23 (82%)	3 (11%)
Resting HR > 100 bpm	2 (7%)	0 (0%)
Normal LV systolic function (EF > 50%)	3 (11%)	0 (0%)
Mild LV systolic dysfunction (EF 45 – 50%)	0 (0%)	0 (0%)
Moderate LV systolic dysfunction (EF 35 – 45%)	7 (25%)	0 (0%)
Severe LV systolic dysfunction (EF < 35%)	12 (43%)	3 (11%)
Sinus rhythm on resting ECG	25 (89%)	3 (11%)
Atrial fibrillation on resting ECG	0 (0%)	0 (0%)
QRS width >140 ms	13 (46%)	2 (7%)
FAP resting systolic BP (mean ± 2SD mmHg)	105.01±31.76	98.85±25.10
Portapres resting systolic BP (mean ± 2SD mmHg)	136.28±34.25	128.46±27.31
Potassium level in mmol/l (mean ± 2SD)	4.5 ± 1.1	4.4 ± 0.8
Calcium level in mmol/l (mean ± 2SD)	2.26 ± 0.4	2.54 ± 0.5
Magnesium level in mmol/l (mean ± 2SD)	0.92 ± 0.28	0.80 ± 0.2
Normal renal function (Cr <120 mmol/l)	14 (50%)	2 (7%)
Moderate renal impairment (Cr 120 - 200 mmol/l)	9 (32%)	1 (3.5%)
Severe renal impairment (Cr > 200 mmol/l)	2 (7%)	0 (0%)

Table 2.1: **Patients' baseline characteristics.**

Abbreviations:
2SD: Two standard deviations, **TC:** Total cholesterol, **mmol/l:** Milli moles per litre, **IHD:** Ischaemic heart disease, **PCI:** Percutaneous coronary intervention, **CABG:** Coronary artery bypass grafting, **DCM:** Dilated cardiomyopathy, **HCM:** Hypertrophic cardiomyopathy, **HR:** Heart rate, **LV:** Left ventricle, **FAP:** Femoral arterial pressure, **BP:** Blood pressure, **Cr:** Creatinine

Patients' usage of cardiac medications is detailed in table 2.2 below:

Table 2.2

Patients N = 28	Males N = 25 (89%)	Females N = 3 (11%)
ACE inhibitor	22 (77%)	3 (11%)
Beta blocker	23 (82%)	2 (7%)
Amiodarone	18 (64%)	0 (0%)
Digoxin	2 (7%)	0 (0%)
Furosemide	19 (68%)	2 (7%)

Table 2.2: Usage of cardiac medications by study patients

The clinical indications for conducting the electrophysiological VT stimulation studies are listed in table 2.3 below:

Table 2.3

Patients N = 28	Males N = 25 (89%)	Females N = 3 (11%)
Recurrent monomorphic primary VT	6 (21%)	0 (0%)
Recurrent syncope or palpitations plus NSVT shown on 24-hour ambulatory ECG monitoring	7 (25%)	1 (3.5%)
Recurrent pre-syncope plus poor LVEF of <35% and NSVT on 24-hour ambulatory ECG monitoring	12 (43%)	2 (7%)

Table 2.3: Clinical indications for VT Stimulation studies

Abbreviations:

Primary VT: Ventricular tachycardia occurring not within the context of acute myocardial ischaemia, and has no obvious reversible precipitant.

NSVT: Non-sustained ventricular tachycardia.

LVEF: Left ventricular ejection fraction (Normal LVEF: 50 – 75%)

2.1 Methodology

2.1.1 ***Transventricular impedance:***

All 28 patients underwent routine, clinically indicated VT stimulation electrophysiological studies as part of assessing their risk of sudden cardiac death. Procedures were performed electively in the cardiac electrophysiology (EP) laboratory with the patients supine and in the non-sedated post absorptive (fasting) state. Under aseptic conditions, the right (or left) groin area was locally anaesthetised using approximately 10 ml of 1% lidocaine (lignocaine) injectable solution. Two Desi-Valve sheaths (6 French & 7 French gauge) were inserted into the femoral vein. Through those two sheaths and under direct fluoroscopic guidance, a 6 French quadripolar pacing/recording electrode (Bard UK) was inserted and then positioned at the right ventricular apex (RVA) and a 7 French decapolar deflectable catheter (Daig UK) was positioned inside the coronary sinus (CS) as far distally as possible (Figure 2.1).

Figure: 2.1

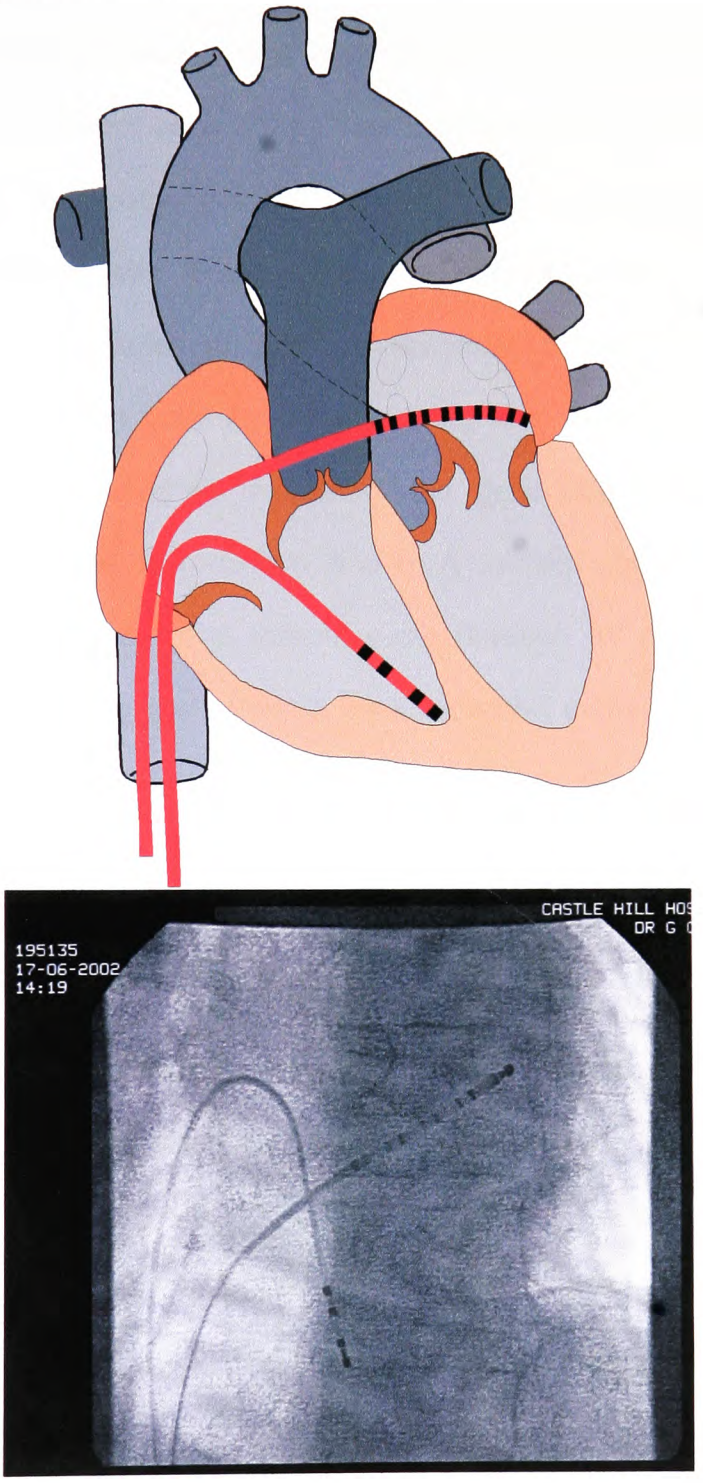


Figure 2.1: **Right ventricular (RV) & coronary sinus (CS) catheter positions**

Top: Schematic drawing: lead positions of the quadripolar catheter in the RV apex and of the decapolar catheter in the Coronary Sinus.

Bottom: Radiological confirmation of the catheters in the left anterior oblique (LAO) position showing the decapolar coronary sinus and the quadripolar right ventricular apical catheters.

An externally positioned, non-modified, implantable Inos^{2}CLS dual chamber pacemaker was then directly connected to the proximal and distal poles of each of the two catheters (four connections) and was used for both current injection and impedance measurement. Impedance was measured by first injecting a sub-threshold biphasic rectangular pulse of 600μA (micro-Ampere) current between pole 1 (distal) of the coronary sinus catheter and pole 1 (distal) of the RVA catheter, and then measuring the generated voltage between CS catheter pole 10 (proximal) and RVA catheter pole 4 (proximal) (Figure 2.2). The alternating current pulse duration for each polarity was 15 microseconds (μs). Pulses were repeated every 8 milliseconds (ms). This measured the impedance value generated across the intraventricular blood of both ventricles (but mainly the left ventricle), hence the term "Transventricular impedance". The impedance data were then transmitted from the external Inos pacemaker via standard magnet telemetry to a pacing programmer (Boitronik, PMS1000+ with "FlexMeas" customised software – programmer cartridge type 9 B-KIF.V.A). The programmer then generated an impedance-proportional analogue output signal. Using a compatible cable connector (RK 21-E), the analogue output impedance signal was then transmitted from the pacing programmer to the electrophysiology (EP) computer system where its waveform was transformed into digital format and was continuously recorded and also displayed in real-time on the screen of the EP computer system throughout the entire VT induction procedure.

Figure: 2.2

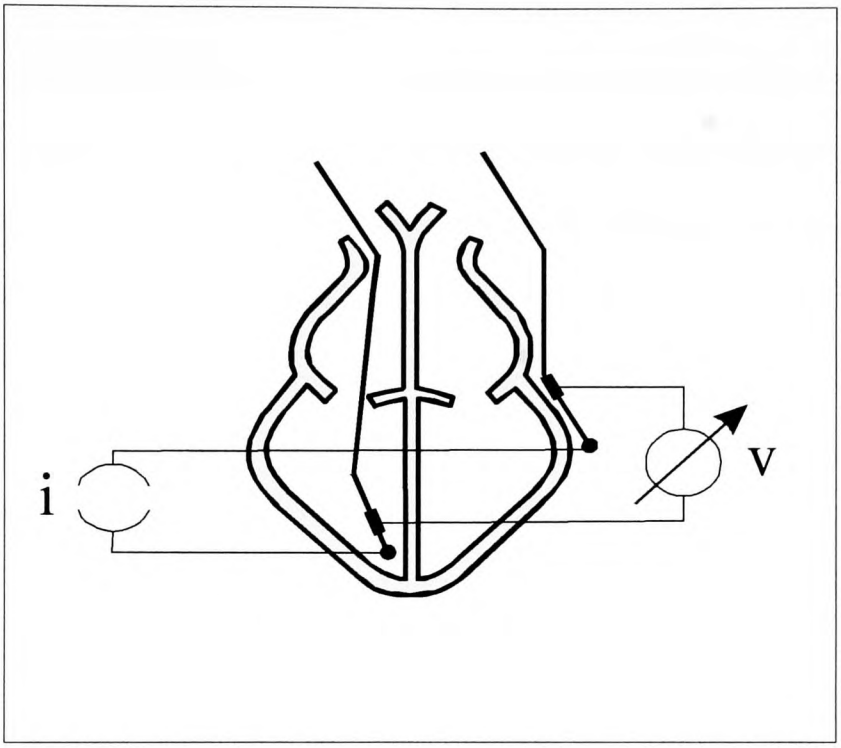


Figure: 2.2

The current (i) & voltage (v) configuration used for LV transventricular impedance measurement

The alternating current (**i**) was injected between the distal poles (poles number 1 & 1) of the RVA and CS electrode catheters. The proximal poles (pole 4 of RVA catheter and pole 10 of CS catheter) were used to measure the voltage (**v**) and the transventricular impedance.

The size – not the morphology – of the impedance waveforms generated by the pacing programmer has been noted to vary considerably between individual patients (i.e. although the morphological appearances of the impedance waveforms looked generally similar to each other for all the patients, some waveforms were much larger – or smaller – in size than others). Initial impedance gain adjustment was therefore performed for some patients – at the stage of the pacing programmer, prior to transmitting the impedance signal onto the EP computer system – in order to standardise the size of the impedance waveform before transmitting the signal onto the EP computer system for recording the measurements. This variable gain of the impedance waveform has no effect on the study outcome since we are studying the relationship between the *change* in stroke impedance (SZ – see below) and the *change* in blood pressure at different heart rhythms. Since we are not studying the *absolute* value of impedance, the absolute gain of the impedance waveform does not matter. After those adjustments, we did not change the final acquired impedance gain setting for the rest of the procedure and no further alterations were performed.

2.1.2 ***Invasive BP (Femoral Arterial Pressure – FAP):***

Continuous haemodynamic monitoring of all studied patients was conducted invasively using femoral arterial pressure (FAP) lines. A 4-French Desi-Valve sheath was inserted into the femoral artery (usually on the ipsilateral side of the impedance catheters) under local

anaesthesia (1% lidocaine) and using aseptic technique. The sheath was connected to a fluid-filled transducer (Medex Medical, model No: MX9604) for FAP signal detection. The transducer was then connected to the EP computer system, to which the FAP analogue signal was transmitted for digitalising, recording and display of its pressure waveform. Transducer zeroing was achieved by manually positioning its line level with the horizontal plane of the femoral artery prior to attaching it to the intra-arterial sheath.

2.1.3 ***Non-invasive BP (Finger Plethysmography - Portapres):***

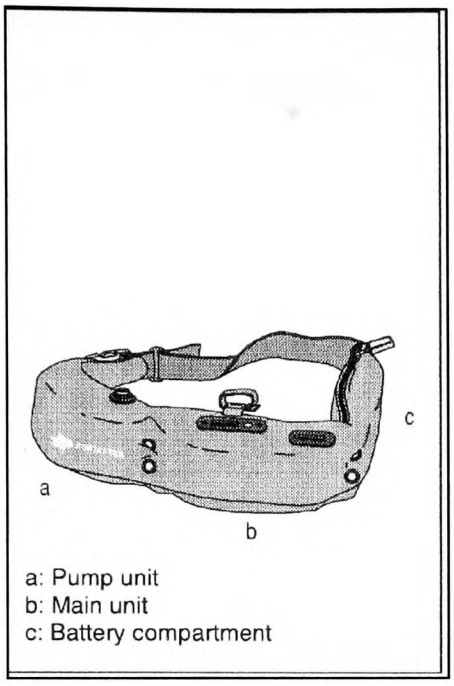
In 20 of the above study patients, in addition to invasive femoral arterial pressure monitoring, simultaneous finger plethysmography was performed using a specially designed continuous non-invasive BP measurement and recording system (Portapres model-2, TNO-TPD Biomedical Instrumentation / Amsterdam). The Portapres system uses the volume-clamp method (developed by J Peñáz in 1973) [155]. The method is based on the development of the dynamic pulsatile loading and unloading of the finger arterial walls. In this method, the circumference of the finger artery being monitored is kept constant (clamped) at a certain diameter despite the changes in arterial pressure during each heart beat. The Portapres device detects changes in arterial diameter by means of an infra-red photo-plethysmograph built into the finger cuff. During systole, when an increase in finger arterial diameter is detected, the cuff pressure is immediately increased by a rapid pressure servo-controller system to prevent the diameter change. To fully

accomplish this without compressing the artery dameter or allowing it to increase (i.e. to maintain a constant arterial diameter during both systole, diastole and throughout the entire cardiac cycle of each heart beat), the cuff pressure needs to be kept *equal to* the finger intra-arterial pressure at all times. As a result, the magnitude of the Portapres-produced finger cuff pressure should be *equal* to that of the finger intra-arterial pressure. Since the resting diameter of the finger artery is itself a variable that constantly alters in response to changes in stress and tone of smooth muscles in the arterial wall, the Portapres system is equipped with a dynamic servo set-point adjuster for the purpose of regularly defining and then re-setting (calibrating) the diameter at which the finger artery should be clamped (Wesseling *et al.* 1995) [156]. This results in the measurement of blood pressure being temporarily interrupted at times when the system is recalibrating itself for setting a new reference vessel diameter. During such periods, the Portapres BP waveform remains flat for the duration of the calibration process, which usually occurs once every two to three minutes and lasts for up to ten seconds at a time.

The Portapres device is contained in a belt that has three compartments containing a pump unit, a main unit, and a battery compartment (Figure 2.3). A small box is placed on the patient's wrist with a strap and is connected to the main and pump units with an electric cable and an air hose, respectively. A small blood pressure cuff is applied to the middle phalanx of the middle finger, and is connected via an air hose to the wrist box. Patient's details (age, sex, weight and height) are entered into

a control panel that is built in the main system unit. This allows the system to calibrate its blood pressure measurements for each individual patient. Zeroing is automatic. The Portapres system is also equipped with a hydrostatic height correction unit that allows for free hand movement, which is particularly useful in ambulatory applications but was not needed here as our patients were not mobilising during the study. Patients' hands were kept warm under a blanket throughout the procedures to reduce the chance of losing the Portapres signal from cold-induced peripheral vasoconstriction. The Portapres analogue BP signal was then transmitted via a connection cable to the same EP computer system of the impedance and femoral BP signals, where it was digitalised, recorded and its waveform displayed on the monitor screen. Waveforms of both BP signals were recorded and displayed simultaneously, along with the impedance and surface ECG signals, on the EP computer system.

Figure: 2.3



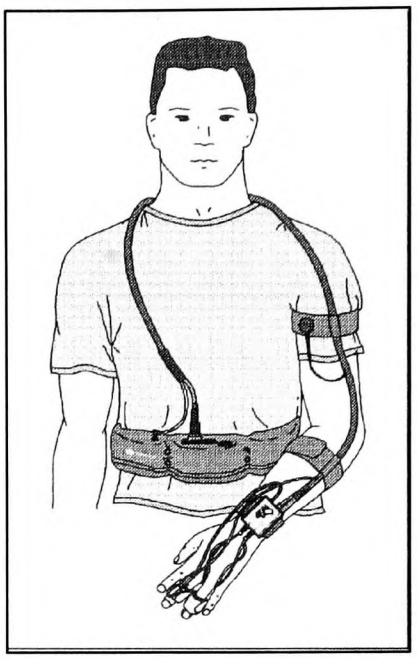


Figure: 2.3

The three main compartments of the Portapres device (left). A small box is placed on the patient's wrist with a strap and is connected to the main and pump units with a cable and an air hose, respectively (right).

2.1.4 ***Study protocol:***

Figure 2.4 shows a schematic representation of the different equipments used in the study. For all patients, we used "Modified Wellens protocol" for programmed VT stimulation. This protocol involves stimulating VT in the EP laboratory by delivering pacing train cycles of 8 paced beats at a rate of 600 ms (100 beats per minute) via the right ventricular apex electrode catheter followed by up to two or three additional paced beats (extra-stimuli) with progressively shortening coupling intervals. Following

each pacing train cycle of 8 beats, the 1st extra-stimulus is delivered closer and closer to the 8th paced beat until it either induces VT or no longer captures the ventricle (i.e. reaches the point of refractoriness). If no VT is induced despite reaching refractoriness, the 1st extra-stimulus is – thereafter – delivered constantly at the shortest coupling interval (between it and the 8th beat of the pacing train) that would produce ventricular capture. A 2nd paced extra-stimulus beat is then delivered after the 1st one and is brought progressively closer to it – in consecutive pacing train cycles – until either VT is induced or refractoriness is reached. The above whole sequence of modified Wellens Protocol is repeated with a pacing train of 400 ms (150 beats per minutes). See figure 2.5 below.

As detailed above, in this study, during routine clinical VT provocation up to 2 or 3 extra-stimuli were delivered during sinus rhythm, and during right ventricular apical (RVA) pacing at 600 ms & 400 ms.

