ARTERIAL STIFFNESS
IN HIGH CARDIOVASCULAR RISK PATIENTS

Ph.D. Thesis Summary

by

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1. Introduction

Atherosclerotic cardiovascular (CV) disease (ASCVD) is the leading cause of morbidity and mortality worldwide. In the last few decades effective and safe risk factor evaluation methods and available treatment options have been developed to decrease CV risk, including population-based approaches and actions directed at high-risk individuals. In general, the higher the absolute CVD risk, the higher the absolute benefit of risk factor treatment, thus recognising patients with very high CV risk profile is the principal of prevention goals. Patients with clinically established ASCVD and most adults with type 2 diabetes mellitus (T2DM) are at very high risk of recurrent CVD events. Population-based CVD risk estimation is feasible for screening and identifying these patients, however, further personal CV risk assessment provides information for tailored prevention and intervention strategy on an individual level.

Our investigations focused on vascular biomarker assessments feasible for detecting arterial stiffness, defined as the reduced arterial elasticity in response to pressure changes indicating both functional and structural changes of the arterial wall. Pulse wave velocity (PWV) is considered the gold standard parameter of arterial stiffness. Besides PWV, arterial augmentation index (Aix) is commonly measured in clinical practise. Elevated stiffness has been associated with the development of several diseases, such as AS, hypertension (HT), chronic coronary syndrome (CCS), T2DM and kidney disease. Increased aortic stiffness has been shown to be a strong predictor of mortality in the general population, in diabetic and in post-infarcted patients. Elevated PWV was found to be an independent predictor of major adverse cardiovascular events (MACE) and it has suggested as a prognostic parameter for risk stratification in patients after ST-elevation MI (STEMI). Consequently, the evaluation of arterial stiffness has a crucial part of risk stratification of these very high CV risk patients for the assessment of prognosis and to maintain proper, individual secondary prevention treatment.

Despite the sufficient amount of available prognostic evidence, the use of arterial stiffness for future CVD risk prediction is not widespread in clinical practise, mainly because of technical measurement difficulties and substantial discrepancies in stiffness values measured by different methods. Applanation tonometry based carotis-femoral (cf)PWV is considered the gold standard technique for the non-invasive measurements, with a cut-off value of 10 m/s to evaluate CV risk. Nevertheless, an introduction into daily clinical practice has not been applied further due to the absence of a complex, standardized methodology and a lack of established reference values based on a large population.

Conforming these technical and methodological prospects, a significant increase in the number of stiffness assessing methods available for clinical use and research have been developed. Techniques that evaluate aortic PWV from waveform analysis (such as oscillometric devices), offer the potential for simplification of PWV assessment, permitting widespread, user-friendly application in clinical settings. However, regarding superficial assessment of pulse wave travel distance, overestimation in travel distance and thus in PWV calculation could occur. Moreover, due to altered technical basis of the applied stiffness

evaluating tools and the different range of the calculated absolute PWV values, the use of established, adjusted, method-specific cut-off values should be recommended for each techniques to improve individual risk stratification.

Cardiac magnetic resonance imaging (CMR) provides accurate non-invasive measurements of aortic length, and thus allowing correct calculation of PWV. Phase contrast imaging (PCI) technique permits precise assessment of the blood flow velocity with an excellent accuracy and reproducibility. The clinical relevance of CMR is crucial in post-infarcted patients, for the assessment of LV function, structure and infarct size. PCI with a slight adjustment to the routine protocol can be performed, allowing an additional CV risk stratification. Based on these, CMR derived PWV evaluation is a promising technique, however, the use of CMR for calculating PWV is not widespread, due to high financial, technical and personal requirements.

Recent guidelines on the management of ASCVD propose the use of prophylactic medicines for event prevention, combined with anti-ischemic drugs to alleviate symptoms. Several studies showed the beneficial effects of different pharmacologic agents on stiffness, such as antihypertensives, statins, antidiabetics, anti-inflammatory drugs, endothelin-A receptor antagonists, and vasopeptidase inhibitors. The effects of these medications on arterial stiffness are usually slight or modest, but most of the drugs have effect on both the dynamic and structural element of arterial stiffness. Although, it is questionable whether there is a need to treat impaired arterial stiffness parameters, and which medications are suitable for this indication, and whether we could trace the effect of these drugs on the changes of stiffness data in patients with documented ASCVD. Medications with metabolic modulator properties, such as trimetazidine also indicates improvement in endothelial function due to non-haemodinamical, anti-ischemic effects. Investigations of stiffness adjusting effects of trimetazidine and new therapeutic approaches to decrease arterial stiffness are highly desirable.

2. Objectives

The overall purpose of our research was to investigate the role of arterial stiffness parameters (PWV and Aix) in patients with high CV risk profile, regarding to methodological considerations, target values evaluation, major CV outcomes prediction and therapeutic approaches.

2.1. Comparison of two non-invasive techniques for PWV evaluation

We aimed to compare an invasively validated oscillometric based method (Arteriograph - AG) and a CMR based phase contrast imaging technique for calculating PWV in 75 consecutive patients in whom routine CMR examination was performed on a clinical indication.

2.2. Arterial stiffness parameters for major adverse CV events prediction in post-infarcted patients

We aimed to evaluate the cut-off PWV and Aix values for AG and CMR based methods for predicting major adverse cardiovascular events (MACE) and validating the prognostic value of high stiffness parameters in 49 patients suffered from previous ST-elevation myocardial infarction. Patients received a 6 years follow-up for MACE comprising all-cause death, non-fatal MI, ischemic stroke, hospitalization for heart failure (HF) and coronary revascularization.

2.3. Therapeutic effect of trimetazidine on arterial stiffness

We aimed to assess the effectiveness and safety of 6-month trimetazidine treatment in 737 patients with high CV risk due to CCS and T2DM. Furthermore, our purpose was to evaluate the effect of trimetazidine on arterial stiffness parameters (PWV and Aix) measured by AG in a subgroup of 122 patients with angina pectoris and T2DM.

3. Methods for arterial stiffness assessment

3.1. Oscillometric technique by Arteriograph

The invasively validated Arteriograph (AG) device (TensioMed, Budapest, Hungary) measures aortic PWV based on an oscillometric method analysing arterial pressure curves registered in the upper arm. The basic principal of this occlusion technique is based on pulse wave reflection concept. As the ejected direct pulse wave reflects from the bifurcation of the aorta, a second systolic peak is generated. The device measures the time interval between the direct and the reflected systolic wave (return time). A careful, direct tape measure was used for compute the distance between the jugulum and the symphysis. The distance travelled by the pulse wave divided by the difference in time in milliseconds between the beginning of the first and reflected waves defines the aortic PWV in m/s. The software also evaluates the augmentation index as the proportion of pressure augmentation caused by wave reflection to local pulse pressure.

