Doctoral Thesis

Advances in cardiovascular magnetic resonance velocity and turbulence quantification

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ADVANCES IN CARDIOVASCULAR MAGNETIC RESONANCE VELOCITY AND TURBULENCE QUANTIFICATION

A thesis submitted to attain the degree of

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(Dr. sc. ETH Zurich)

presented by

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Abstract

Valvular pathologies in general and aortic stenosis in particular are accompanied by abnormal flow in the heart and larger vessels. Turbulent flow may result, which is associated with a higher dissipation of kinetic energy and therefore an increased workload of the heart.

Phase-Contrast Magnetic Resonance Imaging enables the spatially and time-resolved acquisition of velocity vector fields (4D Flow MRI) and quantification of Turbulent Kinetic Energy (TKE). It has been hypothesized that by quantifying the turbulent losses in the aorta a novel marker for disease severity can be obtained, which may aid in decision making regarding aortic valve replacement.

Generalized 4D flow MRI measurements using four-point velocity encoding enable the acquisition of both the velocity vector field and turbulent kinetic energy. However, the narrow dynamic range and the need for an estimate of the highest velocities limit the clinical practicability. An approach using multiple velocity encoding steps per velocity encoding direction combined with Bayesian analysis is presented in this work, addressing these issues. The technique is tested in silico, in vitro and in patients with aortic valve replacements. It is shown that with a single scan a comprehensive hemodynamic assessment is possible.

In order to achieve clinically acceptable scan times with 4D flow measurements, accelerated imaging techniques have to be employed. Since data undersampling impacts noise levels and temporal depiction fidelity, an analytical g\textsubscript{sf}-factor formulation is derived. The formulation expands the conventional g-factor to include the temporal domain. The method was
validated for k-t SENSE and k-t PCA using pseudoreplica analysis. It is shown that temporal fidelity was better preserved in k-t PCA than in k-t SENSE. The g*fr*-metric is furthermore valuable to compare k-t methods with frame-by-frame parallel imaging reconstruction techniques.

The model for estimating TKE using Phase-Contrast MRI is based on a number of assumptions. In particular, a Gaussian distribution of velocities in a voxel is assumed and the spatial resolution is required to be sufficient to correctly distinguish between turbulence and velocity gradients of the mean field. Simulated Phase-Contrast MRI measurements based on Particle Tracking Velocimetry data revealed errors <15% for TKE estimation with scan settings feasible in clinical practice. In contrast, viscous losses, which have been proposed as an alternative marker of energy loss, were found to be significantly underestimated at clinically feasible spatial resolutions.

In a study of 51 patients and 10 healthy volunteers the feasibility of TKE quantification in clinical routine is demonstrated. The study allowed for a direct comparison of TKE levels to Doppler echocardiography derived measures. TKE values were significantly elevated in patients with aortic dilatation and/or bicuspid aortic valves compared to patients with normal geometries. This distinction between the groups was not possible using Doppler echocardiography and promises additional diagnostic information.

In conclusion, in this thesis methods for the quantification of turbulent kinetic energy and blood flow velocities have been developed, validated and their clinical feasibility shown. Errors due to assumptions underlying the signal models could be quantified and allowed for conclusions regarding spatial and temporal resolution. A larger study in patients revealed potential additional diagnostic information compared to Doppler echocardiography.


Um für den klinischen Betrieb geeignet kurze Messzeiten von 4D Fluss-Aufnahmen zu erreichen, müssen Verfahren zur beschleunigten Bildgebung eingesetzt werden. Da eine Unterabtastung der Daten sowohl den Rauschpegel als auch die zeitliche Wiedergabetreue beeinflusst, wurde eine analytische Formulierung eines $g_{sf}$-Faktors abgeleitet. Der $g_{sf}$-Faktor erweitert den konventionellen Geometrie ($g$-)Faktor um die Dimension der zeitlichen Frequenzen. Die Methode wurde mittels Pseudoreplikationsanalyse für $k$-$t$ SENSE und $k$-$t$ PCA validiert. Es konnte gezeigt werden, dass die zeitliche Wiedergabetreue in $k$-$t$ PCA besser erhalten bleibt als in $k$-$t$ SENSE. Darüber hinaus erlaubt die $g_{sf}$-Metrik Vergleiche mit Rekonstruktionsmethoden welche jeden Zeitpunkt einzeln betrachten.


In einer Studie mit 51 Patienten und 10 gesunden Probanden wurde die TKE Quantifizierung in der klinischen Routine untersucht. TKE-Werte wurden hierzu mit konventionellen Ultraschall-basierten Parametern verglichen. TKE-Werte waren in Patienten mit Aortendilatation und bikuspiden Aortenklappen im Vergleich zu Patienten mit normaler Geometrie signifikant erhöht. Diese
Unterscheidung zwischen den Gruppen war mittels Doppler-Echokardiographie nicht möglich. Entsprechend bietet die TKE Quantifizierung einen möglichen diagnostischen Mehrwert.

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Chapter 1

Introduction

With each beat, the average human heart pumps about 80 ml of blood simultaneously through the lungs and the rest of the body (1). To control the direction of blood flow, four unidirectional valves are located at the inlet and the outlet of the ventricles. The aortic and the mitral valve are found in the left side of the heart, and the pulmonary and tricuspid valve in the right. A healthy aortic valve allows blood to pass from the left ventricle into the aorta during systole and prevents it from reentering the ventricle during diastolic filling. Pathological thickening of the valve’s leaflets and subsequent restricted valve opening is called aortic stenosis (AS), the most common valvular disease (2). This constriction leads to an increased cardiac load and higher intraventricular pressures. AS is a progressive disease. Over time, calcification of the leaflets increases and therefore the orifice area of the valve is decreased. At an early stage of the disease the heart can adapt to the higher pressure by thickening of the myocardium (3). The so-caused ventricular hypertrophy does not pose a problem for the heart initially, but in severe AS these adaptive processes fail and patients might start to experience symptoms including angina, dyspnoea and syncope (4). The onset of these symptoms is accompanied by a sharp rise in mortality, and intervention becomes necessary. A replacement of the aortic valve is highly effective in extending the life expectancy of patients with AS (5).

To assess the severity of AS, Doppler echocardiography is employed (6, 7). The velocities across the valve are measured and the valve area and pressure gradient across the valve are determined. However, in most cases the ultimate decision for aortic valve replacement is based on the patients experiencing
symptoms (7, 8), which can be problematic especially in elderly patients with reduced mobility or comorbidities. Currently no quantifiable parameter exists which could indicate a valve replacement on its own.

Phase-Contrast Magnetic Resonance Imaging (PC-MRI) is increasingly being used to quantify velocities in the cardiovascular system (9). The development of accelerated acquisition methods such as SENSE (10), GRAPPA (11) or k-t SENSE (12)/k-t PCA (13) has enabled time resolved 3D flow imaging (4D Flow MRI, (14)), allowing to acquire the velocities in the entire aortic arch or the heart in one scan. From this data a number of parameters can be deduced, such as peak or average velocity, stroke volume, streamlines/pathlines or wall shear stress estimates. Compared to 2D slices, 4D Flow MRI allows for simplified planning and an arbitrary positioning of the investigation volume after the scan (15). As the velocities in the entire volume of interest are acquired, only a single scan is necessary to provide comprehensive and volumetric information about the flow fields.

1.1 Motivation

While the phase information of PC-MRI is now widely used to measure velocities it has also been proposed to relate signal attenuation in the magnitude images to quantify turbulence intensities (16-18). Determining the energy dissipated in turbulent flow as well as losses due to viscous friction could enable the quantification of the total energy lost due to a stenotic valve, and therefore the assessment of the additional workload of the heart (19). This could provide a non-subjective measure on AS severity and a tool to decide whether valve replacement is indicated.

As the signal magnitude decreases exponentially with increasing velocity fluctuations present in turbulent flow, a dedicated acquisition and data
processing scheme to increase the dynamic range is required. Dynamic range extension becomes possible by adding more velocity encoding steps, which in turn increases scan time. To achieve clinically feasible protocols, high data undersampling factors and sophisticated reconstruction techniques have to be employed. However, the effect of accelerated imaging on both noise level and temporal fidelity needs to be quantified, as it could violate the assumptions made by turbulence models.

In general, the quantification of the energy stored in turbulent velocity fluctuations (Turbulent Kinetic Energy, TKE) is based on a number of modelling assumptions which have not been validated yet: First, the equation used to model the signal implies a Gaussian distribution of velocities within a voxel. This is known to be true for high Reynolds numbers and small voxels, but it has been unclear whether it would hold for blood flow in the aorta. Second, the limited resolution of PC-MRI might lead to an overestimation of TKE values due to spatial velocity gradients mistakenly being classified as turbulence. Furthermore it is important to understand whether viscous or turbulent losses are the key contributor to the total dissipated energy in AS.

In a preliminary study it was shown that a significant difference in TKE between controls and patients (20) exists and a correlation between TKE and disease severity is indeed present. However, it remained unclear how TKE values are distributed in a more heterogeneous patient population, and whether there is any diagnostic advantage over conventional echocardiographical parameters. Likewise, it remained to be demonstrated that the measurement protocol does work reliably in a larger number of subjects.
Chapter 1 - Introduction

1.2 Outline

Chapter 2 provides a general introduction to energy dissipation in laminar and turbulent flows, followed by an overview of quantification methods.

In Chapter 3 the pathophysiology and treatment options of aortic stenosis are described and energy dissipation as a marker of disease severity is introduced. A summary of current diagnostic parameters is provided.

The basics of velocity and Turbulent Kinetic Energy measurements using Phase-Contrast MRI are given in Chapter 4. A Bayesian framework for concurrent flow and turbulence mapping is presented in Chapter 5.

A formalism to describe the impact of accelerated imaging methods on noise levels and the temporal fidelity is presented in Chapter 6. It is shown that higher undersampling factors do not necessarily lead to prohibitively low signal-to-noise ratios but do cause temporal blurring. In Chapter 7 the discrepancies in energy loss quantification between Phase-Contrast MRI and Particle Tracking Velocimetry are analyzed. Furthermore the validity of the modelling assumptions is tested.

The results from a study in 51 patients and 10 healthy controls are presented in Chapter 8. It is shown that Turbulent Kinetic Energy shows only weak correlation with traditional parameters describing disease severity. While no difference in peak velocities could be found in subgroups with dilated ascending aortae or bicuspid valves, turbulence levels were significantly higher.

Chapter 9 summarizes the findings of this thesis and gives an outlook on potential future developments.
1.3 Contribution of the Thesis

To accurately quantify velocities and Turbulent Kinetic Energy over a large dynamic range, measurements with multiple encoding velocities are required. The Bayesian framework proposed herein allows for a SNR-efficient combination of the acquired values.

For the method to be feasible in vivo, accelerated imaging has to be employed. Using the $g_{sf}$-factor metric presented the effects of such undersampling can be quantified analytically.

The quantification of Turbulent Kinetic Energy using Phase-Contrast MRI is based on several assumptions, which cannot be verified without an external reference method. Particle Tracking Velocimetry allows for a detailed study of the fluid dynamic processes. Using a realistic phantom setup, quantitative information about the flow downstream of an aortic stenosis was obtained and analyzed in detail.

To prove the clinical feasibility of the methods and to investigate differences in diagnostic information compared to Doppler echocardiography a patient study was carried out. The developed framework is shown to enable the quantification of Turbulent Kinetic Energy in a larger patient population. The study furthermore indicates that valve geometry also impacts turbulence levels, something which is not quantifiable using conventional diagnostic methods.
Chapter 2
Energy Dissipation in Laminar and Turbulent Flows

Any flow of a fluid with non-zero viscosity is accompanied by energy dissipation (21). The amount of this dissipation into heat (or “loss”) is determined by a number of factors. The predominant mechanisms are deterministic, however upon transitioning to turbulent flow random processes start to prevail. This chapter aims to give an overview of mechanisms and methods to quantify energy dissipation.

2.1 Laminar Flow

The existence of velocity gradients leads to shear forces acting on fluid particles with differing velocities \( v \). According to Newton’s law of viscosity, the amount of shear is determined by the viscosity \( \mu \) of the fluid and the velocity gradient (22):

\[
\tau = -\mu \frac{dv}{dx}
\]

Eq. 2.1

To maintain flow and velocity gradients, a constant force is required. When fluid is pumped, pressure is required and work is performed. The losses associated with friction due to these shear forces will be analyzed in the following.

2.1.1 Flow in a straight pipe

The simple case of a non-compressible, Newtonian fluid flowing in a straight horizontal pipe allows for an introduction to sources of energy loss in laminar
flows. Given a pipe with radius $R$ represented in a cylindrical coordinate system, a volume flow rate of $Q$, and a no slip condition at the wall ($v_{wall} = v(R) = 0$) a parabolic flow profile will develop (22):

$$v(r) = v_{center} \left[ 1 - \left( \frac{r}{R} \right)^2 \right]$$

Eq. 2.2

with $v_{center}$ being the maximum velocity at $r = 0$. The shear stress $\tau$ according to Eq. 2.1 is then also a function of the position on the radius $r$. The mean velocity is $v_{center}/2$, and therefore the flow rate $Q = 0.5v_{center}R^2\pi$. The parabolic flow profile also minimizes shear stress given a certain $Q$ and $v(R) = 0$ (21).

Over a length $L$ of said pipe the pressure loss is given by the Hagen-Poiseuille equation (22):

$$\Delta p = \frac{8\mu LQ}{\pi R^4}$$

Eq. 2.3

It is worth noting that in laminar flow the pressure difference required to drive the flow is only dependent on the viscosity and the flow rate of the fluid, the smoothness of the pipe wall is of no concern.

### 2.1.2 General laminar flow

As the results from straight pipe flow are instructive in terms of sources of loss, a more general formulation has to be found for biomedical applications such as the flow in the aorta.

Using a momentum balance approach to analyze the changes of momentum in a volume element of the flow, it is possible to derive its “equation of motion” (21):
2.1 Laminar Flow

\[
\frac{\partial}{\partial t} \left( \frac{1}{2} \rho v^2 \right) = - \nabla \cdot \left( \frac{1}{2} \rho v^2 \mathbf{v} \right) - (\nabla \cdot \rho \mathbf{v}) - p(\nabla \cdot \mathbf{v}) - (\nabla \cdot [\mathbf{\tau} \cdot \mathbf{v}]) - (-\mathbf{\tau} : \nabla \mathbf{v}) + \rho (\mathbf{v} \cdot \mathbf{g}) \quad \text{Eq. 2.4}
\]

with \( \mathbf{\tau} \) being the viscous stress tensor, \( \rho \) the density of the fluid and \( \mathbf{g} \) gravitational acceleration.

Most terms of Eq. 2.4 describe a reversible conversion of different forms of energy. It also follows that given the viscosity and the 3-dimensional velocity vector field the energy dissipated into thermal energy can be calculated (21):

\[
(-\mathbf{\tau} : \nabla \mathbf{v}) = \frac{1}{2} \mu \sum_i \sum_j \left[ \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right] - \frac{2}{3} \left( \nabla \cdot \mathbf{v} \right) \delta_{ij} + \kappa \left( \nabla \cdot \mathbf{v} \right)^2 \quad \text{Eq. 2.5}
\]

with \( i, j \) ranging over the principle directions 1, 2, 3. Under the assumption of an incompressible fluid the flow field is divergence-free and therefore the term \((\nabla \cdot \mathbf{v}) = 0\).

Integrating Eq. 2.5 over the volume of interest, the net energy loss due to viscous dissipation can be obtained.

For the above case of laminar pipe flow with a parabolic velocity profile \( v_z = v(r) \) given in Eq. 2.2, the viscous losses in cylindrical coordinates (see appendix B of (21)) are given by the following:

\[
\mu \int_0^L \int_0^{2\pi} \int_0^R r \left( \frac{\delta v_z}{\delta x_r} \right)^2 dr d\theta dl = \mu \int_0^L \int_0^{2\pi} \int_0^{v_{\text{center}}(r)} r^4 \left( \frac{R^2}{r} \right) dr d\theta dl = \mu 2\pi L v_{\text{center}}^2 \quad \text{Eq. 2.6}
\]
which agrees with the energy loss of a fluid with flow rate $Q$ and resulting pressure drop $\Delta p$ according to Hagen-Poiseuille (Eq. 2.3):

$$\Delta p Q = \frac{8 \mu L Q}{\pi R^4} = \frac{8 \mu L}{\pi R^4} \left( \frac{V_{\text{center}}}{2} \pi R^2 \right)^2 = \mu 2 \pi L v_{\text{center}}^2 \quad \text{Eq. 2.7}$$

Again this holds true only for laminar flow.

### 2.2 Turbulent Flow

In laminar flow with a constant flow rate, the velocity at a given point is stationary and does not change over time (23). As the velocities increase, the flow becomes increasingly instable – random velocity fluctuations start to occur (Fig. 2.1). The Reynolds number Re can serve as a guide to indicate the state of the flow:

$$Re = \frac{L_0 \rho v}{\mu} \quad \text{Eq. 2.8}$$

Flow above Re~2000 enters the transitional regime, and a further increase leads to fully turbulent flow. Here $L_0$ is the characteristic length scale of the flow, for a circular pipe $L_0=2R$. The introduction of random fluctuations prevents an analytical description of the exact velocity at a certain point in time and space, even if all boundary conditions are known. Also the energy loss is increased. While in the laminar regime it scales with $Q$, in fully turbulent flow energy loss is proportional to $Q^2$ (22).
2.2 Turbulent Flow

Fig. 2.1: Velocities at a single point in space for three different flow states. While laminar flow shows no fluctuations over time, in transitional flow small disturbances might lead to fluctuations which subside. In fully turbulent flow velocities fluctuate throughout time.

2.2.1 Statistical description of turbulence

As these fluctuations are a random process statistical analysis enables a mathematical description. To separate velocity fluctuations $v'$ from the mean velocity $\bar{v}$, the Reynolds decomposition is employed (23):

$$v = \bar{v} + v'$$

Eq. 2.9

The mean flow can now be treated in a similar fashion as in the laminar case and from the fluctuations with zero mean statistical measures can be derived, i.e. the standard deviation.

If a three-dimensional velocity vector field is considered also the covariances of the velocity fluctuations in different principal direction carry a physical meaning – they are related to turbulent shear stresses. The elements of the Reynolds stress tensor $\mathbf{R}$ are given as (23)

$$R_{ij} = -\rho \bar{v}_i v'_j$$

Eq. 2.10
with \( ij = 1, 2, 3 \). The main diagonal of this second order tensor are the normal stresses, and the off-diagonal elements are the shear stresses. The shear stresses play an important role when forces on particles in the flow (i.e. red blood cells) are considered and the normal stresses indicate the turbulence intensity. The so called turbulent kinetic energy (TKE) is defined as half of the first invariant of \( \mathbf{R} \): \( \sum_{i=1}^{3} \left( \overline{v_i' v_i'} \right) \) \( J / m^3 \) Eq. 2.11

This describes the mean kinetic energy stored in the fluctuating velocity field. The main portion of this TKE is then dissipated into heat, however TKE itself does not provide information about the rate of dissipation. To better understand the production and dissipation of TKE it is necessary to describe the “source” of the velocity fluctuations, namely eddies at different scales.

2.2.2 Kolmogorov scales

Lewis F. Richardson first described the concept of the energy cascade in turbulent flows as follows: “Big whirls have little whirls that feed on their velocity, and little whirls have lesser whirls and so on to viscosity – in the molecular sense.” (24)

Larger eddies are driven by the main flow and pass their kinetic energy to smaller and smaller eddies, where finally viscous friction converts the kinetic energy (KE) into heat (Fig. 2.2).
Hypotheses on these smallest scales and the corresponding properties of turbulence have been formulated by Andrei N. Kolmogorov in 1941 ((25), re-issued in English (26)). He argued that the statistics of the small-scale motions are uniquely determined by the kinematic viscosity $\eta = \mu/\rho$ and turbulent dissipation rate $\varepsilon$. The Kolmogorov length scales $l_k$ are defined as

$$l_k \equiv \left( \frac{\eta^3}{\varepsilon} \right)^{1/4} \tag{Eq. 2.12}$$

Turbulence at this scale is isotropic, so all information about mean flow or geometry is lost. The length scale of the largest eddies $l_0$ is comparable to $L_0$. 

Fig. 2.2: Schematic diagram of the turbulence energy cascade for high Reynolds numbers. Large eddies are formed by the gradients of the mean flow which in turn drive consequently smaller eddies. On the Kolmogorov microscale the kinetic energy is converted into heat by viscous dissipation.
the characteristic length scale of the flow. The ratio between \( l_o \) and \( l_k \) scales inversely proportional to \( \text{Re}^{3/4} \).

On the side of turbulent production, \( P \) is determined by the spatial gradients of the mean flow \( \mathbf{V}_i \) (23):

\[
P = -v'_i v'_j \frac{\partial V_i}{\partial x_j}
\]

Eq. 2.13

TKE “feeds” off the kinetic energy of the mean flow, the stronger the velocity gradients the higher turbulent production. However, a part of TKE can also be fed back into the main flow, so for steady flows generally \( P/\varepsilon < 1 \).