Figure: 2.4

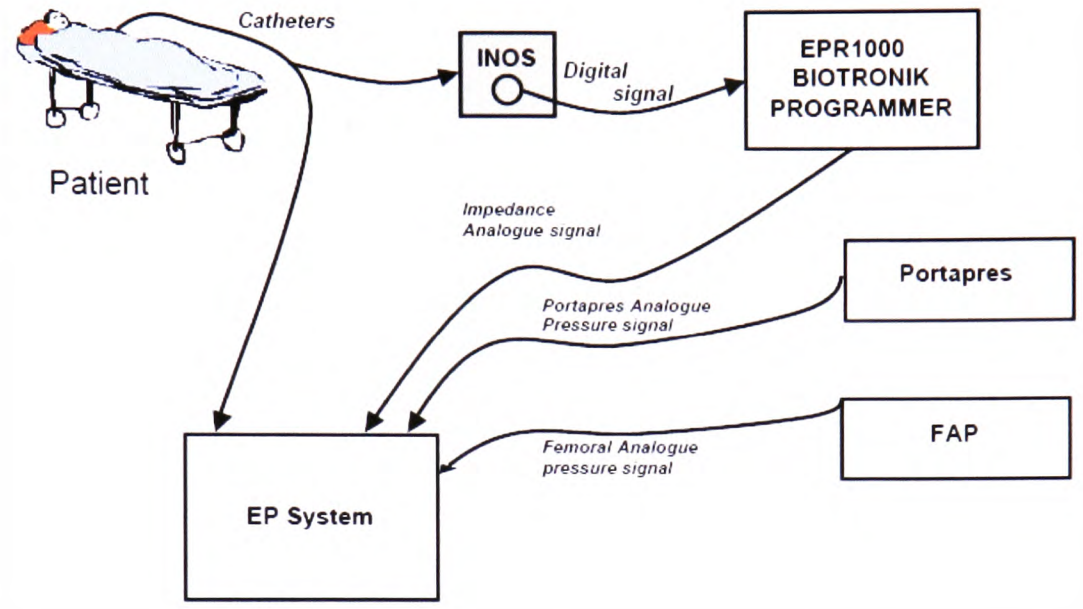


Figure: 2.4: A schematic representation of the study set up and the various equipments used for conducting the procedures in the EP laboratory.

The digital impedance signal was transmitted from the Inos^2 CLS pacemaker via telemetry to the pacing programmer, which in turn generated an impedance-proportional analogue output signal that was transmitted to the EP system. Both invasive and non-invasive BP signals {FAP and Portapres} were transmitted in analogue forms to the EP computer system. All signals were then digitalised and displayed on the EP system monitor screen along with surface ECG and intracardiac electrogram signals.

Figure: 2.5

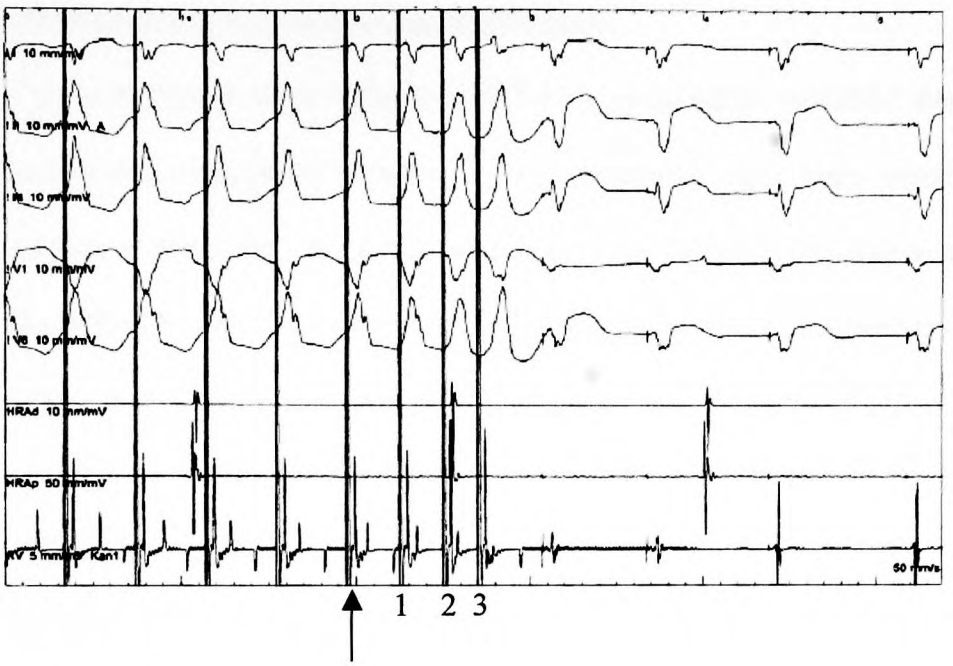


Figure: 2.5

Modified Wellens Protocol with programmed right ventricular apical (RVA) stimulation (arrow marks the end of the RVA drive pacing train) followed by three programmed extra-stimulus beats: 1, 2 & 3. This has still not induced VT in this case.

As an additional part of this study (i.e. in addition to modified Wellens protocol), ventricular drive pacing for a period of one minute at a rate of 400 ms was also performed in patients who had not had VT induced by modified Wellens protocol described above.

The arrhythmias were initially *induced* by using either modified Wellens arrhythmia stimulation protocol or by prolonged rapid right ventricular pacing. If and when an arrhythmia was *induced*, we then *observed* and recorded its effect on the continuously monitored stroke impedance and blood pressure (both invasive and Portapres). If the patient having the arrhythmia remained conscious with stable and sustained perfusion pressure, we would class the arrhythmia as haemodynamically stable. On the other hand, if the arrhythmia resulted in loss of consciousness & cessation of effective cardiac output we would class it as haemodynamically unstable, in which case we would intervene by external defibrillation to terminate it.

RVA pacing was delivered via an external stimulator (UHS 20) through poles 2 and 3 of the RVA electrode catheter, thereby avoiding pacing through the poles used by the Inos^{2}CLS pacemaker for current injection and impedance sensing (poles 1 and 4). This is in order to prevent recording of artefacts on the recorded impedance signal, as has been shown to be the case when we initially attempted to use the pacemaker for both impedance measurement and RVA pacing. By using an external stimulator, the electrodes for pacing and for impedance sensing were kept strictly separated, and impedance measurement was performed unsynchronised to the stimuli and could not therefore be blanked during

stimuli of the UHS 20. Such artefacts would have been recorded on the impedance channel, and may have affected the final results if the Inos^{2}CLS pacemaker was used for RVA pacing using the same impedance recording electrode poles. Data obtained from measurement of stroke impedance (SZ), surface ECG, invasive femoral artery blood pressure (FAP) and non-invasive finger plethysmographic blood pressure (Portapres) were recorded synchronously during the study at a sampling rate of 1000 Hertz (Hz) per channel. Figures 2.6, 2.7, 2.8 & 2.9 represent respective data recordings from individual patients during sinus rhythm, right ventricular pacing, stable and unstable VTs. A low-pass filter (0-500 Hertz) was used for filtering the impedance and both blood pressure channels. All remaining signals were filtered using band-pass filters (the filters were needed in order to reduce the noise interference on – and thereby improve the waveform quality of – all the recorded channels (impedance, invasive BP and Portapres).

Figure: 2.6

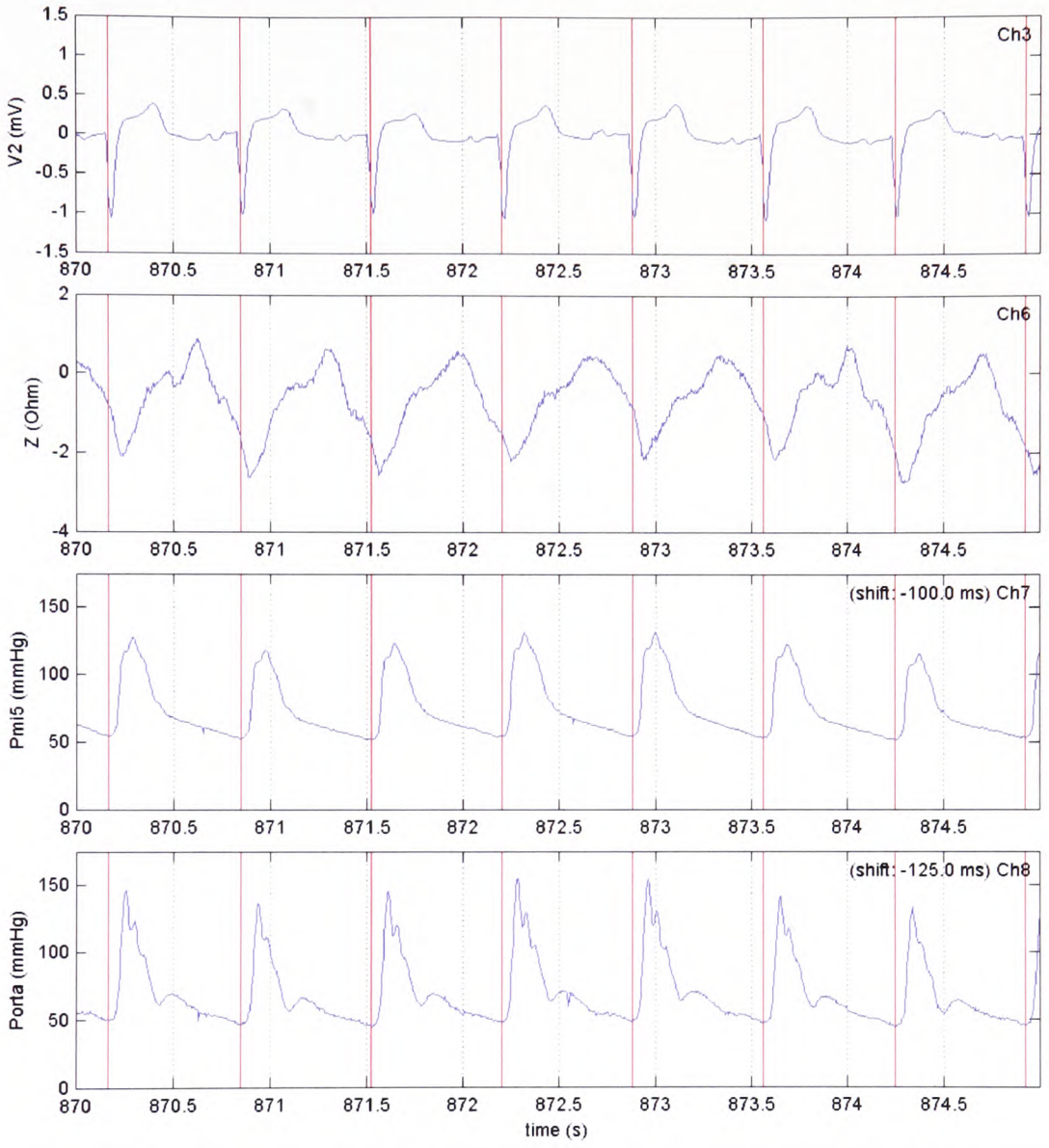


Figure: 2.6 **Sinus Rhythm**

Patient "15" during sinus rhythm. The signals simultaneously displayed on the EP system monitor screen from top to bottom are: Surface ECG, Intracardiac impedance (Z), femoral arterial BP (Pmi5), and Protrapres signal (Porta).

Figure: 2.7

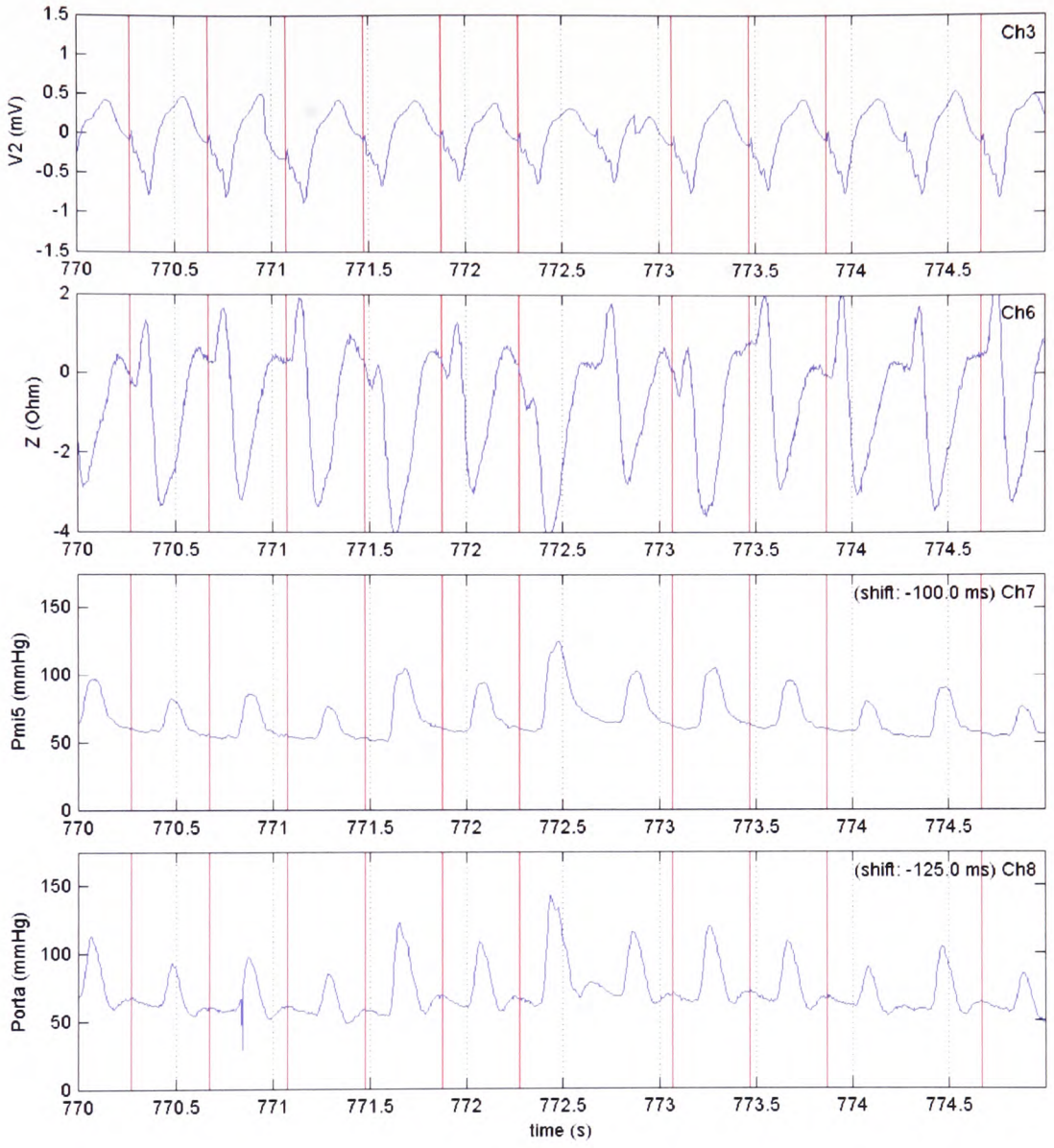


Figure: 2.7 **Rapid RAV pacing**

Patient "15" during rapid RVA pacing at 400 ms. The signals simultaneously displayed on the EP system monitor screen from top to bottom are: Surface ECG, Intracardiac impedance (Z), femoral arterial BP (Pmi5), and Protrapres signal (Porta).

Figure: 2.8

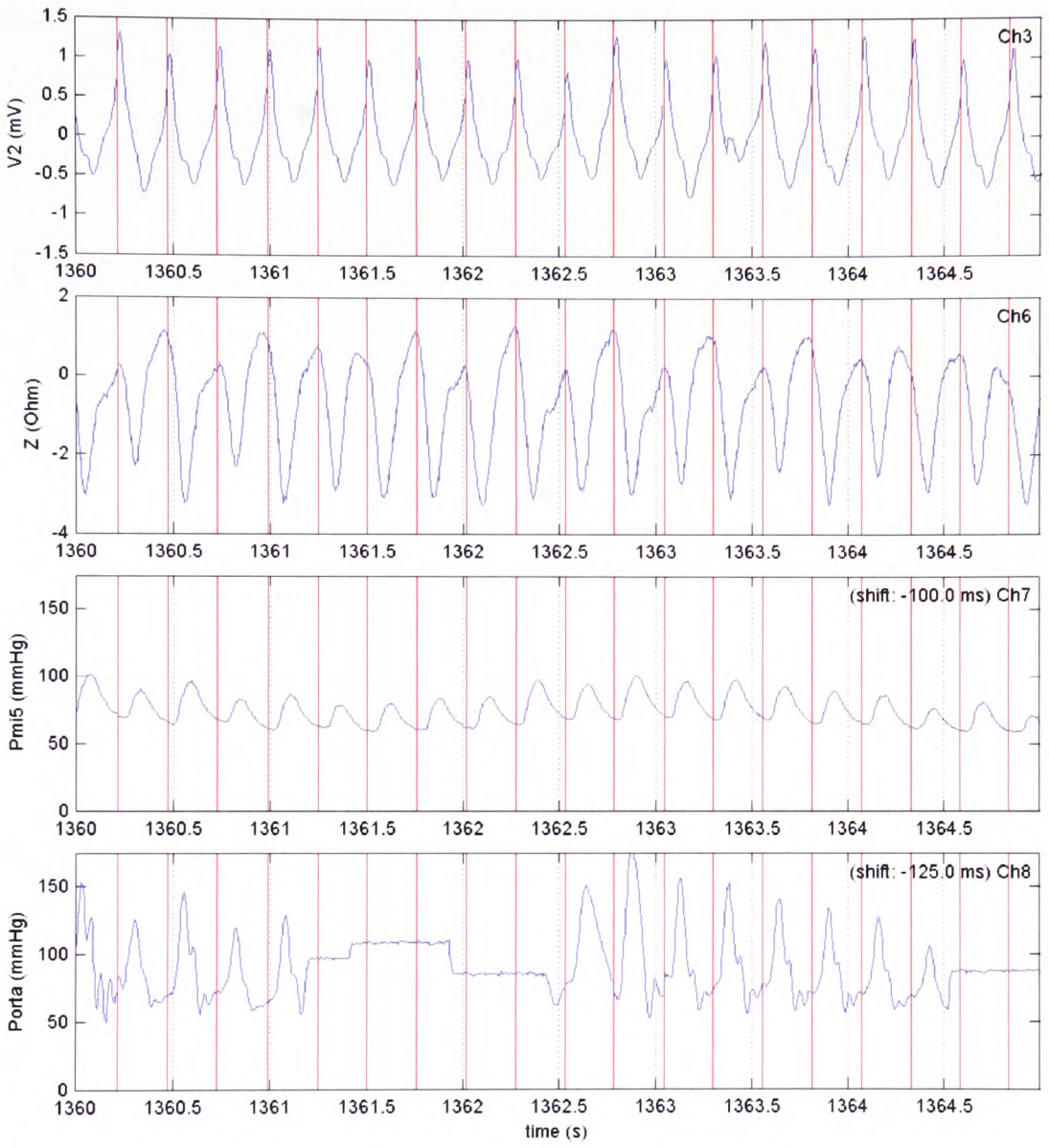


Figure: 2.8 **Stable VT**

Patient "18" during stable VT. The signals simultaneously displayed on the EP system monitor screen from top to bottom are: Surface ECG, Intracardiac impedance (Z), femoral arterial BP (Pmi5), and Protrapres signal (Porta). Note the flat segments in the Portapres waveform. These are times of device auto-calibration and were later excluded from the data analysis.