All measurements were performed in a supine position after 5 minutes of rest. Two separate measurements were performed and for statistical analysis, the mean PWV and Aix values of the two measurements were used.

3.2. Phase contrast imaging CMR technique

CMR based PWV assessment was carried out in patients in whom routine CMR examination with the need of contrast agent administration was performed on a clinical indication: myocardial viability assessment after MI or suspected cardiomyopathy. CMR was

performed on a 1.5 T MRI scanner (Magnetom Avanto, Siemens, Erlangen, Germany). In the course of CMR imaging a three dimensional (3D) aortic angiography was carried out. Velocity encoded PCI was applied to measure the through-plane flow at two predefined locations in the ascending aorta and at the descending aorta proximal to the renal arteries. The aortic path lengths among these planes were determined along the centreline of the aorta. With the novel module of MASS analytical software (MASS, v2020 EXP, Leiden University Medical Center, Leiden, The Netherlands), which was developed for the request and cooperation of our research group, the flow curves from the planes were delineated simultaneously with a real time shift. For the time delay calculation, the time-to-max-upslope approach was applied. The PWV (expressed in m/s) was calculated automatically by dividing the aortic length by the calculated transit time.

LV volumes and function were calculated on short-axis cine images by using the semi-automated QMassMR method with a special algorithm for trabeculation detection - MassK mode technique (QMassMR, version 7.6, Medis Medical Imaging Systems, Leiden, the Netherlands). The typical ischemic (subendocardial or transmural) pattern of hyperenhancement was visually evaluated on LGE images. The volume of MI was quantified with a semiautomatic approach using the threshold of 5 standard deviations (SD) above the average of the normal myocardium. Infarct size as a percentage of LV myocardium was then determined. LV scar score (LVSS) and wall motion score index (WMSI) was also performed.

4. Comparison of oscillometric and CMR based methods for PWV calculation

4.1. Study population and methods

We investigated 75 consecutive patients (56 men and 19 women, average age mean ± SD: 55±11 years) in whom routine CMR examination was performed on a clinical indication: myocardial viability assessment after previous MI or suspected cardiomyopathy. 49 patients suffered previous STEMI and 26 patients had no CCS in the medical history. All patients had concomitant measurements of PWV by Arteriograph and PCI by CMR.

4.2. Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows (Version 27.0, IBM Corp, Armonk, NY, USA). The comparison between the methods was tested by the Spearman correlation coefficient, Mann-Whitney analysis and Bland-Altman analysis. Bland-Altman test was carried out using MedCalc Statistical Software (version 20.014, MedCalc Software bv, Ostend, Belgium). Stepwise multivariate linear regression analysis was carried out to compare how PWV measurements were related to physiological variables. P-values of less than 0.05 were considered statistically significant.

4.3. Results

75 patients were investigated for PWV assessment by CMR of whom 71 had analysable data from pulse wave analysis using the AG device. In comparison of the two methods, we found a significant, positive correlation between the PWV measures (Spearman's rho: 0.332, p: 0.005). However, absolute values of PWV were significantly higher for AG compared with CMR findings (mean ± SD: 10.35 m/s ± 1.77 m/s vs. 6.73 m/s ± 1.59 m/s; median(IQR): 10.4 m/s (9.2-11.9 m/s) vs. 6.44 m/s (5.64-7.5 m/s);$p < 0.001$). Bland Altman plot showed that in general the mean difference between the two measures was 3.6 m/s (upper and lower limit of agreement: -0.2 and 7.5 m/s). The coefficient of variation was 43.9 % **(Figure 1.)**.

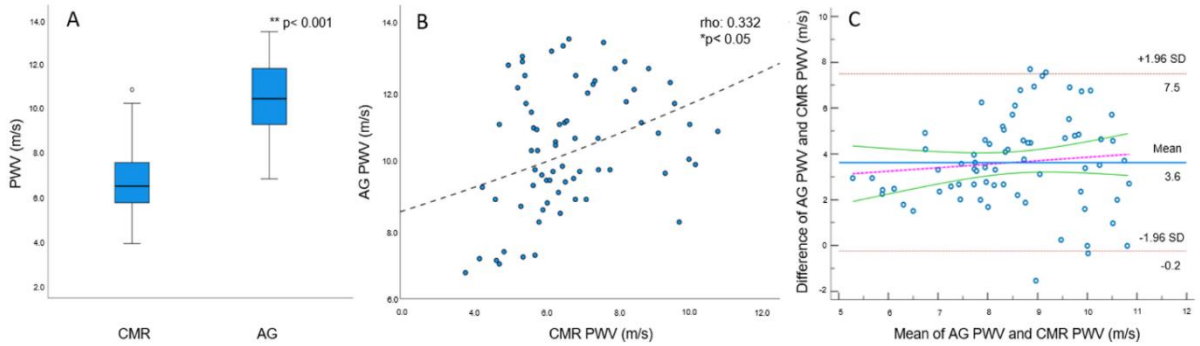

Figure 1.: Comparison of PWV values measured by AG and CMR; Mann-Whitney analysis shows the difference in absolute PWV values (A), and Spearman correlation represents a significant correlation between the measures (B), and the comparison of the two methods by Bland-Altman analysis (C).

We also investigated the correlations of AG and CMR derived PWV parameters with patients' characteristics and CMR-based volumetric and functional data. PWV data derived by both methods yielded a significant correlation with age and systolic BP ($p < 0.05$, respectively), however, we did not find any gender-related differences. Multivariate linear regression analysis revealed that age, BMI and heart rate had a predictive value for PWV derived by CMR ($p < 0.05$, respectively). In the case of using AG device, only age was significantly related to PWV measures as an independent factor ($p < 0.05$).

4.4. Discussion

Recently, novel instrumental solutions have been emerged allowing PWV assessment in clinical routine, such as CMR or oscillometric methods. In our study, these two validated, non-invasive PWV measuring technique were compared for in 75 patients. The results showed a suitable correlation and Bland-Altman analysis revealed an acceptable agreement between the two measures. However, the absolute PWV values were significantly lower measured by PCI CMR compared to AG.

Each methods use the "transit-time" method for PWV calculation, however, AG uses oscillometric arterial pressure waves, while the PCI CMR is based on flow curve

measurements. Moreover, the applied travel distance measurements are diverse, while AG used an estimated travel distance so called jugulum-symphysis distance, in CMR technique a precise aortic centreline distance calculation could be acquired. Several methodological considerations were published according to distance calculations (such as the 80 % method or the subtraction methods), since devices operating with direct body surface distance measurements overestimate real anatomic pathway. In our study, recalculating the PWV values using the CMR aortic length along with the AG transit time, a significantly reduced mean difference of PWV values was found (3.6 m/s versus 1.4 m/s, $p < 0.05$). Although, the recalculated AG PWV values were still higher comparing to CMR derived PWV data. Thus, several additional factors could influence the agreement between the two methods; such as measurement conditions, differences in the assessed vessel segments (altered regional elastic properties of aorta) or in the transit time calculation (wave-to-peak detection vs. the max-upslope method, simultaneous approach contrary to ECG gated CMR sequential records).