As mentioned, dissipation \( \varepsilon \) of turbulent kinetic energy occurs on the smallest scales and can be described by (23)

\[
\varepsilon = 2\eta s_{ij}s_{ij} \quad \text{with} \quad s_{ij} = \frac{1}{2} \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)
\]

Eq. 2.14

\( s_{ij} \) is the fluctuating rate of strain. This also highlights the difficulties of measuring the dissipation rate locally – the velocity fluctuations at the smallest scale have to be known.

Again care has to be taken as these hypotheses assume sufficiently high Reynold’s numbers.

### 2.3 Quantification Methods

To experimentally quantify the energy dissipated over a length of a pipe, the easiest way is to measure the pressure differential between the in- and outlet if their cross-sectional areas are equal. If they differ, a correction using Bernoulli’s principle can be performed.
This approach however only states the total energy dissipated and provides no information about where exactly, or by which loss mechanisms (viscous losses of the mean flow field, turbulence) the energy is lost.

When analyzing pipe systems in engineering practice, analytical solutions using formulas mentioned in the previous chapter are often sufficient. In addition to the major energy loss due to friction/turbulence, sudden changes in geometry such as expansions or pipe bends lead to additional pressure drops. These can be estimated by approximate formulas such as the Borda-Carnot-equation (27) or empirical loss coefficients established in literature (22). Another approach which does not employ an analytical solution but rather a simulated one is Computational Fluid Dynamics (28), where the velocity field is simulated given the geometry of the vessel and the velocities at the inlet.

To quantify or estimate viscous losses spatially-resolved in laminar flow, the velocity vector field has to be known with a sufficiently high spatial resolution. The following list is not exhaustive but should provide a quick overview of most frequently used imaging modalities:

- Doppler echocardiography is the recommended imaging modality for valvular pathologies (8), however in its most common application it is limited to 2D flow. Methods to register 3D Doppler images with differing velocity encoding directions to obtain the full velocity vector field have been proposed recently (29).
- Phase-Contrast MRI, in particular 4D Flow MRI (14) is the only available method to quantify a 3D velocity vector field in-vivo without having to register several acquisitions. Typical temporal and spatial resolutions are on the order of 40 ms and 2 mm isotropic, which might not be sufficient to quantify viscous losses in complex flows as found in the aorta ((30), see also Chapter 7).
Particle Tracking Velocimetry (PTV) uses high frame-rate cameras to capture the movement of fluorescent particles immersed in the fluid (31). Both temporal and spatial resolution exceed 4D Flow MRI, however as it is an optical method the target object has to be transparent. This limits the technique to in-vitro studies (32).

Particle Image Velocimetry (PIV) is comparable to PTV but differs in the post-processing (33). While in PTV individual particles are tracked and their motion described, PIV captures the velocity field via correlation analysis of two images. PIV is primarily used for 2D imaging, but approaches for 3D have been proposed (34).

All the methods listed have also been applied for the investigation of turbulent flows (18, 32, 35, 36). It might also be of interest to quantify turbulent intensities point-wise, for which two additional methods are available:

- Hotwire anemometry was the first technique to investigate turbulence in-vivo (37, 38). By measuring temperature fluctuations of a heated wire via changes in resistance, velocity fluctuations at a point in space can be captured with a very high temporal resolution. However due to its invasive nature and lacking spatial information its application was in most cases limited to in-vitro or animal studies.

- Laser Doppler Anemometry derives information about velocities from the Doppler shifts in the frequency of a laser beam which is scattered by particles immersed in a moving fluid. It is also feasible to perform in-vivo experiments via fiber optics (39).
Chapter 3
Aortic Stenosis

There are a number of valvular pathologies, with the constriction of the aortic valve (aortic stenosis - AS) being the most common one (2). This chapter focuses on AS, however some of the findings can be translated to constrictions of the pulmonary valve as well. For the mitral and the tricuspid valve, valve insufficiency rather than stenosis is of concern clinically.

3.1 Prevalence, Pathophysiology and Treatment

Aortic stenosis is a progressive disease which occurs largely in elderly patients. Different studies provide a wide range of prevalence values, however a meta-study (40) concluded that 12.4% of people aged 75 and older are afflicted by AS, while 3.4% suffer from severe AS. Of these patients, 75.6% showed symptoms.

Apart from congenital defects such as bicuspid valve geometry, the mechanisms for valve calcification are similar to the ones contributing to atherosclerosis (4). Also the risk factors are similar and include inflammation, hyperlipidaemia and age. Rheumatic fever can also be the cause of AS.

3.1.1 Pathophysiology

The opening of a healthy aortic valve is approximately 3 cm$^2$, however as the disease progresses this area can decline to less than 1 cm$^2$. While the survival rate for asymptomatic patients is close to the healthy population, mortality distinctively increases as soon as symptoms develop (Fig. 3.1a). Upon the onset
of the hallmark symptoms angina, dyspnea and/or heart failure the mortality is close to 25% per year (5). This striking difference can partly be explained by looking at the compensatory processes taking place in the myocardium.

As the valve orifice decreases, the obstruction of the blood flow leads to a progressively higher pressure overload for the left ventricle. The myocardium compensates the increase in wall stress by thickening (41), modeled by the Laplace equation:

\[ T = \frac{P \cdot r}{2h} \quad \text{Eq. 3.1} \]

with \( T \) being wall stress, \( P \) pressure, \( r \) the radius of the ventricle and \( h \) the thickness of the myocardium. From Eq. 3.1 it follows that upon an increase in pressure the wall thickness has to increase to keep the wall stress constant.

However, this compensatory mechanism is not available unlimitedly. First of all, hypertrophy impairs the coronary blood-flow reserve. In healthy subjects, this reserve is 500-800% over resting flow, in concentric hypertrophy only 200-300% remain (42). This reduction could explain angina, a symptom otherwise associated with coronary artery disease.

The onset of dyspnea can also be related to an advanced hypertrophy. While normalizing wall stresses, increased wall thickness impairs diastolic function. In concentric hypertrophy, the passive filling of the ventricles is delayed, reducing the time for blood to shift from atrium to ventricle (43). Additionally, augmented pressure is needed to achieve the same level of diastolic filling, leading to pulmonary congestion and dyspnoea (44).
3.1 Prevalence, Pathophysiology and Treatment

Fig. 3.1: While mortality is low in asymptomatic patients with aortic stenosis, the onset of symptoms also marks a significant drop in survival rates (a). If left untreated, symptomatic AS leads to death within 3 years in more than 75% of patients. However, aortic valve replacement (AVR) can lower this number to less than 20%. Figures adapted from Bonow and Greenland (45) and Schwarz et al (5).

The exact mechanism of the third hallmark symptom of AS, syncope, remains unclear. In some patients with cardiac hypertrophy and AS the left ventricular ejection performance is diminished compared to healthy controls (46). In the physiological case blood pressure rises during exercise, whereas in some subjects suffering from severe AS blood pressure drops (47). This effect was postulated to be caused by the physiological decrease in arterial resistance when exercising in combination with a diminished stroke volume. The consequential decrease in blood pressure might cause syncope.

3.1.2 Treatment

Medical treatment in the form of statins to prevent progression of the disease was investigated, however according to current guidelines not enough evidence has been presented to indicate statin therapy (7, 8).

Surgical treatment is effective in reducing the mortality in patients with symptomatic aortic stenosis (Fig. 3.1b). More than 75% of patients die within the first three years upon onset of symptoms if left untreated. In contrast,
Aortic Valve Replacement (AVR) drastically reduces this risk to less than 20% (5).

Artificial aortic valves can be grouped into three categories. Mechanical valves are made of non-biological materials such as pyrolytic carbon and nowadays have either a bileaflet design (i.e. St. Jude Medical Regent™, Medtronic Open Pivot™) or a monoleaflet/tilting disk design (Medtronic Hall™). Caged-ball valves have been discontinued due to unfavorable hemodynamic performance but are still found implanted in patients (48). Mechanical valves require open-chest surgery (sternotomy) and lifelong anticoagulation therapy, however due to their long-time durability they are the recommended choice for patients aged 60 or younger (8).

Bioprosthetic valves consist of bovine or porcine leaflets and mimic a native aortic valve (48). They are either stented (i.e. Medtronic Mosaic®) or non-stented (Shelhigh SuperStentless®) and also require either sternotomy or minimally invasive heart surgery, but no antithrombotic therapy is necessary (8).

The third category is related to the second, with the main difference being the implantation technique. Ballon-expendable (Edwards Sapien®) or self-expandable (Medtronic CoreValve®) bioprosthetic valves allow for insertion of the valve via catheter, so-called Transcatheter Aortic Valve Implantation (TAVI). In TAVI, a catheter is guided either through the apex or through the femoral artery and the valve is placed “within” the diseased one (49). Upon expanding, the calcified leaflets are not removed but simply pushed to the wall. This procedure is indicated for elderly patients with high operative risk (7, 8).
3.2 Current Diagnostic Parameters

The most common first diagnosis of AS is made upon cardiac auscultation when a systolic murmur and a single or paradoxically split second heart sound is found. A normally split second heart sound excludes the possibility of severe AS (8).

Upon abnormal auscultation or the occurrence of symptoms indicative of AS a Transthoracic Echocardiogram (TTE) is indicated. Imaging reveals a possibly bicuspid valve and a first evaluation of valve leaflet mobility can be made. As manual measurements of the valve area are highly operator dependent, Doppler echocardiography is recommended for clinical decision making (7). The main diagnostic parameters are the maximum transvalvular velocity $v_{\text{max}}$, the Mean Pressure Gradient (MPG) according to the simplified Bernoulli equation (50)

$$PG = 4v^2$$  \hspace{1cm} \text{Eq. 3.2}

where PG is averaged over systole, and the Aortic Valve Area (AVA) determined using the continuity equation (6):

$$AVA = A_{\text{LVOT}} \frac{VTI_{\text{LVOT}}}{VTI_{\text{VC}}}$$  \hspace{1cm} \text{Eq. 3.3}

Here $A_{\text{LVOT}}$ is the cross sectional area of the Left Ventricular Outflow Tract, and $VTI_{\text{LVOT}}$ and $VTI_{\text{VC}}$ are the velocity time integrals over systole for the LVOT and the vena contracta (VC), respectively. Here also the peak velocities can be used, however the VTI is more robust (6). The AVA can be normalized to Body Surface Area, with $AVA_i = AVA/BSA$.

Echocardiography also provides information about the systolic function of the left ventricle. The ejection fraction (EF) can be determined and LV hypertrophy detected (8).
Aortic Stenosis is then classified as mild, moderate or severe AS with or without symptoms, see Table 3.1.

For patients with a normal systolic function (EF >50%) and severe AS, valve replacement is recommended if they exhibit symptoms or are scheduled for other cardiac surgery. In patients with low-flow low-gradient AS (MPG<40 mmHg, EF<50%) surgery should be considered also if they do exhibit symptoms. Exercise testing can also be employed for decision making (7, 8).

If echocardiographic data are non-diagnostic, cardiac catheterization is recommended. Hereby the pressure gradient across the valve can be measured directly (46).

Another echocardiographic parameter which is not yet considered in the guidelines but should be mentioned here is the Energy Loss Index (ELI) by Garcia et al (51):

\[
ELI = 4v_{max}^2 \left(1 - \frac{AVA}{A_A}\right)^2
\]

Eq. 3.4

with \(A_A\) being the cross-sectional area of the sinotubular junction. The ELI adjusts for a potential overestimation of disease severity due to pressure recovery (see Chapter 3.3) (52). In a prospective study it could be shown that ELI provides independent and additional prognostic information compared to conventional echocardiographic measures (53).
### Table 3.1 Stages of Aortic Stenosis

<table>
<thead>
<tr>
<th>Severity</th>
<th>( v_{\text{max}} )</th>
<th>MPG</th>
<th>AVA / AVAi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;2.9 m/s</td>
<td>&lt;20 mmHg</td>
<td>-</td>
</tr>
</tbody>
</table>
| Moderate | 3-3.9 m/s            | 20-39 mmHg | >1.0 cm\(^2\) \>
|          |                      |          | >0.6 cm\(^2\)/m\(^2\) |
| Severe   | \( \geq 4 \) m/s     | \( \geq 40 \) mmHg | \( \leq 1.0 \) cm\(^2\) \>
|          |                      |          | \( \leq 0.6 \) cm\(^2\)/m\(^2\) |

Based on the AHA/ACC Valvular Heart Disease Guidelines (8). MPG, Mean Pressure Gradient; AVA, Aortic Valve Area; AVAi, indexed Aortic Valve Area.

### 3.3 Energy Loss in Aortic Stenosis

The amount of work the heart has to supply is determined by the created pressure and the amount of blood transported. As already mentioned, an increased workload will lead to adaptation of the myocardium as a response to increased stresses. The type of adaptation depends on the kind of pathological loading (41). In the case of valvular insufficiency an elevated volume load will induce eccentric hypertrophy, while a stenotic valve will result in pressure overload and concentric hypertrophy. This chapter focuses on constrictions only.

#### 3.3.1 Energy conversion in a stenosis

To fully understand the shortcomings of conventional echocardiographic measures it is necessary to review the predominant forms of energy in the left ventricular outflow tract and the aorta (19). In the anatomical structures leading up to the stenosis (part A in Fig. 3.2), the potential energy in the form of pressure, which is generated by the contracting myocardium, is converted into kinetic energy as the blood is accelerated. In the next section (B) with a gradually constricting diameter the valve opening and vena contracta (VC) can
be found. The VC is defined as the point with the smallest diameter and therefore highest velocities, not necessarily coinciding with the valve opening. The potential energy has in large parts been converted to kinetic energy. In sections A and B the energy losses are mainly due to viscous losses and comparatively small. Echocardiographic measures are based on the velocities measured at the VC, i.e. the Mean and Maximum Pressure Gradients based on the simplified Bernoulli equation (50) describe the pressure needed to accelerate the blood flow from an assumed \( v = 0 \) in the left ventricle to \( v = v_{vc} \) in the vena contracta. This pressure gradient only provides an indication about the energy converted from potential to kinetic energy, not the energy lost. From Eq. 3.2 it follows that the geometry of the AAo bears no impact on the parameters.

The main determinant of energy loss is section C (19). Here the main dissipative processes occur due to viscous losses and turbulent mixing. However not all of the difference in kinetic energy between VC and AAo is dissipated, a fraction is converted back to pressure – a phenomenon termed “pressure recovery”.

### 3.3.2 Pressure recovery

The extent of pressure recovery is dependent on a multitude of factors. Arguably the most important and also best-described is the geometry of the aorta. The energy loss in a sudden expansion was first empirically described 200 years ago by the Borda-Carnot equation (27) which relates the area of two different cross sections of a pipe:

\[
\Delta E = \frac{1}{2} \rho \left( 1 - \frac{A_1}{A_2} \right)^2 v_1^2
\]

Eq. 3.5
Fig. 3.2: Schematic representation of the flow through a stenosed valve and the corresponding energy budget. At first velocities are low (A), but rapidly increase near the valve (B). Kinetic energy is highest at the vena contracta (VC). The main contributor to energy loss is section C, where turbulent mixing occurs. In the sinuses and the ascending aorta pressure recovery (PR) leads to an increase in potential energy. Figure adapted from (19) and (51).

From Eq. 3.5 it follows that the smaller the ratio between the area of the vena contracta and the area of the AAo, the higher the energy loss and therefore the smaller the pressure recovery. The increased energy loss in dilated aortae is explained by a higher extent of turbulent mixing found at the borders of the jet. The Borda-Carnot equation is also the basis of the ELI metric (51).
While the above relation is only valid for sudden expansion of straight pipes, the extent of pressure recovery also depends on the angle of the jet (21). This was not described analytically, but experimental studies showed an increase in jet angle decreases pressure recovery. As the shape of the aortic arch also influences the flow field and turbulent mixing, it is reasonable to assume that the curvature of the aorta will affect the amount of energy loss.

As pressure recovery is not accounted for in MPG and AVA metrics, clinical Doppler echocardiography might hence overestimate disease severity (54).
This chapter details the principles of quantitative velocity and turbulence measurements using MRI. It also gives an overview of necessary post-processing steps and possible acceleration techniques.

4.1 Principles of Phase-Contrast MRI

Flow encoding sequences are based on conventional imaging techniques such as gradient echo or spin echo, which are then sensitized to motion by the application of a flow-encoding gradient (55). Such a gradient is a bipolar gradient waveform with a net area $A$ of 0 (Fig. 4.1), and it is added to the axis of interest, i.e. the slice encoding axis for mapping through-plane motion. As spatial encoding gradients can also act as flow-encoding gradients, it is advisable to use a velocity-compensated sequence as a basis.

The flow-encoding gradient causes spins to acquire a phase depending on their motion. More precisely, the phase $\phi$ of a spin at a time point $t$ is related to the experienced magnetic field at the position $x$ in the time interval $[0, t]$:

$$\phi(t) = \gamma \int_0^t G(u)x(u)du$$

Eq. 4.1

where $\gamma$ is the gyromagnetic constant and $G$ is the gradient strength. Using a gradient moment expansion, Eq. 4.1 can be stated as (56):

$$\gamma \int_0^t G(u)x(u)du \approx \gamma \left( \sum_n \frac{m_n}{n!} \left( \frac{d^n x}{dt^n} \right)_{t=0} \right) \approx \gamma \left( m_0 x_0 + m_1 v_0 + \frac{1}{2} m_2 a_0 \right)$$

Eq. 4.2
As stated above, the zeroth moment (area) \( m_0 \) is 0, so the phase is independent of the initial position \( x_0 \). Remaining are the velocity \( v_0 \) and acceleration \( a_0 \), which are encoding according to the gradient’s first and second moments. Higher order motion is assumed to be negligible. Acceleration can be disregarded if the expansion point of the Taylor series is set to the center of gravity (CG) of the bipolar gradient waveform, and correspondingly \( v = v_{CG} \). Then the acquired phase at echo time \( TE \) can be expressed as

\[
\phi = \gamma m_1 v = \gamma ATv
\]

with \( T \) being the temporal distance between the lobes. It can be shown that Eq. 4.3 is valid for any pair of lobes with arbitrary but equal shape (56).

The phase of an MR image is also influenced by field inhomogeneities which prohibit velocity quantification using a single acquisition. By subtracting the phase of two images with differing \( m_1 \) an elimination of this effect is possible (Fig. 4.1b). The velocity is then calculated by

\[
v = \frac{\phi_{net}}{\gamma |\Delta m_1|} = \frac{\phi_{net}}{\pi} v_{enc}
\]

with

\[
v_{enc} = \frac{\pi}{\gamma |\Delta m_1|}
\]

The encoding velocity \( v_{enc} \) is important as it determines the maximum uniquely resolvable velocity. Velocities exceeding \( v_{enc} \) will result in phase-wraps and will therefore be calculated incorrectly – velocities of \( v_{enc} + a \) will be mapped to \( -v_{enc} + a \). It is possible to correct such phase-wraps in post-processing, however it is advisable to choose \( v_{enc} \) such that it is equal or greater than any occurring
velocity. The choice of $v_{\text{enc}}$ also impacts noise as will be described in Chapter 4.3.

There are two strategies for creating a difference in $m_1$ for the two measurements. The first is to acquire a flow-compensated reference image ($m_1=0$) and a second image with $m_1 = \Delta m_{1,\text{req}}$. This is termed asymmetric encoding. With symmetric encoding on the other hand, flow encoding gradients are present in both acquisitions, with $m_1 = \Delta m_{1,\text{req}}/2$ and $m_1 = -\Delta m_{1,\text{req}}/2$, respectively. Symmetric encoding therefore requires only half of the gradient strength, possibly shortening TE.

**Fig. 4.1**: a) The bipolar velocity encoding gradient and the resulting phase of two spins with different velocities. While the stationary spin does not accumulate any net phase, the moving spin with constant velocity $v$ experiences a different magnetic field throughout the time the gradient is played out, resulting in a net phase. b) Subtraction of two phase maps of the aorta of a healthy volunteer yields the net phase which can then be mapped to velocities. Figure adapted from (56).
4.1.1 4D Flow MRI

For the acquisition of three-dimensional velocity vectors, measurements in all three spatial directions are required. Compared to the one-directional case where two acquisitions ("segments" or "points") are subtracted, at least four such velocity encoding points are required in 3D as the reference has to be acquired only once. Therefore scan time only doubles, not triples relative to one-directional 3D velocity measurements.