Figure: 2.9

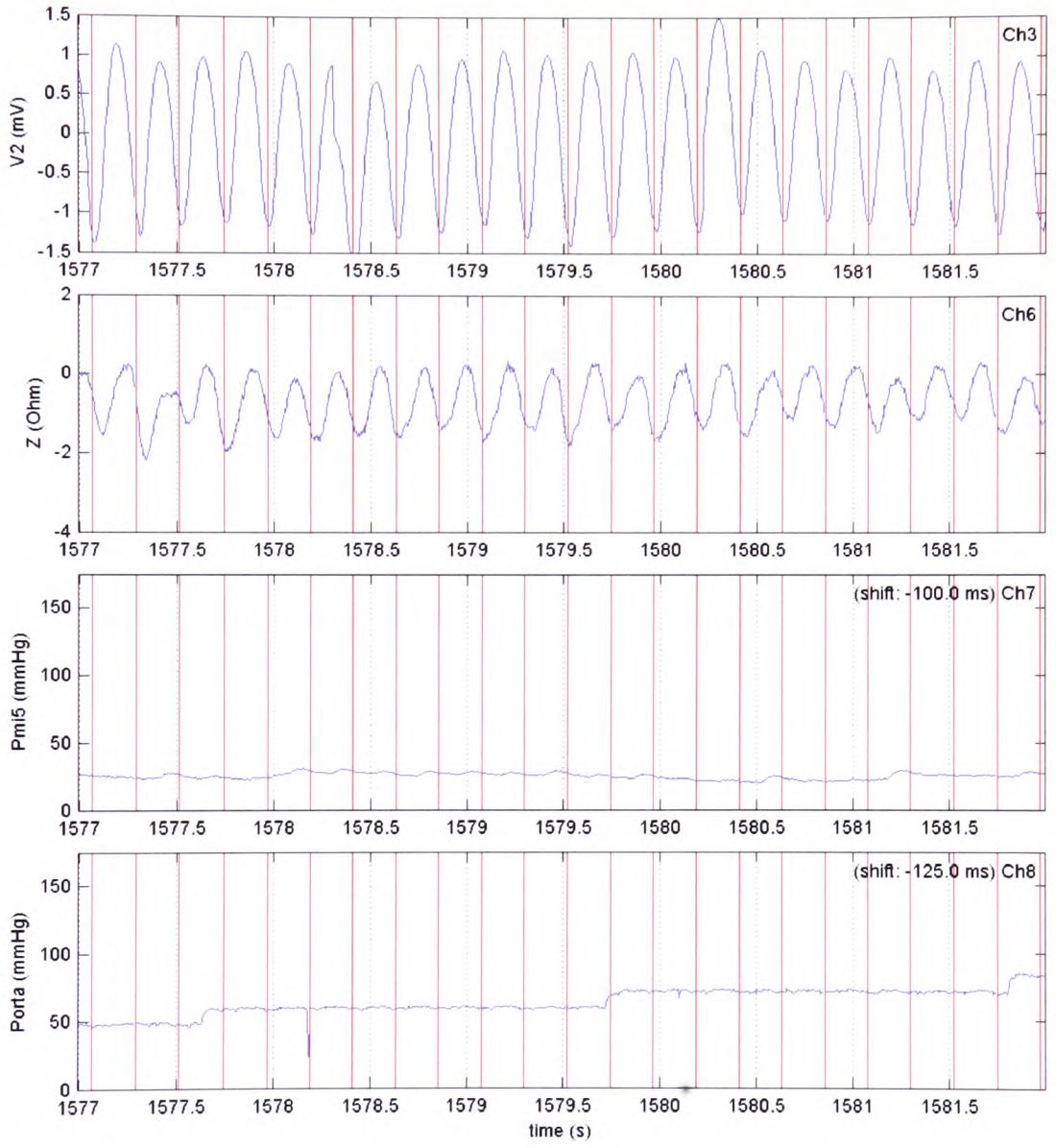


Figure: 2.9 **Unstable VT**

Patient "4" during unstable VT. The signals simultaneously displayed on the EP system monitor screen from top to bottom are: Surface ECG, Intracardiac impedance (Z), femoral arterial BP (Pmi5), and Protrapres signal (Porta). Note the complete flattening of both BP signals indicating haemodynamic instability.

Figure: 2.10

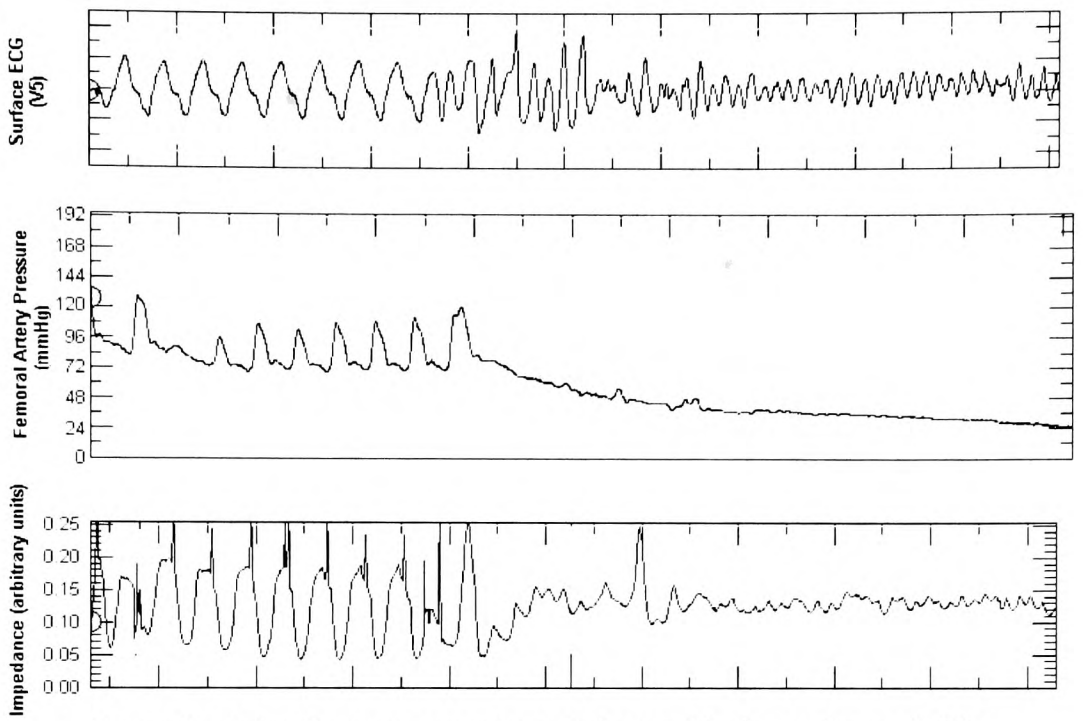


Figure: 2.10 **Onset of unstable VT and VF**

Patient "28". Signals displayed from top to bottom: Surface ECG, invasive femoral arterial pressure, and intracardiac impedance. Rapid ventricular pacing resulted in unstable polymorphic VT initially, which soon degenerated into ventricular fibrillation. Note the almost instantaneous flattening of both the BP and impedance signals immediately after the onset of the unstable arrhythmias.

2.1.5 ***Data Processing and Analysis:***

Data processing

From each procedure a digital data set was generated. All data sets were coded and numbered. Data pre-processing and analysis were performed with custom made tools in the MatLab (Mathworks Inc.) computing language. During the procedures, digital data of all the tested variables (surface ECG, IEGMs, impedance, FAP and Portapres) were recorded online onto optical discs in the EP computer system. Data were then retrieved (off line) and downloaded in ASCII Format on Re-Writable CDs (TDK 700MB-RW). Other data on patients' details such as their name, gender, age, LV function, indication for procedure, ...etc were manually entered on pre-prepared case report forms (CRFs). Printouts of the recorded log file data were also obtained for each patient. The digitally recorded data plus the CRFs and the log files printouts were then analysed offline using MatLab statistical analysis computer programme.

Prior to analysing the data, the following processing steps were performed for each data set (patient):

- Data were converted from ASCII into MatLab format. Different data channels (surface ECG, impedance, Portapres, and invasive BP) were combined and one MatLab file was produced per data set (patient).
- Both pressure curves (Portapres and invasive BP) were shifted backwards in time for the whole recording by about 10

ms (0.01 sec), which was all that was required in order to line them up with their corresponding cardiac cycles (i.e. the onset of QRS complex on the surface ECG was lined up level with the onset of the upstroke of both blood pressure curves). For invasive BP, this shift compensated for the time delay that the pressure signal took between the onset of cardiac contraction and the arrival of the pressure waves at the pressure sensor plus the transducer time required for signal processing and transmission onto the EP system. For Portapres BP, this shift compensated for the time delay in the various steps that the device took in signal recording, transmission and digitalisation prior to waveform display on the EP system screen. The compensatory delay was essentially the same for all the data sets, and it was determined by simply measuring the time difference between the QRS onset and the onset of its corresponding pressure signals (usually 10 ms $\pm$ 0.5 ms). We thought that the error value of 0.5 ms (0.0005 seconds) was extremely small to affect the study outcome in any significant way, and we have therefore ignored it for the purpose of reducing the complexity of data analysis.

- For all data channels besides impedance, the scaling factor was taken from the printouts of the EP-system (the data log files) listing the value range for each channel. The same scaling was used for all patients. For the impedance channel in particular however, the scaling depended on the

programmed impedance gain on the Inos^{2}CLS pacemaker, which was different for each individual patient as explained earlier in page 78. The full measurement range of the Inos^{2}CLS was converted to a voltage scale of a range of ± 1.95 Volts by the analogue output of the PMS1000+ programmer. Scaling for the impedance channel was adjusted for each individual data set according to the Inos^{2}CLS sensor gain settings for impedance measurement. Therefore, although the absolute impedance values may vary by a factor in the range of 1/4 - 4 for those patients, the relative evaluations remain valid for the purpose of the study as explained earlier in this chapter.

- Each data set was subdivided into different sections, each of which contained one heart rhythm type (i.e. sinus rhythm, right ventricular apical (RVA) pacing at different rates, and stable & unstable ventricular arrhythmias). This subdivision was performed according to the documented procedure findings for each patient, obtained from the "EP-log file" printouts.
- Out of all the recorded rhythms for all the patients, not all heart cycles were eventually analysed. For recorded heart cycles to be included in the analysis, the following criteria were applied:
    - For paced rhythms: a stimulation marker must be present. Also, the heart rate of the cycle being analysed and the subsequent cycles must be equal to

the programmed stimulation rate. This is to ensure that the heart was being captured by the pacing impulses.

- For intrinsic rhythms (sinus rhythm and VT): pacing stimulation markers should not be present. Cycles that contain intermittent premature ventricular complexes (PVCs) were excluded from the analysis.
- For Portapres recorded pressure channels: device calibration sequences were excluded (see below for details).
- For femoral invasive pressure channels: cycles with "spikes" in the pressure curve were excluded (see below for details).
- Cycles where the impedance signal showed significant artefact clipping, were excluded.

- Respiration has caused significant noise artefacts affecting the impedance channels in particular. This rendered any beat-to-beat analysis of the impedance data virtually un-interpretable. To minimise the effect of respiration and in order to generally reduce noise, the pressure and impedance curves were averaged for every 8 consecutive valid heart cycles within each rhythm. All further evaluation steps were based on these averaged pressure and impedance curves. The averaging over 8 cycles was implemented for all heart rates, as it appeared to reduce the respiration-induced noise signals down to an acceptable level. Slightly less respiratory

noise was detected on channels with slower heart rates (e.g. sinus rhythm and RVA pacing at 600 ms) compared to other data channels with faster heart rates (VT and RVA pacing at 400 ms). However, we felt that this slight difference in the acceptable levels of respiratory noise between slower and faster heart rate channels was rather insignificant and did not necessitate the need for different averaging settings for the different heart rate channels. The samples resulting from the averaged curves of each heart rhythm were further averaged for all patients to form a single data point for that particular rhythm. For all heart rhythms, the same number of averaged curves was used in order to get equal statistical weight for each data set (i.e. the rhythm with the smallest number of data points determined the sample size included in each data point.

Data analysis

From the pre-processed impedance and pressure curves the target quantities were extracted. Those were: stroke impedance (SZ – see below), mean arterial BP, and BP amplitude (Pulse Pressure).

Invasive femoral intra-arterial monitoring (FAP) was used for BP assessment for all studied patients. Portapres blood pressure was used as an additional non-invasive BP monitoring tool in 20 patients. The mean arterial BP (perfusion blood pressure) is normally closely related to the haemodynamic status: for a stable SVT the mean BP tends to generally show no significant relevant reduction, whereas it tends to

drop significantly for an unstable VT of sufficient duration. The mean arterial BP is calculated by averaging the blood pressure values for each cardiac cycle using the physiological equation: MABP = Diastolic BP + 1/3(Systolic BP – Diastolic BP). (Figure: 2.11).

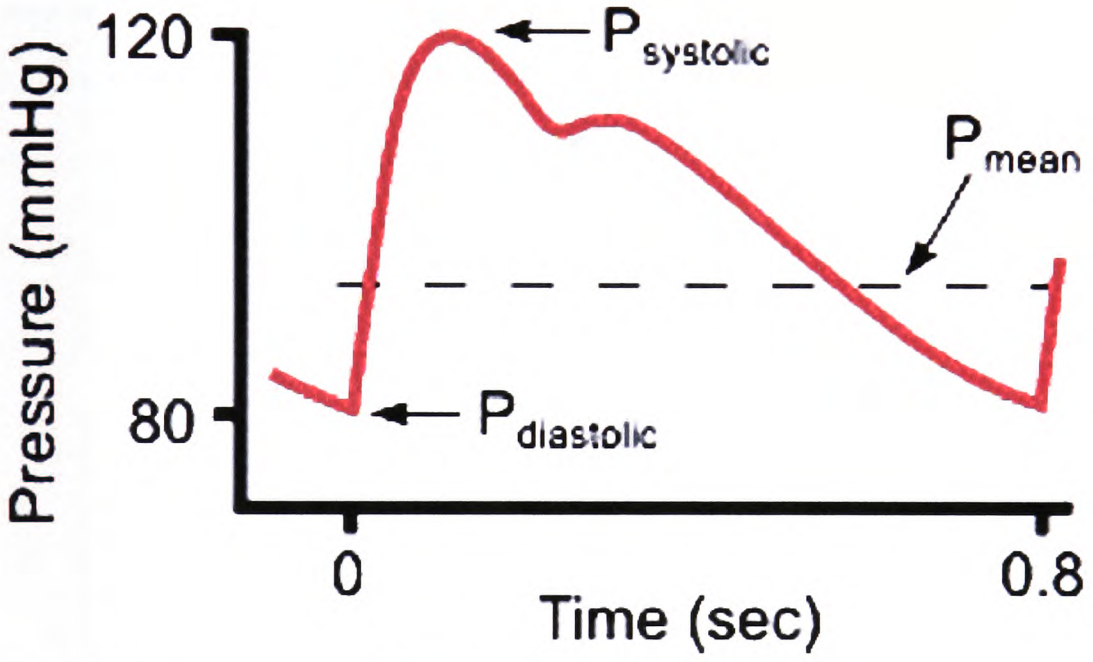


Figure: 2.11 **Mean Arterial blood pressure**

Mean arterial blood pressure (MABP) is calculated by averaging the BP values for each cardiac cycle using the following equation:
MABP = Diastolic BP + 1/3(Systolic BP – Diastolic BP). "P" in the figure stands for "Pressure"

On the other hand, the blood pressure amplitude – pulse pressure – is a rather rough estimate for changes in the stroke volume. Non-linear relationship, but rather a monotonic one, between BP amplitude and stroke volume is expected. BP amplitude is the difference between the maximum and the minimum blood pressure values within each cardiac cycle {BP amplitude (pulse pressure) = Systolic BP – Diastolic BP}.

As explained earlier in the thesis, trans-ventricular impedance value depends on the blood volume within the ventricular cavities at any given point in time. A large impedance value corresponds to a small volume (end systole) and a small impedance value corresponds to a large volume (end diastole). In order to extract a value that correlates with the pumping efficacy of the heart, a stroke volume proportional impedance value would be desirable. The impedance value extracted here is called the stroke impedance (SZ), which is defined as the difference between maximum impedance measured at end systole and the minimum impedance measured at end diastole (Figure 2.12).

Figure 2.12:

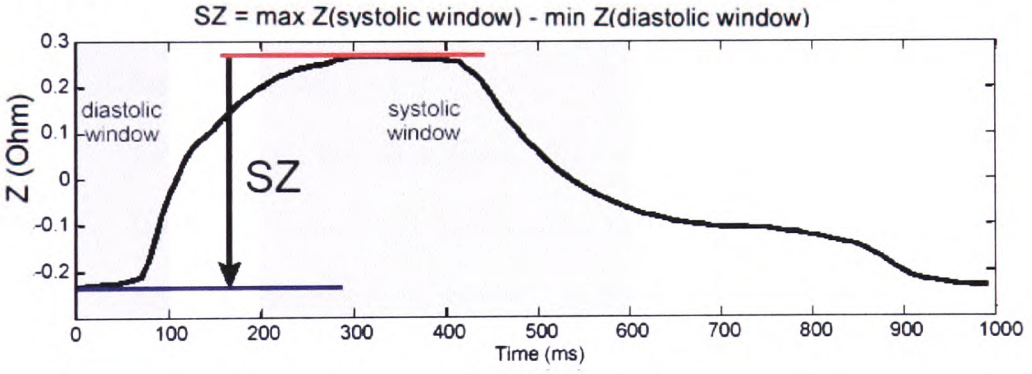


Figure 2.12: Stroke impedance (SZ)

Stroke impedance was defined as the difference between the maximum impedance at an end systolic time window and the minimum impedance at an end diastolic time window.

Extracted values from the respiration-averaged SZ and BP curves (for every consecutive 8 heart cycles) were correlated with each other. For all the data sets analysed, the stroke impedance and both pressure

evaluations were calculated as ratios or percentages relative to their respective values in sinus rhythm.

For each individual data set (patient), the following correlations were calculated:

- BP Amplitude versus heart rate; this investigated the effect of rapid pacing and induced tachy-arrhythmias on BP amplitude.
- Mean arterial BP versus heart rate; this investigated the effect of rapid pacing and induced tachy-arrhythmias on mean arterial BP.
- Mean arterial BP versus BP amplitude; this investigated the relationship between these two BP variables during different heart rhythms.
- SZ versus BP amplitude; this examined the relationship between SZ and BP amplitude, and checked whether stable and unstable arrhythmias could be separated on the impedance scale.
- SZ versus mean arterial BP; this investigated whether arrhythmia-induced changes in mean arterial BP were reflected on the impedance scale.

For each patient, the heart cycle sequences to be included in the analysis were identified by markers set during the procedure. Those markers were entered manually into the computer system along with the other data collected in real time. They defined certain time-points of the procedure; e.g. the beginning of the whole data recording, the beginning

and end of each pacing train, and the beginnings of periods of Portapres BP recording following periods of automatic device re-calibration. Those calibration sequences were recognised by their flat waveform during data analysis and were subsequently excluded from the analysis. This re-calibration occurred automatically at an average frequency of once every two to three minutes, lasting for up to ten seconds at a time. As explained earlier, those calibrations were necessary for the Portapres system to regularly re-define the continuously changing finger artery reference diameter.

The following variables were measured:

1. Systolic BP: maximum pressure during the complete heart cycle
2. Diastolic BP: minimum pressure during the complete heart cycle
3. Mean Arterial BP (MABP): Average BP value during the entire cardiac cycle
4. BP Amplitude (Pulse pressure): Systolic BP – Diastolic BP

The above values from each heart cycle were evaluated as follows:

Cardiac cycle sequences for each heart rhythm (i.e. sinus rhythm, RVA pacing at varying heart rates, and cardiac arrhythmias) were analysed. An average pressure curve of these cycles was calculated for each rhythm and the mean, systolic, diastolic and pulse blood pressures were calculated from those averaged curves. Bland-Altman plots were generated for the comparison of both measurement methods. The bias and the 2*SD values were determined for the pooled data of all patients to determine the expected systematic and stochastic deviations between both measurements. For each patient, the *changes* in BP during

different heart rhythms (pacing at different rates, stable and unstable VT) were calculated as *differences* (in mmHg) to their corresponding BP values during sinus rhythm (each patient served as their own control).