The technical easiness of oscillometric device offering the potential as an applicable tool for daily clinical practice. On the contrary, we assume that the high financial and technical requirements of CMR scanning prohibit the frequent use of it in the indication of PWV assessment. However, for patients undergoing CMR scanning for any clinical indications, the supplementary PWV evaluation for routine CMR examination could provide an additional information about the patient CV risk status.

According to previously mentioned findings, we emphasize that PWV values derived by different non-invasive methodologies show good agreements and similar trends, but due to the altered range of absolute values, the data are not interchangeable and the use of adjusted cut-off values and reference range assessment are recommended for each PWV measuring techniques to improve individual risk stratification.

5. Arterial stiffness parameters for MACE prediction in post-infarcted patients

5.1. Study population and methods

49 patients suffered previous STEMI were investigated. CMR with contrast agent administration was performed to evaluate the remained LV function, myocardial scar extension and myocardial viability. All patients underwent arterial stiffness evaluation by CMR and then by AG. To demonstrate advanced arterial stiffness in this high CV risk population, the PWV values of the post-infarcted patients were compared with a “control group” of 26 patients without CCS and no CMR evidence for any cardiomyopathy.

To validate the prognostic value of high stiffness parameters (PWV and Aix) in patients after STEMI, the post-infarcted patients (N: 49) received a 6 years follow-up using personal medical documentary to investigate major CV events, comprising all-cause death, non-fatal MI, ischemic stroke, hospitalization for HF and coronary revascularization. Furthermore, we

evaluated the cut-off PWV values for each applied methods and the optimized Aix threshold value of AG for predicting MACE-free survival.

5.2. Statistical analysis

Statistical analysis was performed using SPSS 27 statistical software package (SPSS Inc., Chicago, Illinois, USA). Mann-Whitney analysis or independent-samples t-test or Kruskal-Wallis test were applied for testing of statistically significant differences between the different groups. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off points of PWV and Aix values for the prediction of MACE. Outcome functions were expressed by Kaplan-Meier graphs, and groups were compared using the log-rank test. Univariate and multivariate Cox regression analysis was performed to identify outcome predictors. P-values of less than 0.05 were considered statistically significant.

5.3. Results

5.3.1. Arterial stiffness parameters in post-MI patients and in the control group

Altogether 75 patients were evaluated, of whom 49 patients suffered previous STEMI and 26 patients had no CCS in their medical history. The post-MI group and patients without CCS (control group) did not differ in average age, actual systolic and diastolic BP and heart rate. Comparing the CMR derived LV volumetric and functional data between post-MI and non-CCS control group, significantly lower ejection fraction (EF), stroke volume index (SVi) and cardiac output index (COi) were assessed in post-MI patients ($p < 0.05$, respectively).

We found significantly higher PWV values by both methods (AG and CMR) in the high CV risk, post-MI patients, (median(IQR) AG: 11.0 m/s (9.7-12.2 m/s) vs. 9.05 m/s (7.3-10.1 m/s), MRI: 6.85 m/s (5.9-8.1 m/s) vs. 5.79 m/s (4.9-6.5 m/s), $p < 0.001$, respectively) as data were compared to control (non-CCS) patients. Furthermore, in post-MI patients significantly higher Aix values were measured by AG compared to non-CCS control group (Aix median (IQR) AG: 40.6 % (29.1-48.1 %) vs. 26.4 % (18.4-45.3 %), $p < 0.05$).

Spearman correlation of arterial stiffness parameters with baseline patients' characteristics and volumetric and functional LV data revealed a significant correlation between AG-PWV and ESVi, SVi and EF in the all patient cohort, however, CMR-PWV did not show any correlations with LV volumetric and functional data. Moreover, PWV derived by both methods did not correlate with any LV function indicating parameter in neither the post-MI, nor the non-CCS groups. In case of Aix, a significant correlation with age and systolic BP was revealed in both the all patients cohort and the post-MI group, however, in the control patients the BMI was correlated with Aix. Furthermore, a significant correlation was found with heart rate in all the three groups. We also detected a strong significant correlation with COi in all patients cohort ($p < 0.001$), moreover, this correlation was also found in both post-MI and control patients groups with lower level of significances ($p < 0.05$, respectively).

Typical ischemic pattern of LGE (subendocardial to subepicardial extension or transmural scar) was found in 69 % (34/49) of post-MI patients. In patients with LGE significantly lower EF (p: 0.001) and significantly higher indexed end-systolic, end-diastolic volumes (ESVi, EDVi) ($p < 0.001$, respectively) and LV mass index ($p < 0.05$) were evaluated compared to post-MI patients without LGE. Neither the PWV values assessed by each methods, nor the Aix values show significant differences regarding the presence of LGE in the post-MI group (CMR PWV p: 0.305, AG PWV p: 0.576, AG Aix p: 0.601). However, if we compared patients with LGE to the controls (non-CCS patients), then significantly higher PWV values were detected by both methods in the attendance of MI (AG $p < 0.001$, CMR $p < 0.05$). Although, Aix values did not differ in post-MI patients showing LGE compared to control patients (p: 0.291).

Calculating the infarct size as the percentage of LV myocardium with a threshold limit of 5 SD showed strong positive correlation with LVSS, WMSI (rho: 0.82; 0.63, both $p < 0.001$) and ESVi, EDVi (rho: 0.52; 0.35, $p < 0.001$ and $p < 0.05$, respectively) along with a strong negative correlation with EF (rho: -0.59, $p < 0.001$). However, any arterial stiffness parameters, neither the PWV values derived by either methods, nor the Aix values correlated with the infarct size**.** Although, the infarct size as the percentage of the myocardium did not correlate with the stiffness parameters, we assessed the possible association between the transmural extension of the scar and the PWV or Aix values. According to the 3-point scale of LVSS (no LGE, < 50 % of transmurality (TM) and ≥ 50 % of TM) no significant differences were found between AG and CMR derived arterial stiffness data and TM expansion using Kruskal-Wallis test (CMR PWV p: 0.224; AG PWV p: 0.297, AG Aix p: 0.158).

5.3.2. The role of PWV in MACE prediction in post-MI patients

To evaluate the prognostic values of PWV, post-MI patients received a long-term, 6 years follow-up for MACE. During the follow-up period totally 51 MACE events occurred at 31 post-MI patients. 14 patients had only 1, the other 17 patients suffered 2 or more major adverse events. **Table 1.** shows all the MACE during the follow-up period.