Again symmetric and asymmetric encoding is possible: In asymmetric encoding sequences no flow encoding gradient is present in the reference segment, and for the other segments it is applied on each axis separately. Symmetric encoding employs flow encoding gradients on each axis for each acquisition, with a sign reversal on a single axis for the corresponding directions. This can be expressed via matrix $A$, where the rows correspond to measurements 1-4 and the columns to directions x, y, z:

$$
\begin{bmatrix}
A_{sym} & = & \begin{bmatrix}
0 & 0 & 0 \\
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix}, & \\
A_{sym} & = & \begin{bmatrix}
-1 & -1 & -1 \\
+1 & -1 & -1 \\
-1 & +1 & -1 \\
-1 & -1 & +1
\end{bmatrix}
\end{bmatrix}
$$

An alternative encoding strategy is balanced encoding, where all four points encode all three directions. Here $A$ is given by a Hadamard matrix (57):

$$
\begin{bmatrix}
A_{Hadamard} & = & \begin{bmatrix}
-1 & -1 & -1 \\
+1 & +1 & -1 \\
+1 & -1 & +1 \\
-1 & +1 & +1
\end{bmatrix}
\end{bmatrix}
$$

Balanced encoding is beneficial in terms of SNR compared to symmetric/asymmetric encoding, however the correction of phase-wraps becomes non-trivial as they do not strictly amount $2\pi$ rad.
The fourth dimension in the term “4D Flow” refers to time, as the acquired signals are synchronized with the heartbeat. To achieve such synchronization, the electrocardiogram is recorded simultaneously with the MRI measurement. A desired number of heart phases $n_t$ is defined by the operator, and the temporal resolution is then given by the length of the R-R interval divided by $n_t$. Under the assumption of similarity between heartbeats, the k-space lines for a single heart phase are acquired over multiple beats. Techniques like arrhythmia rejection void any data measured in conditions where this similarity is clearly not given, such as extra systoles. Artifacts due to breathing motion are usually suppressed by the use of navigator gating, where the position of the diaphragm is determined after each R peak, and data is only acquired during exhalation.

### 4.2 Estimation of Turbulent Kinetic Energy

The presence of multiple velocities in a voxel while a flow encoding gradient is applied causes dephasing and therefore a loss in signal can be observed (58). While the velocity distribution in laminar flow is very narrow, the higher the level of turbulence the broader the range of velocities found (see also Chapter 2). Assuming a Gaussian distribution of velocities with a standard deviation $\sigma_v$ and a mean velocity $\overline{V}$, the signal for a gradient with a given velocity frequency $k_v = \gamma m_1 = \pi/\nu_{enc}$ can be modeled as (18):

$$S(k_v) = S(0)e^{-\frac{k_v^2 \sigma_v^2}{2}}e^{ik_v\overline{V}}$$

Eq. 4.8

By acquiring a flow encoded image $S(k_v)$ and a non-flow encoded reference image $S(0)$, the variance of the intravoxel velocity distribution is obtained:
\[ \sigma_v^2 = \frac{2}{k_v^2} \ln \left( \frac{|S(0)|}{|S(k_v)|} \right) \]  
Eq. 4.9

If this is repeated for all three spatial directions, the Turbulent Kinetic Energy analogous to Eq. 2.11 can be obtained (59):

\[ TKE = \frac{\rho}{2} \sum_{i=1}^{3} \sigma_{v,i}^2 \]  
Eq. 4.10

From Eq. 4.8 it also follows that the drop in signal magnitude depends on \( k_v^2 \) and \( \sigma_v^2 \), therefore the dynamic range for a specific \( k_v \) value will be limited. This is also illustrated in Fig. 4.2. A possible solution is Multipoint encoding with multiple \( v_{\text{enc}} \) values, which will be discussed in Chapter 5. The influence of voxel size and the validity of the assumption of a Gaussian velocity distribution will be investigated in detail in Chapter 7.

Fig. 4.2: Signal magnitude as a function of \( v_{\text{enc}} \) for three different turbulence levels, assuming isotropic turbulence. The \( v_{\text{enc}} \) with the highest sensitivity is marked for each curve.
4.2.1  **Estimation of Turbulent Shear Stresses**

Under the assumption of a Gaussian velocity distribution in a voxel, the full Reynolds’s stress tensor $R$ can be acquired by adding three measurements along the axes bisecting the three principal directions (60) and thereby obtaining $\sigma_{x+y}$, $\sigma_{x+z}$ and $\sigma_{y+z}$. The off-diagonal elements of $R$, $v'_{i}v'_{j}$ with $i \neq j$, can then be computed with the following expression:

$$v'_{i}v'_{j} = \sigma_{i+j}^{2} - \left(\sigma_{i}^{2} + \sigma_{j}^{2}\right)/2$$  

Eq. 4.11

This approach increases scan time by 75%. As the shear stresses will be smaller than the principal stresses higher SNR is required. Also a violation of the assumed velocity distribution will impact the accuracy of shear stress estimation more severely than estimation of TKE. Recently an approach adapting the ICOSA6 encoding scheme for Diffusion Tensor Imaging was presented (61), improving the SNR dependency of the quantification of the shear stress elements.

4.3  **Noise considerations**

Like all MRI acquisitions, the results obtained using PC-MRI are affected by noise. As the main goal is velocity quantification also the uncertainty introduced by noise should be determined, and parameters affecting this uncertainty identified.

The standard deviation in the phase maps $\sigma_{\text{phase}}$ in radians is inversely proportional to the SNR of the magnitude image (55):

$$\sigma_{\text{phase}} = \frac{1}{SNR_{\text{mag}}} \ [\text{rad}]$$  

Eq. 4.12
For Phase-Contrast MRI two phase images are subtracted and assuming equal SNR the resulting increase in standard deviation is $\sqrt{2}$. This standard deviation in rad directly translates to velocities given the encoding velocity $v_{enc}$:

$$\sigma_{vel} = \frac{\sqrt{2} \sigma_{phase} v_{enc}}{\pi} \left[ \frac{m}{s} \right]$$  \hspace{1cm} \text{Eq. 4.13}$$

A parameter comparable to SNR is the ratio between the velocity of the fluid and the standard deviation of the noise, the so called Velocity-to-Noise Ratio (VNR):

$$VNR = \frac{\Delta \phi}{\sqrt{2} \sigma_{phase}} = \frac{\pi v / v_{enc}}{\sqrt{2} \sigma_{phase}} = \frac{\pi}{\sqrt{2}} \text{SNR}_{mag} \frac{v}{v_{enc}}$$  \hspace{1cm} \text{Eq. 4.14}$$

Here $v$ can be the mean velocity in the volume of interest, or also the velocity at a given location. In the latter case a VNR map is created where the VNR can vary widely within the acquisition volume.

From Eq. 4.13 and Eq. 4.14 it immediately follows that a lower $v_{enc}$ results in a higher VNR. Therefore, $v_{enc}$ should not be chosen arbitrarily, but rather as close as possible to the highest occurring velocities in order to avoid both phase aliasing and VNR penalties.

Eq. 4.14 is valid for conventional 2D PC-MRI, for 4D Flow with different flow encoding strategies this factor may vary (57).
4.4 Post-processing

After the acquisition of the data systematic errors have to be removed to improve accuracy of quantitative analysis. For 4D Flow data also a variety of options for visualization is available.

4.4.1 Correction of systematic errors

Two major contributors to a potential bias in the data are gradient non-linearities (62) and concomitant gradient fields (63). The resulting phase offsets can be corrected or calibrated with predetermined parameters (64).

Another source of systematic errors are gradient induced eddy-currents (65). These eddy-currents lead to first- or higher-order phase offset dependent on a number of parameters which is not determinable analytically. In order to compensate for this, the background phase offset has to be determined in post-processing, with two options available. The first comprises of a linear or 2nd order fit over static tissue such as the chest wall or the back. Here care has to be taken that enough static tissue is available in order to avoid overfitting. Alternatively, a separate scan of a gel phantom with identical scan parameters can be obtained and the fit subsequently performed on this dataset. The background phase offset obtained with either of the two methods is then subtracted from the dataset. The assessment of the offsets for each acquired heart phase is recommended (14).

4.4.2 Visualization

Phase-Contrast MRI acquisitions, in particular 4D Flow, offer a vast amount of underlying information which can be challenging to display.

The most basic visualization involves single slices color-coded according to speed. For 3D/4D volumes the user should be able to interactively browse
through the volume of interest. Vector maps can help understand flow patterns (66).

Another technique to visualize the instantaneous flow field are streamlines (66), Fig. 4.3a. Related to vector maps, streamlines are paths through the velocity field which are tangent to the velocity vectors at all spatial coordinates. Usually a starting point is defined from where the paths originate. Streamlines depict the flow pattern at a single point in time and for pulsatile flow do not coincide with the path particles travel. This drawback is overcome by the use of pathlines (67), Fig. 4.3b. They follow the path a massless particle would take if released at a given point in space and time. For both streamlines and pathlines color coding lends itself to achieve an intuitive overview of the velocities present in the flow field.

Fig. 4.3: Streamlines (a) and pathlines (b) in a patient with aortic stenosis.
4.5 Accelerated imaging

4D Flow acquisitions of a large volume of interest such as the aortic arch require up to 20 min of net scan time, being prohibitively long for clinical scans. Therefore, it is necessary to employ techniques which shorten scan time.

4.5.1 Undersampling and SENSE reconstruction

If fewer k-space points than required by the Nyquist theorem are acquired, signal fold-over occurs. These will have different appearances depending on the way the k-space is filled: With Cartesian sampling a (equidistant) reduction in the number of acquired k-space points $n_{acq}$ is comparable to a reduction of the field-of-view, therefore the object will show the commonly known fold-over artifacts. With radial sampling streaks will occur, and spiral sampling leads to aliasing in spiral form. Different sampling strategies require different reconstruction methods. In the following we will focus on undersampling of Cartesian data.

As the readout in frequency direction $k_x$ is significantly faster than in phase directions $k_y$ and $k_z$, undersampling will in most cases be limited to the latter two directions. Defining the undersampling factor $R$ as the ratio of k-space points in the fully sampled case $n_{full}$ to the actually acquired ones $n_{acq}$, $R = n_{full}/n_{acq}$, regular undersampling implies that only every $R^{th}$ phase encode is acquired. As mentioned above, this will lead to $R$ points folding onto each other. Using coil arrays with different sensitivities, these superpositions can be resolved during reconstruction.

More formally, the imaging and reconstruction process can be described using matrix operations. The mapping of the image pixel values $p$ onto the measured data $m$ is expressed via the encoding matrix $E$:

$$ m = Ep $$

Eq. 4.15
where \( \mathbf{p} \) and \( \mathbf{m} \) are vectors of length \( n_{\text{full}} \) and \( n_{\text{acq}} n_c \), respectively, with \( n_c \) being the number of coils. Here it is assumed that the object to be measured is discretized and considered as an image with the same number of data point as the fully sampled k-space. The encoding matrix \( \mathbf{E} \) describes the sampling operation, the Fourier transform and the sensitivity encoding of the individual coils. \( \mathbf{m} \) is a vector filled with the k-space data points measured on the scanner. For image reconstruction, this process has to be inverted:

\[
\mathbf{p} = \mathbf{F d}
\]

Eq. 4.16

The reconstruction matrix \( \mathbf{F} \) follows from \( \mathbf{F E} = \mathbf{I d} \), where \( \mathbf{I d} \) is the identity matrix. As \( n_c > R \) the reconstruction problem becomes overdetermined, and the sampling noise matrix \( \tilde{\Psi} \) can be utilized for SNR optimization (10). The final reconstruction matrix for SENSE then reads

\[
\mathbf{F} = \left( \mathbf{E}^H \tilde{\Psi}^{-1} \mathbf{E} \right)^{-1} \mathbf{E}^H \tilde{\Psi}^{-1}
\]

Eq. 4.17

where superscript \( H \) denotes the transposed complex conjugate.

**4.5.2 Local noise amplification – the g-factor**

As fewer data points in k-space are acquired, the general SNR will be reduced by a factor of \( \sqrt{R} \). The noise amplification however also depends on the coil geometry, more specifically the separability of aliased signals given by the orthogonality of the coil sensitivities (10). This amplification varies spatially and is called the geometry (g-) factor \( g_x \), which for SENSE is given by

\[
g_x = \sqrt{\left[ \left( \mathbf{S}^H \tilde{\Psi}^{-1} \mathbf{S} \right)^{-1} \right]_{x,x} \left( \mathbf{S}^H \tilde{\Psi}^{-1} \mathbf{S} \right)_{x,x}}
\]

Eq. 4.18
where $S$ is the coil sensitivities matrix and $Ψ$ the receiver noise matrix. The final SNR of the reconstructed image at a specific location $x$ is then given by

$$SNR_{x}^{red} = \frac{SNR_{x}^{full}}{g_x \sqrt{R}}$$

Eq. 4.19

For frame-by-frame reconstruction methods such as SENSE or GRAPPA, $g_x \geq 1$. For methods which also exploit temporal correlation of time-resolved signals this does not necessarily hold true, as demonstrated in Chapter 6.

The geometry factor also increases with $R$, with an exponential increase for larger $R$ (68). This limits obtainable reduction factors to 2-4 for PC-MRI (69).

### 4.5.3 k-t SENSE and k-t PCA

One of the techniques which also takes the temporal dimension into account is k-t PCA (13). It extends k-t BLAST/k-t SENSE (12) by applying a Principal Component Analysis (PCA) on the temporal frequencies in the data.

The concept behind the three reconstruction methods is the inclusion of prior knowledge in the unfolding process. The center of k-space is sampled fully, yielding a low-resolution dataset called “training data”. This data is then used to obtain signal estimates for all positions and temporal frequencies by computing the signal covariance matrix $M^2$. While for k-t BLAST and k-t SENSE reconstruction is performed in x-f space, for k-t PCA the training data $P_{\text{train}}$ is subjected to a PCA calculating temporal basis functions $B$ and training weights $W_{\text{train}}$, giving

$$P_{\text{train}} = W_{\text{train}}B$$

Eq. 4.20

The temporal basis functions describing the training data are assumed to be the same as the ones for the full dataset. This may not hold true for the
dynamics of small objects not captured due to the low resolution of the training data. The signal covariance matrix is then composed by the entries in $\mathbf{W}_{\text{train}}$ (13).

Reconstruction for all methods is then performed according to:

$$\mathbf{w}_x = \mathbf{M}_x^2 \mathbf{E}_x^H \left( \mathbf{E} \mathbf{M}_x^2 \mathbf{E}_x^H + \lambda \mathbf{I} \right)^+ \mathbf{P}_{\text{alias},x}$$  \hspace{1cm} \text{Eq. 4.21}

where $+$ indicates the Moore-Penrose pseudo-inverse, and $\lambda$ a regularization term derived from the noise covariance matrix $\mathbf{\Psi}$ (12, 13). The resulting weights and $\mathbf{B}$ are then used to obtain the reconstructed image. k-t SENSE reconstruction can also be expressed by Eq. 4.21 and setting $\mathbf{B}$ to the identity matrix sized $n_f \times n_f$, with $n_f$ being the number of temporal frequencies.

Due to the exploitation of both spatial and temporal correlations, k-t based methods allow for a higher acceleration factor than frame-by-frame based reconstruction techniques.
Chapter 5
Bayesian multipoint velocity encoding for concurrent flow and turbulence mapping

5.1 Introduction

Many cardiovascular diseases are associated with changes in blood flow patterns. However, in clinical practice the evaluation of flow parameters is limited (70), mostly because comprehensive and accurate flow quantification remains difficult to achieve (71, 72). In research, Phase-Contrast (PC) MRI is becoming more and more accepted as a tool for determining the flow conditions in vivo. In an increasing number of publications the link between disturbed flow and various diseases of the cardiovascular system has been investigated (73-75).

In general, turbulent flows do not occur under physiological conditions. However, in stenotic or artificial heart valves the losses due to turbulence can considerably exceed those due to viscous effects found in healthy subjects (19). For a statistical description of turbulence, a decomposition in mean and fluctuating velocities can be performed (23). The mean kinetic energy in the fluctuating velocity field is termed turbulent kinetic energy (TKE), and can serve as a measure for energy loss due to turbulence. A method to determine this turbulent kinetic energy using conventional PC-MRI was proposed (17, 18, 59). The approach is based on the relation between different first gradient

---

moments and the resulting signal losses if multiple velocities are present in a voxel (58). TKE also offers an estimation of the shear stresses in the fluid (76), making it possible to determine the risk of hemolysis. A PC-MRI method to quantify these shear stresses directly was proposed (60). Validation of MRI based shear stress measurements with particle image velocimetry (PIV) has been attempted, but shear stress results showed pronounced deviations from the PIV data. On the contrary, results for the intra-voxel standard deviation and therefore turbulent kinetic energy agreed well with the PIV measurements, showing that an estimation of TKE with PC-MRI is feasible.

PC-MRI approaches (59, 60) require a trade-off between scan time and dynamic range. For the original method, an estimate of the expected turbulence intensity is necessary to achieve optimum sensitivity. The optimal first gradient moment for TKE measurements (59) usually differs from the optimal setting for velocity measurements, leading to ambiguities in the form of velocity-induced phase wraps when velocity information is extracted from the same acquired data. These phase wraps have to be corrected for in post-processing, using either statistical methods (77) or additional reference data without phase aliasing (78). The successive application of multiple first gradient moments results in an increased dynamic range (60) for TKE measurements, yet it also prolongs the scan time. Subsequently, this approach was improved by using a weighted rather than a standard least squares combination (79), however, no in vivo measurements have been reported. Bretthorst (80) has proposed a framework for Bayesian statistical analysis for nuclear magnetic resonance (NMR) spectroscopy and applications to NMR diffusion and flow measurements followed (81). Again, multiple first gradient moments are used, resulting in a probability map of the mean velocity and the diffusion coefficient in a voxel. This approach has been applied in vivo on anaesthetized rats, with a total scan time of approximately 90 min (82).
The objective of the present work is to propose and validate a Bayesian approach for multi-point velocity encoding. It will be demonstrated that the method is optimal in terms of signal-to-noise ratio (SNR) efficiency and results in improved accuracy of velocity and TKE quantification relative to methods using conventional velocity encoding as presented previously. It will furthermore be shown that the sampling of multiple velocity encoding points permits for efficient extension of the alias-free velocity range. Accordingly, velocity aliasing can be avoided in many practical applications and hence adjustment of the maximum encoding velocity on a patient-by-patient basis is no longer necessary. Using simulations and in vitro measurements it will be demonstrated that the increased accuracy of the Bayesian method outweighs the reduction in SNR by accelerated imaging, which is employed to achieve imaging times comparable to conventional phase-contrast measurements. In vivo feasibility will be demonstrated for aortic flow assessment in healthy subjects and patients with aortic stenosis and valve replacement.

### 5.2 Theory

In PC-MRI bipolar velocity encoding gradients induce a velocity dependent phase. If multiple velocities are present in a voxel, dephasing occurs, leading to attenuation of the signal magnitude. Accordingly, the signal model for generalized PC-MRI assuming a Gaussian distribution of velocities with standard deviation \( \sigma \) is given by (18):

\[
S(k_v) = S_0 e^{-\frac{\sigma^2 k_v^2}{2}} e^{-ik_v \bar{v}}
\]

Eq. 5.1

where \( \bar{v} \) denotes the mean velocity in a voxel, and \( k_v \) is related to the first gradient moment by \( k_v = \gamma \int_0^T tG(t)dt \), with \( T \) being the time of application.
of a gradient with strength \( G \). Typically one reference image without flow encoding is acquired, as well as one flow encoded image per direction. For a 3D velocity vector field is it therefore necessary to acquire 4 points in the three-dimensional \( k_v \) space, and hence the method is frequently referred to as four-point (4P) measurement.

Considering such a 4P experiment and Gaussian noise, the sensitivity for both mean velocity \( \bar{v} \) and velocity standard deviation \( \sigma \) is given by:

\[
\text{Sensitivity} = k_v e^{-\frac{\sigma^2 k_v^2}{2}}
\]

Eq. 5.2

Up to the value \( k_v = \frac{1}{\sigma} = \frac{\pi}{v_{\text{enc}}} \) an increase in first gradient moment and thereby \( k_v \) improves the accuracy of the parameter estimation. Beyond this maximum encoding strength, the signal magnitude drops sharply and the noise begins to predominate. For conventional 4P measurements the \( k_v \) values are typically adjusted such that phase wraps are avoided. Accordingly, the encoding velocity \( (v_{\text{enc}}) \) is set higher than all velocities present in the fluid.

In \( N \)-point measurements, Eq. 5.2 can be used to weight the contribution of individual encodes, for example in a weighted least square sense. However, the weights depend on a target parameter, therefore a first estimation and subsequent iterative optimization is required.