CHAPTER 3

CHAPTER 3

RESULTS

The following statistical methods were used for data analysis:

Linear regression:

For each patient, data points for each heart rhythm (sinus rhythm, pacing and induced tachyarrhythmias) were averaged to form one data point per rhythm per patient. These data points were then combined for all patients and a regression line was plotted. Correlation coefficient (*r*), statistical significance (p) and the standard error of estimation (sigma) were calculated. Linear regressions were calculated with Matlab computer statistical software programme.

T-Test:

The data were separately grouped for each of the different heart rhythms. The pressure amplitude (pulse pressure) and the stoke impedance (SZ) data points were averaged to form one value per patient for each heart rhythm applicable for that patient.

Two-sided paired t-tests were then performed for each of the abnormal heart rhythms (pacing and tachyarrhythmias) and their corresponding sinus rhythm values (for both pulse pressure and SZ). These t-tests were done with Excel computer programme.

Analysis of Variance (ANOVA):

The **AN**alysis **O**f **VA**riance (ANOVA) method is generally used when more than two groups need to be compared simultaneously in order to

determine whether they are statistically different. In this study, we compared three main groups (haemodynamically unstable VT, haemodynamically stable VT, and rapid RV pacing) using the ANOVA method. As variance homogeneity is a precondition for the ANOVA test, this has been first tested and confirmed by the Levene test and no significant differences have been found between the variances in the three groups (Levene test passed). The ANOVA test was performed with SPSS (Statistical Package for the Social Sciences) and MatLab statistical analysis computer programmes, which both generated the same results.

Bland-Altman plots:

The pressure channels (Portapres and invasive BP) were divided into short strips, each corresponding to one heart cycle. For each patient, 16 strips were analysed for each rhythm type (sinus rhythm, rapid RVA pacing, in addition to HSVT & HUVT if induced) and then averaged to form one average BP curve per rhythm per patient for each of the Portapres and invasive BP channels. Averaged BP variable values – for systolic, diastolic, mean BP and BP amplitude – were calculated for each averaged BP curve.

We generated 4 Bland-Altman plots that contain the absolute values of the pressure variables during sinus rhythm and the other three rhythm types (rapid RVA pacing, stable ands unstable VT). Each plot contained one data point per patient per heart rhythm. We plotted the average of Portapres and invasive BP measurements (X-axis) against the

difference between the two channels (Y-axis), and then calculated the bias and the standard deviation values for each plot (see page 122).

3.0 Results

We initially enrolled a total of 37 patients into the study, 9 of whom were later excluded from the analysis due to difficulty placing the coronary sinus electrodes. Out of the remaining 28 studied patients, 5 unstable VT's, 5 stable VT's and 2 stable SVT's were observed.

3.1 Correlation with FAP

3.1.0 Transventricular stroke impedance (SZ) and correlation with Femoral Arterial Pressure (FAP):

A total of 28 (25 males) patients' data — were analysed. Of these, 5 patients had inducible, haemodynamically unstable VT (HUSVT), 5 had haemodynamically stable VT (HSVT) and 2 had haemodynamically stable SVT. To simulate intrinsic VT, right ventricular apical (RVA) pacing at a rate of 400 ms (150 beats per minute) for a period of 60 seconds was performed in 22 patients. The mean age = 61$\pm$11 years, mean left ventricular ejection fraction (LVEF) = 36%, and median LVEF = 28%. The results are shown in Table 3.1, and figures 3.1 to 3.7 below. For all patients, all the resulted SZ and BP values were expressed as either fractions or percentages of their corresponding sinus rhythm values. During HUSVT, SZ dropped to 22% of its original sinus rhythm value (standard deviation = 15 – 32%) and this was associated with a simultaneous drop in mean arterial BP down to 13% of its original sinus rhythm value (standard deviation = 3 – 36%), $p < 0.001$. During HSVT,

SZ dropped to 58% of its original sinus rhythm value (standard deviation = 33 – 88%) and this was associated with a simultaneous drop in mean arterial BP down to 55% of its original sinus rhythm value (standard deviation = 24 – 77%), p = 0.008. During SVT, SZ dropped to 50% of its original sinus rhythm value (standard deviation = 49 – 51%) and this was associated with a simultaneous drop in mean arterial BP down to 76% of its original sinus rhythm value (standard deviation = 74 – 77%). During prolonged RVA pacing at 400 ms, SZ dropped to 25% of its original sinus rhythm value and this was associated with a simultaneous drop in mean arterial BP down to 30% of its original sinus rhythm value (standard deviation = 14 – 52%), $p < 0.001$.

There was generally good correlation between SZ and BP amplitude: correlation coefficient $r = 0.907$, $r^2 = 0.822$, $p < 0.001$(figure 3.4). Mean arterial BP appeared to correlate less well with SZ (figure 3.3).

Within the first 5 seconds of the onset of HUSVT, SZ dropped by 80% of its original sinus rhythm value but did stabilise thereafter. Mean arterial BP and BP amplitude exhibited similar patterns of behaviour as – within the first 5 seconds of HUSVT onset – they dropped by average percentages of 60% and 80% of their original sinus rhythm values respectively before reaching a plateau phase thereafter (figure 3.5).

Table: 3.1

Rhythm	Mean SZ (fraction of sinus rhythm value)	*P* value	Mean BP (fraction of sinus rhythm value)	*P* value	Heart rate* (bpm)	N
SVT	0.50 (0.49 - 0.51)	N/A	0.76 (0.74 – 0.77)	N/A	162 (156 - 167)	2
Stable VT	0.58 (0.33 – 0.88)	0.010	0.55 (0.24 – 0.77)	0.008	149 (112 - 228)	5
Unstable VT	0.22 (0.15 - 0.32)	<0.001	0.13 (0.03 - 0.36)	<0.001	225 (177 – 272)	5
V. pace 150 bpm	0.25 (0.05 - 1.4)	<0.001	0.30 (0.14 – 0.52)	<0.001	150	22

Table 3.1

Changes in mean stroke impedance (SZ) and mean arterial pressure (mean BP) expressed as fractions of their sinus rhythm values and mean heart rate during the studied arrhythmias. Values in parentheses show the range min-max. There was a significant fall in SZ during unstable VT and V. pacing at 400ms compared with sinus rhythm.

Figure: 3.1

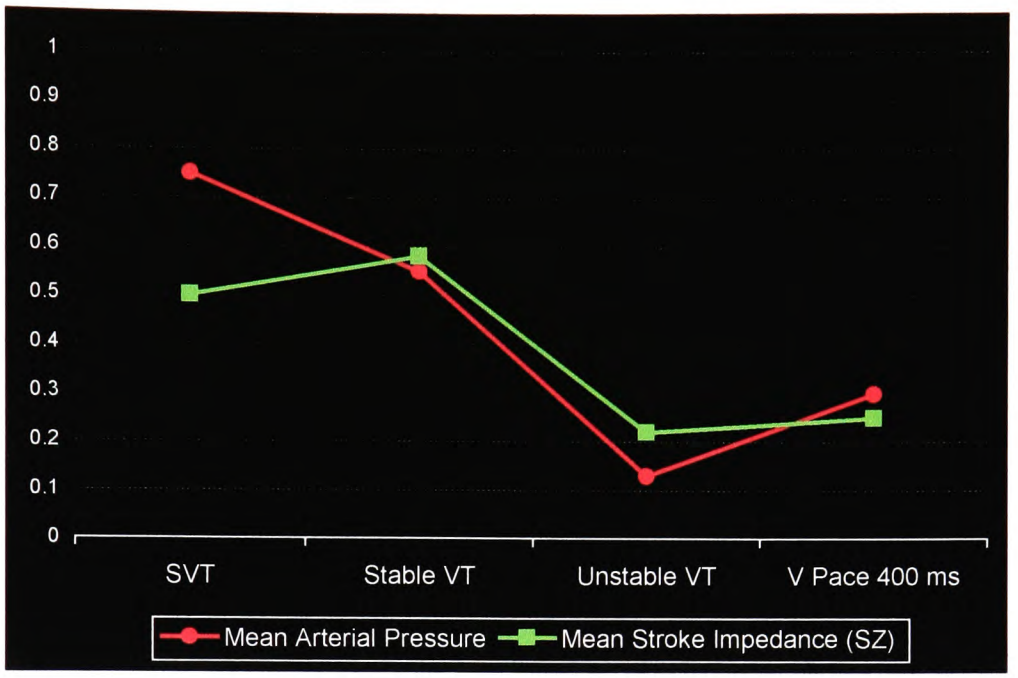


Figure 3.1

Mean values of stroke impedance (SZ) and invasive arterial pressure, expressed as fractions of their corresponding sinus rhythm values during supraventricular tachycardia (SVT), stable and unstable ventricular tachycardia (VT) and during ventricular (V) pacing at 150 beats per minute (400 ms).

Figure: 3.2

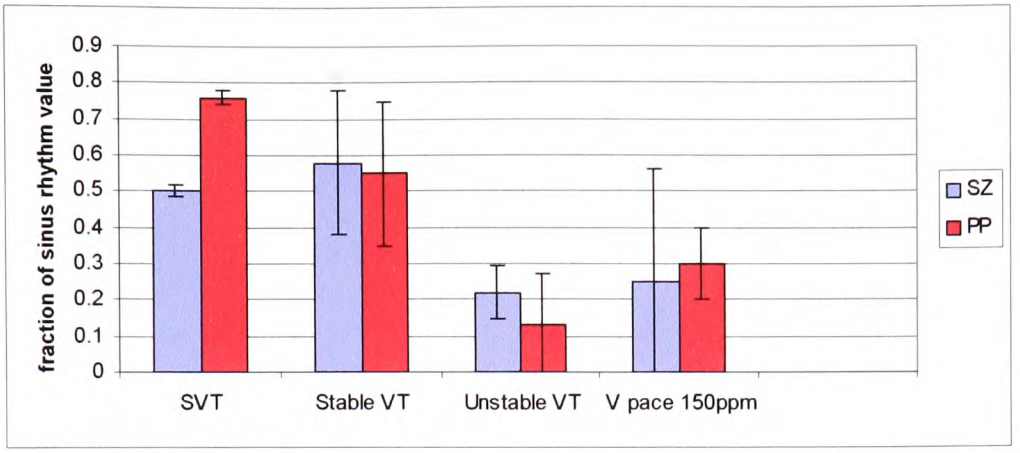


Figure: 3.2

Mean values and standard deviations of stroke impedance (SZ – blue bar) and mean arterial pressure (perfusion pressure PP – red bar) as fractions of the corresponding sinus rhythm values during supraventricular tachycardia (SVT n=2), stable (n=5) and unstable ventricular tachycardia (VT n= 5) and during ventricular (V) pacing at 400 ms (n=22).

Figure: 3.3

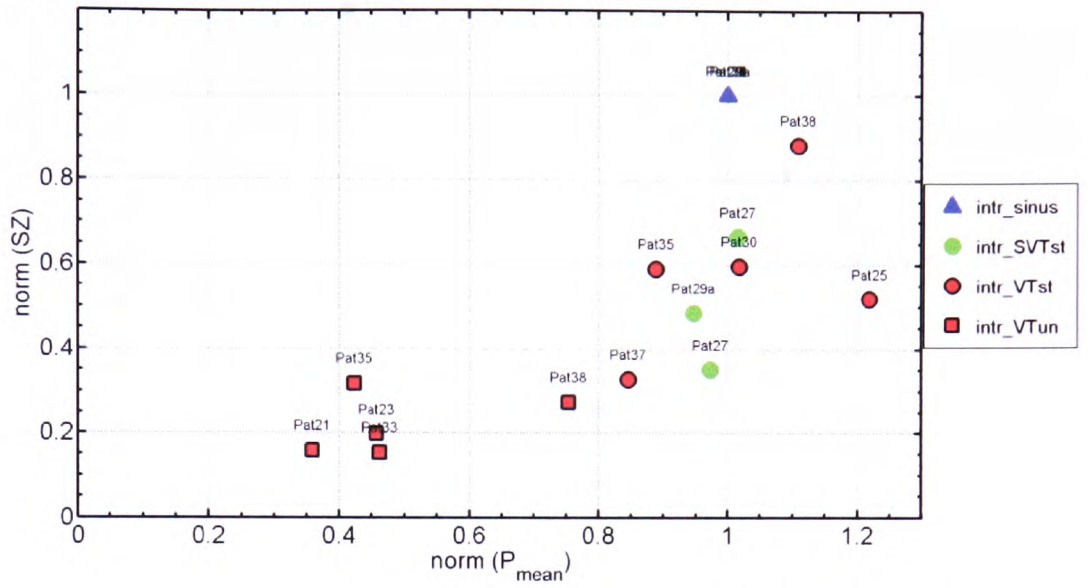


Figure: 3.3 Stroke impedance (SZ – Y-axis) versus mean arterial BP (X-axis) during induced arrhythmias (SVT, stable and unstable VT).

Each data point represents a patient. For each patient, SZ and BP values are expressed as fractions of their corresponding sinus rhythm values. Haemodynamically unstable VT appears to be associated with small SZ and Mean BP values (bottom left) whereas SVT and stable VT (which are both haemodynamically stable arrhythmias) appear to be associated with higher SZ and mean BP values (middle and top right).

Abbreviations:

Intr_sinus:	Intrinsic sinus rhythm
Intr_SVTst:	Intrinsic stable SVT
Intr_VTst:	Intrinsic stable VT
Intr_VTun:	Intrinsic unstable VT

Figure: 3.4

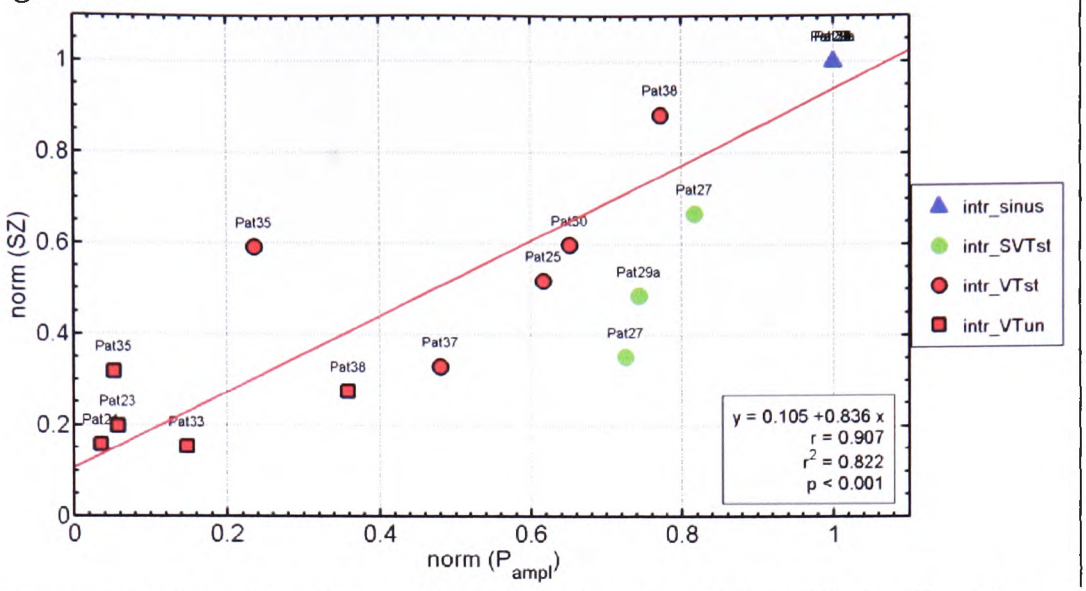


Figure: 3.4 Stroke impedance (SZ – Y-axis) versus BP amplitude (X-axis) during induced arrhythmias (SVT, stable and unstable VT).

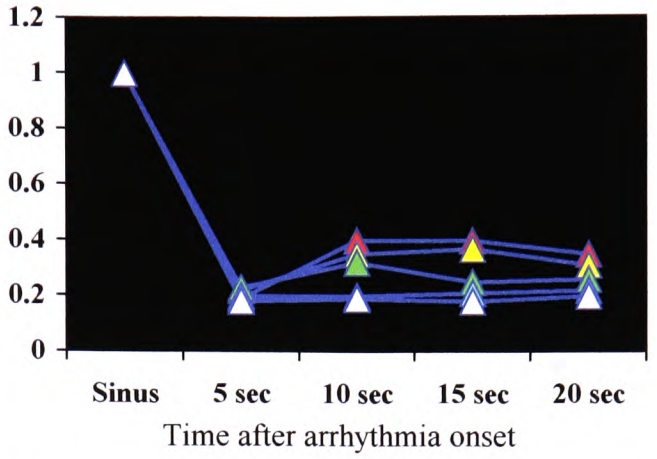
Each data point represents a patient. For each patient, SZ and BP values are expressed as fractions of their corresponding sinus rhythm values. Haemodynamically unstable VT appears to correlate well with small SZ and Mean BP values (bottom left) whereas SVT and stable VT (which are both haemodynamically stable arrhythmias) appear to correlate with higher SZ and mean BP values (middle and top right). Correlation coefficient (r) = 0.907, p <0.001

Abbreviations:

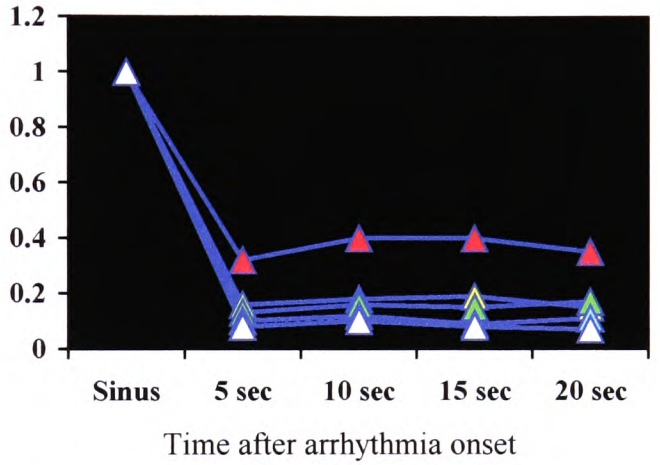
Intr_sinus:	Intrinsic sinus rhythm
Intr_SVTst:	Intrinsic stable SVT
Intr_VTst:	Intrinsic stable VT
Intr_VTun:	Intrinsic unstable VT

Figure: 3.5

Stroke Impedance (SZ)



BP amplitude (Pulse BP)



Mean BP

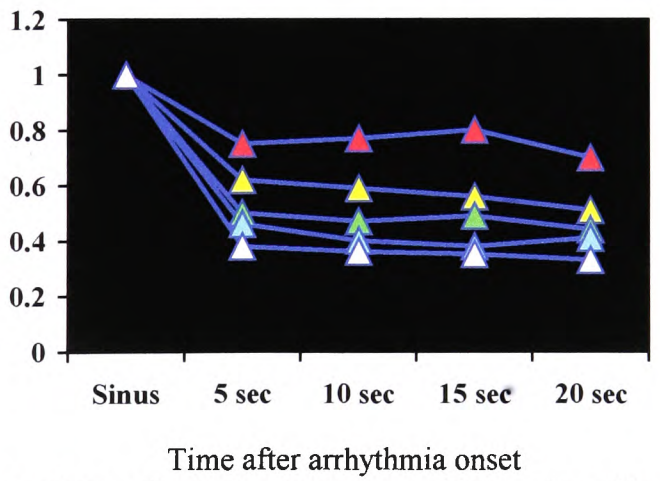
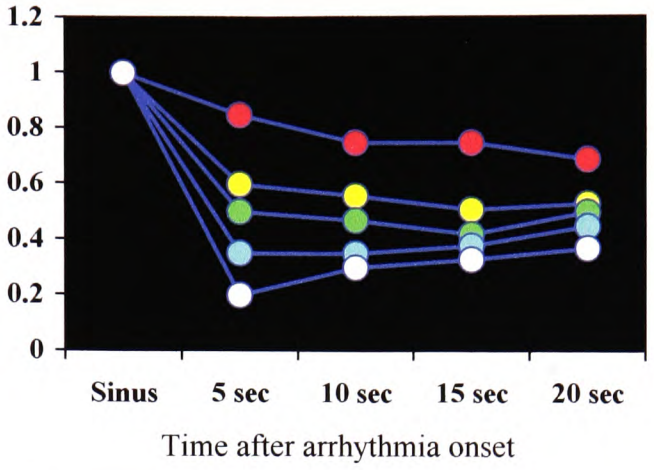


Figure: 3.5 Behaviour of stroke impedance (SZ – top diagram), BP amplitude (middle diagram) and mean BP (bottom diagram) following the onset of haemodynamically unstable VT.

