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BLOOD PRESSURE IN ATRIAL FIBRILLATION

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BLOOD PRESSURE IN ATRIAL FIBRILLATION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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ABSTRACT

Introduction

Hypertension is a leading risk factor for cardiovascular morbidity and premature death. Prevalence of hypertension in the adult population in Sweden has been estimated to 27%. Atrial fibrillation (AF) is the most prevalent sustained arrhythmia of clinical relevance with an estimated prevalence of at least 2.9% among adults in Sweden. Similarly to hypertension, AF is independently associated with an increased risk for cardiovascular morbidity and with a two-fold increased risk of death. The underlying mechanisms responsible for this association however, are not fully known. Both conditions may impose a heavy burden upon affected patients as well as on the health care system. AF and hypertension are closely intertwined and often coexist. Hypertension is the major risk factor for AF development and conversely, AF affects blood pressure (BP). The irregular heart rhythm in AF is one factor influencing BP, but also other factors may play a part. Furthermore, the presence of AF has implications for conventional BP measurement. AF-related effects on BP are studied to a very limited extent. Possibly, AF-induced BP effects may have pathophysiological consequences and may also influence BP measurement accuracy. Consequently, these factors may negatively influence risk assessment and prognosis in patients with AF.

The aims of this thesis were 1) to systematically quantify beat-to-beat BP variability in patients with AF compared to sinus rhythm (SR); 2) to study how BP, as measured with different techniques, is affected by the presence of AF; 3) to investigate the relationship between peripheral and central intra-arterial BP, in patients with AF compared to SR; 4) to evaluate the accuracy of conventional BP measurement in relation to peripheral and central intra-arterial BP, in patients with AF and compared to SR.

Methods and results

In the prospective study I, patients scheduled for a coronary angiography were recruited. Participants included 21 patients in AF and 12 patients with SR. Intra-arterial BP was recorded from the radial and brachial artery and from the ascending aorta. The primary outcome measure was beat-to-beat BP variability, defined as average systolic and diastolic BP difference between consecutive beats, at each site of measurement. A significant difference ($p<0.001$) in BP variability, in AF compared to SR, was observed for all locations of measurement. Systolic BP variability was roughly doubled in patients with AF (4.9 vs 2.4 mmHg), whereas diastolic BP variability was approximately six times as high (7.5 vs 1.2 mmHg) in patients with AF compared to SR.

Study II was a retrospective registry analysis based on data from electronic medical records. 487 patients, treated with electrical cardioversion (ECV) for persistent AF, were included in the study. Information regarding auscultatory sphygmomanometric BP and rhythm, on the day before and 7 days after ECV, was obtained. The primary outcome measure was BP change in patients with restored SR after ECV. In this group with restored SR, systolic BP increased by 9 mmHg ($p<0.01$), whereas diastolic BP decreased by 3 mmHg ($p<0.01$).

Furthermore, the proportion of patients with a hypertensive BP-level (≥140/90) increased by 40% in this group.

In study III, 98 patients with persistent AF undergoing ECV were prospectively recruited. BP was evaluated with 24-h ambulatory BP monitoring before and approximately one week after ECV. The primary outcome measure was BP change in patients with restored SR after ECV. Among 60 patients maintaining SR, mean systolic 24-h ambulatory BP increased by 5.6 mmHg ($p<0.001$) and mean diastolic 24-h ambulatory BP decreased by 4.7 mmHg ($p<0.001$). Accordingly, a 10.4 mmHg (25%) increase in pulse pressure was observed among patients with restored SR.

Study IV comprised the same individuals as study I. Conventional BP (auscultatory sphygmomanometric and automated oscillometric) and intra-arterial BP was measured simultaneously. The first aim was to investigate how intra-arterial BP changes throughout the arterial tree in patients with AF in comparison to patients in SR. The second aim was to evaluate the accuracy of conventional BP measurement in patients with AF in comparison to central and peripheral intra-arterial BP, and in comparison to patients in SR. BP changes throughout the arterial tree was similar in patients with AF compared to SR. Conventional BP was in general very accurate in comparison to diastolic intra-arterial BP, both in AF and SR. In patients with AF, oscillometric blood pressure overestimated systolic intra-arterial brachial (4.1 mmHg, $p=0.07$) and central (5.0 mmHg, $p=0.04$) BP. With measurement bias in SR taken into account, oscillometric BP over-estimated systolic intra-arterial brachial BP by 14.1 mmHg ($p<0.01$) and central BP by 9.0 mmHg ($p=0.01$) in patients with AF.

Conclusions

Beat-to-beat BP variability is increased in patients with AF compared to SR. According to the results from studies in this thesis, systolic BP is lower and diastolic BP is higher in AF compared to SR, as measured by auscultatory sphyghmomanometry or by oscillometric 24-h ambulatory BP monitoring. As a consequence, pulse pressure is markedly lower in AF compared to SR. Intra-arterial BP change throughout the arterial tree is similar in patients with AF and SR. Conventional BP measurement was accurate in relation to diastolic intra-arterial BP, but oscillometric BP measurement overestimated intra-arterial brachial and central systolic BP in patients with AF, in particular when compared to patients in SR.

The presence of AF affects BP. This may have implications for the accuracy of conventional BP measurement and may possibly also have pathophysiological consequences. Suboptimal understanding, measurement and treatment of BP may negatively influence prognosis in patients with AF.

LIST OF SCIENTIFIC PAPERS

I. Olbers J, Gille A, Ljungman P, Rosenqvist M, Östergren J, Witt N.
High beat-to-beat blood pressure variability in atrial fibrillation compared to sinus rhythm.
Blood Pressure. 2018;27(5):249-255.

II. Olbers J, Jacobson E, Viberg F, Witt N, Ljungman P, Rosenqvist M, Östergren J.
Systolic blood pressure increases in patients with atrial fibrillation regaining sinus rhythm after electrical cardioversion.
Journal of Clinical Hypertension. 2019;21(3):363-368.

III. Olbers J, Östergren J, Rosenqvist M, Skuladottir H, Klavebäck S, Ljungman P, Witt N.
Changes in 24-h ambulatory blood pressure following restoration of sinus rhythm in patients with atrial fibrillation.
Journal of Hypertension. August 21, 2020, published ahead of print.
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IV. Olbers J, Östergren J, Ljungman P, Rosenqvist M, Witt N.
Differences in conventional and intra-arterial blood pressure in atrial fibrillation and sinus rhythm.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
BP	Blood pressure
bpm	Beats per minute
CVAR	Coefficients of variation
ECG	Electrocardiogram
ECV	Electrical cardioversion
ESC	European Society of Cardiology
GCP	Good clinical practice
LVEF	Left ventricular ejection fraction
MBP	Manual blood pressure (auscultatory sphygmomanometry)
mmHg	Millimeters of mercury
OBP	Oscillometric blood pressure
RAAS	Renin-angiotensin-aldosterone system
SBU	Swedish agency for assessment of health technology and assessment of social services
SNA	Sympathetic nerve activity
SR	Sinus rhythm

1 RESEARCH QUESTION AND RATIONALE

Atrial fibrillation (AF) is common and the prevalence in Sweden has been estimated to be at least 2.9% among the adult population.[1] Hypertension is even more frequent with prevalence estimates ranging from 20-50%.[2–4] AF is independently associated with increased cardiovascular morbidity and mortality,[5,6] whilst hypertension counts as the leading risk factor for premature death.[3,4] Blood pressure (BP), hypertension and AF are closely intertwined.[2] Hypertension is a major risk factor for AF developement[7,8] and consequently, AF and hypertension very frequently coexist.[2,9] Conversely, AF affects BP[10] and BP measurement accuracy.[11] However, whereas the impact of AF on BP measurement accuracy is studied to some extent, the AF-related effects on BP itself are only studied to a very limited extent. Possible pathophysiological and clinical consequences of such AF-related effects on BP are barely studied at all. It is unknown what constitutes an optimal BP level for AF patients since this is not specifically and prospectively studied.[2,12] AF rhythm may potentially, in itself, be causally linked to the observed increase in cardiovascular morbidity and mortality.[13] However, underlying pathophysiological mechanisms responsible for such a possible causal connection are unknown. Thus, several aspects regarding the interplay between AF, blood pressure and hypertension is insufficiently studied, and its importance may be underappreciated.

In this thesis some yet unanswered research questions pertaining to BP in AF were addressed. We aimed in particular to study how AF may affect BP and to evaluate how the presence of AF affects accuracy of conventional BP measurement.

2 INTRODUCTION

2.1 WHAT IS BLOOD PRESSURE?

Blood pressure is an elemental physiological parameter, used in everyday clinical practice. However, in clinical practice, blood pressure (BP) is often merely perceived as being a peak systolic and a nadir diastolic value, non-invasively measured in millimeters of mercury (mmHg) from a conduit artery (usually the brachial artery). From a research perspective it is thus important to consider how BP is more complex than this. BP may best be conceptualized as a continuous pressure-curve (see figure 1) from which several other parameters, in addition to systolic and diastolic BP, may be derived.

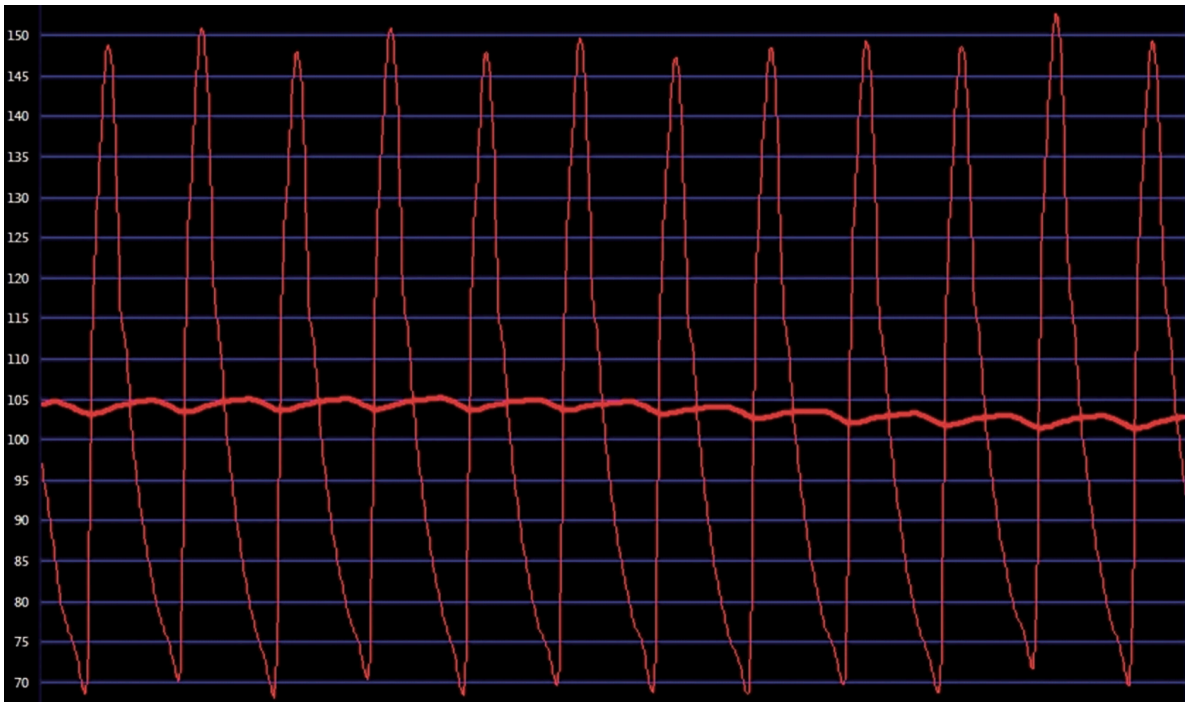

Figure 1. Intra-arterial blood pressure recording from patient in sinus rhythm.

The pressure curve changes over time (short- and long-term) and depending on the location of measurement. It is also important to consider that blood pressure and blood flow has a pulsatile component because of the nature of the pump (the heart), as well as a steady component.[14] The steady pressure component is represented by the mean arterial pressure whereas the pulsatile pressure component is represented by systolic and diastolic pressure.[14] The elastic properties of large arteries have important implications for the BP waveform. The energy released from the left ventricle into the arterial system with every systole is, through the elasticity of large arteries, partly stored, only to be released as kinetic energy during diastole and thus partly transforming pressure and flow from pulsatile to a more continuous one.[15] As with the rest of the human body, arteries age over time, thus losing some of its elastic ability, referred to as arterial stiffening.[16,17] This process in turn affects BP in so forth

that systolic BP increases whereas diastolic BP decreases from middle age and onwards.[18] Disease processes such as hypertension affect the properties of arteries and the process of arterial stiffening.[16,19]

Another important concept that needs mentioning is that of reflected waves.[20] The BP wave is reflected at various sites in the arterial tree, causing a reversed pressure-wave that is directed from the periphery towards the heart. This reflected pressure wave acts as a pressure amplifier, in particular increasing systolic BP to different degrees along the arterial tree.[15,21] One consequence of this is often referred to as arterial pulse pressure amplification,[21] i.e., the phenomenon that systolic pressure and pulse pressure increase from central to peripheral arteries.

2.2 ELEVATED BLOOD PRESSURE - HYPERTENSION

Blood pressure is a continuous physiological parameter and the threshold for when it is too high in a certain individual is not clear-cut. The different categories of BP according to the European Society of Cardiology (ESC) guidelines on hypertension[22] is presented in table 1.

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Table 1. Different categories of blood pressure, according to the European Society of Cardiology.