In order to combine data from \( N \) measured \( k_v \) points, Bayesian analysis can be employed (80). Thereby a joint probability map for both parameters \( \{ \bar{v}, \sigma \} = \theta \) can be obtained. The resulting posterior probability at a voxel given the model \( I \) and the measured image data \( D \) is
5.2 Theory

\[ P(\theta | D, I) \propto \frac{1}{\lambda} \left[ 1 - \frac{h_1^2 + h_2^2}{\sum_{i=1}^{N} \left[ d_R(k_v,i)^2 + d_I(k_v,i)^2 \right]} \right]^{1-N} \]  

Eq. 5.3

with

\[ h_1 = \frac{1}{\sqrt{\lambda}} \sum_{i=1}^{N} \left[ \left( d_R(k_v,i) \cos(vk_v,i) - d_I(k_v,i) \sin(vk_v,i) \right) e^{-\frac{\sigma^2 k_v,i^2}{2}} \right] \]  

Eq 5.4

and

\[ h_2 = \frac{1}{\sqrt{\lambda}} \sum_{i=1}^{N} \left[ \left( d_R(k_v,i) \sin(vk_v,i) + d_I(k_v,i) \cos(vk_v,i) \right) e^{-\frac{\sigma^2 k_v,i^2}{2}} \right] \]  

Eq. 5.5

as well as

\[ \lambda = \sum_{i=1}^{N} e^{-\sigma^2 k_v,i^2} \]  

Eq. 5.6

In equations [1.3-5] \( d_R(k_v,i) \) and \( d_I(k_v,i) \) denote the real and imaginary part of the measured image data at the \( i \)th \( k_v \) value (\( i=1,2...N \)) and term \( h_1^2 + h_2^2 \) is the mean square projection of the data onto the model. Each data point can be regarded as a sinusoid with a specific frequency and amplitude according to its \( k_v \) value. The velocity that results in a common maximum of most sinusoids has the highest probability. Probability further depends on how well the reduction in signal magnitude with increasing \( k_v \) is explained by the intra-voxel velocity standard deviation \( \sigma \). The contribution of each measurement is intrinsically weighted according to its magnitude and resulting sensitivity to errors due to noise. Phase wraps are inherently accounted for as long as one of the velocity encoded images is free of aliasing. Velocity ambiguities caused by wraps are given by \( v = v_{\text{true}} \pm 2*m* v_{\text{enc}} \) \( m=1,2,\ldots,\infty \). Using a single \( v_{\text{enc}} \) value, all velocities
with $m=1,2,\ldots,\infty$ are explained equally well by the model and can therefore not be resolved. If multiple $v_{\text{enc}}$ values are used, these ambiguities are reduced to $v = v_{\text{true}} \pm 2^m \cdot \text{LCM}(v_{\text{enc},i})$, with LCM($v_{\text{enc},i}$) being the least common multiple of all encoding velocities. By setting one $v_{\text{enc}}$ higher than the highest velocity in the flow field the true velocity $v_{\text{true}}$ can be recovered.

Based on the Reynolds decomposition of the velocity vector field $v$ into mean velocity field $\overline{v}$ and a fluctuating velocity field $v'$, $v = \overline{v} + v'$, the kinetic energy of the flow can be assessed (23). Considering the density of the fluid $\rho$ and the mean velocity $\overline{v}_i$ in direction $i$, the mean kinetic energy MKE is given by

$$MKE = \frac{\rho}{2} \sum_{i=1}^{3} \overline{v}_i^2$$

Eq. 5.7

For a Gaussian distribution of velocities in a voxel the kinetic energy stored in velocity fluctuations, which is referred to as TKE, is related to the velocity standard deviation $\sigma$:

$$TKE = \frac{\rho}{2} \sum_{i=1}^{3} \overline{v}_i' \overline{v}_i' = \frac{\rho}{2} \sum_{i=1}^{3} \sigma_i^2$$

Eq. 5.8

TKE is the first invariant of the Reynolds stress tensor $\rho v'_i v'_j$ and is comparable to a sum over the Reynolds normal stresses in all three directions. Both the TKE and the MKE are direction-independent.
5.3 Methods

Computer simulations

To evaluate the performance of the method at different noise levels and over a wide dynamic range a numerical flow phantom was designed. Based on Computational Fluid Dynamics (CFD) data (ANSYS CFX, ANSYS Inc., Canonsburg, PA, USA, with a k-ε turbulence model) a stenotic u-bend (Fig. 5.1) was modeled, yielding a 3D velocity vector field as well as TKE values. The unconstricted and constricted diameters of the numerical flow phantom were 20 and 9 mm, respectively. The radius of the bend was 50 mm, and entry and outflow lengths of 1.5 m resulted in fully developed laminar flow at the in- and outlet with a flow rate of 150 ml/s. PC-MRI measurements were simulated based on Eq. 5.1, and Gaussian noise was added in order to achieve signal-to-noise ratios in the range of 3 to 30. The voxel size was 1 mm isotropic, and the applied first gradient moments were similar to those used in vitro for the modified St. Jude Medical valve (Table 5.1). The results were compared to 4P PC measurements with $v_{enc}$ set to 150 cm/s, assuming that one-time phase

![Fig. 5.1: Numerical flow phantom of a stenotic U-bend, middle slice, a) velocities in vertical direction (m/s), b) TKE-values in J/m³.](image)
wraps can be resolved in post processing. In order to simulate comparable scan times, the SNR of the N-point measurements was reduced by the square root of a hypothetical undersampling factor N/4. This is justified by the fact that N-point encoding leads to N/4 times longer scan times relative to a conventional 4-point phase-contrast measurement. Accordingly, an N-point measurement yields $\sqrt{N/4}$ times higher SNR compared to the 4-point methods.

**Scan Parameters**

<table>
<thead>
<tr>
<th></th>
<th>FOV (mm³)</th>
<th>Resolution (mm³)</th>
<th>$v_{\text{enc,min}}$ (cm/s)</th>
<th>$v_{\text{enc,max}}$ (cm/s)</th>
<th>Relative $k_v$ values</th>
<th>Scan time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoreValve, 19P</td>
<td>304x210x50</td>
<td>2x3x2</td>
<td>20</td>
<td>240</td>
<td>1, 2, 4, 6, 9, 12</td>
<td>53.9</td>
</tr>
<tr>
<td>SJM valve, 19P</td>
<td>240x128x60</td>
<td>2x2x2</td>
<td>20</td>
<td>160</td>
<td>1, 2, 3, 4, 6, 8</td>
<td>59.2</td>
</tr>
<tr>
<td>SJM (mod.), 22P</td>
<td>320x200x66</td>
<td>2x2x2</td>
<td>30</td>
<td>300</td>
<td>1, 2, 3, 5, 6, 8, 10</td>
<td>118.4 (1x)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.9 (8x)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.1 (12x)</td>
</tr>
<tr>
<td>SJM (mod.), 13P</td>
<td>320x200x66</td>
<td>2x2x2</td>
<td>30</td>
<td>300</td>
<td>1, 2, 5, 10</td>
<td>13.5 (6x)</td>
</tr>
<tr>
<td>SJM (mod.), 10P</td>
<td>320x200x66</td>
<td>2x2x2</td>
<td>30</td>
<td>300</td>
<td>1, 3, 10</td>
<td>14.9 (4x)</td>
</tr>
<tr>
<td>SJM (mod.), 4P</td>
<td>320x200x66</td>
<td>2x2x2</td>
<td>300</td>
<td>300</td>
<td>1</td>
<td>16.1</td>
</tr>
<tr>
<td>CoreValve Pat., 10P</td>
<td>304x192x100</td>
<td>2x2x2.5</td>
<td>50</td>
<td>300</td>
<td>1, 3, 6</td>
<td>8.6/18.2 (8x)</td>
</tr>
<tr>
<td>Stenosis Pat., 10P</td>
<td>304x172x100</td>
<td>2x2x2.5</td>
<td>50</td>
<td>400</td>
<td>1, 2, 8</td>
<td>7.7/13.7 (8x)</td>
</tr>
<tr>
<td>Volunteers</td>
<td>~340x210x70</td>
<td>1.5x1.5x2 – 2x2x2.5</td>
<td>30-50</td>
<td>180-250</td>
<td>1, 3, 5/6</td>
<td>7-10/13-20 (8x)</td>
</tr>
</tbody>
</table>

**Table 5.1**: Scan parameters for the in vitro and in vivo experiments. In all experiments 24 heart phases were acquired. The encoding velocities corresponding to the relative $k_v$ values can be calculated by $v_{\text{enc}} = v_{\text{enc,max}}/k_v$-value, i.e. for the patient with the CoreValve they would be 50, 100 and 300 cm/s in each direction, respectively (see also Fig. 5.3). For in-vivo scans, nominal and actual scan times (including navigator efficiency) are reported. Undersampling factors are given in brackets.
5.3 Methods

**In vitro experiments**

For the in vitro measurements a pulsatile flow phantom was constructed (Fig. 5.2). The inner diameter of the inlet and outlet were 24 and 40 mm, respectively. A St. Jude Medical Standard® bileaflet valve (St. Jude Medical Inc, St Paul, MN, USA, 21 mm diameter) and a Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA, 27 mm diameter) were fitted into the phantom setup. Pulsatile flow was generated using a centrifugal pump (BG-GP 636, Einhell Germany AG, Germany) in combination with a controllable magnetic valve, resulting in a heart rate of 67 bpm and a stroke volume of 85 ml. All measurements were performed on a clinical 3.0 T scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands), using a cine 3D gradient echo sequence with bipolar velocity encoding gradients. A list of scan parameters is found in Table 5.1. The total number of $k_v$ encodes acquired in each experiment is quoted. A pictorial description of one particular $k_v$-$k_y$-$k_z$-$t$ sampling scheme is given in Fig. 5.3 ($k_y$ and $k_z$ corresponding to the phase and slice encoding direction, respectively). In vitro a long scan time is acceptable, therefore a higher number of $k_v$ values than in typical in vivo scans was used (7 vs. 3 $k_v$ steps, respectively – Table 5.1). The lower limit of the $k_v$ range (the highest $v_{enc}$) was set to 130% of the highest velocity expected, allowing for an unaliased phase image to be acquired. The upper limit of the $k_v$ space determines the quantification accuracy at lower levels of TKE as well as the echo/repetition time (TE/TR), depending on the performance of the gradient system. We found that $k_v$ values with corresponding $v_{enc}$ of 20-25 cm/s provided a good trade-off between sequence timing (TE/TR of about 3.6/5.1 ms) and accuracy. The choice of the $k_v$ values in between depends on the number of acquired steps. If only a few points are acquired, a uniform coverage of $k_v$ space is advisable in order not to neglect ranges of velocities/turbulence. With more steps available...
it is possible to focus on accuracy at higher levels of TKE, so a more densely sampled center of the $k_v$ space was chosen. The detailed settings for each experiment are listed in Table 5.1.

**Fig. 5.2**: Schematics of the flow phantom setup used for the in vitro measurements. A pump (A) was placed outside the scanner room, connected to a magnetic valve (B), which in turn was connected to a square waveform generator. Non-compliant tubing into the scanner room ensured preservation of the pulsatile flow up to the flow chamber (C) wherein the valves were placed. The fluid was then directed back to the reservoir (D). Also depicted is the waveform at the inlet of the flow chamber.
For the comparison of different acceleration factors one leaflet of the St. Jude Medical valve was fixated in the closed position in order to simulate a defective valve and generate a wider range of TKE. The accelerated scans employed a reduced set of \( k_v \) values to match typical in vivo scans. A fully sampled scan with 22 \( k_v \) points was combined using the Bayesian algorithm and taken as a reference. The number of acquired training profiles was 15 in \( k_y \) and 7 in \( k_z \)-direction, resulting in net acceleration factors of 3.6, 5.2, 7.0 and 9.8 for 4x, 6x, 8x and 12x undersampling, respectively.
**In vivo experiments**

Data were acquired in 5 healthy volunteers as well as in two patients with a stenotic aortic valve (valve area 0.9 cm², mean gradient 34 mmHg) and a Medtronic CoreValve in aortic position using the velocity-sensitized cine 3D gradient-echo sequence. Navigator-based gating and 8-fold acceleration using k-t PCA (13) was used, resulting in scan times of approx. 7-10 minutes (excluding navigator efficiency). In vivo only three kv values in each direction plus a reference scan were acquired to keep the scan time short. The lowest $v_{enc}$ was chosen higher than in the in vitro scans because turbulence quantification accuracy at higher levels of turbulence was prioritized (Table 5.1). A 6 channel cardiac coil array was used for signal reception, partial echo and partial Fourier encoding (factor 0.75) were applied. Written informed consent was obtained from all subjects according the institutional review and ethics boards.

**Data analysis**

Linear phase offset errors were corrected for by fitting the phase of stationary tissue to a linear function of the image pixel coordinates and subsequent subtraction of this plane. Phase errors introduced by concomitant magnetic fields (83) were also corrected in post processing.

For the estimation of the velocities and velocity standard deviations the Bayesian approach according to Eq. 5.3 was implemented in Matlab (The MathWorks Inc., Natick, MA, USA), and a voxel-wise search for the maximum probability was performed using the built-in Nelder-Mead simplex algorithm (84).
5.4 Results

The relative Root-Mean-Square Error of the velocities (RMSE\(_v\)) was computed by

\[
RMSE_v = \sqrt{\frac{1}{m} \sum_t \sum_x (|v_{measured}(x,t)| - |v_{true}(x,t)|)^2}
\]

where \(m\) denotes the number of voxels of interest (x) multiplied by the number of time points \(t\). All voxels within the lumen of the phantom were defined as volume of interest. The RMSE of TKE values was computed accordingly. Visualization of the results was performed using Matlab.

5.4 Results

Numerical simulations

Fig. 5.4a shows the performance of different algorithms over a wide range of velocities. At lower values the Bayesian approach proved to be more accurate, while at higher velocities the 4P PC approach showed slightly smaller errors. This coincides with the fact that in this numerical phantom most velocities above 60 cm/s occur in areas with turbulent flow. Voxels with high levels of turbulence contain little to no signal at higher \(k_v\) values, and therefore do not contribute to the velocity estimation of the Bayes approach. The root-mean-square error at various SNR regimes can be seen in Fig. 5.4c. The N-point Bayesian approach resulted in a relatively uniform error level for most TKE values (Fig. 5.4b), while the errors of the PC approach were significantly larger. The same finding was observed for different noise levels (Fig. 5.4d). Bayesian analysis requires a minimum SNR of 6 and 9 for maximum root-
mean-square error levels of 10% and 20% of mean velocity and TKE values, respectively. In contrast, conventional 4P PC-MRI requires a minimum SNR of 9 for velocity quantification with 10% error while an SNR of at least 30 is indicated if quantification of TKE with errors smaller than 20% is desired.

**Fig. 5.4:** Numerical simulations. The dynamic range of velocity (a) and TKE (b) measurements is described by the root-mean-square error. The performance of the algorithms over a wide range of noise levels is shown, and the minimum SNR for an error of 10% and 20% is indicated for velocities (c) and TKE (d), respectively. All results have been normalized for scan time.
5.4 Results

**In vitro**

The comparison of the in vitro data using different acceleration factors in Fig. 5.5 shows root-mean-square errors over the entire range of velocities and TKE values. The limited dynamic range of 4P PC-MRI measurements is especially pronounced in the assessment of turbulent kinetic energy (Fig. 5.4b). Also, the lower velocities exhibit significant error levels. Fig. 5.5c shows that the temporal low pass filtering effects of spatiotemporal acceleration methods can be kept to a minimum using k-t PCA.

The stroke volume determined by Bayesian analysis differed by 0.4% to 1.3% from the true value (4x k-t PCA with 10 k_v points and 6x k-t PCA with 13 k_v points, respectively), whereas 4P PC-MRI led to an underestimation of 8.4%.

The spatial distribution of turbulence and velocity patterns in the phantom is depicted in Fig. 5.6. The jet of the CoreValve extends further downstream than the two jets directed sideward of the St. Jude Medical valve. Peak velocities are also higher in the CoreValve (150 vs 120 cm/s). The isosurface view in Fig. 5.7 illustrates the shape of the jets. Highest TKE values can be found where the jet breaks down. Stroke volume was 85 ml in both valves.

![Fig. 5.5](image.png)

**Fig. 5.5:** In vitro measurement. Comparison of the relative root-mean-square error of a) velocities and b) TKE using PC and Bayesian analysis with different acceleration factors. The number of total k_v points is stated for each series and the relative scan time is given in brackets. The increase in TR with lower encoding velocities is accounted for, leading to a 34% increase in scan time between v enc 300 and 30 cm/s. The temporal profile of the velocities (c) in a voxel show that little to no smoothing due to k-t PCA acceleration occurs.
Fig. 5.6: Comparison of the St. Jude Medical valve (upper row) and a CoreValve (lower row) during systole. Velocity patterns (a) show jet formation in both valves. TKE maps (b) show highest level of TKE in the regions where the jets break down. The overall TKE level is lower in the SJ Medical valve. At the position of the valves (z=30 and z=45, respectively) signal loss occurs. Flow is shown in positive z-direction.

Fig. 5.7: TKE isosurfaces and streamlines of the St. Jude Medical valve (upper row) and the CoreValve (lower row). Significantly higher levels of TKE can be seen in the CoreValve (lower row). The isosurfaces colors correspond to TKE values as follows: red (50 J/m³), orange (100 J/m³) and yellow (150 J/m³) (both rows).
In vivo

Exemplary streamline visualization of the flow and isosurface rendering of TKE values in a volunteer and both patients are shown in Fig. 5.8. Pronounced helical flow is visible in the patient with the stenotic valve. The maximum TKE values found in the group of healthy volunteers were 149±12 J/m³. In patients maximum TKE values were significantly higher at 950 J/m³ and 540 J/m³ for the stenotic and the artificial valves, respectively. Peak flow velocities reached 3 m/s in the patient with the stenotic aortic valve, and 2.3 m/s in the patient with the CoreValve implanted. Stroke volumes in the patients and volunteers were 68 ml, 80 ml and 87±18 ml, respectively.

Fig. 5.8: Streamlines and TKE maps in a healthy volunteer (a), a patient with a CoreValve implanted two years prior measurement (b) and a patient with a stenotic aortic valve (c). Significant differences in flow patterns and levels of TKE can be observed. TKE values in healthy volunteer were below 250 J/m³ and hence not apparent given the color range used. Seeding points were placed on a plane upstream (volunteer, stenotic patient) or downstream the valve (patient with CoreValve).
5.5 Discussion

In this work a method to determine flow velocity and turbulence intensity based on multi-point PC-MRI encoding has been presented. Using Bayes' theorem, multiple measurements of velocity vector components are incorporated to derive information about velocity distributions including mean and standard deviation. The feasibility of the measurement and the validity of the underlying signal model has been investigated in previous work using conventional 4P PC-MRI (59, 85-87). Numerical simulations as well as comparison with Laser Doppler Anemometry revealed good agreement of the measured turbulent kinetic energy relative to data obtained with the reference methods (18, 87). The possibility of N-point sampling was briefly examined in previous work (79), but not followed up further. As the model of the effects of turbulence on the signal magnitude is based on an assumption about the characteristic time scales of turbulence (58), further validation is required. To this end, a comparison of MRI and Particle Tracking Velocimetry (PTV) (88, 89) in a heart phantom is warranted.

The distribution of velocities in the turbulent regime has been assessed both experimentally (90) and analytically (91). Resulting data suggest that the probability density function of the velocity fluctuations can be approximated by a Gaussian distribution. The model used in the present study assumes that velocity fluctuations about the mean velocity are caused by turbulence. This assumption holds if the spatial resolution is sufficient i.e. the width of the Gaussian distribution of velocities within a voxel equals the root mean square of the velocity fluctuations (eq. 5.8). While this statement is valid in in the lumen, it does not apply to voxels near the vessel wall, where high velocity gradients result in elevated TKE values.
In the present work, $N$-point sampling of $k_v$ space in combination with Bayes’ analysis has been demonstrated to result in lower errors of velocity and TKE quantification relative to previous methods, in particular at low SNR. Accordingly, spatiotemporal undersampling techniques could be employed to shorten the long scan times associated with $N$-point $k_v$ encoding.

Sampling of multiple $k_v$ points has been shown to be of importance to guarantee a relatively uniform error across a large dynamic range for both velocity and TKE. A minimum number of 3 $k_v$ values in each direction was found to be a reasonable lower limit when studying aortic flows. Higher numbers of $k_v$ values may, however, be used to improve the accuracy of velocity and TKE assessment, i.e. for shear stress measurements.

The $N$-point Bayes’ approach greatly simplifies user interaction, as the error of velocity and TKE quantification remains low and relatively constant over a wide dynamic range. To this end, a single protocol can be used to measure flows in different subjects and in different parts of the body without the need to adjust the $v_{enc}$ value on a scan-by-scan basis. In contrast, conventional 4P PC-MRI measurements require the $v_{enc}$ to match peak velocities to obtain optimum velocity sensitivity. At the same time such a setting may not guarantee optimal sensitivity of TKE assessment. While the $N$-point Bayes’ approach outperforms conventional 4P PC-MRI in general, it can become inferior if high velocities and high TKE levels are encountered in the same voxel. This is seen in Fig. 5.4a, where the Bayes’ velocity estimation outperforms PC-MRI up to velocities of 0.6 m/s, but then deteriorates. In this particular dataset all higher velocities are accompanied by turbulence at the same spatial position. Hence measurements with high $k_v$ values exhibit strong signal loss in these voxels and do not contribute to the final velocity estimation as much as they would do in laminar flow.
In a practical setting, however, such a condition may be limited to intermediate velocities since turbulence develops typically in regions of fluid deceleration and hence reduced velocities. This theory is supported by the in vitro results presented in Fig. 5.5a.

The relative gain of the $N$-point Bayes' approach was found to be greater for TKE than for velocity quantification. This finding agrees with the fact that the decrease in signal magnitude is dependent on $k_v^2$, whereas the phase has a linear dependency on $k_v$. The results also show that a high number of $k_v$ steps in combination with a higher acceleration factor is advisable. The Bayes' approach permits for a 25% reduction in scan time relative to 4P PC-MRI, which allows for acquisitions of e.g. the entire aortic arch with scan times of about 7 min.