Patients suffered MACE were older (60.2 ± 6.9 vs. 52.7 ± 5.5 years, $p < 0.05$), and had higher calculated PWV values derived by both methods (CMR: 6.98 (6.5–8.6) vs. 6.20 (5.69–7.39) m/s, AG: 11.5 (9.95–12.63) vs. 10.1 (9.23–11.18) m/s, $p < 0.05$, respectively). Moreover, significantly higher ESVi (31.46 (19.73–42.22) vs. 20.75 (17.84–31.33) mL/m^2, $p < 0.05$) and lower EF (53.7 (46.7–63.9) vs. 66.3 (47.9–70.3) %, $p < 0.05$) was detected in patients underwent any MACE events. However, no statistically significant differences were found between patients with and without MACE for the following parameters: sex, BMI, mean diastolic BP and heart rate, history of T2DM and smoking, infarct size or other volumetric CMR parameters.

MACE events in post-infarcted patients	All post-MI patients (N: 49)	CMR PWV (N: 49)		AG PWV (N: 46)	
		< 6.47 m/s	≥ 6.47 m/s	< 9.625 m/s	≥ 9.625 m/s
Numer of patients with MACE, N (%)	31 (63)	7 (14)	24 (49)	6 (13)	22 (48)
Total number of MACE, N	51	10/51	41/51	8/48	40/48
All cause death, N (%)	8 (15)	0	8 (20)	1 (12.5)	7 (17.5)
Cardiovascular death, N (%)	3 (6)	0	3 (7)	0	3 (7.5)
Non-fatal myocardial infarction, N (%)	6 (12)	0	6 (15)	1 (12.5)	5 (12.5)
Hospitalisation for coronary revascularisation, N (%)	28 (55)	9 (90)	19 (46)	5 (62.5)	20 (50)
Hospitalisation for heart failure, N (%)	6 (12)	1 (10)	5 (12)	1 (12.5)	5 (12.5)
Ischemic stroke, N (%)	3 (6)	0	3 (7)	0	3 (7.5)

Table 1.: The incidence of major adverse cardiovascular events (MACE) in all post-infarcted patients cohort and after grouping patients by the PWV cut-off values derived by each methods, during the 6 years follow-up.

In the first place, for predicting the MACE-free survival in post-MI patients ROC analysis was performed and optimized PWV cut-off values were calculated for each methods (CMR: 6.47 m/s; area under the curve (AUC) of 0.697, 95 % confidence interval (CI) 0.57–0.82, sensitivity: 0,710, specificity: 0,300); AG: 9.625 m/s; AUC: 0.682, 95 % CI: 0.56–0.81, sensitivity: 0,871, specificity: 0,475) **(Figure 2.)**. The major CV events occurred significantly more often in post-MI patients with high PWV (CMR PWV ≥ 6.47 m/s 24 patients (49 %) vs. 7 patients (14 %); AG PWV ≥ 9.625 m/s 22 patients (48 %) vs. 6 patients (13 %); $p < 0.05$ respectively) during the 6 years follow-up period **(Table 1.)**.

Survival analysis using Kaplan-Meier curves was performed and MACE-free survival time counted till the first MACE occurred. We found a significantly shorter MACE-free survival time in patients with high PWV derived by both methods (mean survival time (95 % CI) CMR: 2.99 (2.16–3.83) vs 4.60 (3.90–5.39) years, AG: 3.22 (2.47–3.97) vs 5.05 (4.32–5.76) years, $p < 0.001$, respectively) **(Figure 2.)**.

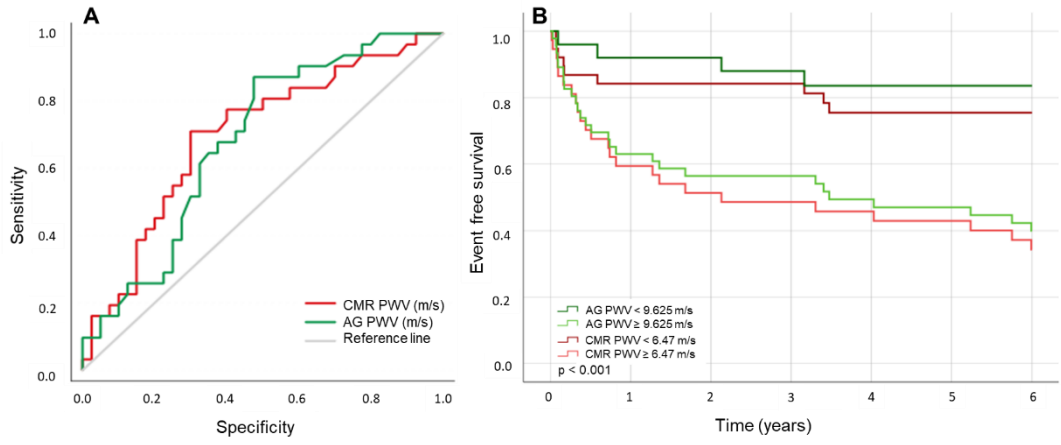

Figure 2.: ROC analysis (A) of PWV derived by AG and CMR for the prediction of MACE. PWV cut-off values are calculated: CMR: 6.47 m/s; AG: 9.625 m/s. Kaplan-Meier curves (B) for the occurrence of MACE stratified by PWV cut-off values.

Univariate Cox regression indicated age, history of HT, HF, LV volumetric and functional parameters (EDVi, ESVi, EF, LGE) and PWV absolute values derived by both methods as predictors of MACE. Multivariable Cox regression analysis including PWV by both methods together with age, sex, mean arterial blood pressure (MAP), BMI, smoking revealed age, CMR and AG PWV as an independent predictor of MACE (CMR PWV HR: 1.31 (1.07-1.66), AG PWV HR: 1.24 (1.01-1.53), $p < 0.05$, respectively).

5.3.3. The role of Aix in MACE prediction in post-MI patients

According to the pulse wave analysing potential of AG device, we also investigated the impact of Aix on CV outcome prediction. On the same post-MI patient cohort we evaluated the optimized Aix cut-off value by ROC analysis and afterwards survival analysis was performed. ROC analysis revealed an Aix cut-off value of 34,225 % (AUC: 0.673, 95 % CI: 0.55–0.80, sensitivity: 0.774, specificity: 0.375). Correspondingly to our findings with PWV values, we found a similar significantly lower MACE-free survival time in patients with high Aix using Kaplan-Meier analysis (mean survival time (95 % CI): 3.37 (2.57–4.17) vs 4.84 (4.06–5.62) years, p: 0.003).

Furthermore, univariate Cox regression showed a 1.031 HR of Aix (CI: 1.004-1.059, $p < 0.05$), and multivariable Cox regression analysis including Aix together with age, sex, MAP, BMI and smoking, revealed age and Aix as an independent predictor of MACE (age HR: 1.037 (0.09-1.09), Aix AG HR: 1.043 (1.01-1.08), $p < 0.05$, respectively).