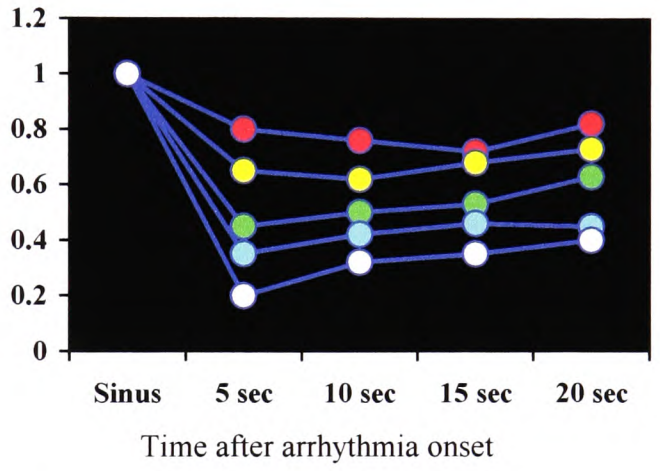
Each data point represents a patient. SZ and BP values are expressed as fractions of their corresponding sinus rhythm values. Within the first 5 seconds following the arrhythmia onset, both SZ and BP amplitude dropped acutely to about 20% of their original sinus rhythm values but sustained no further significant reduction thereafter. Mean BP only dropped to about 60% of its original sinus rhythm value within the first 5 seconds of arrhythmia onset, and sustained no further significant drops thereafter.

Figure: 3.6

Stroke Impedance (SZ)



BP amplitude (Pulse BP)



Mean BP

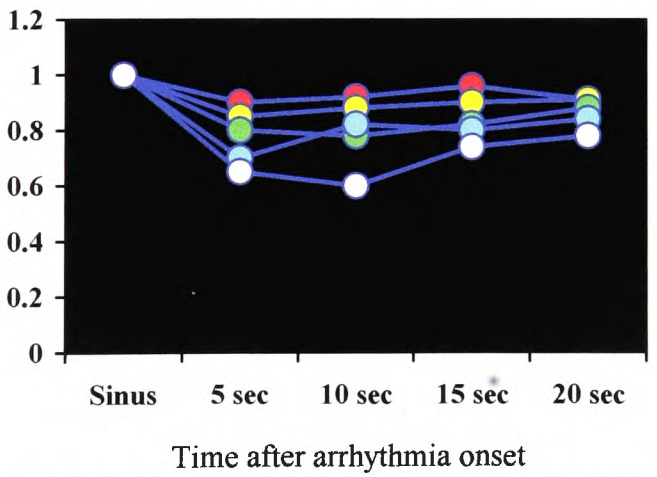
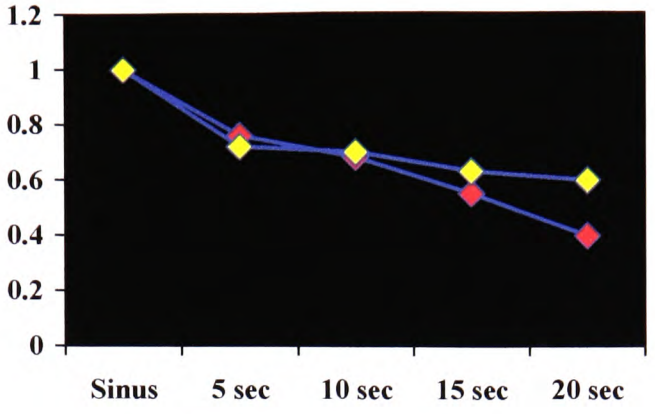


Figure: 3.6 Behaviour of stroke impedance (SZ – top diagram), BP amplitude (middle diagram) and mean BP (bottom diagram) following the onset of haemodynamically stable VT.

Each data point represents a patient. SZ and BP values are expressed as fractions of their corresponding sinus rhythm values. Within the first 5 seconds following the arrhythmia onset, both SZ and BP amplitude dropped comparably for individual patients to about 20-80% of their original sinus rhythm values but then reached a plateau with subsequent partial recovery thereafter. Mean BP only showed minimal change within the first 5 seconds of arrhythmia onset, and continued to remain stable thereafter.

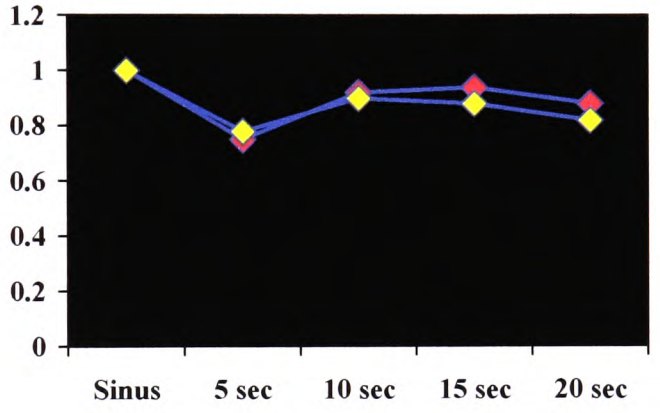
Figure: 3.7

Stroke Impedance (SZ)



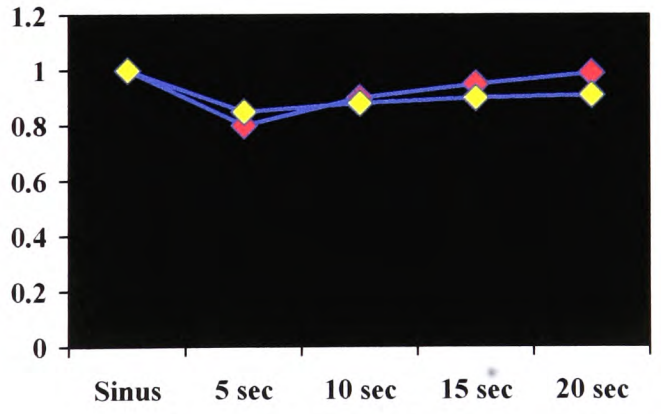
Time after arrhythmia onset

BP amplitude (Pulse BP)



Time after arrhythmia onset

Mean BP



Time after arrhythmia onset

Figure: 3.7 Behaviour of stroke impedance (SZ – top diagram), BP amplitude (middle diagram) and mean BP (bottom diagram) following the onset of haemodynamically stable SVT.

Each data point represents a patient. SZ and BP values are expressed as fractions of their corresponding sinus rhythm values. Within the first 5 seconds following the arrhythmia onset, there was no significant change in SZ, mean BP and BP amplitude. Thereafter, both BP variables continued to remain stable over time, whereas values of SZ appeared to steadily drop to about 40 –60% of their original sinus rhythm values.

3.1.1 ***Portapres and correlation with invasive BP:***

All 28 patients studied had their BP monitored invasively. In addition, 20 had their BP monitored both invasively (FAP) and non-invasively (Portapres).

All 20 patients had their invasive and Portapres BP recorded during sinus rhythm and right ventricular pacing at 400 milliseconds (ms). Out of those 20 patients, VT was induced in 8 patients, of whom 5 were haemodynamically unstable. We compared the averaged *absolute values* of both BP measurements (table 3.2). We also studied the correlation between the *changes* in both BP measurements (figures 3.8 – 3.11).

Comparison between the averaged *absolute* BP values (mmHg) of Portapres and FAP (table 3.2):

1. Systolic BP:

Sinus rhythm:	FAP: 101.93±28.43,	Portapres: 132.37±30.78
All paced rhythms:	FAP: 78.58±19.14,	Portapres: 100.01±21.25
Stable VT:	FAP: 86.42±1.15,	Portapres: 89.88±10.06
Unstable VT:	FAP: 35.00±23.55,	Portapres: 55.64±17.39

2. BP Amplitude:

Sinus rhythm:	FAP: 58.40,	Portapres: 69.80
All paced rhythms:	FAP: 31.41,	Portapres: 39.92
Stable VT:	FAP: 36.11,	Portapres: 43.10
Unstable VT:	FAP: 9.43,	Portapres: 14.67

3. Diastolic BP:

Sinus rhythm:	FAP: 43.53±24.63, Portapres: 62.56±21.03
All paced rhythms:	FAP: 47.17±15.07, Portapres: 60.09±17.15
Stable VT:	FAP: 50.31±1.73, Portapres: 46.78±0.53
Unstable VT:	FAP: 25.57±19.19, Portapres: 40.97±14.99

4. Mean Arterial BP:

Sinus rhythm:	FAP: 64.36±26.30, Portapres: 87.73±21.93
All paced rhythms:	FAP: 69.99±16.76, Portapres: 72.85±17.36
Stable VT:	FAP: 59.73±2.69, Portapres: 64.38±0.19
Unstable VT:	FAP: 29.50±20.58, Portapres: 47.38±15.03

Correlation between *the changes* in BP measurements (Portapres versus invasive BP):

1. Systolic BP (Figure 3.8):

$r = 0.961$, $r^2 = 0.924$, $p < 0.001$, N = 62

2. BP Amplitude (Figure 3.9):

$r = 0.964$, $r^2 = 0.929$, $p < 0.001$,N = 72

3. Diastolic BP (Figure 3.10):

$r = 0.853$, $r^2 = 0.728$, $p < 0.001$,N = 62

4. Mean Arterial BP (Figure 3.11):

$r = 0.968$, $r^2 = 0.937$, $p < 0.001$,N = 62

Table: 3.2

		Systolic BP	BP amplitude	Diastolic BP	MABP
Sinus Rhythm **N = 1571**	*Portapres*	132.37±30.78	69.80±22.83	62.56±21.04	84.73±21.93
	Invasive BP	101.93±28.43	58.40±18.53	43.53±24.63	64.36±26.30
Right ventricular pacing at 400 ms (150 beats per minute) **N = 2827**	*Portapres*	100.01±21.25	39.92±15.16	60.09±17.15	72.85±17.05
	Invasive BP	78.58±19.14	31.41±11.44	47.17±15.07	58.12±16.76
Stable VT **N = 123**	*Portapres*	89.88±10.06	43.10±5.50	46.78±0.53	59.73±2.69
	Invasive BP	86.42±1.15	36.11±3.76	50.31±1.73	64.38±0.19
Unstable VT **N = 295**	*Portapres*	55.64±17.39	14.67±13.80	40.97±14.99	47.38±15.03
	Invasive BP	35.00±23.55	9.43±18.62	25.57±19.19	29.50±20.58

Table: 3.2 Portapres versus Femoral invasive BP.

Comparison between the averaged *absolute values (mmHg)* of the different BP components (systolic BP, diastolic BP, mean arterial BP {MABP} and BP amplitude) for both Portapres and invasive BP. "N" stands for the number of averaged heartbeats.

Figure: 3.8

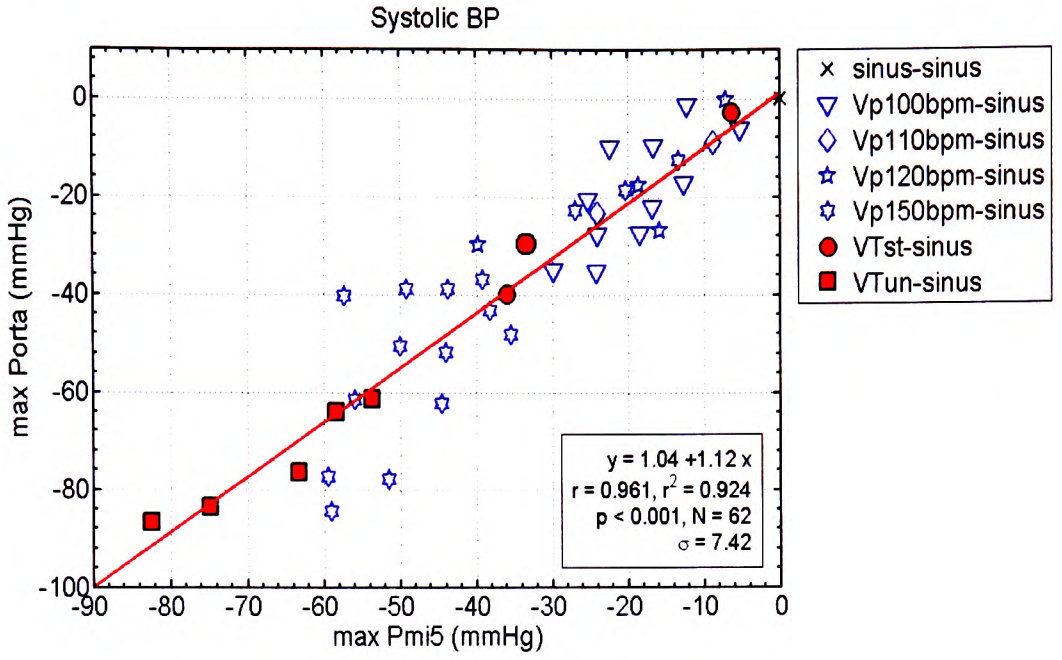


Figure: 3.8

Correlation between *changes* in systolic BP measurements of Portapres (Porta) (Y-axis) versus femoral invasive BP (Pmi5) (X-axis)

Each data point represents a patient. Values are expressed as *changes* (in mmHg units) from their original sinus rhythm value (x), which is positioned at intercept point of "0 mmHg". For haemodynamically unstable VT, haemodynamically stable VT, and for right ventricular paced rhythms, the *change* in systolic BP of Portapres appear to correlate well with that of invasive BP (correlation coefficient $r = 0.961$, N = 62, $p < 0.001$). "N" stands for the averaged heart beats per patient.

Abbreviations

Sinus-sinus:	Sinus rhythm
Vp100bpm-sinus:	right ventricular pacing at 100 beats per minute
Vp110bpm-sinus:	right ventricular pacing at 110 beats per minute
Vp120bpm-sinus:	right ventricular pacing at 120 beats per minute
Vp150bpm-sinus:	right ventricular pacing at 150 beats per minute
VTst-sinus:	Haemodynamically stable VT
VTun-sinus:	Haemodynamically unstable VT

Figure: 3.9

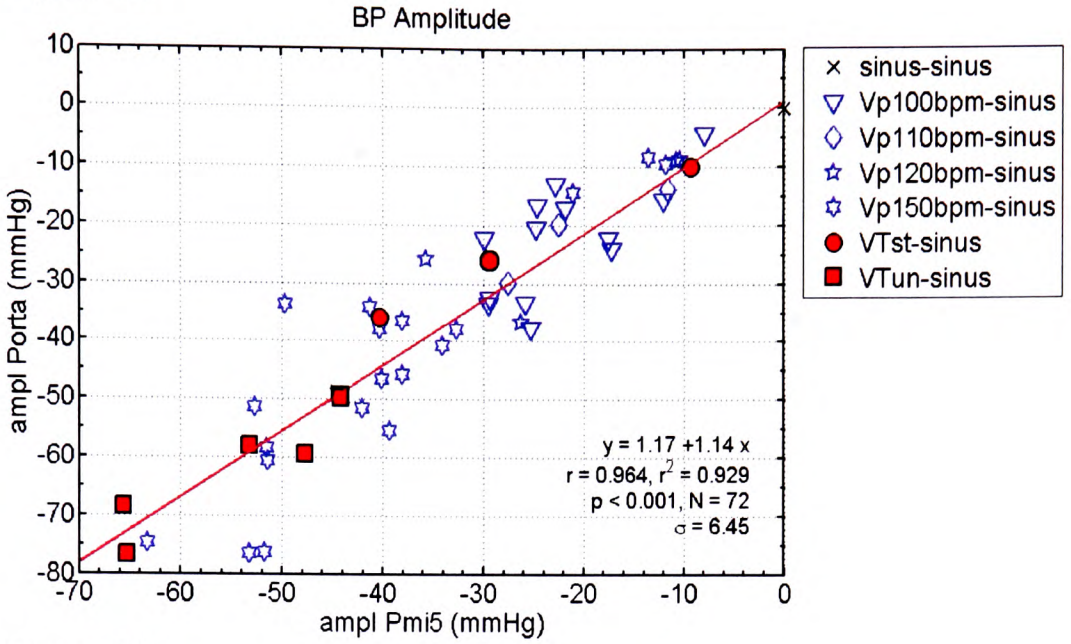


Figure: 3.9

Correlation between *changes* in BP amplitude measurements of Portapres (Porta) (Y-axis) versus femoral invasive BP (Pmi5) (X-axis)

Each data point represents a patient. Values are expressed as *changes* (in mmHg units) from their original sinus rhythm value (x), which is positioned at intercept point of "0 mmHg". For haemodynamically unstable VT, haemodynamically stable VT, and for right ventricular paced rhythms, the *change* in BP amplitude of Portapres appear to correlate well with that of invasive BP (correlation coefficient $r = 0.964$, N = 72, $p < 0.001$). "N" stands for the averaged heart beats per patient.

Abbreviations

Sinus-sinus:	Sinus rhythm
Vp100bpm-sinus:	right ventricular pacing at 100 beats per minute
Vp110bpm-sinus:	right ventricular pacing at 110 beats per minute
Vp120bpm-sinus:	right ventricular pacing at 120 beats per minute
Vp150bpm-sinus:	right ventricular pacing at 150 beats per minute
VTst-sinus:	Haemodynamically stable VT
VTun-sinus:	Haemodynamically unstable VT

Figure: 3.10

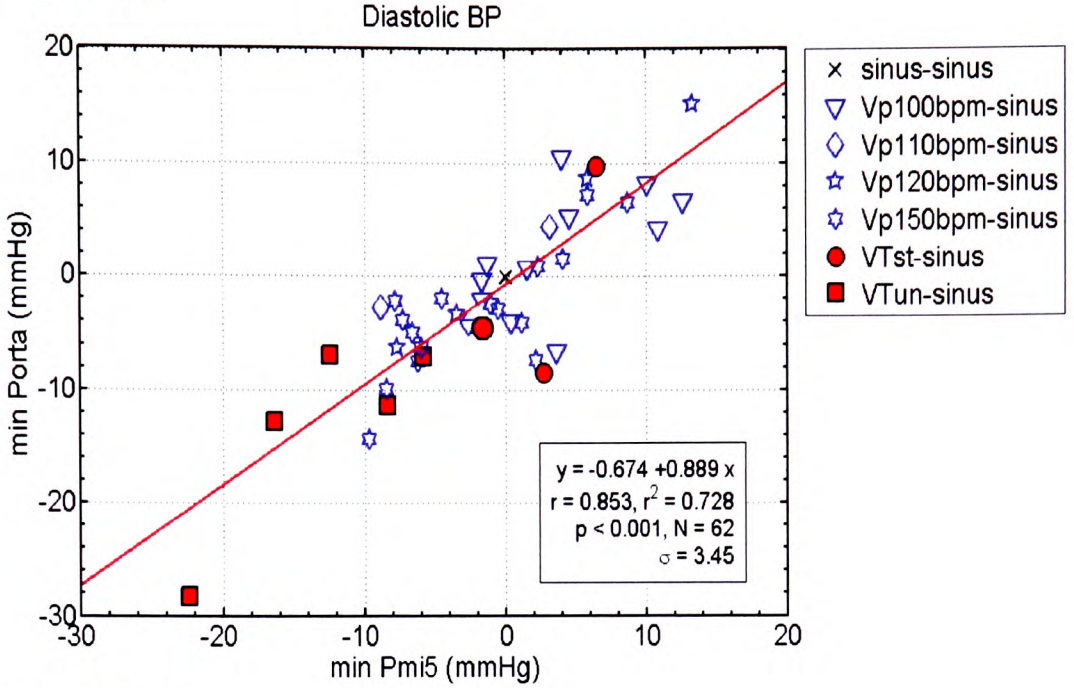


Figure: 3.10

Correlation between *changes* in diastolic BP measurements of Portapres (Porta) (Y-axis) versus femoral invasive BP (Pmi5) (X-axis)

Each data point represents a patient. Values are expressed as *changes* (in mmHg units) from their original sinus rhythm value (x), which is positioned at intercept point of "0 mmHg". For haemodynamically unstable VT, haemodynamically stable VT, and for right ventricular paced rhythms, the *change* in diastolic BP of Portapres appears to correlate well with that of invasive BP (correlation coefficient $r = 0.853$, N = 62, $p < 0.001$). "N" stands for the averaged heart beats per patient.