The most used definition for the clinical diagnosis of hypertension is a sustained resting office BP ≥140/90 mmHg, which is the definition also used by the ESC.[22] This of course, is an arbitrary threshold and may be viewed as the BP level over which intervention (life style intervention and in most cases pharmacological intervention) can be expected to be beneficial for the individual in question. This BP threshold is derived from a plethora of large randomized clinical intervention trials, as are the evidence regarding the benefits from therapeutic intervention in hypertensive patients.[23–26] Of note, BP-levels below the threshold for hypertension are categorized as high normal (130-139/85-89 mmHg) or normal (120-129/80-84 mmHg), whereas optimal BP is defined as <120/80 mmHg. This implies that

although a BP level of 120-139/80-89 mmHg may not warrant pharmacological intervention, it may still not be an optimal BP-level with regard to long term risk for cardiovascular morbidity. This is also reflected in the 2017 ACC/AHA hypertension guidelines in which hypertension is defined as BP ≥130/80.[27] With this definition, 46% among all US adults and up to 63% of those aged 45-75 are defined as hypertensive.[28,29]

The underlying mechanisms responsible for the development of hypertension are multifactorial, and include life style factors as well as genetical disposition.[30,31] An unphysiologically elevated blood pressure over time harms the arterial endothelium,[32] increasing the risk for atherosclerosis and its potential deleterious effects.[33] Hypertension is the leading global risk factor for premature death.[30,34,35] Prevalence is high and according to a report from 2004 by the Swedish agency for health technology assessment and assessment of social services (SBU), 27% of the adult population has hypertension. Globally, estimates of hypertension prevalence in different regions ranges from 20-50%.[2–4]

2.3 BLOOD PRESSURE MEASUREMENT

As described above, BP changes over time and throughout the arterial tree. Thus, a single blood pressure measurement is an estimate of the BP at a specific point in time at a certain arterial location. Furthermore, for all methods of measurement, there is a potential for measurement bias.

The original, clinically useful, method for BP measurement was developed by Riva-Rocci in the late 19th century and the method was later improved by the addition of the use of Korotkoff sounds.[36,37] With this method, a mercury or aneroid sphygmomanometer and a stethoscope is used[38] and this has been the predominant way of measuring BP, at least up till recently.

With the oscillometric method, pressure waveforms are derived from oscillations in the artery (usually the brachial artery), which is then analyzed to estimate BP. Automatic oscillometric BP devices was introduced in the 1980s and has since been increasingly used in clinical practice.[38–40]

Office BP usually refers to BP measured by a professional within health care, either with the manual auscultatory sphyghmomanometric or the automated oscillometric method.[41] Although several factors with potential to cause measurement bias exist in relation to manual auscultatory office BP, this has been the predominant method for BP measurement in randomized intervention trials.[41]

A single BP measurement provides a snapshot estimate of BP at that specific point in time whereas the harmful effects of elevated BP is better reflected by the mean BP load imposed on central organs over longer periods time.[42] To this end, various techniques to estimate mean systolic and diastolic BP over time has been developed. 24-h ambulatory BP monitoring, in which automated oscillometric BP is repeatedly obtained over 24 hours, is such a method which is widely used in clinical practice. It has been demonstrated that 24-h ambulatory BP

may be a better predictor than office BP in relation to cardiovascular outcomes.[43–45] The golden standard for reference BP is to obtain intra-arterial BP recordings. Since this method is invasive it is however not feasible for most clinical scenarios.

Conventional BP measurement (auscultatory sphygmomanometric or automated oscillometric) is normally obtained from the upper arm, i.e., the brachial artery. As mentioned, BP however change throughout the arterial tree.[46] Central BP refers to BP in the central arteries such as the ascending aorta, whereas peripheral BP refers to the pressure in the brachial and more peripheral arteries. Central BP may better reflect the true blood pressure load imposed on central target organs such as the heart and the brain.[47–49] In most individuals, diastolic and mean arterial pressure are essentially unchanged throughout the arterial tree, whereas systolic BP increases the more peripheral the site of measurement.[15,21] It has however been proposed that there may be heterogeneity in this pattern with different identifiable phenotypes.[50]

There are different methods for non-invasive estimation of central blood pressure.[51] Since central BP theoretically should be a better predictor of cardiovascular outcomes than conventional peripheral BP, several studies have investigated these methods with regard to prognosis. However, the results of those studies are heterogenous and the superiority of non-invasively obtained central BP over conventional BP has not been unequivocally shown.[52–54] Conventional, peripheral BP measurement thus estimates brachial BP, with a certain (normally unknown) measurement bias. This estimate in turn, could arguably be conceived as a proxy for central BP, which on theoretical grounds should be the BP comprising the most useful data for clinical decision making. However, in the large randomized therapeutic hypertension trials, the predominant method for BP measurement has been conventional office BP. Thus, although concerns against conventional office BP measurement may be raised, this is the method upon which the lion's share of current scientific evidence for when and how to treat hypertension is based.

2.4 WHAT IS ATRIAL FIBRILLATION?

The underlying pathophysiological mechanisms responsible for the development and progression of AF are complex and not fully understood. However, it involves structural and electrical remodeling.[55–57] Structural remodeling refers to the anatomical changes that may be observed in the atria, such as fibrosis, hypertrophy and dilatation. Electrical remodeling refers to processes that affect ion channels and thereby affect depolarization patterns in the atria.[55,58] In SR, depolarization is initiated in the sinus node and the depolarization of the atria occurs in an organized manner. In AF, the sinus node remains inactive and there is constant uncoordinated depolarization and repolarization of the atria. In contrast to SR, where heart rate is normally controlled by the pace of the sinus node, (ventricular) heart rate in AF is primarily governed by the conduction status of the AV node. As a consequence of these prevalent conditions, heart rhythm in AF is irregular and often faster in comparison to the regular sinus rhythm (see figure 2).

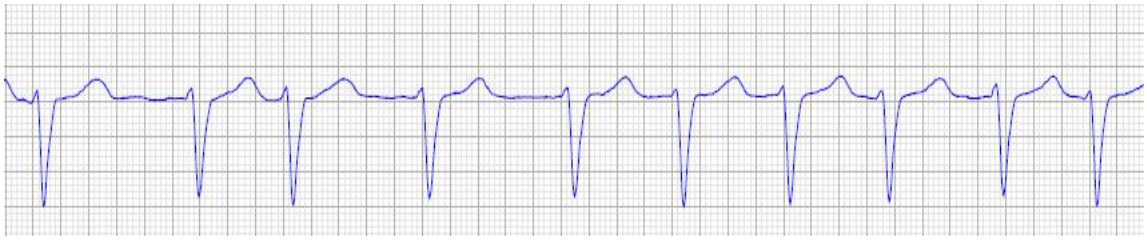

Figure 2. ECG strip from patient in atrial fibrillation.

Another hemodynamic consequence of AF is the loss of synchronized atrial contraction at the end of diastole, potentially decreasing left ventricular filling and stroke volume.[59,60] On a group level, AF is associated with a deterioration of hemodynamic parameters, such as cardiac output and left ventricular filling pressure.[61] A number of factors may contribute to impairment of hemodynamics in AF. Loss of synchronized atrial contraction, increased ventricular heart rate, increased R-R-variability and neurohormonal effects may all play a part.[61,62] Restoration of SR is associated with improved hemodynamic parameters.[60]

AF is the most common arrhythmia of clinical relevance and it has an estimated prevalence of at least 2.9% among adults in Sweden.[1] The incidence increases with age and the prevalence is over 10% in those over the age of 80 years.[1] As for cardiovascular disease in general, AF is more frequent and debuts at a younger age in men compared to women.[63] Except for gender and age, common cardiovascular risk factors such as hypertension, obesity and diabetes are also risk factors for the development of AF.[63,64] With an aging population and an increasing prevalence of AF risk factors, a trend for increasing AF incidence is believed to continue[65] and AF prevalence is projected to double within this century.[65,66] Without preventive anticoagulant therapy, individuals with AF in general run a five-fold increased risk for stroke.[5,6] Although direct hemodynamic effects of AF, such as loss of synchronized atrial contraction, is important for the risk of stroke, other effects on the endothelium and on the coagulative properties of the blood probably also play a part.[67]

AF is associated with an increased cardiovascular morbidity and mortality, which may only to a lesser part be explained by the increase in the risk for stroke.[5,68] Results from several studies imply a two-fold increase in the risk for mortality in patients with AF compared to patients with SR.[5,68] Since AF shares most of its risk factors with other cardiovascular disease, possible direct causal relationships between AF and increased cardiovascular morbidity have been difficult to determine.

Symptoms of AF include shortness of breath, palpitations and reduced exercise capacity.[64,69] For symptomatic patients, different methods are used to restore or maintain SR. Electrical cardioversion (ECV), in which a sedated patient receives a high energy electric shock, is commonly used to restore SR in patients with persistent AF.[64]

2.5 BLOOD PRESSURE AND HYPERTENSION IN ATRIAL FIBRILLATION

In AF the heart rhythm is irregular. During diastole, arterial BP progressively falls until the start of the following systolic left ventricular contraction. A longer R-R-interval results in a more pronounced fall in BP during diastole. At the same time, a longer diastole increases left ventricular filling, resulting in increased stroke volume and increased blood pressure surge during the following systole. As a consequence, there is an increase of beat-to-beat BP variability in AF compared to SR (see figure 3).[10,70]

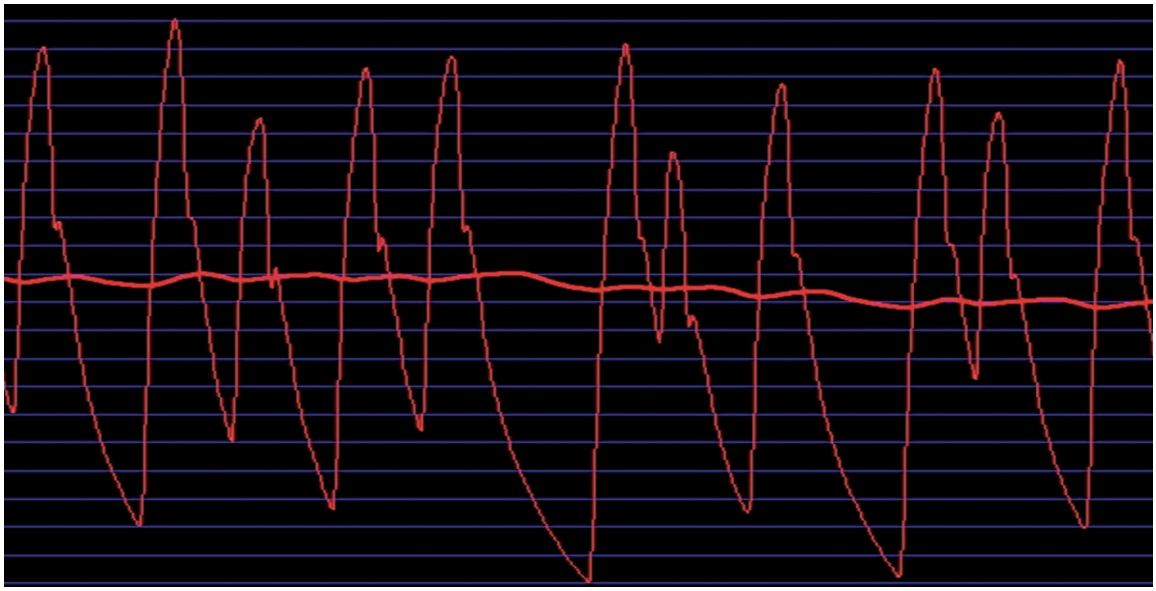

Figure 3. Intra-arterial blood pressure recording from patient in atrial fibrillation.

This phenomenon has implications for BP measurement in AF. A single conventional office BP only provides a single systolic and diastolic BP value from a number of different systolic and diastolic pressures during the BP measurement. Because of this rhythm irregularity, auscultatory BP measurement is often perceived as more difficult and uncertain in AF than in regular sinus rhythm.[11] Furthermore, there is no accepted universal reference standard for BP measurement in AF.[71] Earlier studies evaluating the accuracy of oscillometric BP measurement in AF, mostly using auscultatory sphyghmomanometric BP as reference method, are not conclusive.[72–75] The topic of how to accurately measure BP in the presence of AF is still debated.[76,77] Triplicate measurements are usually recommended and some authors recommend to continue the use of the auscultatory method in clinical practice.[78]

On a population level, hypertension is the most common risk factor for the development of AF.[7,8] Hypertensive patients run an increased risk of incident AF and this risk increases with increasing BP.[63,79–81] Patients with BP in the high-normal range also have an increased risk for incident AF.[82,83] Accordingly, approximately 15% of individuals with hypertension have concomitant AF[84] and hypertension prevalence in patients with established AF may be as high as 60-80%.[2,9] In addition, concomitant hypertension further increases the risk for AF

complications such as heart failure, stroke and bleeding.[64] According to the recently published guidelines for AF by the ESC, in most patients, AF should be regarded as a manifestation of hypertension target-organ damage.[64] ESC guidelines for hypertension and atrial fibrillation recommend that pharmacological treatment of hypertension, regarding both thresholds for initiation and BP treatment goals, should be no different in patients with AF than for other patients with hypertension.[22,64] However, since patients with AF have been systematically excluded from randomized hypertension treatment trials,[11] the underlying evidence for these recommendations are quite thin.

The underlying pathophysiological processes linking hypertension with the development of AF are not fully known but hemodynamic and structural effects are probably involved. Hypertension may cause left ventricular diastolic dysfunction, leading to elevation of left atrial pressure and thus inducing remodeling of the left atrium and thereby providing a substrate for AF development.[2,85]

3 AIMS

The overall aim of this thesis was to evaluate how the presence of AF may affect BP and the accuracy of conventional methods for BP measurement.

The specific aims of the studies were:

Study I: To systematically quantify beat-to-beat BP variability in patients with AF compared to SR.

Study II: To study how BP, as measured with auscultatory sphygmomanometry, is affected by the presence of AF.

Study III: To study how BP, as measured with oscillometric 24-h ambulatory BP monitoring, is affected by the presence of AF.

Study IV: To investigate the relationship between peripheral and central intra-arterial BP, in patients with AF compared to SR. To evaluate the accuracy of conventional BP measurement in relation to peripheral and central intra-arterial BP, in patients with AF and compared to SR.

4 MATERIALS AND METHODS

4.1 STUDY I AND IV

4.1.1 Ethical considerations

Studies I and IV comprised the same individuals. Invasive procedures such as peripheral and coronary artery catheterization always carry a risk for complications. Furthermore, patients undergoing an invasive procedure may experience discomfort and sometimes pain. Patients participating in the study were already scheduled for a coronary angiography by clinical indication. It was deemed that the marginally prolonged procedure, necessary for the BP-recordings in the study, would also only marginally prolong potential feelings of discomfort or pain in study persons. The addition to a routine coronary angiography were short pauses with the catheter resting during the beginning of the procedure, and therefore the risk for medical complications was not expected to be increased by participating in the study. Thus, it was deemed that the scientific benefits of conducting the study would outweigh the potential risk of harm for participants. The study was in accordance with general good clinical practice (GCP) and all participants signed a written informed consent. The study was approved by the Regional Ethics Committee, registration number 2011/788-31.