5.4. Discussion

High aortic PWV is associated with haemodynamic changes and adverse effects on LV myocardium related to haemodynamic biomarkers in post-infarcted patients. The impact of the infarct size on cardiac remodelling and remaining LV dimensions and function has been broadly investigated. In our study, we also aimed to focus the pathophysiological impact of high aortic stiffness on the injured LV myocardium and infarct size.

Corresponding to several studies, we reported significantly higher arterial stiffness values in patients suffered MI. The association between arterial stiffness and CCS severity is controversial in the recent literature. Impaired vascular stiffness was linked to CCS severity in some reports, but other results showed that PWV, but not Aix is associated with CCS extent and severity. However, several other reports did not find any significant correlation between the individual coronary lesion SYNTAX score and regional arterial stiffness parameters (PWV and Aix) in patients with verified CCS. In the present research, PWV derived by both methods and Aix data did not correlate with the infarct size. Moreover, PWV values did not show any connection with any LV function indicating parameter in neither the post-MI nor the control groups. Feistritzer et al. similarly to our results, did not find significant correlation for PWV and LV EF, EDSVi, LVMassi and infarct size. However, in case of Aix, we found a significant correlation between Aix and COi in all groups. We could conclude that although impaired

arterial function and higher PWV and Aix values were measured in patients with CCS and/or with LGE, our results suggest that arterial stiffness parameters cannot provide any additional information about the expansiveness of the MI and vice versa.

Previous meta-analyses have provided evidence on the predictive value of PWV for CV events and all-cause mortality. However, defining the normal range and threshold values for PWV calculation is challenging. The cut-off value of 10 m/s for cfPWV, as a fixed threshold was recommended by an expert consensus focused mainly on healthy population. A recent systematic review and meta-analysis of non-invasive PWV reports demonstrated the importance of arterial stiffness as an indicator of CV risk even in high-risk populations with threshold values between 9.9 and 13 m/s for CV mortality, and from 9.9 to 11.8 m/s for all-cause mortality.

We assessed the optimized arterial stiffness cut-off values for each applied methods for predicting MACE-free survival and support the prognostic value of high PWV and elevated Aix in post-infarcted patients. During the 6-years follow-up period 51 MACE events were reported in post-MI patients. ROC analysis revealed a 6.47 m/s and a 9.625 m/s PWV cut-off values for predicting MACE by CMR and AG methods. Both the AUC values and the sensitivity, specificity of the calculated cut-off values indicate limitations in the test accuracy, although they may be reasonable, due to the high discrepancy of data. Feistritzer et al. reported a comparable, 7.3 m/s cut-off PWV value derived by PCI CMR with a similar AUC value of 0.68 (0.56-0.79) for predicting MACE in post-STEMI patients. However, according to their results the association between PWV and MACE was mostly driven by the occurrence of new congestive HF. In our study, the hospitalisation for coronary angiography and revascularisation exposed the majority of MACE events **(Table 1.)**. Our AG derived PWV results support the recommendations for high-risk populations, as the threshold value in the current study was a 9.625 m/s representing the elevated risk for post-MI patients. In the study of Accus et al. a PWV cut-off value of 10.15 m/s was calculated to predict MACE, which was in a reliable agreement with our results. Furthermore, high aortic stiffness parameters were associated with reduced MACE-free survival at 6 years of follow-up. PWV and also Aix was found to be an independent predictor of MACE even after adjustment for age, sex, MAP, BMI and active smoking.

According to recent prevention guidelines and our present results, we could underscore that both arterial stiffness parameters, but particularly PWV has a prognostic relevance in outcome prediction in post-infarcted patients. All these findings emphasize the clinical significance of the applied methods for aortic stiffness measurements, although, we recommend the use of method-dependent, adjusted cut-off values to improve individual risk stratification and to assist prognostic and therapeutic guidance.

6. Effect of trimetazidine on arterial stiffness parameters in high CV risk patients

6.1. Study population and methods

We assessed a total of 737 patients with angina pectoris and T2DM to evaluate the effectiveness and safety of 6-month trimetazidine treatment. This was a prospective, observational, non-interventional study (OGYI/51534-1/2014).

Eligibility criteria for inclusion were: age > 18 years; T2DM; stable angina pectoris. The investigator decided to initiate treatment with trimetazidine 35 mg tablets (Moduxin® MR, Gedeon Richter, Budapest, Hungary) twice daily in addition to optimal medical therapy (OMT) after patient counselling and consent. Patients with moderate renal impairment (creatinine clearance: 30–60 ml/min) received a reduced dose of trimetazidine 35 mg once daily. Study exclusion criteria were: contraindications included in the trimetazidine summary of product characteristics; symptomatic HF; unstable angina pectoris; Parkinson's disease, extrapyramidal symptoms; severe renal impairment (creatinine clearance < 30 ml/min).

All patients received a followed up of 6 months (three visits in total: baseline status, month 3 and month 6 visits). The clinical status of patients at visits two and three was compared with that observed at the baseline visit; the change in medical condition was assessed by the clinician using the clinician's global impression of change (CGIC; on a scale from 0 to 7). After the final visit, patients continued to receive their medical therapy in accordance with professional guidelines.

The study end points were the following: weekly frequency and severity (Canadian Cardiovascular Society Classification (CCSC) of angina complaints and the amount of short-acting nitrate products used, systolic LV function and estimated left atrial filling pressure, functional status on exercise tolerance test, time to onset of a 1 mm ST-depression, time to onset of angina, changes in arterial stiffness parameters (PWV and Aix) derived by AG device, changes in HbA1c values, CGIC and documentation of adverse events and other safety parameters.

Laboratory tests were performed, at visit one and at the 6 months visit including electrolytes, renal and hepatic function, cholesterol levels, c-reactive protein (CRP), uric acid, blood glucose and HbA1c. Echocardiography was carried out to determine global LV systolic function and estimated left atrial filling pressure (E/Ea). Results of arterial stiffness (PWV and Aix) were recorded with the oscillometric based AG as described above (Arteriograph, TensioMed, Budapest, Hungary). Exercise tolerance test was used to assess functional status (metabolic equivalents; METs) and time to onset of angina or a 1 mm ST-depression.

6.2. Statistical analysis

Collected data were processed in accordance with the European Union Good Clinical Practice/International Conference on Harmonisation (GCP/ICH) standards. Statistical analysis was carried out using SPSS 22 statistical software package (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± SD. Statistical analysis of all clinical and laboratory data was performed using correlation calculations and variance analysis, in case more than 2 time points. Changes between the baseline and final visits are described using 95 % CIs and tested by paired sample Student t-test. We considered a probability level of $p < 0.05$ as statistically significant.

