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Original article

Association of vascular function and estimated cardiovascular risk in patients with rheumatoid arthritis

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ABSTRACT

Objectives: Rheumatoid arthritis (RA) patients should receive cardiovascular (CV) risk assessment. For this purpose CV risk calculators are available. In addition, parameters of vascular function can be measured and used for risk prediction. Aim of the present study was to assess the association of these two concepts.

Methods: 287 RA patients (58.4 ± 12.6 years) and 232 controls (49.9 ± 13.4 years) were included in this cross-sectional study. We calculated 10 year CV risk with SCORE and QRISK2. For SCORE we used the recommended multiplier of 1.5 in eligible RA patients and estimated the risk also in patients younger than 40 years (mSCORE (0–65)). Augmentation index (AIx) and central pulse pressure (PP), markers of vascular integrity and CV risk, were assessed by pulse wave analysis (PWA). Primary endpoint was the correlation of AIx and the estimated CV risk using mSCORE (0–65).

Results: In RA patients AIx showed a statistically significant correlation with mSCORE (0–65) (rho = 0.3374; $p < 0.0001$) and QRISK2 (rho = 0.3307; $p < 0.0001$). The correlations of central PP with mSCORE (0–65) (rho = 0.4692; $p < 0.0001$) and QRISK2 (rho = 0.5828; $p < 0.0001$) were also statistically significant. Increasing quartiles of central PP were associated with an increased odds of being in the "high risk" category according to SCORE (OR 2.18; 95% CI 1.58–3.01) or QRISK2 (OR 2.18; 95% CI 1.75–2.72). In control patients we also found a correlation of AIx and central PP with SCORE (0–65) and QRISK2.

Conclusions: Parameters of central haemodynamics correlate with calculated CV risk. However, both do not give exactly the same information. The question arises whether a combination of both concepts would result in an improved CV risk prediction.

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Associação entre a função vascular e o risco cardiovascular estimado em pacientes com artrite reumatoide

Palavras-chave:
Artrite reumatoide
Análise de onda de pulso
Risco cardiovascular
SCORE
QRISK2

RESUMO

Objetivos: Os pacientes com artrite reumatoide (AR) devem receber uma avaliação do risco cardiovascular (CV). Para este fim, existem as calculadoras de risco CV. Além disso, parâmetros da função vascular podem ser medidos e utilizados para predição do risco. O objetivo deste estudo foi avaliar a associação entre estes dois conceitos.

Métodos: Foram incluídos neste estudo transversal 287 pacientes com AR (58,4 ± 12,6 anos) e 232 controles (49,9 +/- 13,4 anos). Calculou-se o risco CV em 10 anos com o SCORE e o QRISK2. No SCORE, utilizou-se o multiplicador recomendado de 1,5 em pacientes com AR elegíveis e estimou-se também o risco em pacientes com menos de 40 anos [mSCORE (0-65)]. O índice de aumento (AIx) e a pressão de pulso (PP) central, marcadores da integridade vascular e risco CV, foram avaliados pela análise de onda de pulso (PWA). O desfecho primário foi a correlação entre o AIx e o risco CV estimado usando o mSCORE (0-65).

Resultados: Em pacientes com AR, o AIx mostrou correlação estatisticamente significativa com o mSCORE (0-65) (rho = 0,3374; p < 0,0001). A correlação entre o AIx e o QRISK2 também foi significativa (rho = 0,3307, p < 0,0001). As correlações entre a PP central e o mSCORE (0-65) (rho = 0,4692; p < 0,0001) e QRISK2 (rho = 0,5828; p < 0,0001) também foram estatisticamente significativas. Os quartis incrementais da PP central estiveram associados a uma maior probabilidade de estar na categoria de "alto risco" de acordo com o SCORE (OR 2,18; IC 95% 1,58 a 3,01) ou QRISK2 (OR 2,18; IC 95% 1,75-2,72). Nos pacientes do grupo controle também se encontrou uma correlação entre o AIx e a PP central no SCORE (0-65) e no QRISK2.

Conclusões: Os parâmetros de hemodinâmica central se correlacionam com o risco CV calculado. No entanto, ambos não fornecem exatamente as mesmas informações. Questiona-se se uma combinação de ambos os conceitos resultaria em uma melhor predição do risco CV.

Introduction

Previously it could be shown consistently that Rheumatoid arthritis (RA) is associated with an increased cardiovascular (CV) risk.[1,2] This translates into a reduced lifespan of patients with RA of approximately 3–18 years.[3] Therefore, the European League Against Rheumatism (EULAR) recommends regular assessment of CV risk in patients with RA. For this purpose EULAR favours the use of the Systematic COronary Risk Evaluation (SCORE). As the CV risk in RA patients may be underestimated, EULAR also recommends to adjust CV risk score models by introducing a multiplier of 1.5 when RA patients meet two of the following three criteria: (a) disease duration of more than 10 years, (b) rheumatoid factor (RF) or anti-CCP-antibodies positivity and/or (c) presence of extra-articular manifestations.[4] QRISK2 is another validated CV disease risk algorithm, which has the particular advantage of directly incorporating RA into the algorithm of CV risk estimation.[5] Therefore, further adjustment for RA using a multiplier is not indicated.