4.1.2 Study design and participants

In this prospective study, patients referred for routine coronary angiography with right radial artery access, either with persistent AF or SR, were screened for participation. Patients below 18 years of age, with ongoing chest pain and/or ischemia, persisting atrial flutter, left ventricular ejection fraction <30%, hemodynamically significant valvular heart disease, BP difference between right and left arm >20 mmHg or known significant arterial anomaly, were excluded from participation. Patients treated for acute coronary syndrome without evidence of ongoing ischemia were eligible for participation. All patients were examined with echocardiography within the last year of enrollment. Data regarding background clinical characteristics were obtained from the digital medical record and directly from participants.

4.1.3 Data recording procedure

Right and left upper arm sphygmomanometric and oscillometric office BP were obtained on the same day but prior to coronary angiography. Left upper arm circumference was measured and appropriate cuff size was used. BP measurements were performed after at least five minutes of rest in the supine position. After routine preparations for coronary angiography, right radial artery access was established using six French (6F) sheaths and 5F standard diagnostic catheters for all patients. We used adjustable level pressure sets for continuous recording of intra-arterial BP. The pressure transducer was adjusted to match the height of the radial introducer sheath after zeroing arterial pressure to air.

Intra-arterial pressure recordings were obtained using pressure transducer-equipped manifolds (NAMIC®, Navilyst Medical Inc, Marlborough, MA, USA), connected to the RadiAnalyzer Xpress® unit (St Jude Medical, St Paul, MN, USA) for digital storage. Intra-

arterial recordings included at least 15 heart cycles. For conventional BP measurements an upper arm cuff of appropriate size was used. The right and left upper arm were adjusted in height so that they matched the estimated height of the left atrium. Figure 4 is a schematic illustration of the BP measurement procedure.

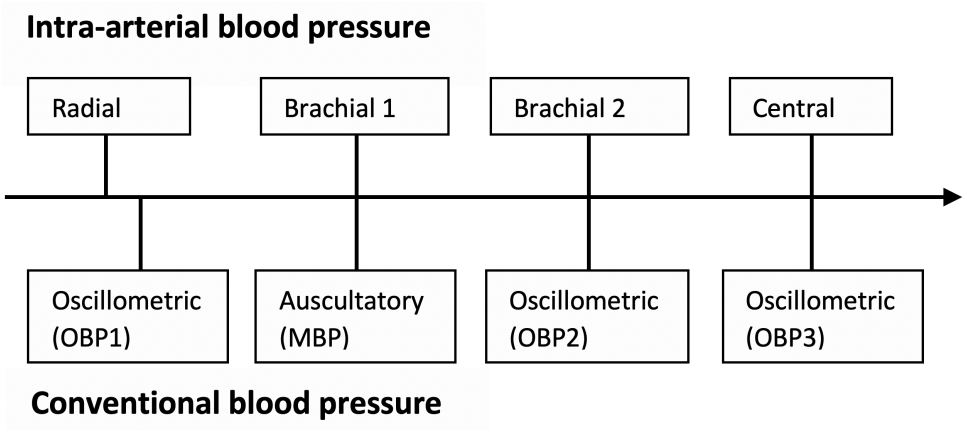

Figure 4. Flow-chart for conventional and intra-arterial blood pressure measurements procedure.

Oscillometric BP measurements were performed using a Philips Easy Care Adult cuff connected to Philips IntelliVue MMS X2 bedside monitoring system (Philips Healthcare, Andover, Ma). The first intra-arterial recording was obtained from the right radial artery introducer sheath. Directly afterwards, oscillometric BP (OBP) from the upper right arm was obtained. Thereafter, the pressure transducer was adjusted to estimated left atrial level and the diagnostic catheter was advanced to the brachial artery. Intra-arterial brachial BP and upper left arm manual sphygmomanometric BP (MBP) were then recorded simultaneously. In a similar manner, intra-arterial brachial BP and upper left arm oscillometric BP (OBP2) were simultaneously recorded. Finally, the diagnostic catheter was advanced to the ascending aorta and simultaneous central intra-arterial and upper left arm oscillometric BP (OBP3) were recorded. Systolic and diastolic BP from conventional measurements were noted in the case report form whereas intra-arterial recordings were digitally stored (RadiAnalyzer Xpress® unit (St Jude Medical, St Paul, MN, USA)) for off-line analysis.

4.1.4 Data analysis

For intra-arterial BP the RadiView 2.2® software (St. Jude Medical, St Paul, MN, USA) was used for data analysis. Systolic and diastolic BP were manually determined from the intra-arterial BP tracings. The absolute systolic and diastolic BP difference from one consecutive beat to the next, regardless of increase or a decrease in BP, was calculated from intra-arterial recordings. The primary outcome variable in study I, beat-to-beat BP variability, was defined as average systolic and diastolic BP-difference between consecutive beats. Maximum beat-to-beat BP-difference was also determined. As an alternative measure of beat-to-beat BP

variability coefficients of variation (CVAR) were calculated for systolic and diastolic pressures.

4.1.5 Statistical methods

Normally distributed data are presented as mean (± standard deviation) or median (25^{th}, 75^{th} interquartile range) for non-normally distributed data. The Shapiro-Wilk's test was used to test for normality of distribution. To test for differences between groups, independent sample t-test or the Mann-Whitney test (depending on distribution of data) was used for continuous data. For categorical data a Chi square test or Fishers exact test was used. A Paired Samples t-test was used to test for differences within groups. A One-Way ANOVA test was used to test for differences in beat-to-beat BP variability between locations. P-values <0.01 (Study I) or <0.05 (Study IV) were considered significant. Statistical analyses were performed using SPSS Statistics, Version 22.0 and 25.0 (IBM Corp. Armonk, NY).

4.2 STUDY II

4.2.1 Ethical considerations

Study II was a retrospective observational register study based on data extracted from digital medical records. As such, patients included in the study were not asked permission for participation. In the process of data collection, the researchers involved in the study accessed and read individual medical records. This constitutes a potential breach of integrity on behalf of participating study persons and furthermore, no additional direct individual benefit was to be expected for participants. However, the potential benefits of conducting the study, for patients with AF in general, were deemed to outweigh the ethical problem of integrity. The Regional Ethics Committee deemed from the application (registration number 2014/2199-31) that the project as such, did not fall under the law for ethics approvals, but further deemed that they could not identify any ethical obstacles for the carrying through with the project.

4.2.2 Study design and data collection

Data from the digital medical records of 487 unique patients with persistent AF, undergoing electrical cardioversion at Södersjukhuset during 2013-2014 was collected and analyzed. A flow chart of the screening and inclusion process is presented in Figure 5.

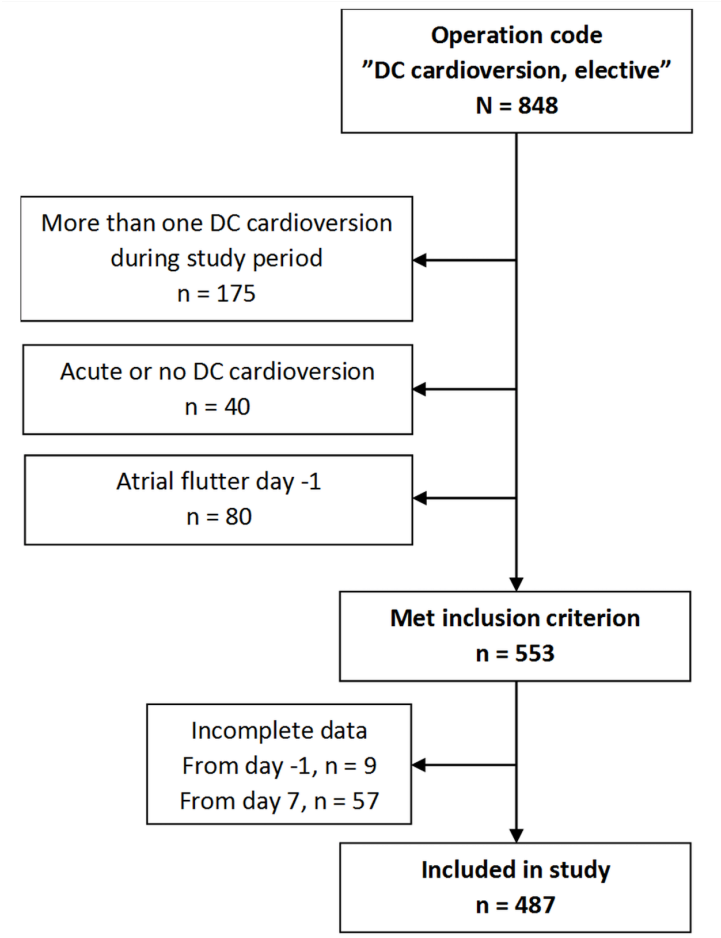

Figure 5. Flow-chart of inclusion process. Reprinted courtesy of Journal of Clinical Hypertension 2019;21:363-368. Wiley Periodicals, Inc.© DC indicates direct current.

According to local clinical routine, patients scheduled for elective cardioversion had a nurse appointment the day preceding cardioversion (day -1) when a 12-lead ECG was recorded and sphygmomanometric office BP was obtained. One week after ECV (day 7), patients had a follow-up visit with repeat 12-lead ECG and office BP measurement. BP measurements and ECG recordings were performed by nurses at the Cardiology outpatient clinic. The same staff and the same methods were used at both visits. Local clinical routine stipulated that BP was measured after at least five minutes of rest in the supine position, using the auscultatory method with an aneroid sphygmomanometer. At each visit, a single BP was noted in the digital medical record. Data on background clinical characteristic, medication and BP were collected from digital medical records whereas data on heart rate and rhythm were obtained directly from ECG-recordings.

4.2.3 Statistical methods

Descriptive data are presented as mean and standard deviation or median and interquartile range according to distribution of data. Comparison of categorical variables was made using the Fisher's exact test. The Shapiro-Wilk test was used to test for normality for continuous variables. For normally distributed data, a Student's t-test was used to test for differences

between groups. For non-normally distributed data, the Mann-Whitney U test and the Wilcoxon signed-rank test were used. P-values <0.01 were considered significant. Statistical analyses were performed using SPSS Statistics, Version 22.0 (IBM Corp. Armonk, NY).

4.3 STUDY III

4.3.1 Ethical considerations

Apart from routine procedures such as office BP measurement and ECG-recordings, study participants underwent two 24-h ambulatory BP recordings, one before and one after ECV. Although 24-h ambulatory BP is generally recommended and frequently used, it may be associated with patient discomfort, disturbed sleep and sometimes pain. On the other hand, a thorough evaluation of BP by means of 24-h ambulatory BP monitoring, may provide additional medical data that is of benefit for the individual. It was deemed that an ethical cost-benefit calculation weighed in favor of conducting study III. The study was in accordance with GCP, all study persons were thoroughly informed about the study and the nature of the procedures involved. All patients signed a written informed consent before inclusion. The study was approved by the Regional Ethics Committee, registration number 2012/1272-31.

4.3.2 Study design and participants

In this prospective study, patients without significant valvular heart disease, undergoing ECV for persistent AF, were eligible for inclusion. The study was conducted at three different sites; Södersjukhuset, Karolinska University Hospital and Danderyd University Hospital. A flow chart of the inclusion process is presented in Figure 6.

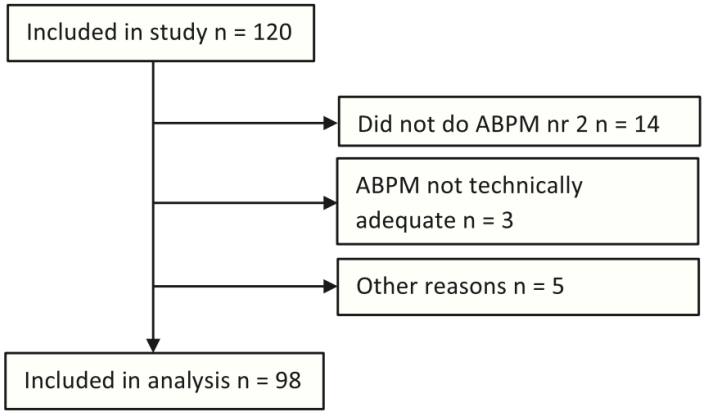

Figure 6. Flow-chart for inclusion process. Courtesy of Journal of Hypertension. August 21, 2020, published ahead of print. doi: 10.1097/HJH.0000000000002623. Wolters Kluwer Health, Inc.© ABPM indicates ambulatory blood pressure monitoring.

At the first study visit, background clinical characteristics regarding lifestyle factors, medical history and medication were obtained from participants and from medical records. A 12-lead ECG was recorded and automated oscillometric and auscultatory sphygmomanometric office BP were obtained. On the second visit, which was scheduled within a week before planned ECV, a 24-h ambulatory BP measurement (SpaceLabs 90217a device; Spacelabs, Snoqualmie, Washington, USA) was conducted. BP measurements were made every 20th minute both during daytime (0600-2200h) and night-time (2200-0600h). On the third visit, scheduled seven days after ECV, an ECG-recording and a 24-h ambulatory BP measurement was repeated. Data regarding heart rate was obtained from 24-h BP monitorings. BP measurements in the study were performed either by trained research nurses or by the researchers involved in the study. Upper arm circumference was measured, and the appropriate cuff size was used for all measurements.

4.3.3 Statistical methods

Comparisons of categorical variables were made using Fisher's exact test. Descriptive data are presented as mean and standard deviation. Independent-samples t-test was used for comparisons between groups and Paired-samples t-test for comparisons within groups. Correlations between dependent and independent variables were tested using linear regression analysis. P-values <0.05 were considered significant. Statistical analyses were performed using SPSS Statistics, Version 25.0 (IBM Corp. Armonk, NY).