6.3. Results

We investigated 737, high or very high CV risk (T2DM) patients. A total of 60 % of patients (442 patients) had a history of CV or cerebrovascular events (acute MI, percutaneous coronary intervention, coronary artery bypass graft, stroke, transient ischemic attack). In addition to stable angina pectoris, 88 % of patients had hyperlipidaemia, 76 % suffered from HT and 35 % of them had peripheral arterial disease (PAD).

During 6 months of treatment with trimetazidine, clinically minor, but statistically significant reductions in systolic (136.1 ± 19.2 vs. 130.2 ± 10.6 mmHg) and diastolic BP (86.4 ± 7.4 vs 78.1 ±7.9 mmHg), and pulse rate (74.6 ± 10.0 vs 71.8 ± 8.0 bpm) were demonstrated compared with baseline values ($p < 0.05$; respectively). However, excluding patients underwent adjustments of anti-ischemic treatment with mainly haemodynamic effect, no statistically significant change in haemodynamic parameters was observable (N: 663 patients, p: 0.20-0.41).

During trimetazidine treatment, the weekly frequency of angina symptoms showed significant reductions at visit two (month 3) compared with baseline, and there was a tendency toward further reductions during 6 months of treatment (2.9 ± 2.4 vs. 1.6 ±1.8 vs 1.1 ± 1.6, $p < 0.05$, respectively). The mean CCSC score (1.9 ± 0.8 vs. 1.4 ± 0.7 vs. 1.2 ± 0.8, $p < 0.05$, respectively) and short-acting nitrate consumption showed a clinically meaningful, significant improvement during the 6-month study period (1.8 ± 1.9 vs. 1.0 ±1.1 vs. 0.6 ± 1.2, $p < 0.05$, respectively).

On exercise tolerance teszt, the 6-month course of treatment with trimetazidine resulted in a clinically effective, significant improvement in functional status (6.1 ± 1.7 vs. 6.5 ± 1.7 METs, $p < 0.05$), time to onset of angina (5.8 ± 2.3 vs. 6.4 ± 2.1 minutes, $p < 0.05$) and time to onset a 1 mm ST-depression (5.5 ± 2.5 vs. 6.5 ± 2.6 minutes, $p < 0.05$). However, no significant change was observed in global LV systolic function (55.9 ± 10.8 vs. 57.0 ± 9.8 %, p: 0.22) and estimated left atrial filling pressure during the 6-month period therapy (9.0 ± 3.4 vs. 8.8 ± 3.0, p: 0.57).

Parameters of arterial stiffness (PWV and Aix) were also determined in a subgroup of 122 patients at the baseline visit and at 6 months. PWV values showed significant improvement

after the 6 months trimetazidine therapy (11.2 ± 2.1 vs. 10.4 ± 2.2 m/s, $p < 0.05$), whereas no significant change in Aix values were observable (41.9 ± 9.6 vs. 41.0 ±10.9 %, p: 0.28).

During 6 months of treatment with trimetazidine, a significant and clinically meaningful 31 % reduction in CRP, 11 % in blood glucose, 7 % in HbA1c levels, and a clinically minimal but statistically significant decrease in total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, uric acid, and creatinine ($p < 0.05$, respectively) were shown; however, no significant change was observed in the other assessed laboratory parameters. We measured the effect of trimetazidine treatment on the extent of CGIC and tolerability, which resulted in substantial (39.8 %), moderate (30.2 %) or mild (19.2 %) improvement in CGIC questionnaire scores; although, a small proportion of patients had no significant change in their status (8.5 %) and in a few cases minimal impairment (2.3 %) was observable.

During the 6 month therapy insignificant number of adverse effects were detectable. Out of 737 patients 1.1 % (8 patients) experienced treatment-related adverse events. Five cases of hospitalization were recorded of whom two cases of acute MI treated with percutaneous coronary intervention, two cases of elective coronary angiography and intervention, and one case of atrial fibrillation were revealed. No deaths were reported during the study period. Trimetazidine therapy was discontinued in a total of three cases due to side effects; hand tremor in two cases and gait disturbance in one case.

6.4. Discussion

In our clinical study we evaluated the effectiveness and safety of trimetazidine in patients with high and very high CV risk due to CCS and T2DM. The effectiveness of trimetazidine was assessed not only by discovering subjective data, but also via extended use of objective, noninvasive cardiology testing parameters.

According to our findings, adding trimetazidine as a symptomatic anti-ischemic therapy to the OMT, resulted in a decrease in clinical symptoms and in an improvement in QoL. In addition to assessing subjective parameters, we used exercise tolerance test to demonstrate both a significant development in the functional status and an extension of the time to onset of provoked ischemia. Our results support the findings of the VASCO-angina study, which gave evidence for the efficacy and tolerability of trimetazidine therapy in improving effort-induced myocardial ischemia and functional capacity in patients with stable angina receiving background medical therapy.

On echocardiography, no significant changes were observable in either the global systolic LV function or the estimated left atrial filling pressure during the 6-month course of treatment. Although, it is important to highlight that patients included in our study were in a stable general condition and the baseline echocardiographic parameters were also in the normal range. Symptoms or echocardiographic results indicating heart failure were in the exclusion criteria.

Until recently, scarce data have been available on the metabolic effects of trimetazidine in patients with concomitant T2DM and CCS. In patients with T2DM and CCS free fatty acid

inhibition with trimetazidine improves myocardial metabolism and myocardial ischemia due to shifting the energy production processes toward the energetically more effective glucose oxidation. Based on available published literature, our study was the first large-scale clinical trial to explore the long-term effects of trimetazidine treatment on serum glucose and HbA1c levels in patients with CCS and T2DM. We found significant, sustained improvement in blood glucose and HbA1c levels during the study period. Furthermore, ameliorating glycemic status may also have a beneficial effect on the occurrence of CV events. Recently published clinical trial (ATPCI) showed no long term beneficial effects on stable CCS patients, however, the trial design and the low endpoint data made the interpretation controversial. Furthermore, larger multicentre clinical studies are warranted to clarify the effect of trimetazidine on the reduction of mortality and MACE.

Arterial stiffness parameters (PWV and Aix) were investigated in a subgroup of 122 patients. Both parameters were increased at the baseline measurements showing ongoing vascular target organ damage in this high CV risk patient cohort. In the course of 6 months of trimetazidine treatment PWV showed significant improvement, however, Aix data remained unchanged during the observation period. The metabolic modulator properties of the medication stabilize intracellular phosphocreatine stores, decrease cellular acidosis and intracellular free calcium levels and protect against damage caused by free radicals, consequently all these pathophysiological mechanisms indicate an improvement in endothelial function. However, some clinical trials yielded inconsistent results in terms of beneficial effect of trimetazidine on endothelial function in chronic HF patients and in patients suffering from PAD. Our study is the first clinical trial to evaluate the long-term effects of trimetazidine on PWV and Aix. Although, PWV values improved during the observation period, the Aix data appeared to be unchanged regardless to trimetazidine medication. Corresponding to our findings, the clinical significance of Aix as a useful vascular stiffness marker in T2DM was not supported in a several studies. The lower value of Aix in case of T2DM patients could be explained by several pathophysiological actions, such as the increased sympathetic activity caused by hyperinsulinemia, or the direct Aix lowering effect of insulin.