The in vitro as well as the in vivo experiments have demonstrated differences in hemodynamics between normal, stenotic and mechanical valves. In the in vitro comparison of the two artificial valves studied, TKE values of the CoreValve during peak flow were found to be almost twice as high as the values measured in the St. Jude Medical valve. Turbulence typically occurs where jet flow breaks down. Given that the trileaflet CoreValve valve emits only one jet with small diameter, whereas the bileaflet mechanical valve forms two slower jets, the results seem plausible. This is also in agreement with results obtained in previous work (86). Given the shape of the phantom, the abrupt expansion of the vessel might favor the bi-leaflet design, leading to a more pronounced disparity between the results measured in the two valve designs. Therefore direct translation of in vitro findings to conditions in vivo is difficult. In vivo, the curvature of the aorta leads to a different transformation of kinetic energy and pressure. Consequently, accurate assessment of valve hemodynamics requires measurements in in-vivo subjects.
One of the limitations of the conducted in vivo study was the extensive processing time of the Bayes framework, which was about 8 hours per dataset on a conventional personal computer. However, it is possible to speed up post processing by parallelizing the computations or by changing the optimization algorithm. Also the limited number of patients in the in vivo study does not allow for statistically significant conclusions about the relationship of turbulence and valve performance prompting for studies in a larger population.

5.6 Conclusion

Bayesian analysis of multi-point PC-MRI provides an increase in accuracy and in dynamic range compared to previous methods for measurement of velocities and turbulent kinetic energy. For same error bounds of velocity and turbulence quantification the $N$-point Bayes’ approach allows for a 25% reduction in scan time relative to conventional 4-point PC-MRI measurements.

Preliminary in vivo data obtained in a patient with aortic stenosis and in a patient with an implanted CoreValve showed considerable differences in turbulent kinetic energy and flow patterns relative to values found in healthy subjects. Further studies with a higher number of subjects are warranted in order to assess the viability of the method as a diagnostic tool.
Chapter 6
A g-factor metric for k-t SENSE and k-t PCA based parallel imaging

6.1 Introduction

Parallel imaging methods enable faster image acquisition without compromising diagnostically relevant image information (10, 11, 92). Scan acceleration is achieved by acquiring only parts of k-space and subsequent image reconstruction infers the missing information by utilizing the spatially varying coil sensitivities of receiver arrays. Besides a reduction in signal-to-noise ratio (SNR) due to fewer data points acquired, there is an inherent spatially dependent noise amplification caused by non-orthogonality of the coil encoding functions.

In order to experimentally quantify the change in SNR imposed by parallel imaging, a large number of repetitions of the same measurement can be performed and pixel-by-pixel noise statistics derived. Besides requiring additional scan time, such an approach assumes geometrical and structural invariance of the object being imaged and is hence often practically infeasible. Alternatively, the reconstruction process is repeated with different realizations of input noise to create “pseudo multiple replica” (93) of the same measurement. If the noise level is determined in a separate scan, it can be incorporated in the reconstruction process to yield an image in SNR units (94).

For many reconstruction methods, it is possible to describe the resulting spatially varying distribution of noise levels analytically. In parallel imaging the geometry (“g-“) factor is frequently used to assess local noise amplification. The g-factor was initially derived for SENSE (10), and subsequently adapted for SMASH (95) and GRAPPA (96, 97). In order to assess ultimate SNR performance of parallel imaging, theoretical g-factor limits based on electrodynamic considerations have been studied (68, 98). Accordingly and depending on field strength, an exponential g-factor increase is observed once a critical reduction is exceeded limiting the applicability of parallel imaging at higher undersampling rates.

In time-resolved imaging, k-t sampling (99) allows to derive coil sensitivity information or reconstruction weights from sliding window reconstruction of the undersampled data without requiring separate coil calibration scans or auto-calibration lines (100). Subsequent image recovery involves frame-by-frame parallel image reconstruction. Examples are TSENSE (101), TGRAPPA (102) and KL-TSENSE/KL-TGRAPPA (103). Joint treatment of spatial and temporal encoding offers additional potential of accelerating imaging sequences beyond the limits inherent to frame-by-frame parallel imaging (100). The gain is based on the observation that most dynamic series of images are compressible or exhibit sparsity upon suitable spatiotemporal transforms. This property has successfully been exploited by a number of reconstruction algorithms such as variations of the UNFOLD technique (104-106), among others. With these methods, a priori assumptions about the signal distribution in the spatio-temporal frequency (x-f) domain are made. In order to relax the restriction, low spatial resolution data may be used to inform about the actual x-f signal distribution. Examples of approaches implementing measured x-f signal estimates for k-t image reconstruction are k-t BLAST and k-t SENSE (12). The ability to resolve aliasing due to k-t undersampling
depends on the signal transform used. While reconstruction of signal in the x-f space has been exploited widely, more efficient transforms allow for better reconstruction accuracy. The concept of partially separable functions (107, 108) has been introduced to describe the x-t signal by spatially dependent weights and time-dependent basis functions thereby compressing signals more efficiently. This idea has been followed up further with the k-t PCA method which exploits low-resolution data to unfold x-f signal in the spatio-principal component (x-pc) domain (13), and with an approach which joins partial separability with sparsity constraints (109).

Besides prior driven reconstruction methods, spatiotemporal redundancy present in the data may be used to improve auto-calibrated parallel image reconstruction as in k-t GRAPPA (110) or PEAK-GRAPPA (111) for which a g-factor metric has been described very recently (112).

The objective of the present work is to describe a g-factor formalism for k-t BLAST, k-t SENSE and k-t PCA as examples for linear k-t image reconstruction methods. Thereby an analytical way of determining SNR performance is made available to analyze local noise enhancement and temporal filtering effects. The framework is an alternative to experimental quantification of both SNR and depiction fidelity requiring fully sampled data, which may not be obtainable in all cases in practice due to timing constraints and compliance in-vivo. It also complements perturbation approaches (113) which employ multiple reconstructions with alterations to the input to derive a modulation transfer function (MTF). A g-factor formalism is further considered valuable for benchmarking developments aiming at reducing temporal filtering effects of k-t methods by adaptive regularization (114) or GRAPPA/SENSE reconstruction of the fully sampled low-resolution calibration data (115, 116).
Using pseudo-replica analysis of cardiac cine data the analytical g-factor description presented here is validated and example data are used to analyze the performance of k-t methods for various parameter settings.

### 6.2 Theory

In parallel image reconstruction, the image pixel values $p$ to recover are expressed as a linear transformation of the measured data $m$ using reconstruction matrix $F$:

$$ p = Fm $$

Eq. 6.1

The noise propagation is then described using noise matrices (10):

$$ X = F\tilde{\Psi}F^H $$

Eq. 6.2

where superscript $H$ refers to the conjugate transpose and $\tilde{\Psi}$ is the sample noise matrix, a diagonal matrix which is obtained by Kronecker multiplication of the receiver noise covariance matrix with the identity matrix. Hereby it is assumed that noise decorrelation (117) has been performed.

Parallel image reconstruction generally leads to a spatially dependent reduction in SNR, which can be expressed using the so called ‘geometry factor’, or ‘g-factor’ (10). This g-factor is defined for a pixel at position $x$ as

$$ g_x = \frac{SNR_x^{\text{full}}}{SNR_x^{\text{red}}} \sqrt{R} = \frac{\sqrt{X_x^{\text{red}}}}{\sqrt{X_x^{\text{full}}}} $$

Eq. 6.3

where $R$ is the undersampling factor. This g-factor is the square root of the ratio between the elements on the main diagonal of the noise matrix of the undersampled data $X^{\text{red}}$ and the diagonal elements of the noise matrix of the
fully sampled data $X^{\text{full}}$, attenuated by the spatially invariant SNR degradation due to the undersampling by factor $R$. Here and in the following $x$ does not necessarily correspond to a point along a single dimension but rather to any point in a multi-dimensional data space. In Eq. 6.3 equally scaled voxel functions are assumed. For a fully sampled scan, the noise matrix $X^{\text{full}}$ is computed using

$$X^{\text{full}} = \left( E^{\text{full}}_s \tilde{\Psi}^{-1} E^{\text{full}}_s \right)^{-1}$$

Eq. 6.4

where $E^{\text{full}}_s$ is the encoding matrix for the fully sampled case. For $k$-$t$ imaging eq. 6.4 remains valid; only the dimensions of the noise matrix change from $n_x n_y \times n_x n_y$ to $n_x n_y n_t \times n_x n_y n_t$ for the two-dimensional case where $n_t$ denotes time frames and $n_x$ and $n_y$ the number of data points in frequency and phase encoding direction, respectively.

**k-$t$ SENSE and k-$t$ PCA**

In $k$-$t$ BLAST/$k$-$t$ SENSE and $k$-$t$ PCA the undersampling pattern is shifted for each time frame (Fig. 6.1), resulting in spatial and temporal aliasing. Simultaneously, the center of $k$-space is fully sampled yielding a low-resolution set of so-called training data, which are used to obtain signal estimates at low spatial but full temporal resolution. The regularized least squares solution to resolve the aliasing at a pixel $P_{\text{alias}}$ yields the relative weights for the aliased pixels, $W^{\text{recon}}$:

$$W^{\text{recon}} = M^2 E^H \left( EM^2 E^H + \tilde{\Psi} \right)^{-1} P_{\text{alias}}$$

Eq. 6.5

where $M^2$ is a diagonal matrix capturing the signal variances obtained from the training data. Regularization strength depends on the sample noise matrix $\tilde{\Psi}$, with $\tilde{\Psi}_{\text{SENSE}} = \tilde{\Psi}$ for $k$-$t$ SENSE (12) and $\tilde{\Psi}_{\text{PCA}} = \tilde{\Psi} n_{pc} / n_f$ for $k$-$t$ PCA (13),
where \( n_f \) and \( n_{pc} \) are the number of temporal frequencies and principal components, respectively.

The solutions to the k-t BLAST/k-t SENSE and k-t PCA problem are mathematically equivalent and only differ in the choice of temporal basis functions (13). While k-t SENSE unfolds data in the x-f domain, k-t PCA operates in the x-pc domain (pc refers to the principle components obtained by applying a principle component analysis, PCA). In both methods it is assumed that the true data \( \mathbf{P} \) of an image in the x-f domain with \( n_t = n_f \) time frames are given by

\[
\mathbf{P} = \mathbf{W} \mathbf{B}
\]

where \( \mathbf{B} \) contains the spatially invariant temporal basis functions, and \( \mathbf{W} \) time-invariant spatial weights for all pixel locations. For k-t PCA \( \mathbf{W} \) and \( \mathbf{B} \) are

---

**Fig. 6.1:** k-t SENSE and k-t PCA acquisition and reconstruction. The diagonal matrix \( \mathbf{M}^2 \) is obtained from the low-resolution training data, which is then used to unfold the aliased data \( \mathbf{P}_{\text{alias}} \). Coil sensitivities are included in encoding matrix \( \mathbf{E} \); \( \Psi \) denotes the regularization parameter based on the sample noise matrix. For k-t PCA, \( \mathbf{E} \) also contains the spatially invariant basis functions \( \mathbf{B} \). All elements only related to k-t PCA are marked by dashed borders.
matrices of size \( n_x n_y \times n_{pc} \) and \( n_{pc} \times n_f \) respectively. \( \mathbf{B} \) contains the principal components (PCs) calculated from the acquired training data \( \mathbf{P}_{\text{train}} = \mathbf{W}_{\text{train}} \mathbf{B} \) in the x-f domain. For k-t SENSE \( \mathbf{B} \) is the identity matrix, and \( \mathbf{P} = \mathbf{W} \) (sized \( n_f \times n_f \) and \( n_x n_y \times n_f \) respectively).

The reconstruction matrix \( \mathbf{F} \) based on the weak condition (10) for both k-t SENSE and k-t PCA is (13)

\[
\mathbf{F} = \mathbf{M}^2 \mathbf{E}^H \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{SENSE/PCA}} \right)^{-1} \quad \text{Eq. 6.7}
\]

Combining Eqs. 6.2 and 6.7 results in the noise matrix for the undersampled data:

\[
\mathbf{X}_{\text{red}} = \mathbf{M}^2 \mathbf{E}^H \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{SENSE/PCA}} \right)^{-1} \tilde{\mathbf{\Psi}} \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{SENSE/PCA}} \right)^{-1} \mathbf{E} \mathbf{M}^2 \mathbf{E}^H \quad \text{Eq. 6.8}
\]

As the g-factor per definition does not account for the global SNR degradation by \( \sqrt{R} \), \( \mathbf{E}_{\text{full}} \) has to be scaled accordingly. Considering this and inserting Eq. 6.8 into Eq. 6.3 yields the g\(_{xf}\)-factor for k-t SENSE:

\[
g_{xf} = \sqrt{\mathbf{M}^2 \mathbf{E}^H \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{SENSE}} \right)^{-1} \tilde{\mathbf{\Psi}} \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{SENSE}} \right)^{-1} \mathbf{E} \mathbf{M}^2 \mathbf{E}^H} \frac{1}{R} \left[ \mathbf{E}_{\text{full}}^H \mathbf{\Psi}^{-1} \mathbf{E}_{\text{full}} \right]_{sf, sf} \quad \text{Eq. 6.9}
\]

From Eq. 6.9 it follows that both the training data and the coil sensitivities influence the g\(_{xf}\)-factor.

For k-t PCA, the reconstruction is performed in x-pc space, therefore a g\(_{xpc}\)-factor is obtained:

\[
g_{xpc} = \sqrt{\mathbf{M}^2 \mathbf{E}^H \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{PCA}} \right)^{-1} \tilde{\mathbf{\Psi}} \left( \mathbf{E} \mathbf{M}^2 \mathbf{E}^H + \tilde{\mathbf{\Psi}}_{\text{PCA}} \right)^{-1} \mathbf{E} \mathbf{M}^2 \mathbf{E}^H} \frac{1}{R} \left[ \mathbf{E}_{\text{full}}^H \mathbf{\Psi}^{-1} \mathbf{E}_{\text{full}} \right]_{xpc, xpc} \quad \text{Eq. 6.10}
\]
This $g_{\text{spec}}$-factor indicates the increase in the standard deviation of the noise for each principal component. Using the summation rule for standard deviations, 

$$\sigma_{A+B} = \sqrt{\sigma_A^2 + \sigma_B^2},$$

the g-factor can now be transformed into x-f space by multiplication with the basis functions:

$$g_{xf} = \sqrt{\sum_{i=1}^{n_{pc}} g_{x,i} 2 \left[ B \right]_{i,f}^2}$$ \hspace{1cm} \text{Eq. 6.11}

In contrast to k-t SENSE, the noise levels of k-t PCA reconstructions can vary between time frames, and therefore it is helpful to state the g-factor in the x-t domain. This $g_{xt}$-factor is obtained as

$$g_{xt} = \sqrt{\sum_{i=1}^{n_{pc}} \left| FT \left( g_{x,i} \left[ B \right]_{i,\bullet} \right) \right|^2}$$ \hspace{1cm} \text{Eq. 6.12}

where $FT \left( g_{x,i} \left[ B \right]_{i,\bullet} \right)$ is the Fourier transform of the $i$th basis function (the $i$th row of B) weighted by its $g_{\text{spec}}$-factor. The result of Eq. 6.12 is a vector with the g-factors for all time frames at a position $x$. This equation also holds true for k-t SENSE, where $[B]_{i,\bullet}$ is the $i$th row of the identity matrix.

In order to obtain the “traditional” $g_x$-factor (2) the root-mean-square average of the $g_{xt}$-factor over all temporal frequencies is applied:

$$g_x^{\text{avg}} = \sqrt{\frac{1}{n_f} \sum_{i=1}^{n_f} g_{x,i}^2}$$ \hspace{1cm} \text{Eq. 6.13}

Thereby noise amplitudes independent of temporal frequency are computed. In k-t SENSE the noise level does not change over time, therefore for all time steps $t \, g_{xt} = g_x^{\text{avg}}$.

If white noise with equal power at all frequencies is assumed as input, the $g_{xt}$-factor also corresponds per definition to the temporal transfer function (TTF):
\[ \text{TTF} = \left| \text{P}^{\text{recon}} \right| \circ \left| \text{P}^{\text{full}} \right|^{(-1)} \quad \text{Eq. 6.14} \]

where operator \( \circ \) denotes the Hadamard product and \( \left| \text{P}^{\text{full}} \right|^{(-1)} \) is the hadamard inverse of the signal magnitude in x-f space for the fully sampled case. The expression describes the ratio of the signal magnitude \( \left| \text{P}^{\text{recon}} \right| \) of the reconstructed data to the signal magnitude of the fully sampled data \( \left| \text{P}^{\text{full}} \right| \) as a function of temporal frequency \( f \) and spatial position \( x \). This concept is comparable to the Modulation Transfer Function known from other imaging systems (118), except for it being applied to measure temporal instead of spatial filtering of the reconstruction.

While \( g_{xf} \) for k-t SENSE reflects the signal attenuation for each frequency \( f \), the \( g \)-factor in \( x \)-pc space represents the reduction of the weight \( \left[ \text{W}^{\text{recon}} \right]_{x,pc} \) of the corresponding principal component in k-t PCA. An estimation of the magnitude of the true weight \( \left[ \text{W}^{\text{true}} \right]_{x,pc} \) for principal component \( pc \) at spatial location \( x \) can be obtained by dividing it by its \( g_{\text{pc}} \)-factor: \( \left[ \text{W}^{\text{true}} \right]_{x,pc} = \left[ \text{W}^{\text{recon}} \right]_{x,pc} g_{xpc}^{-1} \). Consequently, if the TTF is defined as in Eq. 6.14 and \( \left[ \text{P} \right]_x = \left[ \text{W} \right]_x \bullet \text{B} \), for k-t PCA the TTF for all frequencies at a spatial location \( x \) can be written as

\[ \left[ \text{TTF} \right]_x \bullet = \left[ \text{W}^{\text{recon}} \right]_x \bullet \text{B} \circ \left( \left[ \text{W}^{\text{recon}} \right]_x \circ \left[ g^{x_{\bullet}} \right]^{-1} \right) \text{B}^{-1} \quad \text{Eq. 6.15} \]

where \( g_{x_{\bullet}} \) is a vector containing the \( g_{xpc} \)-factors of all principle components.

This estimation of the temporal transfer function relies on an accurate estimation of the weights obtained by image reconstruction, and therefore not only requires the sensitivities and training data, but also the undersampled k-space signals.
6.3 Methods

A fully sampled 2D balanced SSFP scan in short-axis view orientation was obtained in a healthy subject on a 3T whole-body MR scanner (Philips Ingenia, Philips Healthcare, Best, The Netherlands) using a 28-channel coil array. During a single breath hold, 42 heart phases were acquired at a heart rate of 66 beats per minute, resulting in a temporal resolution of 21.6 ms. Spatial resolution was 2x2x8 mm\(^3\) (matrix size of 148x132). Sensitivities and noise variances of each coil were acquired in a separate scan. Informed consent and approval of the local ethics committee was obtained prior to the scan.

**Retrospective undersampling and Pseudo-replica analysis**

Undersampling factors of \( R = 3, 5 \) and 7 were simulated by removing lines in \( k_y \)-space and then performing k-t SENSE and k-t PCA reconstructions. The number of fully sampled training profiles was set to 13. Reconstructions were performed using Eq. 6.7, and the \( g_{xf} \)-factor was calculated according to Eqs. 6.9 and 6.11.

To validate the predicted noise behavior a pseudo-replica analysis was performed. The fully sampled data were first combined using a Roemer coil combination (119) to obtain a reference image. This reference was multiplied with the coil sensitivities, which were assumed to be noise-free. Thereby a fully sampled data set for 28 coils with zero noise correlation was obtained. The reconstructions were then repeated 256 times with different realizations of coil-wise uncorrelated Gaussian noise added. The noise level was set to simulate an SNR of 20 by setting the standard deviation to 5\% of the median signal magnitude of the foreground image. The sensitivities used in the reconstruction were obtained from the training data.
6.4 Results

In order to analyze SNR and depiction fidelity as a function of the number of coils, coil array compression was performed according to (120) to generate sets of virtual coils with different numbers of coil elements. Furthermore, the dependency on the number of training profiles was studied. For Fig. 6.2 and 6.3, a reduced set of 10 coils was used because of the required computation time of the full field-of-view pseudo-replica analysis.

As error metric, the temporal root-mean-square error (tRMSE) was computed in x-t space according to

$$tRMSE(x) = \sqrt{\frac{1}{n_t} \sum_{i=1}^{n_t} \left( \left| \left[ \mathbf{P}_{\text{recon}}^{x,t} \right]_{x,i} \right| - \left| \left[ \mathbf{P}_{\text{true}}^{x,t} \right]_{x,i} \right| \right)^2}$$

Eq. 6.16

with $\mathbf{P}_{\text{true}}$ being the data from the fully sampled scan without any additional noise added.