5 RESULTS PER STUDY

5.1 STUDY I

Twenty-one patients in AF and 12 patients in the SR control group were included in the study. The two groups were similar with regard to age, prevalence of treated hypertension and left ventricular ejection fraction. Resting heart rate was numerically slightly higher in the AF group (71.1 ± 12.1 beats per minute) compared to the SR group (62.4 ± 9.2 beats per minute), although this difference was not statistically significant (p=0.06). Of note, baseline office systolic BP was numerically lower, whereas diastolic BP was numerically higher in the AF group compared to the SR group (128.7/82.9 versus 137.4/77.2 mmHg), these differences were however also not statistically significant. For all but one patient, known or suspected ischemic heart disease was the primary indication for coronary angiography. Five patients were treated for acute coronary syndrome.

The primary outcome variable in study I was beat-to-beat BP variability in AF patients in comparison to patients with SR. Median systolic beat-to-beat BP change, grouped by AF or SR, is presented in figure 7.

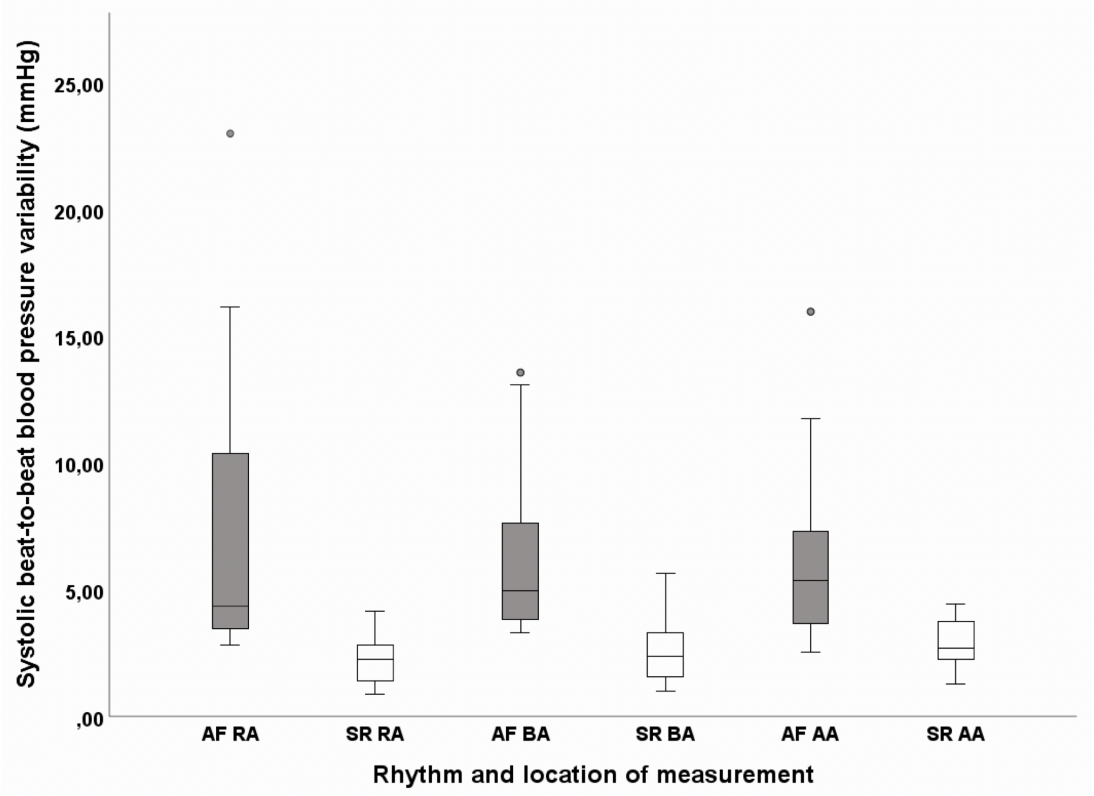

Figure 7. Systolic beat-to-beat BP variability in patients with AF and SR. Reprinted courtesy of Blood Pressure. 2018;27(5):249-255. The authors©. RA indicates radial artery, BA indicates brachial artery, AA indicates ascending aorta.

A significantly higher systolic BP variability in AF patients compared to SR patients was observed for all locations of measurement: (median, interquartile range) 4.3 (3.5-10.4) mmHg vs. 2.2 (1.4-2.8) mmHg at the radial artery level, 4.9 (3.8-7.6) mmHg vs. 2.4 (1.6-3.3) mmHg at the brachial artery level and 5.4 (3.6-7.3) mmHg vs. 2.7 (2.3-3.8) mmHg in the ascending aorta ($p<0.001$ for all comparisons). Systolic BP variability defined as CVAR was also significantly higher in AF compared to SR. Furthermore, maximum systolic beat-to-beat BP change was significantly higher in AF patients compared to SR patients at all locations of measurement. For diastolic BP variability, the absolute and relative difference between AF and SR patients was even more pronounced, see figure 8.

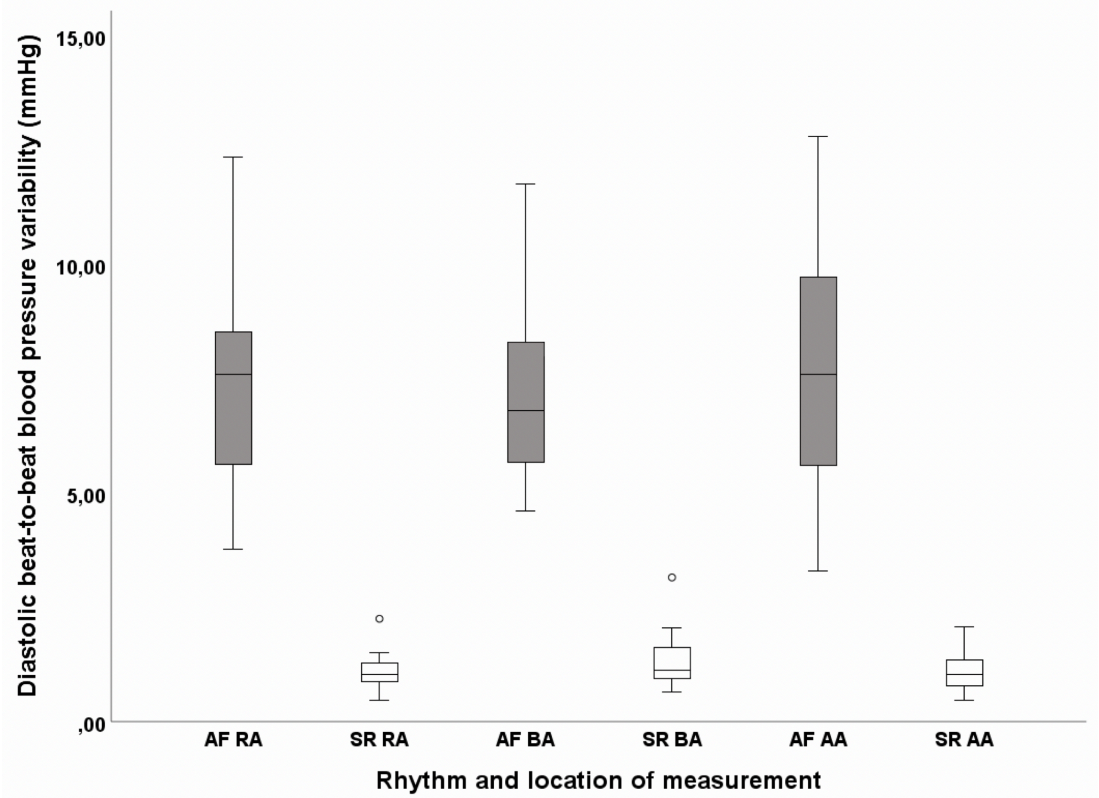

Figure 8. Diastolic beat-to-beat BP variability in patients with AF and SR. Reprinted courtesy of Blood Pressure. 2018;27(5):249-255. The authors©. RA indicates radial artery, BA indicates brachial artery, AA indicates ascending aorta.

Mean beat-to-beat BP variability in AF and SR groups respectively were: 7.4 ±2.2 mmHg and 1.1 ±0.4 mmHg at the radial artery level, 7.2 ±1.9 mmHg and 1.4 ±0.7 mmHg at the brachial artery level and 7.8 ±2.8 mmHg and 1.1 ±0.4 mmHg in the ascending aorta ($p<0.001$ for all comparisons). Diastolic BP variability defined as CVAR as well as maximum diastolic BP change between beats, were both significantly higher in AF compared to SR.

5.2 STUDY II

487 unique patients were included for analysis in the study. At day 7 follow-up, 198 (41%) of patients had relapsed into AF (AF-AF group), whereas 289 (59%) patients remained in SR (AF-SR group). Baseline clinical characteristics were largely similar between the groups except for a diagnosis of heart failure which was more common in the AF-AF group (although LVEF did not differ significantly between groups). The primary outcome variable was BP change after restoration of SR. The main results are presented in table 2.

(A) All 487 patients					
	AF-AF group n = 198		AF-SR group n = 289		Difference between groups
	mm Hg (±SD)	*P*-value[a]	mm Hg (±SD)	*P*-value[a]	*P*-value[b]
Mean systolic BP					
Day −1	133 (±17)		129 (±17)		<0.001
Day 7	133 (±17)		137 (±18)		0.008
Mean change	0 (±14)	0.439	9 (±16)	<0.001	<0.001
Mean diastolic BP					
Day −1	84 (±10)		82 (±9)		0.018
Day 7	84 (±11)		79 (±10)		<0.001
Mean change	0 (±10)	0.319	−3 (±9)	<0.001	<0.001

Table 2. Mean systolic and diastolic BP. Divided according to rhythm after ECV. Reprinted courtesy of Journal of Clinical Hypertension 2019;21:363-368. Wiley Periodicals, Inc.©

A mean increase in systolic BP by 9 mmHg and a mean decrease in diastolic BP by 3 mmHg, following restoration of SR was observed ($p<0.001$ for both comparisons). In contrast, in patients with a relapse in AF (AF-AF group), no change in BP was observed. To test if these BP changes were independent of changes in antihypertensive and antiarrhythmic medication, a subgroup analysis consisting of patients without any such medication changes between the visit before and after ECV was performed. The results from the analysis of these 371 patients were largely consistent with those of the entire cohort. A 9 mmHg increase of systolic BP after SR restoration could be observed. Diastolic BP numerically decreased by 2 mmHg, this difference was however not significant ($p=0.1$). We then analyzed the proportion of patients with a hypertensive BP-level (≥140/90 mmHg) before and after ECV. In the AF-SR group, the number of patients with a hypertensive BP level increased from 115 to 161, representing an absolute 16% increase or a 40% relative increase.

5.3 STUDY III

Of the 120 patients included in the study, 98 patients were included in the statistical analysis. A flow chart of the inclusion process is presented in Figure 4. At the second 24-h ambulatory BP measurement, 62 patients had retained SR after ECV (AF-SR group), whereas 36 patients had relapsed into AF (AF-AF group). The two groups were similar in terms of age. There was a predominance of male participants, a high prevalence of preexisting hypertension and a high usage of b-blocking agents in both groups. The main results of the primary outcome variable (change in 24-h ambulatory BP following restoration of SR) are presented in table 3 and figure 9.

	AF-AF group $n = 36$		AF-SR group $n = 62$[a]		Difference between groups
	mmHg (±SD)	P *	mmHg (±SD)	P *	P **
Mean systolic 24-h ABPM			$n = 60$		
Before ECV	117.0 (±11.2)		118.4 (±13.8)		0.55
After ECV	114.9 (±10.8)		124.1 (±14.7)		0.002
Mean change	−2.1 (±8.3)	0.14	5.6 (±8.4)	<0.001	
Mean systolic daytime ABPM					
Before ECV	121.3 (±10.6)		122.1 (±14.3)		0.76
After ECV	119.2 (±10.3)		128.2 (±15.6)		0.003
Mean change	−2.1 (±8.8)	0.16	6.1 (±10.1)	<0.001	
Mean systolic night-time ABPM			$n = 60$		
Before ECV	109.6 (±12.9)		112.1 (±16.1)		0.36
After ECV	107.4 (±12.5)		116.3 (±16.3)		0.007
Mean change	−2.3 (±8.3)	0.11	4.2 (±9.2)	0.001	
Mean diastolic 24-h ABPM			$n = 60$		
Before ECV	76.8 (±8.5)		76.0 (±9.7)		0.77
After ECV	75.5 (±7.5)		71.3 (±9.8)		0.03
Mean change	−1.3 (±5.6)	0.17	−4.7 (±6.8)	<0.001	
Mean diastolic daytime ABPM					
Before ECV	80.4 (±8.7)		79.3 (±10.2)		0.58
After ECV	79.1 (±7.4)		74.6 (±10.5)		0.02
Mean change	−1.3 (±6.5)	0.23	−4.8 (±8.0)	<0.001	
Mean diastolic night-time ABPM			$n = 60$		
Before ECV	70.2 (±9.6)		70.3 (±10.9)		0.87
After ECV	68.9 (±9.0)		65.4 (±10.2)		0.07
Mean change	−1.3 (±6.2)	0.24	−4.9 (±7.0)	<0.001	

Table 3. Ambulatory blood pressure monitoring (ABPM) before and after ECV. Reprinted courtesy of Journal of Hypertension. August 21, 2020, published ahead of print. doi: 10.1097/HJH.0000000000002623. Wolters Kluwer Health, Inc.©