Abbreviations

Sinus-sinus:	Sinus rhythm
Vp100bpm-sinus:	right ventricular pacing at 100 beats per minute
Vp110bpm-sinus:	right ventricular pacing at 110 beats per minute
Vp120bpm-sinus:	right ventricular pacing at 120 beats per minute
Vp150bpm-sinus:	right ventricular pacing at 150 beats per minute
VTst-sinus:	Haemodynamically stable VT
VTun-sinus:	Haemodynamically unstable VT

Figure: 3.11

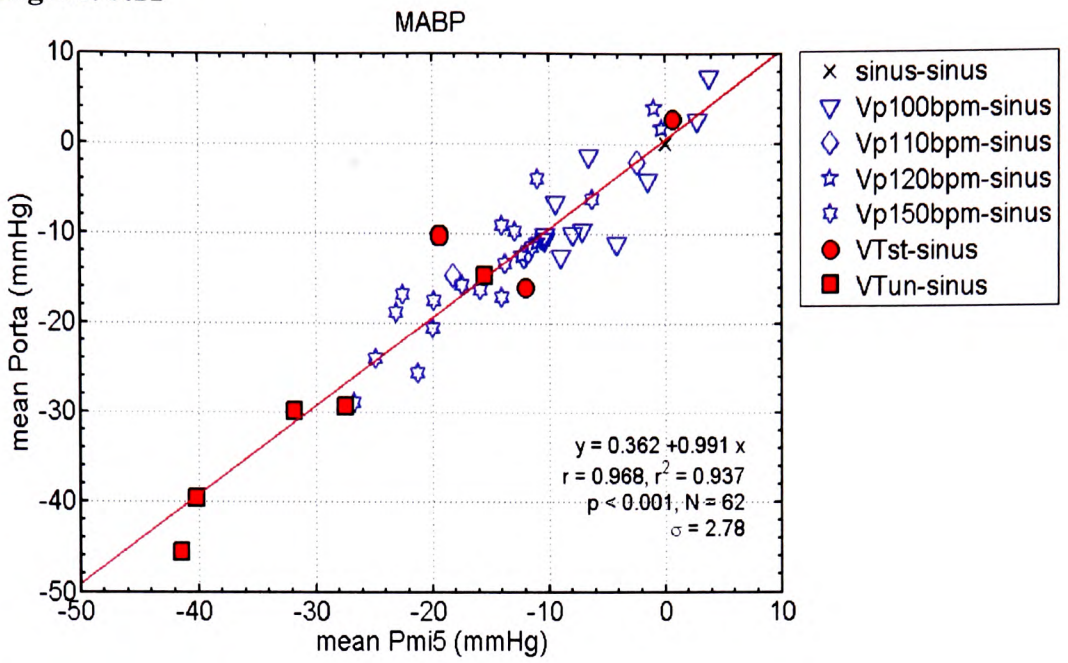


Figure: 3.11

Correlation between *changes* in mean arterial BP (MABP) measurements of Portapres (Porta) (Y-axis) versus femoral invasive BP (Pmi5) (X-axis)

Each data point represents a patient. Values are expressed as *changes* (in mmHg units) from their original sinus rhythm value (x), which is positioned at intercept point of "0 mmHg". For haemodynamically unstable VT, haemodynamically stable VT, and for right ventricular paced rhythms, the *change* in mean BP of Portapres appears to correlate well with that of invasive BP (correlation coefficient $r = 0.968$, $N = 62$, $p < 0.001$). "N" stands for the averaged heart beats per patient.

Abbreviations

Sinus-sinus:	Sinus rhythm
Vp100bpm-sinus:	right ventricular pacing at 100 beats per minute
Vp110bpm-sinus:	right ventricular pacing at 110 beats per minute
Vp120bpm-sinus:	right ventricular pacing at 120 beats per minute
Vp150bpm-sinus:	right ventricular pacing at 150 beats per minute
VTst-sinus:	Haemodynamically stable VT
VTun-sinus:	Haemodynamically unstable VT

Bland-Altman evaluation of Portapres and invasive BP:

Bland-Altman plots – Figures 3.12 to 3.17 – were used to evaluate the average values of Portapres and invasive BP measurements (X-axis) in addition to the differences between the two BP measurements (Y-axis) for each of the 20 patients. This evaluation was done for each of the BP variables (mean BP, BP amplitude, systolic and diastolic BP) during sinus rhythm, right ventricular apical pacing at varying rates, and induced stable and unstable ventricular arrhythmias.

During sinus rhythm (figure 3.12), the average absolute value of mean Portapres and invasive BP measurements (X-value) was around 80 mmHg. The difference between the two BP channels (Y-value) ranged from about -10 to +50 mmHg. The bias (the mean difference between the two BP channels) was 8.26 mmHg, meaning that – on average – the mean Portapres BP was 8.26 mmHg higher than the mean invasive BP during sinus rhythm. 2*SD (twice the standard deviation of the difference between Portapres and invasive BP measurements) was 30 mmHg. This means that statistically – for 95% of cases – the difference between Portapres and invasive mean BP measurements was not greater than 30 mmHg.

Figure: 3.12

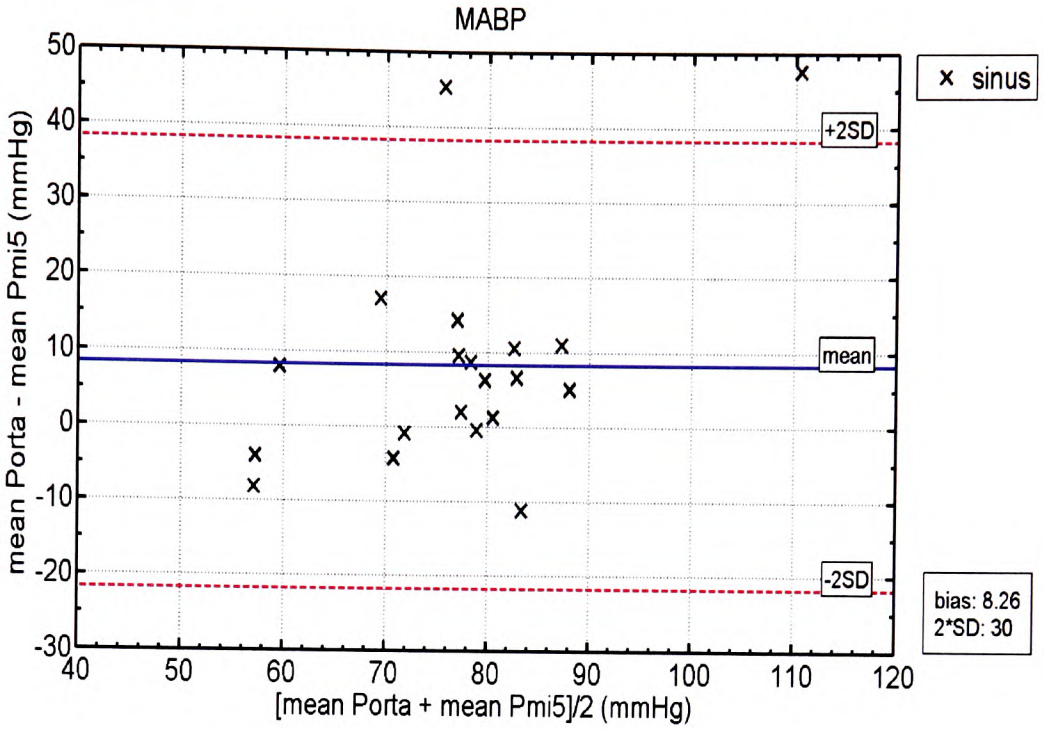


Figure: 3.12 Bland-Altman plotting of mean Portapres (Porta) and invasive BP (Pmi5) during sinus rhythm.

Each data point represents one absolute value for one patient. On the X-axis is the average of Portapres and invasive BP measurements, and on the Y-axis is the difference between the two BP channels. The X-axis values cluster around 80 mmHg. This means, that during sinus rhythm the average of both BP channels is around 80 mmHg.

The difference between both channels (Y-axis) ranges from about -10 to +50 mmHg. The bias, which is the mean difference between the two BP channels, is 8.26 mmHg, meaning that the Portapres value was 8.26 mmHg higher than the invasive value on average. 2*SD, which is defined as: *"twice the standard deviation of the difference between the two BP channels"* was 30 mmHg. This means that for 95% of cases, the difference between Portapres and invasive measurement was not larger than 30 mmHg.

For all the other heart rhythms (paced, stable and unstable VT), the Portapres and invasive BP values plotted on the Bland-Altman diagrams below (Figures: 3.13 to 3.17) were expressed as the *"relative differences"* in BP to their corresponding sinus rhythm values, thus highlighting how the pressure has changed from sinus rhythm to the new rhythm(s).

During right ventricular pacing (Figure 3.13), the average of Portapres and invasive mean BP (X-axis) ranged between –30 and +5 mmHg, meaning that – for right ventricular pacing – the mean blood pressure has *changed* in the range of –30 mmHg (i.e. decreased) to +5 mmHg (i.e. increased) relative to the sinus rhythm value. Furthermore, the pressure reduction measured due to pacing was nearly identical between the two BP measurements. The calculated bias was therefore very small = 0.58 mmHg. 2*SD = 7.3mmHg, meaning that in 95% of cases the *change* in BP measured during pacing differed between the two channels by a maximum of 7.3 mmHg.

Figure: 3.13

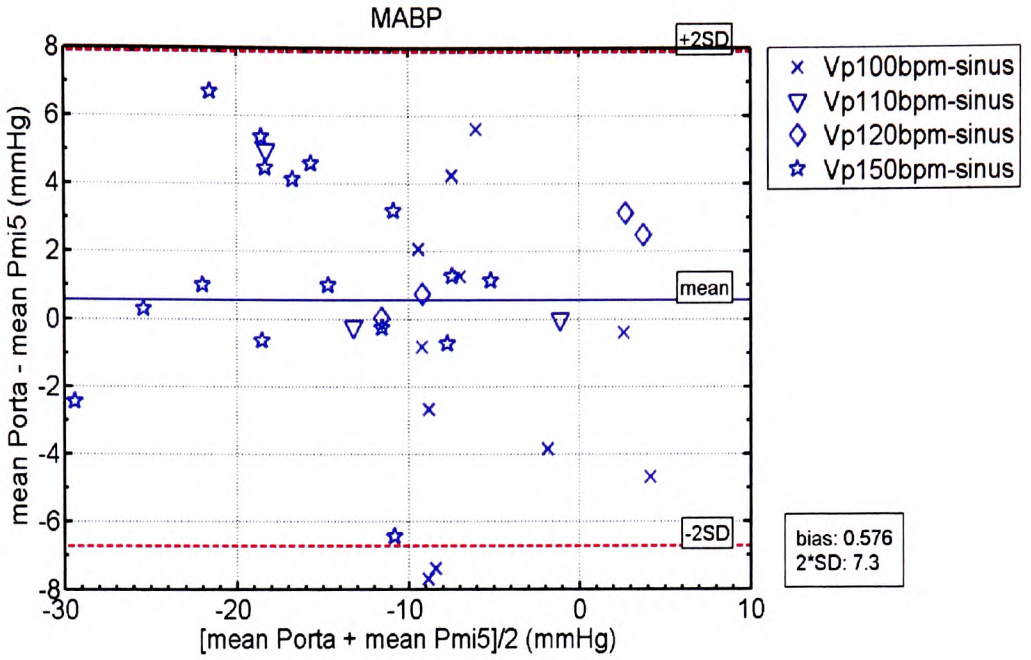


Figure: 3.13 Bland-Altman plot showing the effect of right ventricular pacing on the *change* of mean Portapres (Porta) and invasive BP (Pmi5) measurements *relative* to their sinus rhythm values.

On the X-axis is the average of Portapres and invasive BP, and on the Y-axis is the difference between the two BP channels. The average of Portapres and invasive BP ranged between –30 and +5 mmHg, meaning that – for right ventricular pacing – the blood pressure has changed in the range of –30 mmHg (i.e. decreased) to +5 mmHg (i.e. increased) relative to the sinus rhythm value.

The pressure reduction measured due to pacing was nearly identical between the two BP measurements. The calculated bias was therefore very small = 0.58 mmHg. 2*SD = 7.3mmHg, meaning that in 95% of cases the change in BP measured during pacing differed between the two channels by a maximum of 7.3 mmHg.

Abbreviations:

Vp100-sinus: Right ventricular pacing at 100 beats per minute
Vp110-sinus: Right ventricular pacing at 110 beats per minute
VP120-sinus: Right ventricular pacing at 120 beats per minute
VP150-sinus: Right ventricular pacing at 150 beats per minute

During ventricular arrhythmias (Figure 3.14), the average *change* in Portapres and invasive *BP amplitude* (X-axis) ranged between –72 and –25 mmHg, meaning that – for the combination of stable and unstable VT – the blood pressure amplitude has dropped by 72 mmHg to 25 mmHg from the sinus rhythm value. The bias (mean difference between the two BP measurements) = 2.28 mmHg, 2*SD = 17.7 mmHg.

During ventricular arrhythmias (Figure 3.15), the average reduction of Portapres and invasive *systolic BP* relative to sinus rhythm (X-axis) ranged between zero and –40 mmHg for stable VT, and between –30 and –85 mmHg for unstable VT. For the combination of paced rhythm and all VT, The bias (mean difference between the two BP measurements) = 1.71 mmHg, 2*SD = 17.4 mmHg.

During ventricular arrhythmias (Figure 3.16), the average change of Portapres and invasive *mean BP* relative to sinus rhythm (X-axis) ranged between +6 and –17 mmHg for stable VT, and between –12 and –46 mmHg for unstable VT. For the combination of paced rhythm and all VT, The bias (mean difference between the two BP measurements) = 0.256 mmHg, 2*SD = 6.15 mmHg.

During VTs (Figure 3.17), the average change of Portapres and invasive *diastolic BP* relative to sinus rhythm (X-axis) ranged between +8 and –3 mmHg for stable VT, and between –2 and – 26 mmHg for unstable VT. For the paced rhythms and all VT, The bias (mean difference between the two BP measurements) = 0.588 mmHg, 2*SD = 6.99 mmHg.

Figure: 3.14

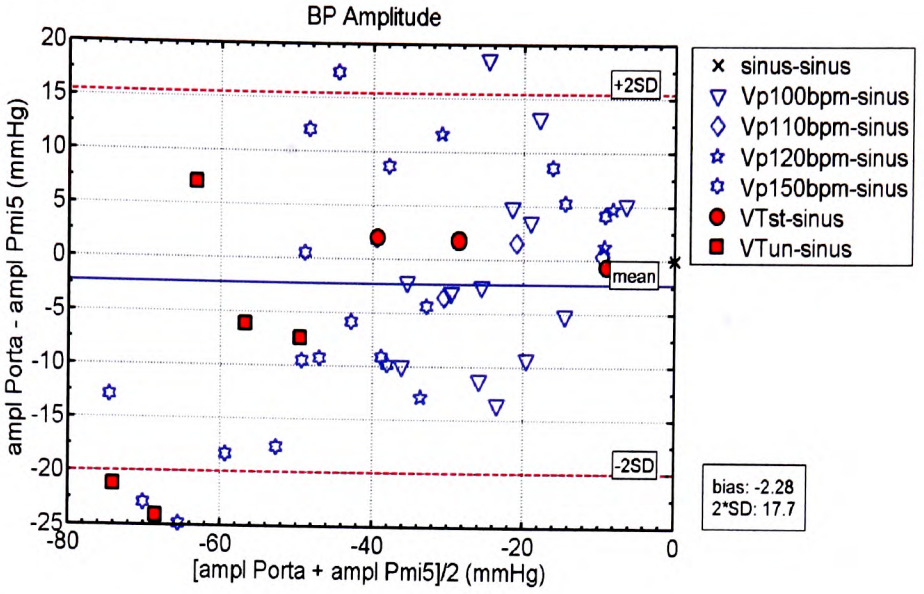


Figure: 3.14 Bland-Altman plot showing the effect of right ventricular pacing and ventricular arrhythmias on the *change* of Portapres (Porta) and invasive BP (Pmi5) amplitude measurements *relative* to their sinus rhythm values.

On the X-axis is the average of Portapres and invasive BP, and on the Y-axis is the difference between the two BP channels. The average of Portapres and invasive BP amplitude ranged between -72 and -25 mmHg, meaning that – for ventricular arrhythmias – the blood pressure amplitude has reduced by 25 to 72 mmHg relative to the sinus rhythm value.

The pressure reduction measured due to pacing and VT was very similar between the two BP measurements, resulting in a small calculated bias = -2.28 mmHg. 2*SD = 17.7 mmHg, meaning that in 95% of cases the change in BP measured during pacing an VT differed between the two channels by a maximum of 17.7 mmHg.

Abbreviations:

Vp100-sinus: Right ventricular pacing at 100 beats per minute
Vp110-sinus: Right ventricular pacing at 110 beats per minute
VP120-sinus: Right ventricular pacing at 120 beats per minute
VP150-sinus: Right ventricular pacing at 150 beats per minute
VTst-sinus: Haemodynamically stable VT
VTun-sinus: Haemodynamically unstable VT

Figure: 3.15

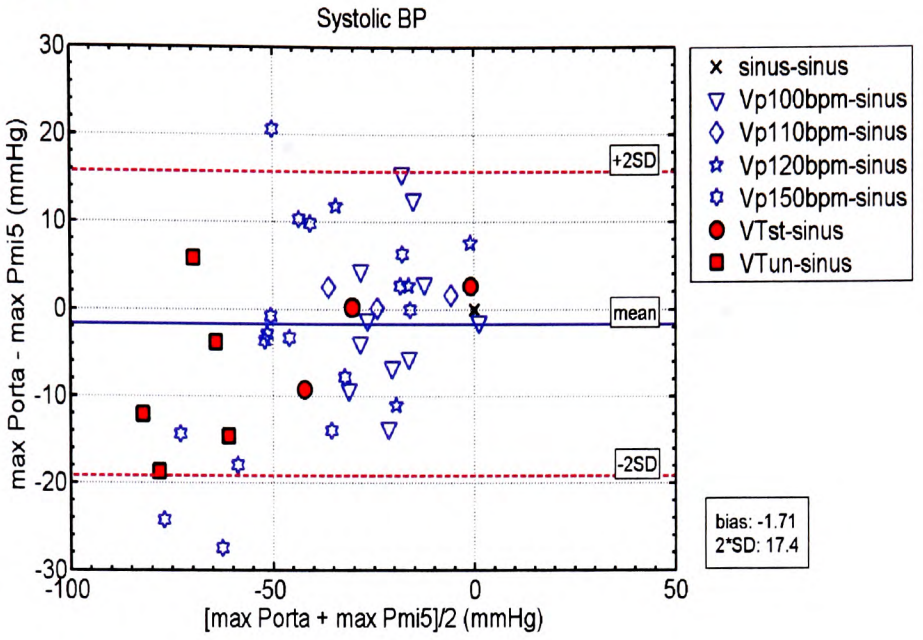


Figure: 3.15 Bland-Altman plot showing the effect of right ventricular pacing and ventricular arrhythmias on the *change* of Portapres (Porta) and invasive systolic BP (Pmi5) measurements *relative* to their sinus rhythm values.