6.4 Results

In Figure 6.2 analytical $g_{xt}$-factor maps are compared with results from pseudo-replica analysis for 5x k-t SENSE and 5x k-t PCA. The error maps show overall agreement of $g_{xt}$-factor and statistical maps revealing similar spatial variations as a function of temporal frequency. For 256 repetitions, the error had zero mean ($<10^{-2}$), with standard deviations of 0.010 and 0.016 for k-t SENSE and k-t PCA, respectively. The root mean square errors were 0.010 and 0.016 for both reconstructions, indicating normally distributed errors with zero mean.
The $g_{sf}$ factors were found to be dependent on temporal frequency. At temporal DC $g_{sf}$-factors result in a distribution of values $\geq 1$ across the field-of-view, similar to conventional $g$-factor maps at low undersampling factors. The maximum $g_{sf}$ value was 1.04 for k-t SENSE, and 1.003 for k-t PCA. With increasing temporal frequency accentuated spatial dependency is observed, with lower $g_{sf}$ values in static regions. Dynamic regions typically exhibit decreasing $g_{sf}$ values at higher frequencies. At the highest temporal frequency ($f=22$ Hz), the maximum $g_{sf}$ values were 0.04 and 0.07 for k-t SENSE and k-t PCA, respectively.

![Fig. 6.2: Comparison of analytical and pseudo-replica (statistical) analysis of $g_{sf}$ and $g_{avg}$ maps for 5x k-t SENSE (upper row) and 5x k-t PCA (lower row). In regions with static tissue low $g_{sf}$ values at temporal frequencies above DC indicate attenuation of noise. While k-t SENSE results in lower $g_{avg}$ values in static regions compared to k-t PCA, k-t PCA yields lower $g_{avg}$ values in dynamic regions when compared to k-t SENSE. The error is in the range of the expected statistical uncertainty due to the finite number of repetitions (N = 256).](image-url)
6.4 Results

For \( k-t \) SENSE with 5-fold undersampling, \( g_{xt}^{avg} \) was found to be in the range between 0.16 and 0.49, which would indicate that the total noise exceeds the noise of a fully sampled scan by 10% in regions with high dynamics (0.49 \( \times \) \( \sqrt{R} = 1.1 \)). The \( g_{xt}^{avg} \) value of 0.16 in static regions corresponds well with the theoretical lower limit of \( 1/\sqrt{n_t} \), where \( n_t \) denotes the number of time frames. This implies an increase in SNR due to averaging of the reconstruction in the time domain. The peak \( g_{xt}^{avg} \) was higher in \( k-t \) SENSE compared to \( k-t \) PCA (0.49 to 0.34).

The temporal noise behavior is shown in Figure 6.3. The signal intensities plotted along the indicated profile illustrate noise reduction in static regions, and temporal blurring in the heart. The \( g_{xt} \) plot shows temporally invariant noise levels for \( k-t \) SENSE, whereas \( k-t \) PCA exhibits small fluctuations over time. For the pixel with the highest temporal dynamics, \( g_{xt} \) ranges between 0.26 and 0.49. Again, the results show good agreement with the pseudoreplica analysis, mean error ± standard deviation was -0.01±0.03 for both \( k-t \) SENSE and \( k-t \) PCA.

Figure 6.4 shows \( g_{xt}^{avg} \) and \( g_{xf} \) maps for \( R = 3, 5, 7 \) for \( k-t \) SENSE and \( k-t \) PCA, illustrating the noise behavior of the reconstruction. Peak \( g_{xt}^{avg} \) values for
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\[ R = 3, 5, 7 \] were 0.52, 0.49 and 0.39 for k-t SENSE and 0.49, 0.36 and 0.34 for k-t PCA, respectively. The decreasing noise levels indicate an increased amount of temporal filtering. The frequency dependence of \( g_{xf} \) is seen in the \( g_{xf} \) maps taken at the vertical profile indicated in the anatomical short-axis view.

In Figure 6.5 the fidelity of temporal depiction of k-t SENSE and k-t PCA is illustrated for \( R = 3, 5 \) and 7 along the same indicated profile. Temporal transfer functions calculated according to eqs. 6.14 and 6.15 are plotted, revealing a larger temporal bandwidth of k-t PCA relative to k-t SENSE.

\[ \text{Fig. 6.4: Comparison of } g_{xf} \text{ and } g_{xavg} \text{ maps along profile indicated for 3x, 5x and 7x undersampled data reconstructed with k-t SENSE and k-t PCA.} \]

\[ \text{Fig. 6.5: Signal intensity (SI) plots and temporal transfer function (TTF) maps along profile indicated for fully sampled data, 3x, 5x and 7x undersampled data reconstructed with k-t SENSE and k-t PCA. Temporal blurring is visible for higher undersampling factors, which corresponds to the reduced temporal bandwidth seen in the TTF maps on the right.} \]
6.4 Results

Fig. 6.6: Analysis of $g_{x,y}$ temporal transfer function (TTF) and signal intensity (SI) curves in a dynamic voxel as indicated (red arrow) for fully sampled data, 3x, 5x and 7x k-t SENSE and k-t PCA relative to pseudo-replica analysis (dashed curves). While the temporal bandwidth is reduced for increasing undersampling factors with k-t SENSE, k-t PCA is found to preserve temporal bandwidth better. This finding is also reflected by the reduced temporal blurring with k-t PCA relative to k-t SENSE as seen in the signal intensity curves.
Figure 6.6 compares analytical $g_{xf}$ values, temporal transfer functions and signal-intensity curves taken at a point with significant temporal dynamics. Analytically derived $g_{xf}$ values and temporal transfer functions for k-t SENSE compare well with results obtained with pseudo-replica analysis. The small discrepancies can be explained by the limited number of repetitions (N=256). It is observed that $g_{xf}$ values are increasingly attenuated with increasing undersampling factors for k-t SENSE, while this effect is less pronounced for k-t PCA. Signal intensity curves show a more accurate depiction of the peak at heart phase 20 for k-t PCA, indicating a higher temporal bandwidth than k-t SENSE. This is also seen in the plot for the temporal transfer function. In Figure 6.7 maps of the temporal root-mean-square error (tRMSE) relative to the fully sampled reference are shown for different undersampling factors for k-t SENSE and k-t PCA revealing residual artifacts primarily at the boundaries of tissue structures.

![Fig. 6.7](image)

**Fig. 6.7:** Maps of the temporal root-mean-square error for different undersampling factors for k-t SENSE and k-t PCA. Residual aliasing is primarily found at the boundaries of dynamic structures. Areas with low signal (lungs) are masked.
6.4 Results

The dependency of the $g_{\text{avg}}$ and tRMSE on the number of coils and training profiles is summarized in Figures 6.8 and 6.9. While k-t PCA results in consistently lower $g_{\text{avg}}$ values for all coil counts relative to k-t SENSE, tRMSE for k-t SENSE is similar to the one found for k-t PCA. In general it is observed that $g_{\text{avg}}$ and tRMSE change only little beyond 8 receive channels indicating the number of effective coil modes available with the coil array used. Increasing numbers of training profiles result in higher $g_{\text{avg}}$ values and lower tRMSE with most improvement seen up to 11-13 training profiles.

**Fig. 6.8:** Dependence of $g_{\text{avg}}$ and temporal root-mean-square error (tRMSE) on the number of coil elements for 5x k-t PCA and 5x k-t SENSE. Both $g_{\text{avg}}$ and tRMSE are found to change little beyond 8 coil elements.

**Fig. 6.9:** Dependence of $g_{\text{avg}}$ and temporal root-mean-square error (tRMSE) on the number of fully sampled training profiles used in 5x k-t PCA and 5x k-t SENSE. Most significant change in $g_{\text{avg}}$ and tRMSE is seen for up to 13 training profiles.
6.5 Discussion

In this work the $g$-factor formalism has been extended to prior driven k-t undersampling methods including k-t BLAST/k-t SENSE and k-t PCA. The $g_{\text{xf}}$ factor not only allows for a description of the spatial distribution of noise, but also permits the study of temporal depiction fidelity of the reconstruction process. The analytical description was validated using pseudo multiple replica analysis on cine cardiac short-axis data.

By taking the root-mean-square of $g_{\text{xf}}$-factor maps over all temporal frequencies, a time-average $g$-factor map ($g_{\text{avg}}$) can be obtained. For k-t SENSE, such maps are similar to conventional $g$-factor maps as in SENSE or GRAPPA. Accordingly back-to-back comparisons become feasible and the performance of k-t methods can directly be compared to frame-by-frame parallel imaging approaches. The time-varying noise in k-t PCA reconstructions may affect post-processing steps which require knowledge of noise statistics. To this end, the $g_{\text{xf}}$-factor provides an estimation of spatially and temporally dependent noise statistics. It is also conceivable to extend existing denoising methods which utilize information about spatially varying noise levels (121) to the time domain.

In contrast to frame-by-frame reconstruction, only moderate noise enhancement is found for k-t SENSE and k-t PCA with increasing undersampling factors as demonstrated by the $g_{\text{avg}}$ analysis. This is due to the reconstruction being regularized by the training data. At the same time, temporal depiction is increasingly compromised with increasing reduction factor as illustrated by the TTF analysis. An accentuated spatial dependency of the $g_{\text{xf}}$-factor at higher temporal frequencies is observed.

While the $g_{\text{xf}}$-factor directly describes signal attenuation as a function of temporal frequency for k-t SENSE, k-t PCA requires additional weighting in
principal-component space. Accordingly, the $g_{xt}$-factor in k-t PCA indicates attenuation of temporal basis function rather than temporal frequencies. This also leads to a temporal dependency of the noise levels in k-t PCA, which can be quantified using the $g_{xt}$-factor.

The close relationship between $g_{xt}$-factor and TTF for k-t SENSE is a consequence of the reconstruction process, which is a least-squares fit of the measured aliased data to a model defined by the training data and the coil sensitivities. As the sensitivities are time invariant, the attribution of signal (and noise) as a function of temporal frequencies closely follows the signal distribution of the training data. Therefore the signal will exhibit the same temporal filtering as the noise. For k-t PCA, this direct relationship does not hold true due to the transformation into principal components space. As attenuation primarily affects higher temporal frequencies for k-t SENSE, lower magnitude weights of k-t PCA will be decreased more prominently. The basis functions of the first few weights and therefore the main principal components of the temporal frequency profiles are attenuated less, resulting in reduced temporal filtering of k-t PCA relative to k-t SENSE. It is, however, noted that small noise-related temporal signal fluctuations, which are present in the original data, were not reconstructed using k-t PCA as the temporal basis functions did not capture these signals. This issue is considered a limitation of the present study as a noisy fully sampled reference was used for comparison. However, it also highlights the critical importance of the resolution of the training data. The determination of temporal basis functions based on the training data implies that any signal time course, which is not captured in the training data and cannot be represented by the determined basis functions, will not be accurately depicted. For typical cardiac imaging such as perfusion or cine imaging a number of 9-13 training profiles should be sufficient, however imaging of small vessels i.e. in the brain could require a higher
training data resolution in order to resolve those small structures. It has also previously been demonstrated that temporal fidelity is improved with increasing training data resolution (122). As demonstrated in Fig. 6.9, this also reduces noise attenuation, resulting in higher $g_{x,\text{avg}}$ values.

The framework presented here is readily applicable to single-coil reconstruction techniques including k-t BLAST as demonstrated by the analysis of $g_{x,\text{avg}}$ and tRMSE as a function of virtual coil elements. In general, the g-factor metric presented here can be adapted to any linear k-t reconstruction technique for which a reconstruction matrix $F$ is available. Further, together with the derived equivalent framework for time-resolved GRAPPA based methods (25), comparison with other approaches of time-resolved parallel imaging is possible. Along the lines of this study, there have also been recent efforts to predict noise propagation for region of interest measurements in frame-by-frame image reconstruction formulation (123). To this end, back-to-back comparison of frame-by-frame and k-t methods can readily be implemented.

6.6 Conclusions

The proposed $g_{xr}$-factor and temporal transfer formalism allows assessing noise performance and temporal depiction fidelity of k-t methods including k-t SENSE and k-t PCA. The $g_{xr}$-factor maps and temporal transfer function analysis require coil sensitivities and training data as input and are hence specific to each object being imaged. The framework enables quantitative comparison of different k-t methods relative to frame-by-frame parallel imaging reconstruction.
Chapter 7

On the accuracy of viscous and turbulent loss quantification in stenotic aortic flow using phase-contrast MRI

7.1 Introduction

The first in-vivo investigations of turbulence in the aortic arch were performed more than 40 years ago (38, 124). Using hot film anemometry, turbulence intensities at different locations in the aorta could be measured. Subsequently the concept of energy loss due to turbulence was developed (125). It was demonstrated that even under physiological conditions blood flow can become turbulent (38). Doppler echocardiography enabled the first non-invasive assessment of velocities across the aortic valve (50). Using the simplified Bernoulli and continuum equations, the pressure gradient (50) and the aortic valve area (126) could be estimated. In today’s clinical practice, Mean Pressure Gradient (MPG) during systole and the Aortic Valve Area (AVA) are the most common disease severity metrics and form the basis of treatment guidelines (127, 128). These parameters, however, do not account for the effect of pressure recovery and thus disease severity may be overestimated (19, 129). To address this issue, Garcia et al. (51) proposed to assess pressure loss based on a combination of velocities measured across the valve and the size of the aorta. The approach has been shown to result in a higher correlation with data from invasive pressure measurements when compared to MPG and AVA (52).
Early theoretical descriptions of the energy loss in the aorta were based on the velocity field being known in all points in the aorta (130). Further studies showed that the energy loss was not solely determined by the velocities and geometry of the valve, but was found to also depend on the geometry of the aortic arch (131).

Advances in Phase-Contrast (PC) MRI have facilitated the acquisition of time-resolved 3D velocity vector fields (4D Flow MRI), potentially enabling a more precise assessment of energy loss in the aorta when compared to 2D echocardiography. Two approaches have been pursued. First, the assessment of energy loss due to turbulent flow and, second, the estimation of viscous losses of the mean flow field.

Turbulent flow leads to attenuation of the signal in PC-MRI measurements (132, 133). This effect may be utilized to assess turbulence intensity (18) to determine the energy stored in turbulent flow, also referred to as Turbulent Kinetic Energy (TKE) (59). Likewise, quantification of velocity fluctuations allows estimating turbulent stresses exerted on blood cells and platelets (134). In-vivo data have been acquired using hot-film anemometry (135) and Doppler echocardiography (136) using 1D or 2D descriptions of turbulence. The 3D determination of TKE using PC-MRI was previously validated against Laser Doppler Anemometry (18) and Particle Tracking Velocimetry (PTV) (137). Besides assessing energy loss based on velocity fluctuations, viscous loss may serve as an indicator of stenosis severity. Viscous losses of mean kinetic energy may be derived using the spatial gradients of the mean velocity vector field obtained from 4D Flow MRI (138). In laminar flow
all dissipated energy is due to viscous losses. However, at high Reynolds numbers the turbulent losses exceed the viscous losses by several orders of magnitude. In aortic stenosis Reynolds numbers of up to 10000 occur and hence viscous losses present a non-negligible contribution to total energy loss.

Notwithstanding the approach, PC-MRI data typically provides spatial resolutions which are coarse relative to the characteristic length scales of turbulent flows. Accordingly, the present work aims at investigating the resolution limits of MR based measurements of viscous and turbulent losses using data obtained from high resolution Particle Tracking Velocimetry in a realistic aortic phantom of stenotic flow.

\section{7.2 Theory}

\textit{Disturbed laminar and turbulent flow}

An essential feature of turbulent flow is that “the fluid velocity field varies significantly and irregularly in both position and time” (23). Due to the random nature of turbulence an analytic description of the flow field is not possible. For a single observation point, the unstable eddies of different time and length scales manifest themselves as velocities fluctuating around a mean value. By performing a Reynold’s decomposition of the flow field $v$ into its mean and a fluctuating part $\overline{v}$ and $v'$, a statistical description of turbulence can be obtained (23). Here, $v'$ describes the standard deviation of the velocity fluctuations. In general it is noted that flow features such as helical flow or recirculation zones are not necessarily indicative of turbulent flow (139). If an obstruction or irregularity is present in a tube and the fluid velocity is small enough, so called ‘disturbed laminar flow’ can occur. In this case, the velocity at any given point does not vary over time for steady flow conditions and the
pressure gradient scales linearly with the flow rate \((139)\). If the flow rate is increased, however, flow can become unstable or ‘turbulent’. In consequence, the relationship between pressure gradient and flow rate becomes non-linear \((139)\). While in turbulent flow particles form unstable eddies and vortices these features should not be confused with vortices or recirculation zones seen in streamline plots \((23)\).

To estimate energy losses associated with turbulent flow the losses due to velocity gradients present in the mean flow (‘laminar viscous losses’) and the energy of velocity fluctuations (‘turbulent kinetic energy) can be determined. Here it has to be noted that the term ‘viscous losses’ is used because it has been established before \((138)\). Strictly speaking also the turbulent kinetic energy is converted to heat due to viscous friction \((23)\).

**Viscous Losses**

Losses due to viscous friction are caused by velocity gradients in the flow field and occur in laminar and turbulent flow. If the 3D mean velocity vector field \(\bar{V}\) is known, the laminar viscous dissipation \(\Phi_v\) can be computed \((138)\):

\[
\phi_v = \frac{1}{2} \sum_{i=1}^{3} \sum_{j=1}^{3} \left[ \left( \frac{\partial \bar{V}_i}{\partial x_j} + \frac{\partial \bar{V}_j}{\partial x_i} \right) - \frac{2}{3} \left( \nabla \cdot \bar{V} \right) \delta_{i,j} \right]^2
\]

Eq. 7.1

where \(x_i\) refers to the spatial position in principal direction \(i\) and \(\delta_{ij} = 1\) for \(i = j\) and \(\delta_{ij} = 0\) for \(i \neq j\). For Eq. 7.1 to be valid, the spatial resolution of the measurement has to be sufficient to resolve gradients of the mean flow velocity. Violation of this condition will lead to underestimation of viscous losses \(\Phi_v\). Furthermore, noise in the images affects the computation of spatial gradients. To mitigate this effect median filtering of the data has been proposed \((138)\).
Turbulent Losses

In turbulent flow, unstable eddies form and are converted into smaller eddies. Accordingly, energy is transferred down the different length scales until it is dissipated into heat at the Kolmogorov scales (23). Turbulence at the end of this ‘energy cascade’ can be considered locally isotropic and the velocity distribution can be assumed as Gaussian. The Kolmogorov length scale $l_k$ is determined by the kinematic viscosity $\eta$ and the dissipation rate $\varepsilon$ (23):

$$l_k = \left(\frac{\eta^3}{\varepsilon}\right)^{\frac{1}{4}} \quad \text{Eq. 7.2}$$

For production of turbulent kinetic energy, the characteristic length $l_0$ and velocity $v_0$ of the largest eddies are decisive, as they are driven by the kinetic energy of the mean flow (23).

More specifically, gradients of the mean velocities determine the production $P$ of TKE:

$$P \equiv -v_i' v_j' \frac{\partial \bar{v}_i}{\partial x_j} \quad \text{Eq. 7.3}$$

The ratio of the smallest and largest scales is given by the Reynolds number $\text{Re}$:

$$l_k / l_0 \sim \text{Re}^{\frac{-3}{4}} \quad \text{Eq. 7.4}$$

In addition to turbulent kinetic energy dissipation and production, inhomogeneous fluxes due to pressure, turbulent advection and viscous diffusion are relevant for the budget of turbulent kinetic energy. These quantities, however, only describe the local displacement of turbulent kinetic energy and do not influence the overall level of TKE in a volume (23). If one
assumes that the produced turbulent kinetic energy is transferred down the energy cascade until it is dissipated, it follows that it is not necessary to sample at the Kolmogorov scales. Instead, the information available in the larger eddies should be sufficient to estimate the energy dissipated into heat. However, assumptions such as Gaussian velocity distribution might be violated when sampling at scales larger than the Kolmogorov scales.

The turbulence intensity $TI$ is calculated by relating the fluctuating velocities $u'$ to the mean flow: $TI = v' / \bar{v}$. The variance of the velocity fluctuations corresponds to the kinetic energy stored in turbulent flow and multiplication with the fluid density $\rho$ yields the Reynolds normal stress (23). The sum of the normal stresses describes the turbulent kinetic energy:

$$TKE = \frac{\rho}{2} \sum_{i=1}^{3} v_i'^2$$  \hspace{1cm} \text{Eq. 7.5}$$

In PC-MRI, spin velocities deviating from the mean velocity within a voxel lead to dephasing and therefore signal loss. The amount of dephasing depends on the first gradient moment $M_i$ of the velocity encoding gradient. The signal can be described by integrating over the spin velocity distribution within a voxel (18):

$$S(k_v) = C \int_{-\infty}^{\infty} s(v) e^{-ik_vv} dv$$  \hspace{1cm} \text{Eq. 7.6}$$

where $k_v = \gamma M_i$, with $\gamma$ being the gyromagnetic ratio. $C$ is a scaling factor to account for differences in signal magnitude caused by relaxation and inflow effects. For small scales, a Gaussian distribution with mean $\bar{v}$ and standard
deviation $\sigma$ can be assumed for $s(v)$, and the signal model can be expressed as (18):

$$ S(k_v) = Ce^{-\frac{\sigma^2 k_v^2}{2}} $$

**Eq. 7.7**

It follows that $\sigma$ can be obtained from two measurements with different $k_v$ values. If a Gaussian distribution is assumed, $\sigma$ equals $v'$ and TKE is given as:

$$ TKE = \frac{\rho}{2} \sum_{i=1}^{3} \sigma_i^2 $$

**Eq. 7.8**

The assumption of a Gaussian velocity distribution, however, might not hold true for the scales resolvable by PC-MRI. In addition, spatial velocity gradients may affect the velocity distribution within a voxel. Accordingly, the *mis*estimation of $\sigma$ due to non-Gaussian velocity distributions and the *over*estimation of $\sigma$ caused by velocity gradients needs to be investigated.