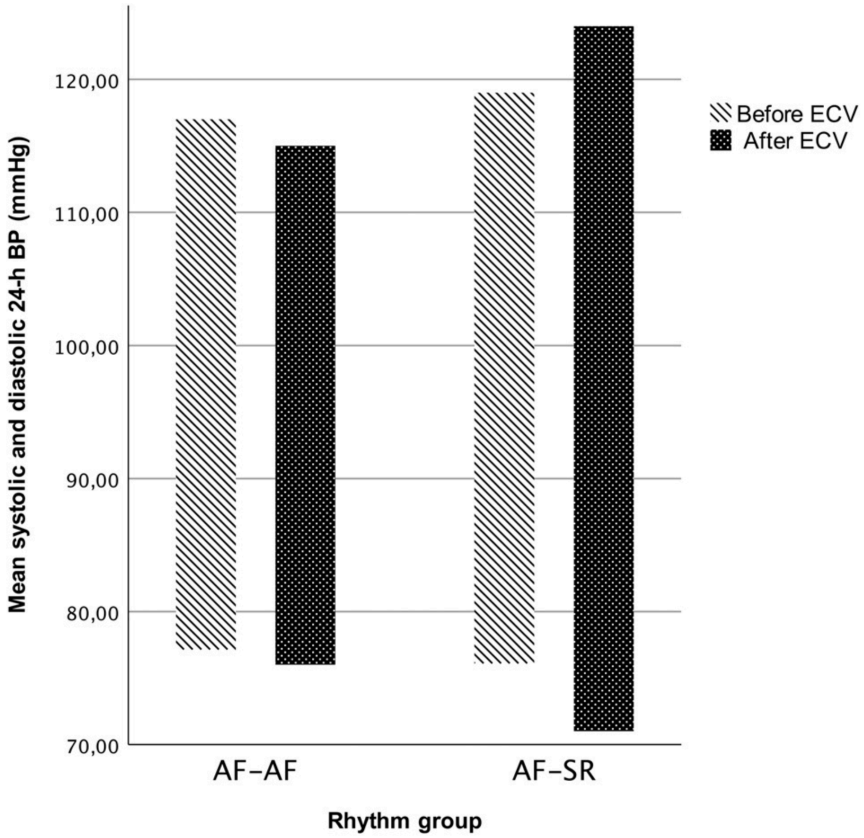

Figure 9. 24-h ambulatory BP before and after ECV. Bar upper margin represents systolic BP, lower margin represents diastolic BP and entire bar length represents pulse pressure. Reprinted courtesy of Journal of Hypertension. August 21, 2020, published ahead of print. doi: 10.1097/HJH.0000000000002623. Wolters Kluwer Health, Inc.©

In the AF-SR group mean systolic 24-h ambulatory BP increased by 5.6 mmHg and mean diastolic 24-h ambulatory BP decreased by 4.7 mmHg ($p<0.001$ for both comparisons). In contrast, both systolic and diastolic 24-h ambulatory BP numerically slightly decreased in the AF-AF group. These changes however, were not statistically significant. Accordingly, pulse pressure was markedly increased (approximately 25%) in patients with restored SR ($p<0.001$), whereas no change in ambulatory PP was observed in the AF-AF group. To evaluate the possible correlation between baseline BP level and the observed BP changes in the AF-SR group, mean arterial pressure (defined as mean 24-h ambulatory diastolic BP + (mean 24-h ambulatory PP/3)) was plotted against ambulatory PP change. As demonstrated in Figure 10, no correlation between mean arterial pressure and relative PP change was observed.

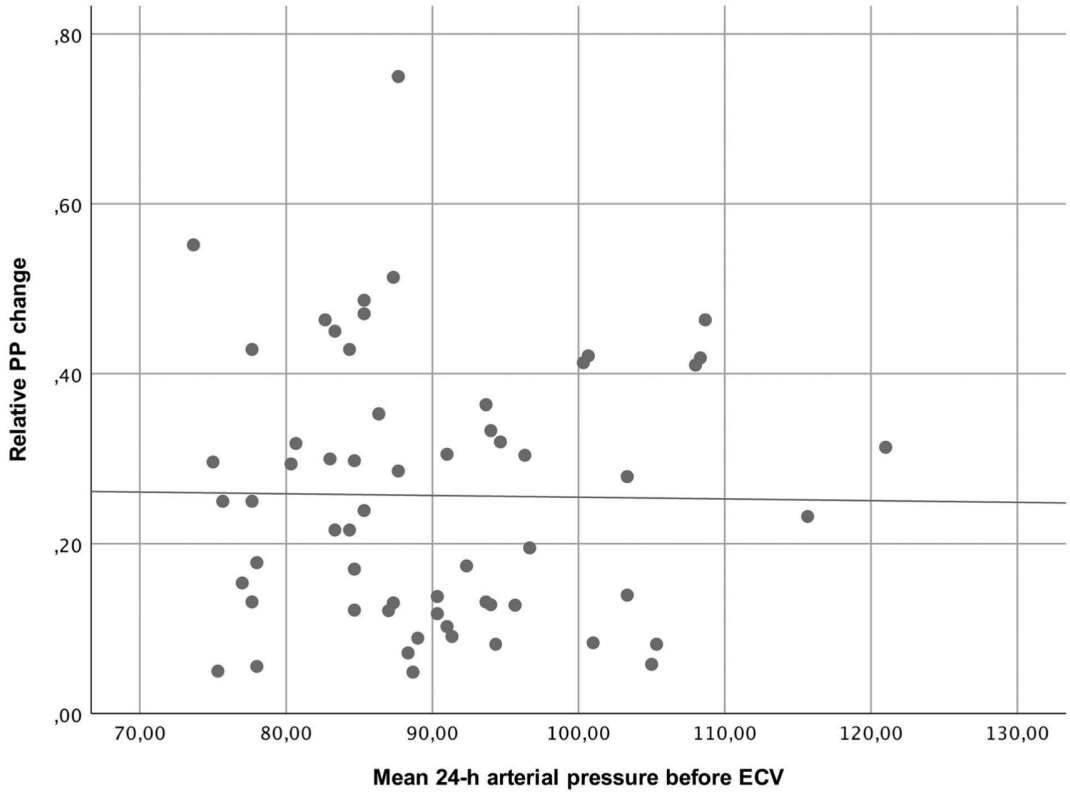

Figure 10. Correlation between relative change in pulse pressure after ECV and mean arterial 24-h ambulatory BP before ECV. Reprinted courtesy of Journal of Hypertension. August 21, 2020, published ahead of print. doi: 10.1097/HJH.0000000000002623. Wolters Kluwer Health, Inc.© PP indicates pulse pressure.

Mean heart rate significantly decreased from 79.5 ±11.5 to 57.6 ±8.7 bpm after ECV, whereas mean heart rate was unchanged in the AF-AF group. In a linear regression analysis, change in systolic 24-h ambulatory BP in the AF-SR group was not significantly correlated with change in heart rate (adjusted R^2 0.045), whereas a moderate correlation (adjusted R^2 0.43) for diastolic 24-h ambulatory BP and change in heart rate was observed.

We then analyzed the proportions of patients with a hypertensive BP level (mean daytime ambulatory BP ≥135 mmHg systolic or ≥85 mmHg diastolic). Before ECV, 36% of patients in the AF-AF group and 31% of patients in the AF-SR group were hypertensive according to daytime ambulatory BP. Among remaining individuals, who were normotensive before ECV, the proportion of hypertensive individuals after ECV was slightly higher in the AF-SR group (6/43) compared to the AF-AF group (2/23).

5.4 STUDY IV

The 33 patients included in the analysis (21 with AF and 12 with SR) are the same as for study I and baseline characteristics are briefly described under results for study I.

The first aim of the study was to evaluate the relationship between intra-arterial peripheral (radial and brachial) and central BP in patients with AF compared to patients with SR. These results are presented in table 4 and figure 11.

	AF, n=21 mmHg (±SD)	SR, n=12 mmHg (±SD)	Mean diff. AF - SR, mmHg	P
Radial, systolic	149.5 (±23.8)	152.5 (±16.7)	-3.0	0.7
Brachial 1, systolic	138.3 (±24.2)	146.8 (±21.4)	-8.5	0.3
Brachial 2, systolic	137.2 (±24.5)	146.7 (±20.4)	-9.5	0.3
Central, systolic	136.1 (±26.1)	141.6 (±19.3)	-5.4	0.5
Radial, diastolic	77.7 (±13.4)	68.6 (±4.9)	9.1	0.03
Brachial 1, diastolic	80.1 (±12.0)	70.2 (±7.6)	9.9	0.02
Brachial 2, diastolic	79.6 (±12.0)	70.2 (±7.2)	9.4	0.02
Central, diastolic	82.5 (±13.6)	72.3 (±7.7)	10.2	0.02
Radial, PP	71.8 (±14.7)	83.9 (±14.7)	-12.2	0.04
Brachial 1, PP	58.2 (±18.1)	76.7(±19.3)	-18.4	0.01
Brachial 2, PP	57.6 (±18.5)	76.5 (±19.1)	-18.9	<0.01
Central, PP	53.6 (±18.7)	69.3 (±15.2)	-15.6	0.02

Table 4. Peripheral and central intra-arterial BP in AF and SR. PP indicates pulse pressure. P indicates p-value.

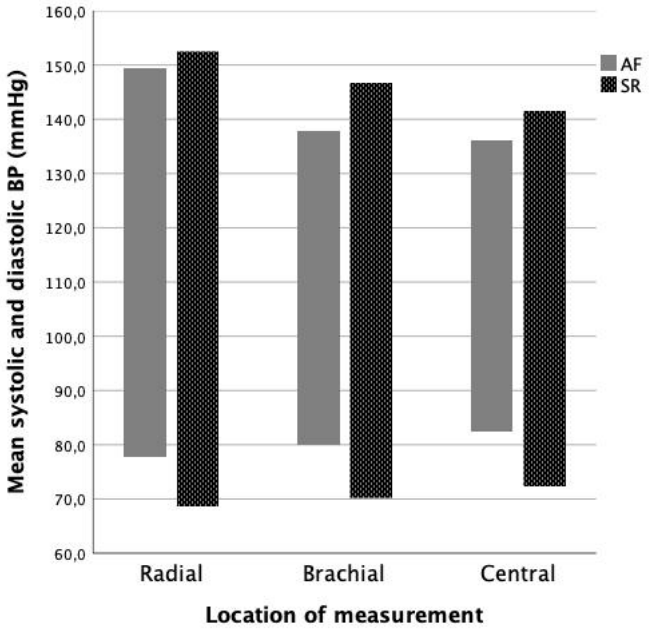

Figure 11. Peripheral and central intra-arterial BP in AF and SR. Bar upper margin represents systolic BP, lower margin represents diastolic BP and entire bar length represents pulse pressure. Brachial is mean from measurements Brachial 1 and 2.

Systolic intra-arterial BP was numerically, albeit not significantly, lower in AF patients compared to SR patients for all locations of measurement. In contrast, diastolic intra-arterial BP was significantly higher in AF compared to SR patients for all locations of measurement. As a consequence, PP was markedly lower in patients with AF compared to SR. In both groups, intra-arterial systolic BP was numerically lower, whereas diastolic BP was higher the more proximal the location of measurement. These BP-changes from peripheral to central, along the arterial tree were however very similar in the AF compared to the SR group and no significant in-between differences regarding intra-arterial systolic (p=0.6), diastolic (p=0.6) or PP (p=0.6) were observed.

The second aim of study IV was to evaluate the accuracy of conventional BP measurement (oscillometric and manual sphygmomanometric) as compared to reference intra-arterial BP at different arterial locations, in AF and SR patients separately and in comparison. See figure 4 for a flow-chart of the measurement procedure. Conventional systolic BP was similar in the AF compared to the SR group, whereas conventional diastolic BP was numerically higher (significantly for some comparisons) in AF compared to SR patients. Results regarding accuracy of conventional BP are presented in table 5.

	AF, n=21 mmHg (±SD)	SR, n=12 mmHg (±SD)	P	Bias AF mmHg	P	Bias SR mmHg	P
OBP 1 syst	137.4 (±25.8)	136.8 (±15.3)	0.9	-12.1	<0.01	-15.8	<0.01
MBP syst	133.9 (±19.8)	135.4 (±15.0)	0.8	-4.4	0.1	-11.4	0.02
OBP 2 syst	141.3 (±24.8)	136.7 (±18.4)	0.6	4.1	0.07	-10.0	0.01
OBP 3 syst	141.2 (±26.1)	137.7 (±17.0)	0.7	5.0	0.04	-3.9	0.09
OBP 1 diast	76.0 (±11.8)	68.7 (±10.3)	0.08	-1.8	0.5	0.1	0.9
MBP diast	79.2 (±10.2)	71.8 (±8.2)	0.04	-0.9	0.6	1.6	0.2
OBP 2 diast	80.3 (±14.1)	70.7 (±11.3)	0.05	0.7	0.8	0.5	0.8
OBP 3 diast	82.6 (±13.7)	69.4 (±10.0)	<0.01	0.1	0.9	-2.9	0.05

Table 5. Conventional BP measurement and bias in comparison to intra-arterial BP at different arterial locations. OBP indicates oscillometric blood pressure, MBP indicates manual auscultatory blood pressure. P indicates p-value.

Measurement biases for conventional diastolic BP were overall small in absolute numbers, both in the AF and SR group. Regarding the accuracy of conventional systolic BP, measurement biases were however larger. In the SR group conventional BP measurement numerically underestimated reference intra-arterial systolic BP at all locations (significantly except for comparison to central BP). In the AF group conventional systolic BP, as in SR, numerically underestimated radial intra-arterial BP but in contrast to SR, oscillometric measurement numerically overestimated intraarterial brachial and central BP. In a comparison of conventional BP measurement bias between groups, oscillometric BP measurement in AF overestimated brachial intra-arterial BP by 14.1 mmHg ($p<0.01$) and central intra-arterial BP by 9.0 mmHg ($p=0.01$), in comparison to patients in SR. These results are presented in figure 12 and 13.

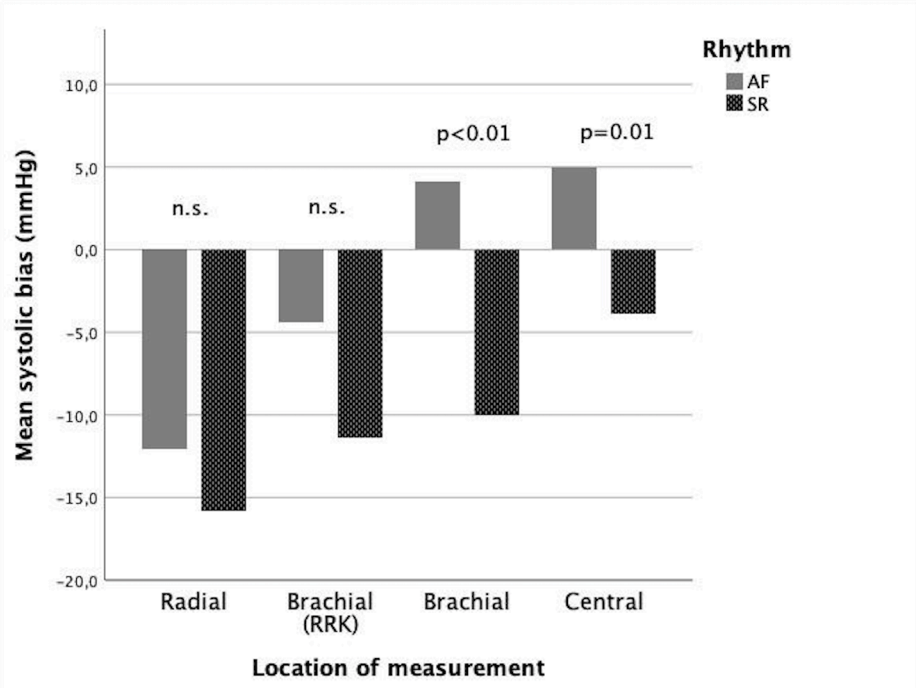

Figure 12. Conventional systolic BP measurement bias in AF and SR. RRK (Riva-Rocci Korotkoff) indicates manual auscultatory BP measurement.