On the X-axis is the average of Portapres and invasive systolic BP, and on the Y-axis is the difference between the two BP channels. During ventricular arrhythmias, the average reduction of Portapres and invasive systolic BP relative to sinus rhythm (X-axis) ranged between zero and –40 mmHg for stable VT, and between –30 and –85 mmHg for unstable VT.

The pressure reduction measured due to pacing and VT was very similar between the two BP measurements, resulting in a small calculated bias = -1.71 mmHg. 2*SD = 17.4 mmHg, meaning that in 95% of cases the change in BP measured during pacing an VT differed between the two channels by a maximum of 17.4 mmHg.

Abbreviations:

Vp100-sinus: Right ventricular pacing at 100 beats per minute
Vp110-sinus: Right ventricular pacing at 110 beats per minute
VP120-sinus: Right ventricular pacing at 120 beats per minute
VP150-sinus: Right ventricular pacing at 150 beats per minute
VTst-sinus: Haemodynamically stable VT
VTun-sinus: Haemodynamically unstable VT

Figure: 3.16

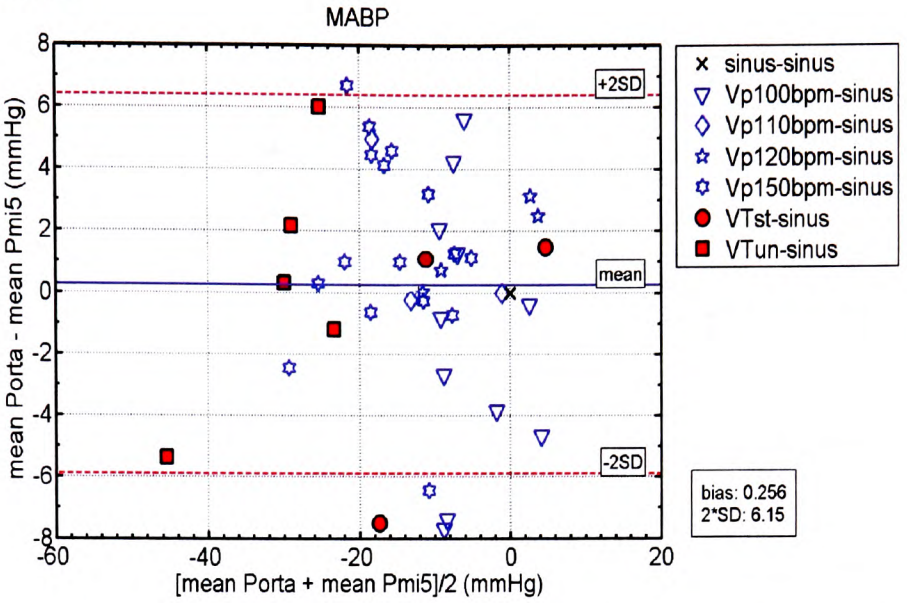


Figure: 3.16 Bland-Altman plot showing the effect of right ventricular pacing and ventricular arrhythmias on the *change* of Portapres (Porta) and invasive mean BP (Pmi5) measurements *relative* to their sinus rhythm values.

On the X-axis is the average of Portapres and invasive mean BP, and on the Y-axis is the difference between the two BP channels. During ventricular arrhythmias, the average change of Portapres and invasive mean BP relative to sinus rhythm (X-axis) ranged between +6 and –17 mmHg for stable VT, and between –12 and –46 mmHg for unstable VT.

The pressure reduction measured due to pacing and VT was almost identical between the two BP measurements, resulting in a small calculated bias = 0.256 mmHg. 2*SD = 6.15 mmHg, meaning that in 95% of cases the change in BP measured during pacing an VT differed between the two channels by a maximum of 6.15 mmHg.

Abbreviations:

Vp100-sinus: Right ventricular pacing at 100 beats per minute
Vp110-sinus: Right ventricular pacing at 110 beats per minute
VP120-sinus: Right ventricular pacing at 120 beats per minute
VP150-sinus: Right ventricular pacing at 150 beats per minute
VTst-sinus: Haemodynamically stable VT
VTun-sinus: Haemodynamically unstable VT

Figure: 3.17

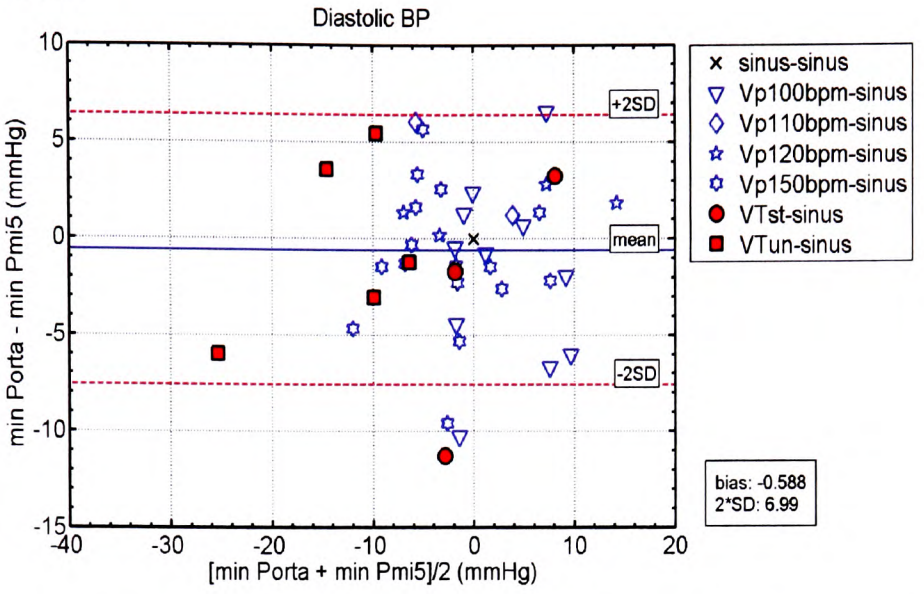


Figure: 3.17 Bland-Altman plot showing the effect of right ventricular pacing and ventricular arrhythmias on the *change* of Portapres (Porta) and invasive diastolic BP (Pmi5) measurements *relative* to their sinus rhythm values.

On the X-axis is the average of Portapres and invasive diastolic BP, and on the Y-axis is the difference between the two BP channels. During ventricular arrhythmias, the average change of Portapres and invasive diastolic BP relative to sinus rhythm (X-axis) ranged between +8 and –3 mmHg for stable VT, and between –2 and –26 mmHg for unstable VT.

The pressure reduction measured due to pacing and VT was almost identical between the two BP measurements, resulting in a small calculated bias = -0.588 mmHg. 2*SD = 6.99 mmHg, meaning that in 95% of cases the change in BP measured during pacing an VT differed between the two channels by a maximum of 6.99 mmHg.

Abbreviations:

Vp100-sinus: Right ventricular pacing at 100 beats per minute
Vp110-sinus: Right ventricular pacing at 110 beats per minute
VP120-sinus: Right ventricular pacing at 120 beats per minute
VP150-sinus: Right ventricular pacing at 150 beats per minute
VTst-sinus: Haemodynamically stable VT
VTun-sinus: Haemodynamically unstable VT

CHAPTER 4

CHAPTER 4

LV TRANSVENTRICULAR INTRACARDIAC IMPEDANCE AND HAEMODYNAMIC CORRELATION (DISCUSSION)

4.0 Introduction

As discussed earlier in the thesis, during myocardial contraction, the impedance continuously increases reaching its maximum in late systole. This impedance increase correlates with right ventricular contractility, and thus, with the inotropic state of the heart. In current commercially available DDDR pacing systems, integrated information from the changing ventricular impedance is used for closed-loop regulation of the rate response. In 1992, Ruiter *et al* [157] tested the stability and dynamic behaviour of pre-ejection interval (PEI) in patients who have "Precept" pacing systems that use right ventricular intracardiac impedance waveform for such haemodynamic evaluation of PEI. This was conducted under various forms of exercise and also during postural changes. Although significant patient-to-patient variability of the sensor values was observed, the chronic stability of PEI was excellent in the total device experience of 147 months. In all patients, PEI shortened significantly during bicycle ergometry and was associated with an increase in pacing rate in all patients. The strong and highly significant correlation between dP/dt*max* and unipolar RV impedance for both ventricular pacing and intrinsic heart rhythm has already been proven as discussed in earlier chapters [133].

Other previous studies have also shown comparable correlations between stroke volume and impedance [158] suggesting that impedance could act as a haemodynamic sensor. However, most studies have examined impedance changes either at rest or during exercise where changes in heart rate were not extreme. To increase the capabilities of modern implantable defibrillators any impedance sensor would need to be effective across a wide range of heart rate changes. In addition, impedance reflects a complex series of changes with the cardiac cycle and it is not currently known which electrode configuration gives the optimal and most stable impedance signal that accurately reflects changes in intracardiac haemodynamics.

As discussed in the first chapter, transvalvular impedance has been found in 1996 to be a potential pacing and sensing validation tool in auto-regulating pacemakers and also for fibrillation recognition in ICDs. In a more recent animal study conducted in 2005 involving male sheep, Chirife *et al* [159] evaluated the efficacy of implanted Sophòs DDDR pacemakers in detecting the transvalvular intracardiac impedance (TVI) waveform in comparison to an external high-resolution impedance measurement device and obtained closely comparable results. Impedance at end diastole was consistently smaller than that at end systole. Furthermore, TVI behaviour during inotropic challenge with Isoprenaline infusion has been found to be physiological as TVI rate matched closely the animals' sinus rate.

Recently, Zima *et al* [160] conducted a small experimental animal study to assess the feasibility of determining left ventricular volume changes by

LV conductance measurements with an implantable device in anaesthetised dogs. Using the two electrodes of a bipolar right ventricular pacing lead for current injection and two LV epicardial leads for voltage measurement, stroke conductance was correlated with the LV stroke volume computed from the aortic flow and a strong correlation was identified (r = 0.97) suggesting that it may be possible in the foreseeable future to use LV intracardiac conductance (the mathematical reciprocal of ohmic resistance) by implantable devices for continuous haemodynamic monitoring.

4.1 Results analyses

4.1.0 ***Mean stroke impedance (SZ) versus mean arterial BP***

During haemodynamically unstable VT, the heart rate rose to an average of 225 beats per minute (bpm) and mean BP dropped to only 13% of its original sinus rhythm value. This was associated with a simultaneous significant drop in SZ to only 22% of its original sinus rhythm value.

Although both stable VT and RVA pacing at 400 ms had similar average heart rates of 149 and 150 bpm respectively, their haemodynamics were significantly different to each other. In stable VT, mean BP dropped to 55% of its sinus rhythm value, and this was associated with a similar modest drop in SZ to 58% of its sinus rhythm value. In contrast, mean BP exhibited a much more significant drop during RVA pacing at 400 ms (down to 30% of its sinus rhythm value), which was associated with a similar significant drop in SZ (down to 25% of its original sinus rhythm value). This indicates that in those two rhythms (stable VT and RVA

pacing at 400 ms), stroke impedance was a better assessment tool of the haemodynamic situation than the arrhythmia heart rate.

Only two patients had haemodynamically stable SVT, so it was therefore difficult to draw any meaningful statistical conclusions from their data. However, we could still conclude that in those two SVT cases, both impedance and BP signals appeared not to significantly change compared to their original sinus rhythm values.

The correlation between SZ and mean arterial BP was, in general, statistically significant (Figure 3.3) with clear separation between sinus rhythm and haemodynamically unstable VT. However, there was less clear separation between stable and unstable VT, suggesting that SZ alone may not be able to reliably discriminate between haemodynamically stable and unstable VT.

4.1.1 ***Stroke impedance (SZ) versus BP amplitude (pulse pressure):***

SZ appeared to have a direct linear correlation with BP amplitude. By plotting the two against each other at different heart rhythms, the most statistically significant correlation was obtained during unstable VT (Figure 3.4). Stable VT and SVT showed a somewhat weaker correlation with some overlap between stable and unstable VT data points, again making it difficult for SZ alone to be used as a reliable haemodynamic discriminator between stable and unstable arrhythmias.

4.1.5 ***Change of stroke impedance (SZ) following arrhythmia onset:***

The maximum haemodynamic effect of an arrhythmia appeared to be exerted within the first few seconds after its onset. Figure 3.5 compares the effect of time after onset of unstable VT on SZ, BP amplitude and mean BP. The first five seconds after arrhythmia onset appear to witness most of the haemodynamic deterioration, with subsequent relative stability and partial recovery in BP and SZ measurements thereafter. There was no further significant drop afterwards in either SZ or BP despite the fact that unstable VT remained sustained at the same fast heart rate for a further 20 to 30 seconds before termination (usually be external DC cardioversion). Five seconds into stable VT (figure 3.6), the variables exhibited a similar pattern, albeit with less dramatic reduction in BP and SZ values than during unstable VT. After arrhythmia onset of both stable and unstable VT, SZ appeared to correlate more closely with BP amplitude than with mean BP. Stable SVT (figure 3.9) was associated with a minor drop in SZ and BP amplitude during the first 5 seconds following arrhythmia onset. Thereafter, a steady decline in SZ continued to be observed for another 60 seconds when it dropped to 50% of its sinus rhythm value. This decline in SZ did not appear to be associated with a similar decline in BP, the maximal drop in which occurred during the initial few seconds of the arrhythmia.

4.2 Discussion

As discussed earlier in the thesis, unipolar intra-cardiac impedance is currently used in commercial systems as a rate sensor assessing changes in the inotropic state of the myocardium [133]. Previous studies using a multipolar electrode catheter placed in the right ventricle have shown a fall in impedance amplitude during arrhythmias in man [153]. The greatest fall occurred in patients with haemodynamically unstable arrhythmias suggesting that impedance could be used as a haemodynamic sensor. However, overall, results have been variable. In a previous study using unipolar impedance we found that although the greatest reduction in impedance occurred during ventricular fibrillation, changes during unstable and stable VT and SVT were less predictable [144] and did not allow reliable haemodynamic differentiation between arrhythmias. There may be a number of reasons for this lack of reliability such as independent catheter tip movement, which can significantly alter impedance measurements. In this study – and also in other previous studies – temporary pacing catheters were used and catheter tip movement and bending of the body of the catheter may have contributed to a variable impedance result, particularly during rapid heart rates where catheter movement may be exaggerated compared to slower heart rates. In commercial systems with permanent leads, fibrosis of the tip will ensure that the lead movement is directly related to movement of the heart. It is likely therefore that any impedance signal will be more stable under those conditions. In addition, impedance data from the right ventricle may be affected by the complex right ventricular

geometry, producing a false positive indication of sufficient pumping activity despite haemodynamic instability. This can originate from strong local wall motion around some of the impedance-measuring electrodes and can occur even when no blood is effectively being pumped by these contractions. Multi-polar impedance with a multi-channel catheter in the right ventricle assesses volume and output changes within the right ventricle [153]. Although there is evidence that right ventricular changes during arrhythmias reflect left ventricular dynamics, RV multi-polar impedance can be distorted by atrial activity due to the location of the catheter poles close to the tricuspid valve [153,161]. Ideally, as the left ventricle (LV) has a more regular geometry than the right and is less deformed during contractions, an impedance sensor that strongly reflects LV changes is desirable. Trans-ventricular impedance, measuring impedance changes across both the left and right ventricles (mainly the left), may be less sensitive to local wall motion artefacts and be suitably insensitive to atrial distortion. The development of bi-ventricular pacemakers allows the future possibility in man of an impedance sensor that uses the coronary sinus pacing lead to measure trans-ventricular impedance.

Intracardiac impedance can be measured by different configurations and each may relate to a different aspect of cardiac function. We therefore investigated configurations other than in the right ventricle that may more accurately represent changes within the left ventricle. In the present study we originally investigated two trans-ventricular configurations. In addition to the main study electrode configuration

described in the methodology chapter above, another one was initially attempted, that of injecting the alternating current between the proximal and distal poles of the CS catheter. This produced a very small voltage between the RV electrodes with an unacceptable signal to noise ratio and as a result could not be used further. That may have been due to the nearly perpendicular orientation of the RV and LV electrodes (the LV electrode was positioned in the coronary sinus), which tends to minimise the measured signal amplitude. If the LV electrode is implanted in a mid LV (preferably lateral) position, both electrodes are nearly parallel, which should then result in an adequate amplitude. The configuration we finally used – the details of which are described in the methodology chapter – produced satisfactory signals and showed a good correlation between SZ and arterial blood pressure. The results implied that as the arrhythmia became "increasingly unstable" there was a corresponding reduction in SZ. In particular, during unstable VT the drop in SZ was accompanied by a corresponding decrease in both pulse pressure and mean BP.

However, the diagnostic window between stable and unstable VT was small and may not allow automatic haemodynamic differentiation based on impedance measurement alone. The addition of the atrial intracardiac electrograms (IEGMs) together with the impedance data may help in the discrimination of haemodynamic instability, although we can't back up this theoretical assumption by sufficient practical data, as there were only 2 patients with SVT in the study. The presence of ventriculo-atrial (VA) conduction during tachycardia in addition to the

impedance data would also aid in the decision as to whether shock therapy should be given or not.

During both stable unstable arrhythmias, we have observed that the blood pressure exhibited its maximum drop at the onset of arrhythmias (or rapid RV pacing) with subsequent significant partial recovery of BP signal within the first five seconds. We think that may be due to the increased magnitude of sympatho-excitation and arterial baroreflex gain that tends to rapidly occur at arrhythmia onset [162]. It was also interesting to observe that SZ appeared to follow a similar partial recovery course to that of BP after arrhythmia onset (Figures 3.5, 3.6 & 3.7)

We conclude that there was generally good correlation between the stroke impedance SZ and arterial pressure, and that SZ for HUSVT was clearly separated from sinus rhythm, which in principle would support the use of impedance as a sensor for determining changes in the haemodynamic stability of arrhythmias. However, in the present study, there was less clear separation in SZ measurement between HUVT and HSVT, suggesting that perhaps impedance alone may not allow real time discrimination of haemodynamics. The results are encouraging however, and further studies are required to determine the optimal impedance signal that would act as a reliable haemodynamic sensor. Further studies – involving patients undergoing bi-ventricular ICD implantation procedures, and thus using permanent pacing electrodes – are also needed to look into the long-term sensitivity and reliability of impedance measurement before any future commercial clinical applications are implemented.

4.3 Study limitations:

The major limitation was the small patient numbers. During the study period the results of MADIT II trial were published and as a result the number of patients with evidence-based clinical indications for routine programmed VT stimulation studies significantly reduced. The positive induction rate for VT stimulation studies is usually low at best and therefore high patient numbers were difficult to recruit.

All patients were studied in the post-absorptive state and in the supine position. The effect of factors such as exercise (sympathetic drive), changes in posture, and changes in the metabolic state on the impedance signal was not assessed and therefore the study findings may not necessarily reflect the behaviour of impedance signal in real life.

Temporary pacing electrodes were used. Although active fixation temporary electrodes are now available these were not available at the start of the study. It is possible that changes in the impedance signal may have given a more predictable result in the presence of active fixation electrodes.