### 7.3 Methods

**Particle Tracking Velocimetry**

PTV experiments were performed on a silicon replica of a human aortic arch (Elastrat, Geneva, Switzerland) which was connected to a pump (BG-GP 636, Einhell Germany AG, Germany) providing steady flow. Fluorescent rhodamine particles with a diameter of 200 $\mu$m were illuminated by a 25 W laser (BeamLok 2080, Spectra Physics, Santa Clara, CA, USA). Particle movement was captured at 7000 fps from four different angles using a high-speed camera (Photron SA5, Photron Inc., Tokyo, Japan), allowing for time-resolved determination of the particles’ path in 3D. A circular constriction with an area of 0.95 cm$^2$ was included to implement a 64% stenosis. A mixture of 37%
glycerin, 48% water and 15% NaCl was used to match the reflective index of silicon. The resulting dynamic and kinematic viscosity were \(5.82 \times 10^{-3} \text{ Pa} \cdot \text{s}\) and \(4.85 \times 10^{-6} \text{ m}^2/\text{s}\), respectively, and the fluid density 1200 kg/m\(^3\). The accuracy of mapping mean velocity in a voxel of 0.625 mm isotropic was determined to be on the order of \(10^{-4} \text{ m/s}\). Accordingly, the corresponding velocity-to-noise ratio was larger than \(10^3\). Fig. 6.1 shows a schematic of the setup and a more detailed description of the PTV imaging process can be found in (140).

**Simulations and Data processing**

Data processing was performed in Matlab (Mathworks Inc, Natick, MA). Different spatial resolutions were obtained by binning neighboring voxels. For example a set of \(4\times4\times4\) original data points resulted in a voxel size of 2.5 mm isotropic. Density correction was performed by random resampling.

For TKE calculations, a standard 4-point PC-MRI sequence using a flow-compensated and a velocity-sensitized measurement with an encoding velocity \((v_{enc})\) of 2 m/s was simulated. The \(v_{enc}\) value was chosen to optimally map TKE values of 730 J/m\(^3\) assuming isotropic turbulence (79). For mapping mean velocities the \(v_{enc}\) value was set to 4 m/s. To simulate PC-MRI in turbulent flow the signals for each of the \(N\) velocity-encoded measurements were summed, analogous to eq. 7.6:

\[
S_{\text{sim}}(k_v) = \sum_{i=1}^{N} e^{-ik_v v_i}
\]

Eq. 7.9

The viscous dissipation of the mean kinetic energy \(\Phi_v\) was computed using Eq. 7.1 (138). To obtain the viscous loss \(EL_{\text{visc}}\) in mW, \(\Phi_v\) was integrated over the investigation volume, multiplied with the voxel volume \(V\) and the dynamic viscosity \(\mu\) of the fluid:
7.3 Methods

\[ EL_{\text{visc}} = \mu \sum_{i=1}^{\text{num voxels}} \phi_{V_i} V_i \]  
Eq. 7.10

To investigate the effects of median filtering, a 3D median filter with a box size of 3×3×3 voxels was used (138).

Turbulent Kinetic Energy was determined according to Eq. 7.8, where the intra-voxel velocity standard deviation \( \sigma \) was calculated according to (18, 132):

\[ \sigma = \sqrt{2 \ln \left( \frac{|S_0|}{S(k_v)} \right)} \]  
Eq. 7.11

\( S_0 \) and \( S(k_v) \) refer to the flow compensated and flow sensitized measurement, respectively, and \( k_v = \pi / v_{\text{enc}} \).

The investigation domain was subdivided into three different flow regions (Fig. 7.2c) and classified as follows: a) “Jet Core” referring to the sub-volume defined by velocities higher than 80% of the maximum velocity, b) “Shear Layer” referring to the sub-volume with velocities lower than 80% of the maximum velocity and TKE values higher than 200 J/m\(^3\), and c) “Recirculation Zone” comprising of the remaining volume.

\[ \begin{array}{c}
\text{Pump} \\
\text{Reservoir} \\
\text{Flowmeter} \\
\text{Stenosis} \\
\text{Laser} \\
\text{Camera} \\
\text{Image Splitter} \\
\text{Mirrors} \\
\text{Investigation Domain} \\
\end{array} \]

**Fig. 7.1:** Schematic of the PTV setup. On the right, one view of the investigation domain is shown as seen by the camera. 100 time frames recorded at a rate of 7000 frames/sec were averaged to visualize the paths of the rhodamine particles.
Two error metrics were computed including the root-mean-square error (RMSE) in %,

\[
RMSE = \sqrt{\frac{\sum_{i=1}^{N_{\text{voxels}}} (TKE_{sim} - TKE_{ptv})^2}{\sum_{i=1}^{N_{\text{voxels}}} (TKE_{ptv})^2}}
\]

Eq. 7.12

and the cumulative error (CE) in %,

\[
CE_{TKE} = \frac{\sum_{i=1}^{N_{\text{voxels}}} (TKE_{sim} - TKE_{ptv})}{\sum_{i=1}^{N_{\text{voxels}}} TKE_{ptv}} \quad \text{and} \quad CE_{visc} = \frac{\sum_{i=1}^{N_{\text{voxels}}} (EL_{visc, sim} - EL_{visc, ptv})}{\sum_{i=1}^{N_{\text{voxels}}} EL_{visc, ptv}}
\]

Eq. 7.13

where \(TKE_{ptv}\) and \(TKE_{sim}\) are the true and the reconstructed TKE values, respectively. \(N_{\text{voxels}}\) denotes the number of voxels in the volume of interest.

**Fig. 7.2:** Mean velocities (a) and TKE maps (b) obtained from the PTV measurements at an isotropic voxel size of 0.625 mm. The velocity distributions for four exemplary voxels (I-IV) in different jet regions are shown (c) including a point of high TKE (I), high velocity in the core of the jet (II), a voxel of jet impingement at the wall (III) and a voxel in the recirculation zone (IV).
7.4 Results

In Figure 7.2 velocity and TKE maps obtained by PTV are shown along with velocity distributions in four different voxels. Maximum measured velocity was 3.7 m/s. TKE integrated over the investigation volume was 9.31 mJ, and turbulent production as determined by Eq. 7.3 was 115 mJ/s. The average number of velocity measurements per voxel was 890.

The viscous losses calculated for the “Jet Core”, “Shear Layer” and “Recirculation Zone” sub-volumes at voxel sizes of 0.625, 1.25, 1.875 and 2.5 mm are analyzed in Figure 7.3a. Integrated over the sub-volumes, viscous losses decreased from 23.2 mW to 7.09 mW at 0.625 and 2.5 mm resolution, respectively. The cumulative error relative to 0.625 mm resolution is shown in Fig. 7.3b. The SNR dependency of viscous loss measurements is reduced by median filtering as shown in Fig. 7.3c, however at the cost of accuracy.

Total TKE values increased from 9.26 mJ at a voxel size of 0.625 mm to 10.66 mJ at 2.5 mm. Cumulative errors were found to be highest in the “Shear Layer” and the “Recirculation Zone” (Fig. 7.4c). Averaged over sub-volumes, the non-Gaussian velocity distribution resulted in an underestimation of TKE values on the order of 2%. The deviation was most prominent in the “Jet Core” with values reaching 12% (Fig. 7.4d). The relative cumulative error due to
increased voxel size was highest in the recirculation zone at 15% (Fig. 7.4e). The absolute cumulative error in mJ is highest in the shear layer (0.9 mJ), as it is the major contributor of TKE (Fig. 7.4a). The effect of different noise levels is shown in Fig. 7.4f.

Two additional cases with differing valve geometry and flow rates were also analyzed and showed similar results, which can be found in Chapter 7.7 as supporting information.

**Fig. 7.4:** Total (a) and mean (b) Turbulent Kinetic Energy (TKE) in the different flow regions. The cumulative error (c) is decomposed into errors due to non-Gaussian velocity distribution (d) and apparent velocity gradients due to insufficient resolution (e). TKE shows smaller cumulative errors than viscous losses, however it is more sensitive to low SNR (f).
7.5 Discussion

In this study the resolution and SNR requirements for laminar viscous loss and Turbulent Kinetic Energy estimation using PC-MRI have been investigated based on high-resolution PTV data acquired in a realistic aortic phantom with stenotic flow.

The error of viscous losses was found to be very sensitive to voxel size with relative underestimation of viscous losses of up to 83% when increasing the voxel size from 0.625 to 2.5 mm. In addition, error levels depend on the flow region and are especially pronounced in the recirculation zones. Therefore, data obtained under different anatomical conditions may not be comparable even if acquired at the same resolution. Median filtering of the velocity vector field (138) was confirmed to reduce the bias introduced by varying noise levels. However, for low resolutions the error of filtering was found to be higher than the error caused by low SNR. In general, viscous losses are not indicative of turbulence as they are based on the mean flow field.

Errors in TKE were found to be less dependent on spatial resolution with up to 19% overestimation when increasing the voxel size from 0.625 to 2.5 mm. Overestimation is attributed to intra-voxel phase dispersion due to velocity gradients. Underestimation due to non-Gaussian intra-voxel velocity distributions was found to be bounded to 13%.

TKE estimation was found to be more sensitive to increasing noise when compared to calculation of viscous loss. In general SNR levels of 20 or higher are advisable for both methods. The use of TKE as a marker for turbulent loss assumes comparable turbulence decay rates across studies, a parameter not obtainable by PC-MRI. Therefore, a direct comparison of viscous and turbulent losses is also not feasible. However, the turbulent production of 115 mW in the
investigation domain indicates that turbulent losses exceed viscous losses by a factor of 4-5.

In relation to the present study, it is noted that not all aspects of viscous and turbulent losses as present in-vivo are assessable using PTV. Both the viscous loss and the TKE metric assume an incompressible Newtonian fluid; an assumption which is only approximately valid for aortic blood flow. TKE values simulated with the setup were lower compared to values measured in severe aortic stenosis (20). Based on the peak velocity measured, the stenosis degree would be classified as ‘moderate’. Accordingly, conditions found in ‘severe’ aortic stenosis could not be assessed. Furthermore, data obtained at the minimum PTV voxel size of 0.625 mm were assumed to serve as reference. To this end, data should be considered in a best-case scenario, i.e. viscous losses cannot decrease with a higher resolution except for the error due to noise in PTV. The latter error should be negligible given the high velocity-to-noise ratio of >1000 in the data. Finally, results obtained here have not been directly compared to measured PC-MRI data. This step is to be performed in a future setting in a way similar to previous studies (137).

7.6 Conclusions

Based on phantom data and simulated PC-MRI measurements it has been demonstrated that viscous losses of stenotic flows are significantly underestimated while turbulent kinetic energy values show smaller errors and reduced sensitivity to spatial resolution. Accordingly, turbulent kinetic energy is considered a preferred metric to assess energy loss associated with stenotic and turbulent flows at spatial resolution feasible with current in-vivo PC-MRI protocols.
7.7 Supplementary Information

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stenosis Geometry</strong></td>
<td>Circular 0.95 cm²</td>
<td>Tricuspid 0.75 cm²</td>
<td>Tricuspid 0.75 cm²</td>
</tr>
<tr>
<td><strong>Flow Rate</strong></td>
<td>271 ml/s</td>
<td>119 ml/s</td>
<td>35 ml/s</td>
</tr>
<tr>
<td><strong>Peak Velocity</strong></td>
<td>3.7 m/s</td>
<td>2.13 m/s</td>
<td>0.52 m/s</td>
</tr>
<tr>
<td><strong>Viscous Loss</strong></td>
<td>24.36 mW (at 0.625 mm res.)</td>
<td>11.55 mW (at 0.67 mm res.)</td>
<td>1.15 mW (at 0.67 mm res.)</td>
</tr>
<tr>
<td><strong>Peak TKE</strong></td>
<td>780 J/m³</td>
<td>515 J/m³</td>
<td>27 J/m³</td>
</tr>
<tr>
<td><strong>Total TKE</strong></td>
<td>9.31 mJ</td>
<td>2.74 mJ</td>
<td>0.11 mJ</td>
</tr>
</tbody>
</table>

**Supp. Table S7.1:** Comparison of different flow parameters for Case 1 (presented in the main document) and two cases with a valve geometry modeled after a 2D cine scan of a patient with a tricuspid valve. For Case 2 and 3, flow rates were lowered compared to Case 1 to obtain different ranges of velocities and TKE values.
Supp. Fig. S7.1: The level of underestimation of viscous losses is similar for all three cases. The effects of median filtering vary, however for all cases an underestimation of more than 70% at clinically feasible resolutions is present. The effects of non-Gaussian velocity distribution and increasing voxel size are comparable for Case 1 and Case 2. The analysis was not performed for Case 3 because of the absence of turbulence. The maximum achievable resolution for the TKE map of Case 2 was 1 mm isotropic due to a lower number of PTV data points. Here the values at 1 mm were taken as a reference, compared to 0.625 mm in Case 1. This causes an offset as seen in the figure on the right.
Chapter 8
Quantification of Turbulent Kinetic Energy using Phase-Contrast MRI for Evaluating Aortic Stenosis Severity

8.1 Introduction

Aortic stenosis (AS) is the most prevalent valvular heart disease in adults of advanced age and, if untreated, is associated with a high mortality when symptoms occur (141, 142). According to current guidelines, the diagnosis of severe AS is based on echocardiographic measures of mean pressure gradient (MPG) and aortic valve effective orifice area (AVA) (7, 8). Class I indications for valve replacement are severe, symptomatic AS or severe AS with reduced left ventricular ejection fraction (7, 8). However, gauging symptoms of AS is highly subjective and can be confounded by various other diseases e.g. coronary artery disease, pulmonary disease and/or orthopaedic disorders. In addition, correct quantification of AS severity by two-dimensional echocardiography is challenging and AS severity is misclassified in a non-negligible portion of the patient population (143, 144). This misclassification has in part been associated with the effect of pressure recovery of the flow field and its dependence on valve and aortic geometry which is not accounted for in

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standard echocardiographic metrics (54, 145, 146).

To compensate for pressure recovery, Garcia et al. (51) introduced the Energy Loss Index (ELI) which takes into account the diameter of the sinotubular junction for the echocardiographic assessment of AS severity. In-vitro and in-vivo, catheter based measurements of pressure gradients showed a better correlation with ELI than with MPG and additional prognostic information for aortic valve related morbidity and mortality has been indicated (52, 53). Differences in aortic flow patterns or valve geometry across patients are, however, not factored in when computing the ELI. Furthermore, a limited acoustic window or an eccentric jet can hamper a parallel alignment of the echo-beam with the flow jet which in turn compromises the accuracy of ELI as well as classical measures of AS severity.

Phase-Contrast Magnetic Resonance Imaging (PC-MRI) allows to acquire time-resolved velocity vector fields of blood flow within the entire aortic arch (4D Flow MRI) (14, 147). Besides the measurement of blood flow directions and velocities, 4D Flow MRI also enables direct investigation of the mechanisms responsible for energy dissipation (30, 148). In particular, the assessment of Turbulent Kinetic Energy (TKE) – the energy stored in turbulent flow – enables gauging energy losses due to AS (149) as TKE is largely dissipated into heat. TKE can be quantified operator independently and reproducibly by 4D Flow MRI, and it has been shown that TKE correlates with pressure loss as evidenced in a pilot study (20).

In the present study, we hypothesized that TKE derived from 4D Flow MRI data provides additional information for the assessment of AS severity beyond echocardiographic measures and thereby has the potential to enhance future classification and stratification of AS patients.
8.2 Methods

Study design

Between September 2012 and November 2014, 55 patients with aortic stenosis (67 ± 15 years, 20 female) and 10 healthy age-matched controls (69 ± 5 years; 5 female) were prospectively enrolled. Exclusion criteria were an ejection fraction <50% and the standard exclusion criteria for MRI.

The study was approved by institutional and local ethics committees. Written informed consent was obtained from all study subjects prior to examination. All subjects underwent a 4D Flow MRI examination in addition to a routine cardiac MRI protocol for the assessment of cardiac function and aortic geometry. Furthermore, patients had a routine echocardiography examination performed on average within 23 ± 33 days of the MRI study.

MRI data acquisition

To obtain 4D Flow MRI data for the calculation of TKE maps, a spoiled gradient echo sequence with 10 different velocity encodings (3 per spatial direction plus 1 reference encoding) was employed. This multipoint velocity encoding strategy (Multipoint 4D Flow MRI) was combined with Bayesian data processing (150, 151), addressing limitations of previous approaches (20). The Bayesian method allows capturing a wide range of velocities without velocity aliasing while simultaneously providing the data necessary for TKE calculation. For each direction, the velocity encoding values were set to 450, 150 and 50 cm/s for patients and 200, 67 and 40 cm/s for the controls. Prospective cardiac triggering and respiratory navigator-based gating allowed for acquisition during free-breathing with an isotropic spatial resolution of 2.5×2.5×2.5 mm³ and a heart rate dependent temporal resolution of 22 to 44 ms. The field-of-view (238-440×240-300×47.5-80 mm³) was adjusted for each subject to cover...
the aortic root and the aortic arch. The acquisition was accelerated using 8-fold k-t PCA (13) with a net acceleration factor of 7.1, resulting in a total scan time of 15 to 30 min depending on navigator efficiency.

**MRI data processing and TKE calculation**

Multipoint 4D Flow MRI data were reconstructed using a custom-made software implemented in Matlab (MathWorks, Natick, MA, USA). Data were corrected for concomitant gradient field effects and background phase errors. Subsequently, Bayesian processing was performed to simultaneously calculate mean velocities and intensities of velocity fluctuations per image voxel along each velocity encoding direction and for each time point in the cardiac cycle. Voxelwise TKE values were then computed according to (148):

\[
TKE = \frac{\rho}{2} \sum_{i=1}^{3} \sigma_{i}^{2} \left[ \frac{J}{m^3} \right]
\]

where \(\sigma_{i}^{2}\) is the variance of the velocity fluctuations for direction i, and \(\rho\) is the fluid density, assumed to be 1060 kg/m\(^3\).

**MRI data analysis**

Data analysis was performed by two blinded readers (CB, AG) with 5 and 6 years of experience in MR imaging. For the TKE analysis the thoracic aorta was segmented semi-automatically to include the ascending aorta, aortic arch and descending aorta up to the level of the right pulmonary artery. TKE was integrated over the investigation volume for each time frame. For analysis, values integrated over systole (Total TKE\(_{\text{sys}}\)) as well as peak systolic values (Peak TKE) are reported, with an assumed turnover time of 70 ms.
To normalize TKE with respect to the hemodynamic work of the heart per beat, Total TKE$_{sys}$ was related to the stroke volume (SV):

$$\text{Normalized TKE} _{sys} = \frac{\text{Total TKE} _{sys}}{SV} \left[ \frac{mJ}{ml} \right]$$  \hspace{1cm} \text{Eq. 8.2}

This value refers to the amount of dissipated TKE per ml SV and represents an indicator for the efficiency of the heart. To display the flow fields, pathline visualization was performed with GTFlow (GyroTools LLC, Zurich, Switzerland).

**Echocardiographic measurements**

To obtain the left ventricular outflow tract (LVOT) and transaortic flow velocity profiles, pulsed-wave (PW) Doppler signal for the LVOT and continuous-wave (CW) Doppler signal for transaortic flow were recorded. MPG was calculated using the modified Bernoulli equation as recommended in current guidelines (6). For determination of ELI, AVA was calculated by the continuity equation. In addition, the diameter of the ascending aorta at the level of the sinotubular junction was measured inner edge-to-inner edge and the cross-sectional area (AA) of the sinotubular junction was calculated. With this data the ELI, indexed to body surface area (BSA), was computed according to Garcia et al. (51):

$$\text{ELI} = \left( \frac{AVA \cdot AA}{AA - AVA} \right) \cdot \frac{1}{BSA} \left[ \frac{cm^2}{m^2} \right]$$  \hspace{1cm} \text{Eq. 8.3}

**Statistical analysis**

Continuous and categorical data are expressed as mean ± SD or as a percentage, respectively. Continuous data were evaluated with one-way
analysis of variance, and Holm-Bonferroni post hoc test. In order to analyze the
effect of bicuspidity and aortic dilatation as well as their interaction on energy
loss, a two-way analysis of variance was performed. Homogeneity of variance
was tested by a Levene's test and a logarithmic transform was applied when
appropriate. For comparison of categorical data a binomial test was used.
Values of $p<0.05$ were considered statistically significant, all statistical tests
were two-sided and performed in R (R v3.2.2, R Foundation for Statistical
Computing, Vienna, Austria).