During the 6-month course of treatment with trimetazidine we found some clinically and statistically significant changes in the laboratory parameters. The level of CRP is significantly decreased in the study period, however, we found the greatest CRP reduction in case of significantly elevated baseline CRP level in a subgroup of patients with coexisting T2DM and PAD. Moreover, the laboratory parameters known to be independent risk factors, such as uric acid, triglyceride and total cholesterol levels showed a clinically moderate but statistically significant reduction during trimetazidine treatment. However, these changes could be explained by several lifestyle changes involving an increase in physical activity owing to pain relief and an improved QoL. All these factors led to a moderate (3.5 %) reduction in body weight and secondary improvement in metabolic status.

Treatment tolerability was considered to be ‘excellent’ or ‘good’ in the majority of patients, QoL represented significant improvements, and minimal overall impairment was

only observed in 2.4 % of patients. Treatment-related adverse CV events were observed in 1.0 % of patients.

In summary, according to our results, anti-ischemic medical treatment with trimetazidine is an effective and safe therapeutic option in symptomatic CCS patients with diabetes. In our study, a 6 months of additional trimetazidine therapy to an optimal ischemic heart disease medical treatment, improved the glucose metabolism, significantly lowered the HbA1c and glucose levels and significantly reduced the PWV data, in patients with CCS and T2DM.

7. Discussion

We aimed to investigate the role of arterial stiffness parameters in patients with high CV risk profile due to CCS and/or T2DM. We assessed PWV with two validated, non-invasive techniques; the oscillometric based AG and the CMR PCI methods, and we also evaluated the Aix as an additional stiffness parameter gained from AG measurements.

The use of arterial stiffness parameters in CV risk estimation is recommended by several studies, however, measurement difficulties and substantial publication bias argue against widespread use of PWV evaluation in daily clinical routine. In the present study, we made a methodological comparison of PWV assessments by AG and CMR. According to the different technical approaches and the altered travel distance computation the absolute PWV data assessed by PCI CMR were significantly lower comparing to AG measures. In generally, we could state, that non-invasive devices applying direct body surface distance measurements overestimate real anatomic pathway. Several methodological considerations have been published according to travel distance calculations providing less estimation errors and similarly reliable PWV values. In our study, we found an acceptable correlation and agreement between the two PWV results. To decrease the inconsistency between the two measures, we also recalculated AG PWV using CMR-derived aortic length, which improved the agreement between the two methods.

According to our findings, we could conclude that although, the oscillometric method could overestimate PWV compared to CMR, it is easy to apply and cost effective advantage makes this technique feasible for everyday clinical routine. However, using CMR, an accurate PWV data could be derived and moreover, CMR also offers the potential for precise LV functional and volumetric determination and infarct size assessment. Hence, in the course of routine CMR examination, an additional arterial stiffness assessment could improve the individual risk stratification, even in high risk, post-infarcted patients. Furthermore, the technical aspect of flow waveform analysis has been improved by the novel, enhanced model of MASS analytical software, providing a user-friendly, commercially available platform for PWV analysis. We emphasize using either of these methods to assess PWV, however, the use of adjusted cut-off values are recommended for different techniques to improve individual risk stratification.

In the subsequent chapter of our research, we aimed to evaluate the cut-off values of arterial stiffness data (PWV and Aix) for AG and CMR based methods for predicting MACE and validating the prognostic value of high stiffness parameters in patients suffered from previous STEMI. Corresponding to several reports, we found significantly higher PWV and Aix values in post-MI patients compared to control group. In a previous study of our research group, we also assessed arterial stiffness parameters (PWV and Aix) derived by AG in two high CV risk categories: 186 patients with verified CCS and 152 patients with T2DM. PWV were similarly elevated in the both CCS and T2DM groups, while T2DM patients showed significantly reduced Aix values when compared to CCS patients. According to other studies, this incoherent result of Aix could be explained by hyperinsulinemia, which produces increased sympathetic activity and consequently, lowers the Aix. However, high aortic stiffness results in an early pulse-wave reflection, which leads to haemodynamic consequences, increased myocardial wall stress and impaired coronary perfusion. Furthermore, high aortic PWV is also linked to adverse effects on LV myocardium, thus directly associated with high plasma levels of biomarkers of myocardial wall stress. We did not find any correlation between the infarct size and aortic stiffness data; neither the PWV, nor the Aix values. PWV values did not show connection with any LV function indicating parameter in neither the post-MI nor the control groups. We could conclude that although, impaired arterial function and higher PWV and Aix values were found in patients suffered previous STEMI, our results suggest that arterial stiffness parameters cannot provide any additional information about the expansiveness of the MI and vice versa.

Previous meta-analyses have provided evidence on the predictive value of PWV for CV events and all-cause mortality. However, defining the threshold values for arterial stiffness parameters is challenging. Cut-off values and normal ranges may differ depending on the applied methods and on the nature and risk factors of the examined population. An expert consensus recommended a cut-off value of 10 m/s for cfPWV as a fixed threshold focused mainly on healthy population. While a recent study demonstrated the importance of arterial stiffness as an indicator of CV risk even in high-risk populations.

We evaluated the optimized PWV cut-off values for each applied methods for predicting MACE-free survival and support the prognostic value of high PWV in post-MI patients during a 6 years follow-up period. ROC analysis showed a 6.47 m/s and a 9.625 m/s PWV cut-off values for predicting MACE by CMR and AG methods. However, the additional statistical data (AUC, sensitivity, specificity) indicate moderate statistical power in the test accuracy. Correspondingly to our findings, Feistritzer et al. calculated a comparable, 7.3 m/s cut-off PWV value derived by PCI CMR with AUC value of 0.68 (0.56-0.79) for predicting MACE in post-STEMI patients. Our AG derived PWV results also support the recommendations for high-risk populations, as the cut-off point was found to be 9.625 m/s representing the increased risk for post-infarcted patients. Accus et al. revealed a PWV cut-off value of 10.15 m/s to predict MACE, which is in a good agreement with our AG PWV findings. Investigating the role of Aix in MACE prediction, we found analogous outcomes to our PWV results; as significantly lower event free survival was detected in patients showing high Aix values corresponding to ROC cut-off calculation. All these findings emphasize the prognostic relevance of high stiffness

(PWV, Aix) in patients with high CV risk. Nevertheless, the role of arterial stiffness, particularly PWV calculation in outcome prediction is not debateable, however, the application of method-dependent, adjusted cut-off values are needed to improve individual risk stratification.