4.4 Summary

Intracardiac impedance, using the right ventricular unipolar configuration, has been used in a number of previous studies in both animal and human models to investigate its link with myocardial contractility and stroke volume and to assess the feasibility of its use as a haemodynamic sensor. By and large, the results of those studies were

encouraging, as they appeared to show consistently good correlation between SZ and blood pressure, albeit with some limitations. Although impedance is successfully being used as a closed-loop haemodynamic sensor for chronotropic response in commercially available pacing systems, its use in implantable defibrillators as a haemodynamic sensor for cardiac arrhythmias is not yet clinically possible. During arrhythmias induced in some of the previous studies, the instability of the temporary pacing leads used for impedance measurement together with the complex right ventricular geometry may have led to distortion of the recorded impedance signal and may consequently have adversely affected the outcome of the studies. We investigated the intracardiac impedance using configurations other than in the right ventricle in man as they may more accurately represent changes within the left ventricle. In the present study the configuration used produced satisfactory signals and showed a good correlation between SZ and arterial blood pressure. The results implied that as the arrhythmia became "increasingly unstable" there was a corresponding reduction in SZ. During unstable VT and right ventricular apical pacing at 400 ms the drop in SZ was accompanied by a corresponding equivalent decrease in pulse pressure. During RVA pacing there was a large fall in arterial pressure comparable to that seen during unstable VT. It is well recognised that pacing the RVA has a deleterious effect on left ventricular output and this study emphasises that the fall in output would appear to be similar to that seen during ventricular arrhythmias. Overall, however, in the current study the diagnostic window between stable and unstable VT

was small and may not allow automatic haemodynamic differentiation based on impedance alone. This effect also may have been partly due to small patient numbers in this study.

There was a good linear correlation between the stroke impedance (SZ) and arterial pulse pressure and the morphology for SZ waveform for HUVT was significantly different from that of sinus rhythm, HSVT & stable SVT. This would support the use of impedance as a sensor for determining changes in the haemodynamic stability of arrhythmias. However, in the present study the changes during arrhythmias were variable and impedance alone may not allow real time discrimination of haemodynamically stable from unstable arrhythmias. The results are encouraging however, and further studies are required to determine the optimal impedance signal needed to act as a reliable haemodynamic sensor. Although there is no requirement for a sensor as far as VF is concerned, as all ICDs are fully sensitive in detecting VF, a haemodynamic sensor particularly for biventricular devices could be a useful adjunct in patient management. Further studies are needed to look into the long-term sensitivity and reliability of impedance measurement before any future clinical applications are implemented.

CHAPTER 5

CHAPTER 5

NON-INVASIVE BLOOD PRESSURE (PORTAPRES) AND HAEMODYNAMIC CORRELATION (DISCUSSION)

5.0 Introduction

Continuous haemodynamic monitoring using invasive intra-arterial blood pressure measurement is widely applied in clinical practice. It provides information about the blood pressure in real time, and – with the aid of measurements obtained from the addition of a central venous catheter – also assesses the degree of peripheral tissue perfusion and oxygen consumption. Patients benefiting from such monitoring include critically ill patients in intensive care or high dependency units, and patients undergoing invasive diagnostic or therapeutic procedures that are likely to affect their haemodynamics. (e.g. coronary angiography and angioplasty, etc). The ability to reliably monitor invasive haemodynamic variables in such patients greatly influences their management, and has led to improved patients care in recent decades [163]. However, securing intra-arterial access is not without risks. Complications such as arterial dissection, formation of pseudo-aneurysms, haemorrhage, limb ischaemia and infections occur in approximately 1% of patients [164] although some studies have quoted a complication rate as high as 13.5% [165]. This limits the full potential that invasive haemodynamic assessment can offer. Furthermore, sophisticated invasive haemodynamic monitoring equipments are only available in specialised or intensive care units and may not therefore be usually immediately

available for acutely sick patients admitted to the accident and emergency departments. If a sensitive and reliable continuous non-invasive haemodynamic monitoring system was developed, such patients would benefit from early non-invasive assessment prior to their transfer to intensive therapy units. The ideal method for haemodynamic monitoring should be a non-invasive approach that is risk free, but at the same time have the same level of efficacy, reliability and sensitivity of the current invasive intra-arterial monitoring systems. Previous studies have examined different non-invasive haemodynamic monitoring methods, such as thoracic electrical bio-impedance and continuous finger plethysmography, and performed simultaneous comparison of those methods to standard invasive techniques. In 1996, Shoemaker *et al* [166] evaluated the feasibility of multi-component non-invasive haemodynamic monitoring in critical emergency patients. Cardiac output (CO) values – measured by the standard thermo-dilution pulmonary artery catheter technique – were compared with simultaneously obtained measurements using a non-invasive bio-impedance method. The investigators concluded that non-invasive monitoring had provided haemodynamic and perfusion information previously that were previously available only by invasive thermo-dilution catheters. In 1998, a multi-centre study [167] investigated the accuracy and reliability of non-invasive haemodynamic monitoring when used as a front end of invasive monitoring in order to supply more complete descriptions of circulatory pathophysiology. The investigators compared a combination of a then new bio-impedance method for estimating cardiac output,

standard non-invasive arterial BP, pulse oximetry, and transcutaneous PO_2 & PCO_2 with simultaneous invasive measurements in acutely ill patients shortly after hospital admission. They concluded that non-invasive monitoring systems gave continuous displays of physiologic data that provided information allowing early recognition of low flow and poor tissue perfusion that were more pronounced in the non-survivors and that such systems may be acceptable alternatives where invasive monitoring is not available. In 1999, Velmahos *et al* [168] used non-invasive monitoring systems (bio-impedance cardiac output monitoring, pulse oximetry and transcutaneous oximetry) to evaluate early temporal haemodynamic patterns after blunt trauma, and compared those to invasive pulmonary artery monitoring. The investigators concluded that multi-component non-invasive monitoring systems had provided continuous on-line, real-time displays of physiological data that allowed early recognition of circulatory dysfunction; and that they also provided similar information to the invasive thermo-dilution method but are easier and safer to use.

Finger plethysmography provides continuous non-invasive BP monitoring but its use as a potential substitute for the invasive method has not been fully previously assessed. The goal of this study is to compare the reliability and accuracy of non-invasive blood pressure measurement with invasive femoral blood pressure during sinus rhythm and arrhythmias in man. There have been a number of small studies, which compared the two methods, albeit in different clinical settings. Finger plethysmography has been found to be a useful complement to

current vascular research techniques when compared with forearm vascular flow in patients with sleep disorders [169]. It has also been found to correlate well with aortic pressure for monitoring of external counterpulsation (EECP) [170]. Closing pressures extracted from carotid tonometry and finger plethysmography have also shown good linear correlation [171]. In cardiac resynchronisation therapy (CRT), finger photoplethysmography has been found to have high specificity in identifying significant changes in aortic pressure and may prove useful in optimisation of AV delay [172]. Many previous studies have also directly compared the two blood pressure measurement forms. In 1989, Parati *et al* [173] compared the blood pressure values obtained by continuous non-invasive finger blood pressure recording via the FINAPRES device with simultaneous intra-arterial monitoring both at rest and during performance of tests known to induce fast and often marked changes in blood pressure – hand-grip, cold pressor test, diving test, Valsalva manoeuvre, intravenous injections of phenylephrine and tri-nitroglycerine, application of lower body negative pressure and passive leg raising – in normotensive or essential hypertensive subjects. The study concluded that beat-to-beat blood pressure recording via FINAPRES provided an accurate estimate of means and variability of radial blood pressure in groups of subjects, and that it represented in most cases an acceptable alternative to invasive blood pressure monitoring during laboratory studies. In 1996, Hirschl *et al* [174] evaluated the accuracy and reliability of non-invasive continuous finger blood pressure measurement in critically ill patients using continuous non-

invasive blood pressure measurement with the use of a finger cuff on the middle phalanx of the second and third fingers. Invasive mean arterial blood pressure measurement was done by cannulation of the radial artery. The conclusion was that the non-invasive finger method provided reliable measurements that were comparable to those obtained invasively, and that it may be useful in most emergency clinical settings. However, there were still large discrepancies (> 10 mmHg) in 8% of all patients between both measurements with a duration of > 3 minutes. In an animal study performed in 1998, Caulkett *et al* [175] evaluated the accuracy of three non-invasive blood pressure monitoring techniques (oscillometric technique, Doppler and optical plethysmography) in comparison with direct invasive intra-arterial monitoring in anaesthetised cats. The investigators concluded that all three techniques were useful for detecting trends and that out of all three non-invasive methods; oscillometric technique provided the most accurate prediction of direct systolic pressure whereas Doppler and optical plethysmography techniques provided a good prediction of mean arterial pressure. In 2000, Gerhardt *et al* [176] conducted a study in critically ill patients comparing cardiac output measurements determined by thermo-dilution technique with simultaneous measurements obtained non-invasively using Portapres finger plethysmography and an aortic impedance model. The investigators concluded that Portapres measurements couldn't replace thermo-dilution cardiac output estimations due to fluctuations of finger arterial perfusion caused by haemodynamic instability in critically ill patients. In 2005, Cua *et al* compared BP

measurements obtained from Vasotrac, a device that provides near-continuous and non-invasive arterial blood pressure monitoring, to those values obtained invasively via an intra-arterial catheter in post-operative children and demonstrated a good correlation [177]. However, all those previous studies were conducted in the predominant setting of underlying sinus rhythm and therefore all the extracted data and results merely reflected invasive and non-invasive BP correlation during sinus – or intrinsic stable – rhythm only. No previous study has looked into the degree of correlation of the two BP measurement methods during different heart rhythms and it has not been shown before if finger plethysmography maintains its good correlation with invasive intra-arterial BP during cardiac tachyarrhythmias.

As explained earlier in the thesis, the Portapres BP measurement system is based on the volume-clamp method, which was initially invented by J Peñáz in 1973, and later developed further by Wesseling *et al.* in 1995.

5.1 Results analyses

As detailed in chapter 2, comparison was performed between simultaneously recorded Portapres and FAP values during different heart rhythms. Four BP components were analysed and had their results correlated.

5.1.0 ***Mean arterial blood pressure (MABP):***

The *absolute* values of Portapres MABP were, consistently, significantly higher than those of FAP throughout all tested heart rhythms but the

change in the two BP measurement systems from sinus to other rhythms still appeared to correlate well with each other. Out of the four blood pressure components evaluated, mean arterial BP achieved the most significant correlation during all tested heart rhythms. Figure (3.11) illustrates the correlation plotting of the *change* in MABP between the two BP monitoring techniques and shows scatter of the data points along the regression line with a strong positive linear trend. It further shows clear separation between sinus rhythm (top right, associated mostly with normal MABP values) and unstable VT (bottom left, associated mostly with significantly reduced MABP values) on the regression line. The separation between the data points of stable VT, pacing at 600 ms, and pacing at 400 ms was less clear, as there were some areas of overlap. Bland-Altman plotting of Portapres versus femoral invasive MABP (Figure 3.12) illustrates that, in sinus rhythm, the measured bias value indicated that the *absolute* Portapres values were generally much higher than those of femoral invasive BP. Despite this however, plotting the effect of right ventricular pacing and ventricular arrhythmias on the *change* of Portapres (Porta) and invasive MABP measurements *relative* to their sinus rhythm values (Figure: 3.16) appeared to show a much smaller bias value than the one calculated during sinus rhythm, suggesting that the *change* in Portapres MABP measured during pacing an VT appeared to closely follow that of femoral invasive BP.

5.1.1 Systolic blood pressure:

As was the case with MABP discussed above, the *absolute* values of Portapres systolic BP were, consistently, significantly higher than those of their FAP counterparts throughout all tested heart rhythms but the *change* in the two BP measurement systems from sinus to other rhythms correlated well with each other (Figures: 3.8 and 3.15).

5.1.2 Diastolic blood pressure:

Again, similar to the mean and systolic BP discussed above, the *absolute* values of Portapres diastolic BP were consistently higher than those of their FAP counterparts throughout all tested heart rhythms but the *change* in the two BP measurement systems from sinus to other rhythms correlated well with each other (Figures: 3.10 and 3.17).

5.1.3 Pulse pressure (Blood pressure amplitude):

BP amplitude measurements followed a similar trend to that of the above discussed other BP components; with significantly higher *absolute* baseline Portapres values during all tested heart rhythms compared to femoral invasive BP but still an overall good correlation between the *changes* in two BP monitoring systems (Figures 3.10 & 3.17).

5.2 Discussion

Although finger plethysmography has been available for some time as a continuous BP measurement tool, its use in clinical practice is gradually gaining greater acceptance as a means of monitoring blood pressure *changes*. Traditional oscillometric and auscultatory devices allow BP assessment only intermittently. This results in lack of detection of a rapid

BP change, which often occurs in cardiac arrhythmias. Continuous non-invasive BP measurement avoids such shortcoming and provides further opportunities to examine the pathological role of other characteristics of BP such as abnormalities of the diurnal rhythm, short-term BP variability and baro-reflex sensitivity. Increasingly patients are anaesthetised during defibrillator implantation and non-invasive monitoring will reduced the risks of the procedure hopefully without compromising patients' safety.

For all the rhythms analysed, when examining the *absolute* BP results, Portapres appears to consistently give significantly higher readings than FAP. This is explained by the fact that the peak of the Portapres waveform tends to adopt a rather pointed morphological appearance compared to a more plateaued FAP peak morphology, but constitutes a major study limitation in the face of future practical implementation as will be discussed below. Despite this marked discrepancy in the *absolute* BP values however, the *changes* in Portapres BP appear to very closely track those in invasive femoral intra-arterial pressure, which indicates that non-invasive BP *can* potentially be a useful future tool for continuous haermodynamic monitoring if the limitations discussed below are adequately addressed.

5.3 Study Limitations

The main limitation was that small patient numbers were studied. Despite the positive correlation results obtained, it remains to be proven that the findings are reproducible in larger groups of patients. Furthermore, patients were studied in the supine posture after having

been fasted for a few hours. This indicates that the correlation between the two BP forms may not necessarily remain as close in different clinical settings; for example, it can't be assumed that the same degree of correlation is maintained in ambulant patients or in the post-prandial state. Although we used each patient to act as their own control, we have not used a separate control group for this study as the setting made this practically difficult to implement. This represents another limitation in the face of clinically applying the positive results obtained. Another major limitation is the marked discrepancy in the *absolute* BP values between Portapres and femoral invasive pressure values obtained, indicating that relying on Portapres alone for continuous BP measurement may still not be clinically possible, for it is likely to provide false high baseline BP readings leading to inaccurate clinical assessment and subsequent wrong management of patients. We think that this discrepancy may be due to the fact that the two BP measurements were taken from two very different locations, and that they in fact measure different forms of BP. The femoral invasive BP was measured from a large central artery, thereby resulting in a central BP waveform, whereas the Portapres was measured from a much smaller peripheral finger artery resulting in a different peripheral BP waveform. This discrepancy may have been partially avoided if the invasive BP was measured from a smaller vessel like the radial artery. We think that until Portapres technology is improved so that it provides much closer *absolute* BP values to that of invasive BP, its practical implementation in the wider clinical arena will be significantly limited.

5.4 Summary

There is a significant linear correlation between the changes in Portapres and femoral invasive BP values, which was maintained during different heart rhythms at almost the same degree of statistical significance. Further studies involving different cohorts of patients with larger numbers (e.g. the critically ill in intensive care units) are needed to confirm such correlation before adopting finger plethysmography as an acceptable accurate and indeed safer substitute for invasive BP monitoring. Furthermore, the absolute BP values of the two monitoring systems were markedly different from each other and this limitation, together with other limitations has to be observed before any routine clinical application of non-invasive BP monitoring systems.

CHAPTER 6

CHAPTER 6

CONCLUSION

SCD constitutes one of the leading causes of mortality in the developed world. Despite the fact that people with underlying LV dysfunction or structural and genetic heart disorders appear to be the worst affected compared to other cohorts of patients, SCD – in terms of absolute numbers – mostly occurs in apparently healthy subjects with no previously known cardiac problems. A significant number of incidents of SCD is caused by malignant ventricular tachycardia that degenerates into VF. Anti-arrhythmic drug therapy can be used either intravenously to terminate an acute but otherwise haemodynamically stable arrhythmias, or for the long-term – in tablet forms – to reduce the recurrence rate of such arrhythmias. However, so for, there is no evidence that anti-arrhythmic drug therapy improves mortality and therefore patients who survived an arrhythmic cardiac arrest and those identified to be at high risk of SCD should not be offered anti-arrhythmic drug therapy alone. On the other hand, device therapy in the form of ICD implantation has been shown in a number of randomised controlled studies to be unequivocally superior to anti-arrhythmic drugs with clear mortality benefit. At present, ICD therapy is the treatment of choice in patients at risk of life-threatening ventricular arrhythmias.

In the early 1980s, ICD implantation was a complex major surgical operation with over 10% mortality. Devices were large and were abdominally implanted under general anaesthesia and connected to the

heart epicardially. Batteries would only last for 1.5 years and available therapy was in the form of high-energy shock only. At present, modern ICD systems are much simpler to implant subcutaneously with trans-venous endocardial lead positioning under local anaesthesia. Procedural mortality is < 1%. Devices have become much smaller with telemetrically programmable therapy options and extended battery longevity of an average of seven years. Delivering inappropriate shocks for supraventricular or haemodynamically stable ventricular arrhythmias remains one of the major limitations of ICD therapy that can lead to major life style restrictions and occasionally severe psychological disturbances. The advent of dual chamber systems and the development of SVT discrimination algorithms such as QRS width & morphology, arrhythmia rate of onset, rhythm regularity and probability density function have reduced, but not completely abolished, the problem of inappropriate shocks, albeit at the expense of increased device cost and complexity.

Developing a reliable sensor capable of discriminating haemodynamically stable from unstable arrhythmias remains a challenging task for cardiac researchers and ICD manufacturers. Multiple previous studies have examined this issue exploring a variety of haemodynamic variables such as maximal systolic right ventricular contractility (dP/dt), mixed venous oxygen saturation (MVO_2), right ventricular and right atrial pressures and coronary sinus blood temperature. Although some of those studies have demonstrated some degree of correlation between the variations in the studied variables and

haemodynamic stability (or instability), there remain concerns about the accuracy, sensitivity, practical applicability and long-term effectiveness of those variables in discriminating stable from unstable arrhythmias.

We studied the feasibility of using intracardiac impedance as a haemodynamic sensor in patients undergoing clinically indicated elective VT provocation studies as part of assessing their need for ICD therapy. We demonstrated a good linear correlation between the stroke impedance (SZ) and arterial blood pressure that would support, in principle, the use of impedance as a sensor for detecting the haemodynamic effects of arrhythmias. However, impedance alone may not allow real time discrimination of haemodynamically stable from unstable arrhythmias as there was some variability in the recorded SZ signal. The results are encouraging however, although further studies are required to determine the optimal impedance signal needed to act as a reliable haemodynamic sensor. If developed and implemented successfully as part of ICD arrhythmia recognition algorithms, such an impedance haemodynamic sensor would provide a huge step forwards in ICD technology. Devices could then be programmed to deliver tiered therapy for stable arrhythmias that do not significantly alter the detected impedance signal, and reserve DC cardioversion and high-energy shocks for more unstable rhythms that result in a significant drop in the detected impedance signal. Furthermore, inappropriate shocking with all the associated adverse psychological and lifestyle restricting effects will significantly diminish or possibly even disappear.

We also studied the feasibility of using non-invasive finger plethysmography (Portapres) as a tool for continuous blood pressure monitoring in the same cohort of patients by comparing it with invasive intra-arterial blood pressure monitoring. We demonstrated significant correlation between the two techniques in monitoring BP *changes*, which was maintained during different heart rhythms at almost the same degree of statistical significance but the baseline *absolute* BP values however were significantly different between the two BP measurement systems. The findings support the view that, in principle, Portapres can potentially replace invasive BP monitoring but many limitations exist and further studies involving different cohorts of patients with larger patient numbers need to be conducted in order to address those limitations and confirm the consistency of our correlation results before finger plethysmography is adopted as an acceptable accurate and indeed safer substitute for invasive BP monitoring.

We believe that our pilot study, although conducted in a small number of patients, has set the foundation for researchers in the field to further examine two of the important issues that lie within the heart of improving the convenience and safety of patients' management: the use of trans-ventricular intracardiac impedance as an ICD haemodynamic sensor for arrhythmias, and the use of non-invasive plethysmographic BP monitoring devices as a safer alternative to invasive BP systems.

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