**Table 8.1. Overview of the study population**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 - severe AS</th>
<th>Group 2 - mild/moderate AS</th>
<th>Controls</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>24</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>male</td>
<td>12 (44%)†</td>
<td>19 (79%)*</td>
<td>5 (50%)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>female</td>
<td>15 (56%)†</td>
<td>5 (21%)*</td>
<td>5 (50%)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>70 ± 12</td>
<td>64 ± 17</td>
<td>69 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87 ± 0.22</td>
<td>1.87 ± 0.20</td>
<td>1.91 ± 0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Indexed Left Ventricular Mass, g/m²</td>
<td>76 ± 23</td>
<td>68 ± 12</td>
<td>n/a</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>147 ± 20†</td>
<td>133 ± 21</td>
<td>134 ± 9</td>
<td>0.045</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>78 ± 9</td>
<td>78 ± 15</td>
<td>84 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter Ascending Aorta, cm</td>
<td>3.54 ± 0.46†</td>
<td>3.9 ± 0.51*</td>
<td>3.49 ± 0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>Diameter &gt;= 4 cm</td>
<td>4 (15%)†</td>
<td>11 (46%)</td>
<td>-</td>
<td>0.0008</td>
</tr>
<tr>
<td>Bicuspid Aortic Valve</td>
<td>5 (19%)</td>
<td>6 (25%)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Valve Insufficiency</td>
<td>2 (7%)</td>
<td>4 (17%)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection Fraction, %</td>
<td>63 ± 7</td>
<td>61 ± 5</td>
<td>n/a</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number of patients (%). *Significant difference vs. healthy
controls, †significant difference vs. Group 2. AS – Aortic Stenosis.
8.3 Results

Patient characteristics

Data acquisition and evaluation was successful in 51 out of the 55 enrolled patients (93%) and in all 10 controls. One scan had to be aborted due to patient discomfort/claustrophobia, two examinations could not be evaluated due to breathing artefacts or lack of compliance and one examination was excluded due to incomplete coverage of the aortic arch. 31 male (61%) and 20 female patients with a mean age of 67±15 years were finally included in the analysis. According to echocardiographic measures, 27 patients had a severe aortic stenosis (MPG ≥ 40 mmHg) and 24 patients had mild/moderate aortic stenosis (MPG < 40 mmHg). Dilatation of the ascending aorta (AAo), defined as AAo-diameter ≥ 4.0 cm as determined by echocardiography, was found in 15 patients and 11 patients exhibited bicuspid aortic valve geometry. In 48 out of the final 51 patients ELI could be determined, 3 datasets had to be excluded for technical reasons. Table 8.1 provides an overview of the baseline characteristics of patients and healthy controls.

Table 8.2. Results of the TKE-based parameters

<table>
<thead>
<tr>
<th></th>
<th>Group 1 - severe AS (MPG ≥ 40 mmHg)</th>
<th>Group 2 - mild/moderate AS (MPG &lt; 40 mmHg)</th>
<th>Group 3 - Healthy Controls</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak TKE, mJ</td>
<td>26.1 ± 9.9***</td>
<td>24.5 ± 10.5***</td>
<td>4.8 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total TKE&lt;sub&gt;sys&lt;/sub&gt;, mJ</td>
<td>95 ± 39***</td>
<td>83 ± 35***</td>
<td>20.6 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalized TKE&lt;sub&gt;sys&lt;/sub&gt;, mJ/ml</td>
<td>1.34 ± 0.53***†</td>
<td>1.10 ± 0.60***</td>
<td>0.32 ± 0.07</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean ± SD. *** indicates a significant difference vs. healthy controls (p < 0.001), † a significant difference vs. Group 2 (p < 0.05). AS – Aortic Stenosis, TKE – Turbulent Kinetic Energy.
Comparison of MRI-based TKE with echocardiographic measures

Peak TKE, Total TKE$_{sys}$ and Normalized TKE$_{sys}$ were evaluated in all study subjects. The reference values, measured in healthy controls were Peak TKE 4.8±1.0 mJ, Total TKE$_{sys}$ 20.6±4.1 mJ and Normalized TKE$_{sys}$ 0.32±0.07 mJ/ml.

All three parameters were found to be highly significantly elevated in patients with aortic stenosis (Peak TKE 25±10 mJ p<0.001; Total TKE$_{sys}$ 90±37 mJ p<0.001; Normalized TKE$_{sys}$ 1.23±0.57 mJ/ml p<0.001). However, between the patient groups with echocardiographic severe and mild/moderate aortic stenosis, no significant difference of Peak TKE and Total TKE$_{sys}$ was found and only Normalized TKE$_{sys}$ was significantly higher in patients with MPG ≥ 40 mmHg as compared to those below 40 mmHg (severe AS: Normalized TKE$_{sys}$ 1.34±0.53 mJ/ml vs mild/moderate AS: 1.1±0.6 mJ/ml; p=0.02). Table 8.2 lists the results of the TKE-based parameters of the different groups. The relations between MPG and Peak TKE as well as MPG and Normalized TKE$_{sys}$ are

![Fig. 8.1: Correlation of MPG versus Peak TKE (left) and Normalized TKE$_{sys}$ (right). A significant but weak correlation is found for the entire study population including both patients and controls, within the patient group MPG and TKE are not correlated. On the right, a possible stratification scheme is outlined: In the green and red sector MPG and Normalized TKE$_{sys}$ are in agreement and patients can be classified accordingly, in the yellow sectors, the discrepancy between energy loss and MPG implies that considering solely the MPG might result in a misleading classification. The limit for Normalized TKE$_{sys}$ was chosen as the average over the healthy controls plus 1.64 SD of the study population, representing the upper 95% quantile.](image)
illustrated in Figure 8.1a and b, respectively. A significant but weak correlation between TKE and MPG was found in the entire study population (Peak TKE vs MPG: $R^2 = 0.26$, $p<0.0001$; Normalized TKE$_{sys}$ vs MPG: $R^2 = 0.32$, $p<0.0001$). No significant correlation was found if the control group was not included in the analysis.

The ELI metric negatively correlated with MPG ($R^2 = 0.49$, $p<0.0001$), however, it did neither correlate with Peak TKE nor with Normalized TKE$_{sys}$ ($p=0.48$ and $p=0.96$, respectively).

To investigate potential causes for the weak correlation between MPG or ELI on the one hand and TKE on the other hand, the flow patterns and TKE distributions within the aortae were visualized. Figure 8.2 displays the flow patterns and TKE distributions of three selected patients. All patients had tricuspid valves, and the AAo of patient A was dilated (4.7 cm diameter). In Figure 8.2a and b data of patients with comparable MPG transitioning to severe AS are shown. Patient A had a MPG of 35 mmHg, Peak TKE of 53 mJ and a Normalized TKE$_{sys}$ of 3.3 mJ/ml, while patient B had a MPG of 40 mmHg, Peak TKE of 16 mJ and a Normalized TKE$_{sys}$ of 0.8 mJ/ml. It is noted that TKE occurs in a large portion of the aortic arch in patient A, while in patient B elevated TKE is limited to a small region distal to the aortic valve. Figure 8.2c depicts data of a patient with echocardiographic very severe AS (MPG 74 mmHg) but only moderately elevated TKE. Here again high TKE values are confined to the region of the flow jet. Of note, patient C was asymptomatic and reported excellent physical fitness. In patient C the post stenotic accelerated flow continues unhindered to the descending aorta, while in patient A the flow jet dissolves into pronounced flow disturbances in the ascending aorta.
Influence of valve and aortic geometry

The group of patients with dilated AAo showed significantly lower MPG values (p=0.03) compared with patients with normal ascending aortae. The echocardiographic determination of the ELI, which accounts for AVA and the aortic diameter at the sinotubular junction, exhibited no significant difference between patients with dilated and normal AAo (p=0.06). In contrast, 4D Flow
MRI documented increased energy loss in this patient cohort with significantly elevated Peak TKE, but non-significantly elevated Normalized TKE$_{sys}$ values (p=0.002 and p=0.19 for Peak TKE and Normalized TKE$_{sys}$, respectively) compared with the normal aorta group (see Figure 8.3).

Patients with bicuspid aortic valves had MPG (p=0.90) and ELI (p=0.06) values similar to those observed in patients with tricuspid aortic valves. However, Peak TKE and Normalized TKE$_{sys}$ were found to be significantly higher in patients with a bicuspid aortic valve (p=0.0002 and p = 0.003, respectively). No significant interaction of bicuspidity and aortic dilatation was seen for the TKE parameters. A graphical comparison between the groups can be found in Figure 8.4. An overview of all results is given in Table 8.3.

**Fig. 8.3:** Comparison of MPG (left), ELI (middle) and Peak TKE (right) in patients with normal and dilated ascending aorta (AAo). The green and red dots represent the data points attributed to subjects with tricuspid and bicuspid aortic valves, respectively. The MPG is significantly lower in the population with dilated AAo. If, however, the varying pressure recovery due to different AAo diameter is factored in by determining ELI, no significant difference can be observed. TKE values indicate a significantly higher energy loss in patients with dilated aorta.
Chapter 8 - Quantification of Turbulent Kinetic Energy using Phase-Contrast MRI for Evaluating Aortic Stenosis Severity

**Fig. 8.4:** MPG (left), ELI (middle) and Peak TKE (right) in patients with tricuspid and bicuspid aortic valves (BAV). Whereas no significant differences are found for MPG and ELI, Peak TKE values are significantly elevated in BAV patients. Highest Peak TKE values were found in patients with BAV and aortic dilatation.

**Table 8.3.** Results from the two-way ANOVA analysis for Valve and Aortic Geometries

<table>
<thead>
<tr>
<th></th>
<th>Dilated AAo</th>
<th>Bicuspid AV</th>
<th>Normal AAo/AV</th>
<th>Interaction, p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPG, mmHg</strong></td>
<td>33 ± 16*</td>
<td>41 ± 21</td>
<td>39 ± 15</td>
<td>0.066</td>
</tr>
<tr>
<td><strong>ELI, cm²/m²</strong></td>
<td>0.83 ± 0.35</td>
<td>0.71 ± 0.34</td>
<td>0.61 ± 0.27</td>
<td>0.553</td>
</tr>
<tr>
<td><strong>Peak TKE, mJ</strong></td>
<td>34 ± 12**</td>
<td>34 ± 11***</td>
<td>20.8 ± 5.5</td>
<td>0.353</td>
</tr>
<tr>
<td><strong>Total TKE&lt;sub&gt;sys&lt;/sub&gt;, mJ</strong></td>
<td>116 ± 41**</td>
<td>122 ± 41***</td>
<td>73 ± 23</td>
<td>0.116</td>
</tr>
<tr>
<td><strong>Normalized TKE&lt;sub&gt;sys&lt;/sub&gt;, ml/ml</strong></td>
<td>1.53 ± 0.8</td>
<td>1.62 ± 0.63**</td>
<td>1.03 ± 0.31</td>
<td>0.226</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Significance level vs. patients with a normal geometry: * p<0.05, ** p<0.01, *** p<0.001. AS – Aortic Stenosis, TKE – Turbulent Kinetic Energy.
8.4 Discussion

This work has evaluated Turbulent Kinetic Energy derived from Multipoint 4D Flow MRI as a measure to gauge energy loss in patients with aortic stenosis. The correlation of TKE metrics to echocardiography based measures of aortic stenosis severity was investigated. TKE was found to be significantly higher in patients with aortic stenosis when compared with healthy, age matched controls. However, only a weak correlation between TKE from MRI and MPG from echocardiography was detected. The similarity of Peak TKE and Normalized TKE\textsubscript{sys} between patients with severe and patients with mild/moderate AS implies that TKE accounts for other AS characteristics than MPG. Indeed, Peak TKE and Normalized TKE\textsubscript{sys} were found to be significantly influenced by aortic geometry and valvular morphology.

In the study population with dilated AAo TKE was significantly increased, while MPG was significantly lower. A theoretical approach to explain this observation is given by the Borda-Carnot equation (27) which is used in fluid dynamics to describe energy losses of a fluid due to sudden flow expansion as it occurs in aortic stenosis. The increased energy loss is related to a higher degree of turbulent flow mixing at the borders of the jet, thereby resulting in higher TKE levels. A simplistic approach to account for this effect when using echocardiographic measures is to compute the Energy Loss Index (ELI) as proposed by Garcia et al. (51). To account for the diameter of the AAo in the echocardiographic assessment, we computed the ELI for our study population. While MPG was lower in the group with dilated AAo, ELI showed no significant difference in predicted energy loss between patients with dilated and normal AAo.

Furthermore, we found that TKE is elevated in patients with bicuspid aortic valves. Using a theoretical approach to fluid dynamics, a previous study revealed that the degree of pressure recovery depends on the angle of the jet
relative to the axis of the vessel (152). As bicuspid valves often cause a more pronounced flow eccentricity and more deflected jet angles, higher energy losses can be expected when compared to flow downstream of tricuspid valves. Although patients with bicuspid valves often have a dilated aorta, no significant interaction of TKE values for valve and aortic geometry could be found in our study population.

The visualization of TKE in the aortic arch of individual patients confirms that energy losses do not only occur directly distal to the stenotic valve. Depending on the interaction of valvular anatomy, aortic geometry and the luminal flow characteristics, patient specific patterns of energy loss can be observed. These patterns range from diffuse TKE in the whole aortic arch over multiple TKE peaks localized at sites of high vorticity, e.g. the branching of the brachiocephalic artery, to flow with high velocities but low spatial gradients which continues efficiently through the whole aortic arch. These effects cannot be assessed by standard echocardiography which is limited to assessing aortic stenosis severity by measuring the jet velocity at the vena contracta (MPG). Likewise an extended evaluation by factoring in the aortic diameter at the sinotubular junction (ELI) will be limited.

Two thirds of the patient population were congruently classified with either low MPG and TKE or elevation of both parameters. The remaining third of the patients exhibited a discrepancy between the MPG, which is the recommended measure for the classification of AS severity according to current guidelines (7, 8), and the energy loss due to aortic stenosis. This implies that a significant portion of patients presenting with AS might benefit from including TKE in their risk stratification. Future research is warranted to evaluate the prognostic value of TKE and to clarify its role in the future management of patients with AS.
8.4 Discussion

Study limitations

Due to the limited spatial resolution of 4D Flow MRI data, velocity gradients at the vessel wall were excluded in the analysis, as they would result in erroneous TKE parameters due to partial volume effects. To this end, care was taken during the semi-automatic vessel segmentation steps not to include the vessel wall. However, inclusion of partial volume voxels in the analysis cannot be entirely ruled out. In patients with eccentric jets high TKE values are also found close to the wall, which in turn are excluded from the analysis. Their impact on the determined TKE parameters however should be negligible as they only constitute a minor fraction of the volume of interest.

In summary, Turbulent Kinetic Energy allows to quantify the influence of valve and aortic geometry on the hemodynamic burden of AS. Elevated Turbulent Kinetic Energy levels, non-invasively quantified by 4D Flow MRI, imply higher energy losses associated with bicuspid aortic valves and dilated aortic geometries that are not assessable by current echocardiographic measures, potentially demanding changes to risk stratification of these patients.
Chapter 9

Summary

Phase-Contrast MRI, in particular 4D Flow MRI, enables the non-invasive assessment of both physiological and pathological blood flow. Its applications span from simple quantification of velocities and stroke volume to advanced methods such as wall shear stress quantification and relative pressure difference mappings (153).

9.1 Discussion

In this thesis a framework for the comprehensive analysis of hemodynamic parameters in the aorta and larger vessels has been presented and its underlying assumptions validated. The technique was subsequently applied in a larger study population of patients with aortic stenosis as well as healthy, age matched controls.

The presented Bayesian framework for multipoint velocity encoding enabled the concurrent acquisition of velocities and TKE with a high dynamic range. The improvement in accuracy exceeds the theoretical SNR penalty introduced by undersampling required to keep the scan times comparable to conventional single-point PC-MRI scans.

The noise performance and temporal fidelity of k-t SENSE and k-t PCA is quantifiable using the $g_{x,t}$-metric introduced in Chapter 6. Pseudoreplica analysis confirmed the analytically determined values and it was shown that temporal fidelity is better preserved in k-t PCA. It was also found that noise
amplification is dependent on the temporal characteristics of the spatial location. For static tissue k-t methods actually allow for a g-factor smaller than 1. The formulation of the g_{rf}-factor for k-t GRAPPA (154) enables the quantitative comparison of the methods.

The analysis of the assumptions underlying the TKE signal model showed acceptable levels of errors for TKE measurement in clinically feasible scan settings. The non-Gaussian velocity distribution accounts for an underestimation of TKE on the order of 5%, and the overestimation due to velocity gradients strongly depends on the resolution. Viscous losses are prohibitively underestimated at spatial resolutions typically used for in-vivo scans.

The TKE framework was also applied in-vivo, where Turbulent Kinetic Energy in patients was significantly elevated compared to healthy volunteers. However, only a weak correlation between TKE and pressure gradients as determined by Doppler echocardiography was found. Bicuspid valves and dilated aortic geometries showed higher energy loss at comparable peak velocities, agreeing with theoretical considerations of fundamental fluid dynamics.

### 9.2 Outlook

This work presented a clinically feasible scan to comprehensively obtain the most relevant hemodynamic parameters in the aorta. However, with 20-30 min total scan time and a strong dependency on the subject’s breathing, additional acceleration would benefit patient comfort. At the moment only the data acquired during exhalation is utilized and the rest discarded, resulting in a respiratory navigator efficiency between 30-50%. Acquisition throughout the
breathing cycle with a subsequent registration of the images would therefore result in a 2- to 3-fold speedup. It would also make the technique more robust against changes in expiration level as some patients tend to exhale more deeply as the scan progresses. Non-linear iterative acceleration techniques could also allow for higher undersampling factors than the 8-fold speedup which is currently used in k-t PCA.

Additional scan time could also be employed to encode velocity not only along the three principal axes but also along the intersecting ones, thereby enabling the estimation of the full Reynolds stress tensor. This information would provide an assessment of the shear stresses red blood cells and platelets experience, and potentially give insights into the mechanism of the acquired von Willebrand syndrome in aortic stenosis (155). The full tensor would also allow to compute the relative pressure loss using the Navier-Stokes equation. Up to now this is only possible in laminar flow as the information pertaining to turbulent losses is not available. Even if the full Reynolds tensor is not available, TKE on its own could provide sufficient information to estimate pressure loss. To validate any model, the phantom setup described in Chapter 7, or its pulsatile version described in (32) is readily extendable to incorporate pressure measurements using catheterization.

For clinical routine post-processing should also be optimized. While image reconstruction time could be reduced to 30 min or less, the segmentation of the aorta is still performed semi-manually and takes 5-10 min per dataset. Here the time requirement is less of an issue than inter-observer variability. Following strict guidelines, it was possible to achieve intra- and inter-observer variability of less than 20%, however the exact delineation of the vessel wall still remains problematic. A fully automated segmentation would facilitate the determination of TKE levels but might prove difficult given the low contrast.
Conceivable approaches to address this issue include administration of blood pool contrast agents (i.e. ferumoxytol) or application of atlas-based segmentation (156).

A major limitation of the presented approach in regards to the assessment of aortic stenosis is the assumption that the energy loss (or additional workload of the heart) is the decisive factor for high mortality or onset of symptoms. As described in Chapter 2, the pathophysiology of aortic stenosis is centered around the myocardium. For any longitudinal study it would certainly be beneficial to include techniques which study the heart itself. Cardiovascular MR provides a number of such methods to describe the myocardium, for example abnormal cardiac motion obtained from 3D tagging data (157), fiber architecture from Diffusion Tensor Imaging (158) or also perfusion values (159) as coronary blood flow might not be sufficient in patients with symptomatic aortic stenosis.

The patient study conducted for this thesis also highlights the difficulties in comparing the diagnostic value of two methods if no clear indication of disease severity exists. For a comprehensive conclusion a longitudinal study following asymptomatic patients until onset of symptoms or death would be required. Up until now the only conclusion which can be drawn is that the diagnostic information obtained by TKE differs from Doppler Echocardiography.

This thesis focused on the most common forms of aortic stenosis. Of further interest is the assessment of particular variations of AS for which no clear indication regarding aortic valve replacement exist. One example is low-flow low-gradient AS where a limited ejection fraction due to diastolic dysfunction leads to low gradients as determined by echocardiography. On the other hand, in paradoxical low-flow severe AS the total volume of the left ventricular
chamber is limited, also leading to lower gradients. For both cases conventional metrics would provide erroneous classification.

The presented technique is not limited to aortic stenosis, it could furthermore provide insight into pulmonary valve stenosis, the hemodynamics resulting from mitral valve insufficiencies or pathological geometries of the larger vessels, i.e. aortic coarctation.
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List of Publications

Journal publications


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12. **Binter, C.**, Ramb, R., Jung, B., and Kozerke, S. *A g-factor metric for k-t SENSE and k-t PCA*. Proceedings of the 21st Annual Meeting of ISMRM, Salt Lake City, UT, USA.


List of Publications


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