In the latter section of our work, we assessed the effectiveness and safety of 6-month trimetazidine treatment in patients with high CV risk profile due to CCS and T2DM. In addition to the large number of patients, the strength of our study came from that the efficacy of the treatment was evaluated not only by assessing subjective parameters and non-invasive cardiology testing methods, but also via arterial stiffness measurements. According to our findings, adding trimetazidine as a symptomatic anti-ischemic therapy to OMT, proved to be effective in clinical symptoms and improvement in QoL. Our study was the first large-scale clinical trial in patients with CCS and T2DM to explore the long-term effects of trimetazidine treatment on laboratory test results regarding to glucose metabolism, such as serum glucose and HbA1c levels. We found significant, sustained improvement in serum glucose and HbA1c levels in our patient cohort. In the pathophysiologic background of these effects an improved myocardial metabolism and myocardial ischemia was found due to the shifted energy production processes. Furthermore, ameliorating glycemic status may also have a beneficial effect on the occurrence of CV events. Therefore, more studies, especially larger multicentre clinical studies, are warranted to clarify the effect of trimetazidine on the reduction of mortality and MACE. Nevertheless, we found some clinically and statistically significant changes in other, risk factor identified laboratory parameters, however, these changes are not completely assignable to the metabolic modulator features of trimetazidine, but to the improved lifestyle changes and consequential weight loss undertaken by the involved patients during the observational period.

Several pathophysiological mechanisms suggest beneficial effect of trimetazidine on the endothelial function, such as antioxidant and metabolic modulator effect. Our study is the first clinical trial to investigate the long-term effects of trimetazidine on PWV and Aix in a subgroup of 122 patients. We found elevated stiffness parameters even at the baseline measurements in this high CV risk cohort. However, during the 6-month therapy of trimetazidine, a significant improvement was determined in PWV data, although Aix values showed no modification during the treatment time. The PWV reduction effect of trimetazidine could be associated with the enhanced endothelial function and the adjusted glucose metabolism, although, the impact of lifestyle changes and the observed weight reduction is also noteworthy. Corresponding to our findings, the clinical significance of Aix in T2DM was also uncertain in a several studies.

In summary, we could conclude, that in diabetic patients with CCS the individualized, optimal antianginal trimetazidine based treatments not just relieved symptoms, but also improve the glucose profile and reduced the PWV value influencing CV risk

8. Conclusions

Effective and safe risk factor assessments and available treatment options have a prominent part in decreasing CV risk, especially in high-risk individuals. The present study confirmed the significant role of arterial stiffness measurements in patients with high CV risk profile, considering methodological aspects, target value evaluation, outcomes prediction and therapeutic approaches.

We found an acceptable agreement between oscillometric and CMR based methods in PWV calculation. Pulse wave analysis by AG is feasible for daily clinical use due to its easy to apply and cost effective nature, however, it could overestimate PWV compared to CMR based measurement. CMR could provide a precise technique for PWV assessment, but requires more technical and financial conditions. We suggest to use both applied methods for PWV assessments, however, due to the different range of absolute values, the use of adjusted cut-off values are suggested for different techniques to improve individual risk stratification.

We have revealed significantly impaired vascular function measured as increased PWV and Aix in patients with high CV risk profile. We have evaluated the optimized cut-off values of arterial stiffness for predicting MACE-free survival. The determined threshold values are found to be in good correlation with the literature data. Survival analyses have supported the prognostic value of high arterial stiffness even in post-MI patients, moreover both PWV and Aix are found to be an independent predictor of MACE.

We have also demonstrated the safety and predominantly beneficial effect of long-term trimetazidine therapy on glucose metabolism and on PWV reduction in patients with CCS and T2DM.

All these findings emphasize the clinical relevance of aortic stiffness evaluation to improve risk stratification even in high CV risk patients, which is crucial for further prognostic aspects and for therapeutic guidance.

9. Novel findings

1. We have confirmed an acceptable agreement between oscillometric based Arteriograph and CMR based phase-contrast imaging methods in PWV calculation.
2. We have participated in the invention of a novel module of MASS analytical software for the analysis of flow waveforms.
3. We have proven significantly different, method-dependent PWV values simultaneously measured by AG and CMR.
4. We have demonstrated the impaired vascular function as elevated PWV and Aix data in patients after STEMI.
5. We have proven a strong positive correlation of infarct size with LV volumes, LVSS, WMSI, along with a strong negative correlation with the global LV systolic function.
6. We have found no correlation between the infarct size or the transmural scar extension and any arterial stiffness parameter.
7. We have assessed the optimized cut-off values of Aix and PWV for both applied methods for predicting MACE-free survival in post-infarcted patients.
8. We have proven the prognostic value of high PWV and elevated Aix in MACE prediction in post-infarcted patients during a 6-years follow-up.
9. We have confirmed the efficacy and safety of 6-month trimetazidine treatment in large number of patients with CCS and T2DM, by assessing subjective parameters and objective, non-invasive cardiology testing methods.
10. We have explored the long-term effects of trimetazidine treatment on laboratory test results regarding to glucose metabolism in patients with symptomatic CCS and diabetes.
11. We have investigated the long-term impact of trimetazidine therapy on arterial stiffness parameters, and we have proven its beneficial effect on PWV reduction.

10. Publications of the author

Impact factor of original papers: **12.447**

10.1. Original research publications related to the thesis

1. **Meiszterics Zs**, Simor T, van der Geest RJ, Farkas N, Gaszner B: Evaluation of pulse wave velocity for predicting major adverse cardiovascular events in post-infarcted patients; comparison of oscillometric and MRI methods. REVIEWS IN CARDIOVASCULAR MEDICINE. 2021 Dec 22;22(4):1701-1710. **Q2, IF: 4.430**

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10.2. Citable abstracts related to the thesis

1. Gaszner B, Simor T, van der Geest RJ, Farkas N, **Meiszterics Zs**: Increased arterial stiffness predict major adverse cardiovascular events in post-infarcted patients. Do parameters and methods matter? EUROPEAN HEART JOURNAL 43: Suppl. 2 p. ehac544.2294 (2022)

2. **Meiszterics Zs**, Simor T, van der Geest RJ, Farkas N, Gaszner B: Evaluation of pulse wave velocity for predicting major adverse cardiovascular events in patients with chronic myocardial infarction. EUROPEAN HEART JOURNAL 42: Suppl.1 pp. 2533-2533., 1 p. (2021)

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10.3. Original research publications not related to the thesis

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10.4. Citable abstracts not related to the thesis

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