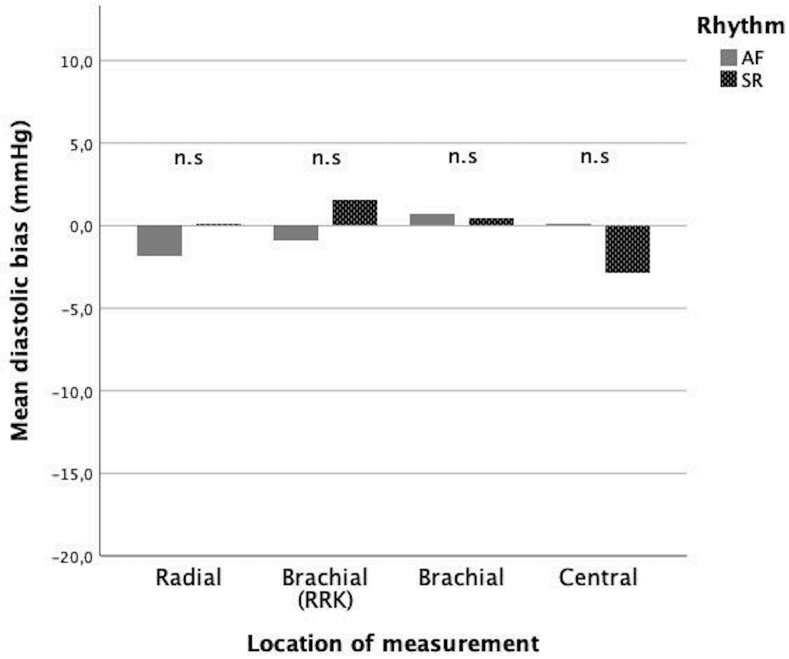

Figure 13. Conventional diastolic BP measurement bias in AF and SR. RRK (Riva-Rocci Korotkoff) indicates manual auscultatory BP measurement.

6 DISCUSSION

6.1 BLOOD PRESSURE IN ATRIAL FIBRILLATION – WHY IS IT OF INTEREST?

Atrial fibrillation has a high prevalence and is closely intertwined with hypertension.[2,12] Both conditions carry an increased risk for cardiovascular morbidity and mortality.[5,6] Hypertension is considered to be the leading risk factor for premature death world-wide.[30,34] The risks and the benefits of therapeutic intervention in hypertension have been thoroughly studied and quantified. However, this body of scientific evidence is primarily based on randomized clinical intervention trials on patients with SR, studies from which patients in AF have been consistently excluded.[11] As shown in the studies included in this thesis,[70,86,87] as well as from other studies, atrial fibrillation may affect BP in several ways. Evidence drawn from interventional hypertension trials conducted on patients with SR, regarding optimal treatment of hypertension, may therefore not be generalizable to patients with AF. Despite adjusting for known cardiovascular risk factors, AF is independently associated with a two-fold increased risk of death,[5,68] for which the underlying pathophysiological mechanisms are not fully understood. Here, suboptimal understanding, measurement and treatment of blood pressure in atrial fibrillation may play a part. This also makes the case for further research into this area and has been an overarching theme for this project.

6.2 BEAT-TO-BEAT BLOOD PRESSURE VARIABILITY IN ATRIAL FIBRILLATION

As previously described, heart rhythm in AF is irregular. As a hemodynamic consequence, there is an increased BP variability in AF compared to SR. Although this is a familiar phenomenon in clinical cardiology, it has previously only been scientifically described in a study from 1940 by Buchbinder and Sugerman.[10] In that study, including eight patients with AF, large variations in beat-to-beat BP were observed, these results were however not systematically quantified. In study I we sought to invasively measure and quantify beat-to-beat BP variability in a cohort of patients with sustained AF in comparison to a control group of patients with SR. In summary, systolic BP variability was roughly doubled and diastolic BP variability was approximately six times higher, in AF compared to SR patients.[70] The exact underlying physiological mechanisms determining the level of BP change between beats were not directly addressed in the study. However, during the diastolic phase, arterial BP progressively falls towards zero until initiation of the following systolic ventricular ejection phase. Consequently, during a longer diastole, arterial BP falls further. At the same time, a long diastolic phase prolongs left ventricular filling time, resulting in increased stroke volume and blood pressure surge during the following systolic phase. Since there is an upper limit for left ventricle filling volume, there is theoretically also an upper limit for the systolic BP surge. In contrast, there is no lower limit (except zero) for how much diastolic BP may fall during a long enough R-R-interval. An intra-arterial BP tracing is presented in figure 14 for illustration. Theoretically, these relationships may explain our finding of a more profound beat-to-beat BP variability for diastolic compared to systolic pressure and this would also

imply that increased rhythm irregularity, as well as bradycardia with long R-R-intervals, would in particular affect the level of diastolic BP variability.

6.3 POSSIBLE IMPLICATIONS FOR BLOOD PRESSURE MEASUREMENT

A single conventional office BP measurement in SR provides a systolic and a diastolic BP value. This may be perceived as an average systolic and diastolic BP during resting conditions since short-term BP fluctuations in regular rhythm can be expected to be small. As shown in study I, short-term BP variability in AF is increased. A conventional BP reading will not be able to account for these BP fluctuations, but instead will only, in a best-case scenario, provide an average systolic and diastolic BP for what is actually a range of varying blood pressures. Furthermore, BP variability in AF most likely leads to an increased inter- and intra-observer variation for auscultatory BP.[88] It has been proposed that this problem may to some extent be mitigated by calculating the mean from triplicate BP measurements.[89,90] However, in study I we also show that maximum BP difference between consecutive beats is markedly higher in AF compared to SR patients, in particular for diastolic BP. These conditions, prevalent in AF, will not be reflected in conventional BP measurement, even if an average from triplicate measurements is calculated.

6.4 POSSIBLE PATHOPHYSIOLOGICAL HEMODYNAMIC CONSEQUENCES

Since the subject of possible negative effects from short-term BP variability in AF has not been specifically studied, a discussion on the topic becomes hypothetical. Hypertension is a fundamental risk factor for the development of atherosclerosis[33] and elevated BP may also act as a trigger for plaque rupture and subsequent vascular events.[91,92] As outlined above, conventional BP measurement in AF will not reflect pressure peaks or troughs (see figure 14). One may hypothesize, that such occasional pressure peaks and troughs could have short- and long-term pathophysiological implications.

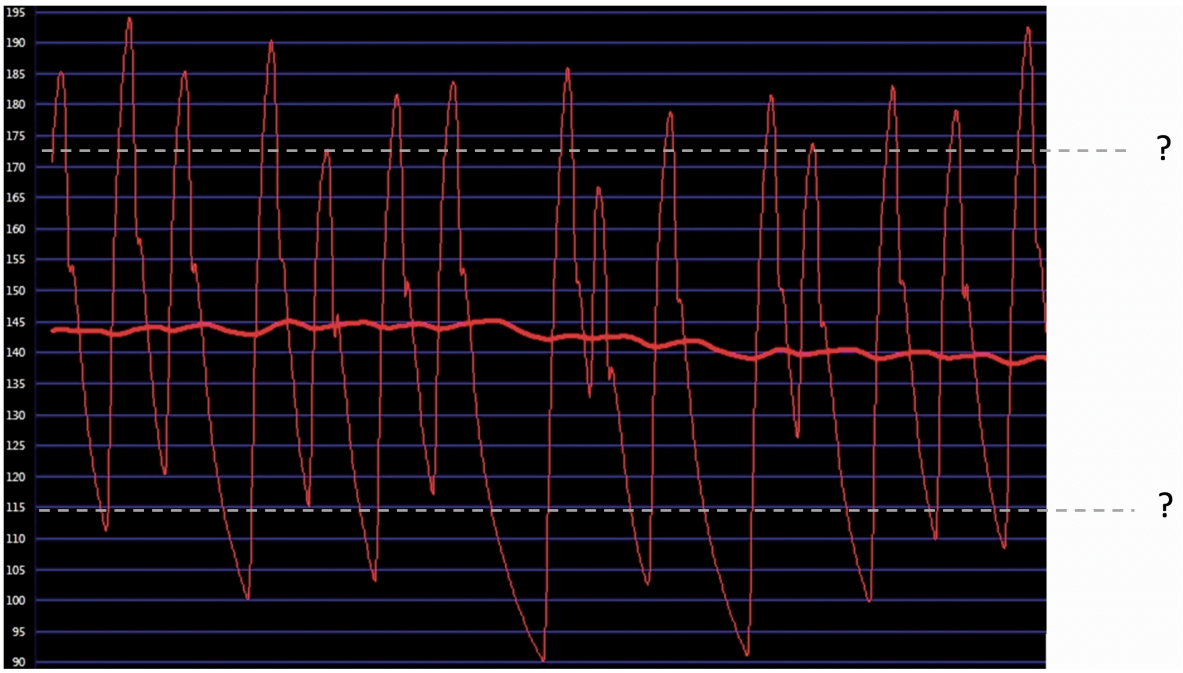

Figure 14. Intra-arterial BP recording from patient with AF. Dashed lines indicate possible mean and/or measured systolic and diastolic BP.

Whether there is a causal connection between AF per se and atherosclerosis is unclear. These conditions share the same risk factors which makes causality difficult to study. However, several studies imply that endothelial dysfunction, which may be viewed as a precursor of atherosclerosis, may be induced by AF[61,93,94] and that this process may be reversed by restoring SR.[95] Inflammation is a fundamental component of atherosclerosis.[96] Earlier studies suggest a bidirectional association between inflammation and AF,[97,98] although it is uncertain if there is also causality. Furthermore, results from other studies have demonstrated an association between AF and increased atherosclerosis, measured as carotid intima-media thickness.[99–101] There also appears to be an association between increasing AF burden with an increased burden of atherosclerosis.[100]

Emerging evidence suggest an association between AF and acute coronary syndrome.[102–104] Systemic inflammation and platelet activation associated with AF has been proposed as drivers, linking AF with an increased risk for myocardial infarction.[105] There has been a longstanding controversy around the so called J-curve phenomenon, referring to findings of a non-linear relationship between diastolic BP and cardiovascular outcomes.[106] There is however consistent evidence suggesting that lowering diastolic BP <70 mmHg in hypertensive patients is associated with an increased risk for coronary events.[107,108] The coronary arteries are perfused during diastole and the likely explanation to these findings are that patients with coronary artery disease have a poor coronary flow reserve, thus making them vulnerable to low diastolic perfusion pressures.[109] In study I we show large beat-to-beat fluctuations for diastolic pressure in particular, meaning that for some heart beats, diastolic pressure was far below average diastolic pressure for that individual during that certain intra-arterial BP-recording. This observation may provide yet another hypothetical

pathophysiological mechanism, linking sustained AF with an increased risk for coronary events. Interestingly, in a pooled analysis, AF was associated with an increased risk for myocardial infarction, despite the fact that AF patients harbored less coronary atherosclerosis at baseline.[110]

Although not specifically studied, it is thus hypothetically conceivable that increased beat-to-beat BP variability in AF patients, with profound pressure peaks and troughs not reflected in conventional BP measurement, may contribute in pathophysiological processes linking AF to an increased risk for atherosclerosis and atherosclerotic cardiovascular events. Such pathophysiological processes may include increased inflammation and endothelial dysfunction, as well as more direct hemodynamic BP-mediated effects possibly affecting plaque stability and impairing myocardial blood flow.

6.5 POSSIBLE AUTONOMIC AND NEUROHORMONAL EFFECTS

Physiological control of BP is complex and involves autonomic and neurohormonal mechanisms. The autonomous nervous system fundamentally influences the regulation of the cardiovascular system, both short- and long-term.[111,112] Short-term it mainly acts by inducing vasoconstriction through increased sympathetic nerve activity (SNA), mediated through baroreflexes.[111] With regard to long term effects it has been proposed that increased SNA may induce endothelial dysfunction, vascular hypertrophy and remodeling, left ventricular hypertrophy and is also associated with cardiovascular disease.[113–116] There may be a bidirectional relationship between increased autonomic nerve activity and AF.[117] Initiation and progression of AF may be induced by increased autonomic nerve activity[117,118] and conversely, autonomic nerve activity may be affected by AF itself.[119] In one study, irregular atrial pacing simulating AF resulted in a 70% increase in SNA compared to regular pacing.[120] This effect is believed to be mediated through arterial baroreflexes.[120] In another study, the level of rhythm irregularity was correlated to the level of increase in SNA.[121] As shown in study I, the irregular rhythm in AF results in rapid beat-to-beat changes in BP. The cardiovascular system strives to uphold a physiologically optimal BP in each moment. A physiological response to these rapid BP changes in AF could be an increase in SNA, mediated through arterial baroreflexes. Thus, hypothetically the BP fluctuations in AF may drive an increase in SNA, which may potentially have negative effects on the vasculature and on long-term cardiovascular risk in AF patients.

AF is also associated with an increased activity of the renin-angiotensin-aldosterone system (RAAS) and a reduction in serum aldosterone after successful restoration of SR by ECV has been demonstrated.[122–124] A reduction in the activity of both the sympathetic nervous system and the RAAS after restoration of SR may thus be correlated to a reduction in BP. Such a mechanism is congruent with our observation in study II and III of a reduction of diastolic BP after SR restoration. It is however incongruent with our findings of increased systolic BP after restoration of SR.

6.6 HOW IS BLOOD PRESSURE AFFECTED BY ATRIAL FIBRILLATION?

The effects of AF on short-term BP variability is discussed above, but does AF affect BP in other ways? Study II is a retrospective study in which BP-effects from AF, measured with conventional sphygmomanometry, was evaluated in a population with persistent AF undergoing ECV.[86] In summary, systolic BP was 9 mmHg lower and diastolic BP was 3 mmHg higher, in AF before ECV compared to in SR one week after ECV. Only a few other studies examining this particular subject exist. BPs in those studies were primarily measured with the oscillometric method (as 24-h ambulatory BP or office BP) and results are not entirely conclusive. In two smaller studies, including 18 and 12 patients respectively, patients undergoing ECV were examined with 24-h ambulatory BP after restoration of SR. Mean diastolic BP decreased from 74 to 70 mmHg[125] and from 81.7 to 75.2 mmHg,[126] whereas mean systolic BP remained unchanged in both studies. In a slightly larger study, 63 patients with restored SR after ECV were evaluated with automated office oscillometric BP. A 5 mmHg decrease in diastolic BP and 4-5 mmHg increase in systolic BP was observed after SR restoration.[90] In another study from the same group of researchers,[127] 54 hypertensive patients with persistent AF were evaluated with 24-h ambulatory BP, before and approximately a month after ECV. In 34 patients retaining SR at one month, mean systolic 24-h ambulatory BP increased by 5.1 mmHg, whereas mean diastolic 24-h ambulatory BP decreased by 2.4 mmHg. The results from this latter study[127] is in line with study III,[87] in which 98 patients with persistent AF were investigated with 24-h ambulatory BP before and approximately one week after ECV. In 60 patients remaining in SR at the second 24-h ambulatory BP monitoring, a significant increase of systolic 24-h ambulatory BP by 5.6 mmHg and a decrease of diastolic 24-h ambulatory BP by 4.7 mmHg, was observed.

Thus, although there is some heterogeneity in earlier results, our results add to the overall evidence, suggesting that systolic BP is lower and diastolic BP is higher in AF compared to SR, according to either auscultatory sphygmomanometric or oscillometric BP measurement. As a result, pulse pressure appears to be markedly lower in AF compared to SR.

6.7 CONVENTIONAL BP MEASUREMENT ACCURACY IN AF

Conventional BP measurement is usually performed either with the auscultatory sphygmomanometric technique or with an automated oscillometric device. There are a number of studies validating oscillometric measurement accuracy in relation to auscultatory sphygmomanometry in individuals with SR.[128,129] Some similar studies have been conducted in patients with AF,[72–75] with heterogenous results. The presence of AF may cause measurement bias also with the auscultatory technique and there is no universal reference standard for how to perform validation studies for automated oscillometric devices in AF patients.[71] However, in a recent meta-analysis it was suggested that the oscillometric method had reasonable accuracy regarding systolic BP, but tended to slightly overestimate diastolic BP, in AF patients in comparison to auscultatory BP.[11]

Intra-arterial BP measurement is typically considered a superior method for reference BP. In study IV, oscillometric and auscultatory sphygmomanometric BP measurements were compared to peripheral and central intra-arterial BP, in patients with sustained AF, and in comparison to patients with SR. Overall, conventional BP measurement was accurate compared to intra-arterial BP for diastolic pressure, both in AF and SR. There was however more heterogeneity regarding the results for systolic BP. In the presence of AF, oscillometric BP measurement overestimated intra-arterial brachial and central BP (by 4.1 and 5.0 mmHg respectively) and with measurement bias for the SR group taken into account, by 14.1 and 9.0 mmHg respectively. Only a few previous studies have investigated oscillometric BP monitoring in AF in relation to intra-arterial reference BP.[89,130,131] These small studies used different methodologies, mainly included patients in an intensive care setting and used intra-arterial radial BP as reference pressure. The results from a meta-analysis that included these invasive studies, suggest that oscillometric BP monitoring in AF underestimate systolic radial intra-arterial BP by 4.1 mmHg and overestimate diastolic radial intra-arterial BP by 6.1 mmHg,[11] which is similar to what has been reported for patients with SR.[132] The methodological differences between previous invasive studies and study IV complicate comparisons. As in previous studies however, oscillometric BP measurement in study IV also underestimated systolic intra-arterial BP, to a similar extent in AF and SR. In contrast to previous studies, oscillometric BP monitoring was however very accurate in relation to intra-arterial radial diastolic BP. The accuracy of conventional BP measurement in the presence of AF has, to our knowledge, not previously been evaluated in relation to intra-arterial brachial and central BP. Since study IV is a small, first study specifically investigating this issue, the results should be interpreted with caution. However, provided these results can be replicated in larger samples, the relatively large measurement biases observed for conventional systolic BP compared to intra-arterial brachial and central BP, in particular in comparison to systolic measurement bias in SR, would be of clear clinical significance.

6.8 IS BLOOD PRESSURE IN ATRIAL FIBRILLATION DIFFERENT PER SE?

In study II and III, diastolic BP was higher whereas systolic BP was lower in AF than after restoration of SR. As a result, pulse pressure was markedly higher in SR after ECV (11 mmHg or 23% for auscultatory sphygmomanometry in study II and 10.4 mmHg or 25% for 24-h ambulatory BP in study III). It is not possible from these studies to determine the underlying mechanisms for this observation. This pulse pressure difference could be related to hemodynamic conditions prevalent in AF, measurement bias that differs in AF and SR, or to a combination of such factors. Of note, in study IV, a substantial difference in pulse pressure between AF and SR patients could be observed also for intra-arterial BP (18.9 mmHg or 33% for brachial intra-arterial BP), although this is an inter-individual comparison in contrast to the intra-individual comparisons made in study II and III.

As discussed above, previously reported measurement biases for conventional BP in AF compared to SR are not of the magnitude to explain this observed difference in pulse pressure. One may consider two hypothetical patients and, in a scientifically unorthodox

manner, apply and combine the results from study III and IV for a rough comparison. Patient 1 (AF-AF) has an oscillometric BP of 120/80 mmHg in AF before ECV, "true" intra-arterial brachial BP is 116/80 mmHg (according to study IV). Since patient 1 remains in AF after ECV, oscillometric and intra-arterial BP are unchanged at follow-up. Patient 2 (AF-SR) has an identical BP in AF before ECV. In SR after ECV, oscillometric BP is 126/75 mmHg (according to BP-changes in study III) and "true" intra-arterial brachial BP is 136/75 mmHg (according to study IV). Hence, according to our results, oscillometric measurement bias cannot explain the observed difference in pulse pressure. On the contrary, this hypothetic calculation would imply that "true" pulse pressure difference is even larger than reflected from oscillometric measurements. Thus, one may hypothesize that BP in AF, as a result of the hemodynamic conditions associated with AF, may be inherently different compared to SR, as indicated by a large difference in pulse pressure. Consequently, BP in AF and SR may not be fully interchangeable entities.

A number of mechanisms potentially affecting hemodynamic conditions and BP differently in AF and SR can be identified. Autonomic and neurohormonal effects that may be associated with AF are discussed above. Loss of synchronized atrial contraction, reduced left ventricular filling, stroke volume, cardiac output and contractility, as well as irregular cardiac activation and endothelial dysfunction are other factors associated with AF that may potentially affect BP.[60–62,133–135] Heart rate, which is often elevated in patients with AF, may be another factor that could affect BP. During normal physiological conditions, heart rate and BP normally moves in tandem.[136] In an exercise test for example, both heart rate and BP increases. The relationship between heart rate and BP during more unphysiological conditions, such as in AF, are more uncertain. In both study II and study III, a significant difference in heart rate between AF and SR was observed (80-82 bpm and 58 bpm respectively, in both studies). One study investigated relationships between different BP parameters and changes of heart rate, induced by right atrial pacing in patients undergoing cardiac catherization.[137] An incremental increase of heart rate was not accompanied by significant changes in peripheral (brachial) systolic or diastolic BP. In the linear regression analysis performed in study III, change in systolic BP was not significantly correlated to change in heart rate, whereas a moderate correlation for change in diastolic BP and heart rate was observed. Although such a correlation does not prove a causal relationship, it implies that differences in heart rate in AF and SR may affect diastolic BP, consistent with shorter R-R-intervals to allow for a drop in diastolic pressure.

True BP at a certain arterial site at a certain point in time is defined by the forward pressure wave, physiological arterial properties and by the timing and amplitude of the reflected pressure wave.[138] The timing and summation of reflected waves onto the forward wave is the main underlying mechanism resulting in the amplification of pulse pressure usually seen from central to peripheral arteries.[139–141] This pulse pressure amplification phenomenon could be observed also in AF patients in study IV. However, as illustrated in figure 14, it is quite evident that beat-to-beat pulse pressure variability is clearly increased in AF, although this has not been specifically quantified. Hypothetically, the irregular rhythm in AF may alter the timing of reflected waves in comparison to regular SR, thereby also affecting pulse pressure

amplification and BP throughout the arterial tree. Although not specifically studied, such a phenomenon could contribute to the observation from study II-IV of a lower pulse pressure in AF compared to SR.

6.9 OPTIMAL BLOOD PRESSURE IN ATRIAL FIBRILLATION

Even when adjusted for known cardiovascular risk factors, patients with AF are at increased risk for cardiovascular morbidity and mortality.[5,68] AF share most of its risk factors with other cardiovascular disease and since these may be difficult to fully adjust for, there is a risk of residual confounding in observational studies. Hence, AF may act as a surrogate marker for increased risk and it is uncertain if and to what extent AF per se, in a causative way increases cardiovascular risk.

There are no randomized clinical trials investigating treatment of hypertension specifically in AF patients and patients with AF have been consistently excluded from prospective hypertension treatment trials.[11] Furthermore, there is very limited data regarding BP available also from earlier prospective trials in patients with AF.[142] However, indirect evidence may still be drawn from randomized studies specifically including patients with AF. In the AFFIRM trial,[143] patients with AF were randomized to either a rhythm or a rate control strategy. In this study, striving for SR with a rhythm strategy was not beneficial over a rate control strategy in terms of mortality. A few other earlier studies were also unable to demonstrate superiority of a rhythm strategy over a rate control strategy.[144,145] However, in the recent and large-scale EAST-AFNET 4 trial,[13] AF patients with cardiovascular conditions randomized to an early rhythm-control therapy had a significantly lower risk of cardiovascular events (including a significant reduction in death from cardiovascular causes) compared to patients randomized to rate-control therapy. These latter results may imply that AF rhythm itself, could have a causal relationship to increased cardiovascular morbidity. The underlying mechanisms responsible for such a possible causative link are not known. However, AF-related effects on BP and BP measurement, may hypothetically play a part.

Even though a large body of evidence exist regarding hypertension treatment goals in patients with SR, controversy still exist pertaining to optimal BP, in general and regarding different subgroups of patients.[146] This may be exemplified by the discussions following the SPRINT trial.[147] There are no randomized trials primarily exploring the topic of optimal BP done specifically in patients with AF. In a post-hoc analysis from the AFFIRM trial, a U-shaped relationship between BP and mortality in patients with a diagnosis of AF was found.[148] The nadir, or optimal BP in relation to risk of death was 140/78 mmHg in that study. However, since many patients were in SR during long periods of time it is uncertain to which extent these findings truly reflect the relationship between BP and risk in patients with persistent or permanent AF. A few other retrospective and post-hoc studies have investigated this topic in cohorts of patients with a diagnosis of AF but also without separating rhythm (AF or SR) at the times of BP measurement.[149–151] In summary, optimal BP level for patients with sustained AF is uncertain.[2,12] In the latest 2018 guidelines on hypertension from the ESC,[22] BP treatment goals are the same for AF patients as for most other patient subgroups (120-129/70-

79 mmHg for individuals below the age of 65 and 130-139/70-79 mmHg for individuals 65 years and older). There is no other specific mentioning of optimal BP in AF, but it is stated that additional BP measurement may be needed in patients with AF and that the manual auscultatory method is recommended. Furthermore, the question "What is the optimal method to measure BP in patients with AF?" is listed under "Gaps in the evidence". In the recently published guidelines on AF from the ESC,[64] there is similarly no mentioning of any subjects pertaining to AF-effects on BP or to BP measuring techniques in patients with AF.

6.10 LIMITATIONS

There are several limitations in relation to the studies included in this thesis. The number of individuals included in study I and IV was fairly low, in particular for the control group of patients with SR. As a consequence, it was not possible to analyze the data in terms of subgroups. Furthermore, the two groups (AF and SR) were not ideally matched and baseline differences between the groups may cause confounding. All patients in study I and IV had a clinical indication for a coronary angiography, which constitutes a selection bias. It should be expected that the prevalence of atherosclerosis and risk factors for atherosclerosis was higher in this population in comparison to an AF population in general. Such conditions may affect BP throughout the arterial tree and possibly also the level of beat-to-beat BP variability. Thus, it is uncertain to which extent the results from study I and IV are generalizable to all individuals with AF. Although study I and IV were prospective studies with a rigorous protocol for how BP measurements were performed, there was an aspect of time constraint since examinations were performed during an invasive procedure. This prohibited the use of even more thorough measurements, such as triplicate cuff measurements at each time, which would otherwise have been desirable. Furthermore, algorithms among different devices for oscillometric BP measurement may differ, and the results may therefore not be generalizable to other devices from other manufacturers. In study IV, a high number of comparisons were made, introducing a possibility of mass significance. However, since comparisons were of similar setup, it should still be possible to get insight from trends, such as when comparing BP measurements from different arterial locations.

Study II was a retrospective analysis which comes with inherent limitations. 57 individuals were excluded due to missing data regarding rhythm and/or BP at follow-up. It is however unlikely that this constituted a systematic selection bias. BP measurements used in the study were obtained under routine clinical circumstances and it was not possible to ascertain to which extent they were performed in accordance with local guidelines for BP measurement. However, BP measurements were performed in the same setting, by the same staff and with the same method before and after ECV, which should make them comparable. Patients with an immediate relapse in AF after ECV were sometimes scheduled for a new ECV attempt right away, after optimization of medical therapy. These patients did therefore not attend a 1-week follow-up and were not included in the study. Thus, the proportion of patients maintaining SR after ECV may therefore have been overestimated.

Study III was a prospective, multi-center study primarily evaluating BP with 24-h ambulatory BP monitoring. The validity of different techniques for BP measurement is uncertain for patients with AF, in particular for 24-h ambulatory BP monitoring. It can therefore not be excluded that systematic measurement bias may have influenced the results. As for study IV, measurement accuracy may also differ between automated oscillometric devices from different manufacturers. All patients in study III had a clinical indication for ECV due to persistent AF. This selection bias means that the results may not be generalizable to other groups of patients with AF.

7 CONCLUSIONS

Beat-to-beat BP-variability is higher in patients with persisting AF compared to patients with SR. Systolic beat-to-beat BP variability is approximately twice as high and diastolic BP variability is approximately six times as high in AF compared to SR. The increased beat-to-beat BP variability in AF may have implications for conventional BP measurement accuracy and could hypothetically also be involved in the pathophysiology behind the increased cardiovascular morbidity and mortality seen in patients with AF.

In patients with persistent AF undergoing ECV, systolic sphygmomanometric office BP as well as 24-h ambulatory BP increased whereas corresponding diastolic BP decreased after restoration of SR. These findings imply that systolic BP and pulse pressure is lower whereas diastolic BP is higher in AF compared to SR. Hypothetically, this difference indicate that BP in AF may be inherently different to BP in SR.

Conventional (oscillometric and sphygmomanometric) BP measurement in patients with persisting AF was accurate in relation to peripheral and central intra-arterial BP regarding diastolic BP. Conventional BP was however insufficiently accurate in relation to peripheral and central intra-arterial BP regarding systolic BP. In particular for oscillometric BP measurement in comparison to intra-arterial brachial and central BP, and with measurement bias in SR patients taken into account. There was no significant difference in pulse pressure amplification between patients with AF and SR.

AF is associated with increased cardiovascular morbidity and mortality, but it is unclear to which extent there is also a direct causal relationship. There are several possible underlying mechanisms potentially linking AF with worse cardiovascular outcomes. AF affects BP but it is still uncertain if this has relevant pathophysiological consequences. Irrespective of the underlying mechanisms, if BP is affected by the presence of AF as indicated in this thesis, these results may have important clinical implications. If BP is different in AF per se, sound evidence for how to manage BP and hypertension in patients with sustained AF is lacking. Our results naturally need to be validated in other studies. Arguably, the broader topic of BP in AF has not received the scientific attention it deserves and more research into this area is warranted.

8 CLINICAL IMPLICATIONS

The ESC guidelines for atrial fibrillation and for hypertension recommend that treatment for hypertension in patients with AF should be no different from in patients with SR. The 2018 ESC hypertension guidelines also state that additional BP measurement may have to be performed in patients with AF and that the manual auscultatory method is recommended. In study II there was a 40% increase in the number of patients with a hypertensive BP-level (≥140/90) that could be identified after restoration of SR. In study III there was also a higher proportion of patients with a hypertensive BP-level (≥135/80 according to mean daytime ambulatory BP) among those with restored SR compared to patients still in AF. These findings suggest that an increased attention to BP after restoration of SR is important in order to achieve an optimal treatment of BP.

9 FUTURE PERSPECTIVE

A number of very important research questions regarding AF and blood pressure in AF remain to be answered. More research is needed to elucidate if AF per se is causally linked to the increased cardiovascular morbidity and mortality observed in AF patients. Earlier studies have not been able to show that maintaining SR reduces mortality. However, in the recently published EAST-AFNET 4 trial, AF patients randomized to a rhythm strategy had a lower risk of cardiovascular outcomes, indicating that maintenance of SR may be beneficial in terms of morbidity and mortality. Hopefully, other prospective trials randomizing AF patients to a rate or rhythm control strategy will be conducted. As therapies for maintaining SR (AF ablation in particular) are improved, the opportunities for conducting such trials and for getting clear results will also improve. If such trials would also include thorough and repeated BP measurements, with specifications regarding rhythm for each measurement, it would potentially also provide important insights regarding the role of BP and cardiovascular outcomes in AF patients.

It will be important to further study the underlying mechanisms linking AF with worse cardiovascular outcomes. Such mechanisms could include hemodynamic, neurohormonal, inflammation and endothelial effects from AF. Patients with persistent AF that undergo therapy such as ECV or ablation in order to restore SR, provide a suitable setting to further study such mechanisms.

The studies in this thesis are hypothesis generating and point to a number of potentially important research topics. From a more mechanistic perspective, it would be of interest to further study the determinants of the level of beat-to-beat BP-variability in AF. No doubt, the degree of irregularity is important but other factors such as heart rate probably also play a part. Such a study could be very similar to study I but in addition to intra-arterial BP, the recording would also need to include a clear time-scale, which was unfortunately lacking in study I.

The results from study II and III, indicating that BP may be inherently different in AF, may have important implications for management and treatment of hypertension in patients with AF. Existing evidence from large randomized hypertension intervention trials, conducted among patients with SR, may not be generalizable to patients with sustained AF. One possible way to study this would be retrospectively from a larger database. This would need to contain information on BP and of rhythm (AF or SR) at the time of BP measurement. Ideally, one would also want to be able to adjust for other patient characteristics and medication. It would also be desirable, but perhaps less feasible, to address this question in a large-size prospective study similar to study III, and with a long follow-up. A third way would be to conduct an invasive study. It may be feasible and ethically acceptable to perform a prospective study on patients with persisting AF, undergoing ECV or AF ablation, with intra-arterial BP-recording. Such a design would provide direct information on how rhythm

affects BP. Ideally, simultaneously performed conventional BP measurements would provide further data regarding measurement bias in AF compared to SR.

Finally, despite there being a substantial number of patients with established AF and concomitant hypertension, there is very little evidence regarding optimal BP in this group of patients. The highest level of evidence would naturally be attained from a prospective clinical trial, randomizing patients with sustained AF to different BP-goals, similar to in the SPRINT-trial. In lack of a randomized trial, important data could also be obtained from retrospective registries comprising information on cardiovascular and other outcomes. As discussed above, information on rhythm at the time of BP measurement is a prerequisite for such studies to achieve clear results.

10 SVENSK SAMMANFATTNING

Bakgrund

Förmaksflimmer (FF) är den vanligaste ihållande hjärtrytmstörningen av klinisk relevans. Det uppskattas att åtminstone 2.9% av den vuxna befolkningen i Sverige lider av FF. Förhöjt blodtryck (BT) – hypertoni är ännu vanligare. I en vetenskaplig rapport av Statens beredning för medicinsk och social utvärdering (SBU) från 2004, beräknades förekomsten av hypertoni i Sverige vara 27% i den vuxna befolkningen. Både FF och hypertoni är associerat med en ökad risk för kardiovaskulär sjukdom. Hypertoni räknas som den globalt ledande riskfaktorn för förtida död, likaså är förmaksflimmer associerat med en tvåfaldig ökning av risken att avlida i förtid. Båda dessa tillstånd kan således innebära ett stort lidande för drabbade patienter och innebär en stor belastning och kostnad för hälso- och sjukvården. Blodtryck, hypertoni och FF är nära sammankopplade. På befolkningsnivå utgör hypertoni den vanligaste riskfaktorn för att också utveckla FF. Omvänt påverkar förekomsten av ihållande FF blodtrycket på individnivå. Vid FF är hjärtrytmen oregelbunden till skillnad från normal, så kallad sinusrytm. Detta innebär en ökad blodtrycksvariabilitet från slag till slag vid ihållande FF, men möjligen påverkas BT även på andra sätt. Dessa förhållanden kan tänkas påverka tillförlitligheten hos vanligt förekommande metoder för att mäta BT, hos patienter med FF. De underliggande orsakerna till att FF är associerat med ökad dödlighet är ofullständigt klarlagda. Hypotetiskt kan FF-orsakad påverkan på blodtrycket och mätosäkerhet av BT vid FF spela in, men dessa områden är vetenskapligt undersökta i endast mycket liten utsträckning.

Syfte

Det övergripande syftet med studierna i denna avhandling var att undersöka hur förekomst av FF påverkar blodtryck och tillförlitlighet hos konventionella metoder för BT-mätning. På sikt kan sådan kunskap öka förståelsen för varför patienter med FF har ökad risk att drabbas av kardiovaskulär sjukdom, kunskap som kan leda till förbättrad behandling och prognos för denna stora patientgrupp.

Syftet med studie I var att undersöka och kvantifiera BT-variabiliteten från slag till slag hos patienter med FF i jämförelse med patienter med sinusrytm. I studie II användes ett retrospektivt material för att undersöka hur blodtrycket förändras när sinusrytm återställs med hjälp av så kallad elkonvertering. Frågeställning i studie III var liknande studie II men denna studie var prospektiv och BT-mätning skedde med så kallad 24-timmars ambulatorisk blodtrycksmätning. I studie IV studerades dels hur förekomsten av FF påverkar blodtrycket i olika delar av artärträdet jämfört med hos patienter med sinusrytm, dels studerades tillförlitligheten hos konventionell blodtrycksmätning i jämförelse med intraarteriell mätning och i jämförelse med patienter med sinusrytm.

Metod och resultat

I studie I rekryterades 33 patienter (21 med FF och 12 med sinusrytm) som var planerade att genomgå kranskärlsröntgen. I samband med kranskärlsröntgen mättes intra-arteriellt BT i arteria radialis (handleden), arteria brachialis (överarmen) och i aorta ascendens (stora kroppspulsådern invid hjärtat). Den huvudsakliga frågeställningen var BT-variabilitet vid FF, vilket definierades som medelskillnaden från slag till slag avseende systoliskt respektive diastoliskt BT. BT-variabiliteten var signifikant högre ($p<0.001$) hos patienter med FF jämfört med hos patienter med sinusrytm vid alla mätlokalisationer. Den systoliska BT-variabiliteten var ungefär dubblerad (4.9 jämfört med 2.4 mmHg) och den diastoliska variabiliteten var cirka sex gånger högre (7.5 jämfört med 1.2 mmHg) hos patienter med FF i jämförelse med patienter i sinusrytm.

Den retrospektiva studie II baserades på journaluppgifter. 487 individer med ihållande FF som genomgick elkonvertering i syfte att återställa sinusrytm studerades. Information avseende hjärtrytm och BT (mätt med vanlig teknik med manschett och stetoskop - så kallad auskultatorisk sphygmomanometri) från dagen före och en vecka efter elkonverteringen inhämtades. Det primära utfallsmåttet var BT-förändring hos patienter med bestående sinusrytm efter elkonvertering. I gruppen med bibehållen sinusrytm ökade det systoliska blodtrycket med 9 mmHg ($p<0.001$) medan det diastoliska blodtrycket sjönk med 3 mmHg ($p<0.001$). Andelen patienter med ett förhöjt BT (≥140/90 mmHg) ökade med 40% i denna grupp.

Studie III hade ett liknande upplägg som studie II men denna studie var prospektiv och blodtryck mättes med 24-timmars ambulatorisk blodtrycksmätning. Det primära utfallsmåttet var blodtrycksförändring hos patienter med bestående sinusrytm en vecka efter elkonvertering. Hos 60 patienter med bestående sinusrytm ökade systoliskt 24-timmars medelblodtryck med 5.6 mmHg ($p<0.001$) medan diastoliskt 24-timmars medelblodtryck minskade med 4.7 mmHg ($p<0.001$). Som en konsekvens av detta ökade pulstrycket (skillnaden mellan systoliskt och diastoliskt BT) med 25% (10.4 mmHg).

I studie IV undersöktes samma individer som i studie I. Konventionellt BT (auskultatorisk sphygmomanometri och automatisk oscillometri) mättes simultant med intra-arteriellt BT. Det första syftet var att studera hur det intra-arteriella blodtrycket förändras från centrala till perifera delar av artärträdet hos patienter med ihållande FF i jämförelse med patienter med sinusrytm. Det andra syftet var att undersöka tillförlitlighet och mätprecision vid konventionell blodtrycksmätning i jämförelse med intraarteriell mätning hos patienter med ihållande FF, och i jämförelse med patienter med sinusrytm. Blodtrycksförändringen längs artärträdet hos patienter med FF skiljde sig inte signifikant från hos patienter med sinusrytm. Konventionell BT-mätning hade god precision i jämförelse med intra-arteriellt BT avseende diastoliskt BT, både hos patienter med förmaksflimmer och sinusrytm. Däremot överskattade automatisk oscillometrisk BT-mätning det intraarteriella blodtrycket i arteria brachialis (4.1 mmHg, $p=0.07$) och aorta ascendens (5.0 mmHg, $p=0.04$) hos patienter med FF. Med hänsyn taget till det uppmätta mätfelet vid sinusrytm överskattade automatisk oscillometrisk BT-

mätning det intraarteriella blodtrycket i arteria brachialis med 14.1 mmHg ($p<0.01$) och aorta ascendens med 9.0 mmHg ($p=0.01$) hos patienter med förmaksflimmer.

Slutsatser

Blodtrycksvariabiliteten från slag till slag är ökad hos patienter med FF jämfört med sinusrytm. Resultaten i denna avhandling tyder på att det systoliska blodtrycket är lägre medan det diastoliska blodtrycket är högre vid FF jämfört med vid sinusrytm, vid mätning med auskultatorisk sphygmomanometri och oscillometrisk 24-timmars blodtrycksmätning. Som en konsekvens av detta är pulstrycket klart lägre vid FF. Blodtrycksförändringen från det centrala till det perifera artärträdet skiljer sig inte signifikant hos patienter med ihållande FF jämfört med patienter med sinusrytm. Resultaten i denna avhandling tyder på att konventionell blodtrycksmätning har hög tillförlighet i jämförelse med intraarteriellt blodtryck hos patienter med FF, avseende diastoliskt BT. Automatisk oscillometrisk BT-mätning överskattade dock systoliskt intraarteriellt BT i arteria brachialis och aorta ascendens hos patienter med FF, speciellt med hänsyn taget till uppmätt mätfel vid sinusrytm.

Förekomsten av förmaksflimmer hos en individ påverkar blodtrycket. Detta kan ha betydelse för tillförlitligheten hos konventionella metoder för BT-mätning och det är tänkbart att det också påverkar risken för kardiovaskulär sjuklighet hos patienter med FF. Effekter på blodtrycket av förmaksflimmer är väldigt lite studerat och mer forskning på området behövs.

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