CV risk calculators are not uniformly precise.[6] Beside CV risk calculators vascular markers for CV risk assessment are available.[7] Whatever the reason: if the integrity of the vessel is compromised, its function is impaired and CV risk is increased. Pulse wave analysis (PWA) is a frequently used method to detect vascular dysfunction and increased CV risk. During systole the pulse wave spreads out along the vessels and is finally reflected. This reflected wave augments central systolic blood pressure. The proportion of augmentation of the central pulse pressure (PP) can be expressed as augmentation index (AIx). PWA allows determining parameters of central haemodynamics such as AIx and central PP non-invasively.[8,9] From a pathophysiological point of view central pressures play a crucial role in the pathogenesis of CV diseases, as inner organs are exposed to these pressures.[10–12] Previously we and others demonstrated that patients with RA have a significantly higher AIx than patients without RA[13,14] and that this increased risk is independent of the presence of traditional CV risk factors.[15] Of interest, little is known whether in RA patients measured parameters of central haemodynamics correlate with the estimated CV risk derived by risk calculators. Aim of the present study was to assess the association of these two concepts. In an ancillary analysis we investigated the correlation of the same parameters in a control group.

Methods

Study design and setting

We report results of a cross-sectional study. The study was performed in a tertiary referral centre.

Participants

In the present study we included a total of 287 patients with a diagnosis of RA according to the 1987 American College of Rheumatology criteria.[16] In addition, we included 232 non-RA patients (=control group). The study was approved by the local ethics committee (Ethikkommission Land Oberösterreich) and is in accordance with the Declaration of Helsinki. All patients and controls gave written informed consent to participate in the study. For each RA patient we assessed traditional CV risk factors. Smoking habits and antihypertensive medication were registered as provided directly by the study participants and as determined by evaluation of the medical records. We diagnosed patients with diabetes (DM) according to the Guidelines of the Austrian Diabetes Association.[17] In addition, all patients receiving any form of antidiabetic treatment were considered to have DM. In all patients we evaluated disease duration, current and previous treatment with disease modifying anti-rheumatic drugs (DMARD), the presence of rheumatoid factor, any extra-articular RA manifestations as well as the disease activity score 28 (DAS 28).[18]

Pulse wave analysis

We performed PWA in all patients as previously reported.[15] In short, we used radial applanation tonometry with a high-fidelity micro-manometer (SPC-301, Millar Instruments, Houston, TX, USA). We measured blood pressure immediately before PWA with an automated oscillometric method (boso medicus, Bosch + Sohn GMBH, Jungingen, Germany; validated and certified by the German Society for Hypertension). A previously validated generalized transfer function integrated in the system software of the Sphygmocor apparatus (AtCor Medical, version 6.31, Sydney, Australia) allows the calculation of parameters of central haemodynamics.[19,20] For AIx we give the normalized index for 75 beats per minute to exclude the influence of heart rate on the AIx.[21] We only included high-quality readings as determined by the Sphygmocor apparatus in the analyses. Each PWA measurement was taken twice and the mean of both was used for further statistical analysis.

Risk calculators

Two CV risk estimation models were applied on all applicable patients. SCORE is the CV risk model recommended by the European Society of Cardiology (ESC).[22] SCORE estimates the 10-year risk of a fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other. The risk can be calculated for people aged 40–65 years.[23] For our calculations in RA patients we used four different versions of SCORE. First, we used the original SCORE values as given in the model. Second, we implemented the multiplier of 1.5 as recommended in the EULAR guidelines for applicable patients and derived an modified mSCORE.[4] Third, as the age group for which SCORE can be estimated is quite narrow and patients younger than 40 years of age have a SCORE risk lower than the highest risk in those aged 40 years we set the SCORE risk to 0% for all patients younger than 40 years. We named this SCORE (0–65). Fourth, the same applies to mSCORE, where the multiplier of 1.5 will not result in any difference when the baseline risk is 0%. We called this variable mSCORE (0–65). For controls we used SCORE and SCORE (0–65) in the same way as described above.

QRISK2 was developed and validated in an UK population using a very large cohort of patients. In contrast to SCORE it does not estimate fatal CV events but the 10 year risk of developing CV disease as defined by coronary heart disease (angina and myocardial infarction), stroke, or transient ischaemic attacks. It is applicable for a broad range of people aged between 25 and 84 years. One of the unique features of QRISK2 is that – besides other risk factors – RA is directly incorporated in the algorithm of risk prediction. Therefore, the application of the multiplier of 1.5 in RA patients recommended by EULAR[4] is not indicated. The Townsend deprivation score, an optional parameter in QRISK2, was not available for our patients.[5] Not all patients were applicable for risk calculation for SCORE or QRISK2. This was the case if some of the relevant parameters were outside the particular valid range of the risk calculator (e.g., age, blood pressure or lipids). For all particular correlations we give the number of available patients.

Statistical methods and management of quantitative variables

Primary endpoint was the correlation of AIx and the estimated CV risk using mSOCRE (0–65). The Null hypothesis was that there is no association between AIx and mSCORE (0–65). The alternative hypothesis was that there is an association. Secondary endpoints included the correlations of AIx as well as central PP with QRISK2, SCORE, SCORE (0–65), mSCORE and mSCORE (0–65). By definition all secondary endpoints were tested exploratory, not confirmatory. For descriptive analyses we present means and standard deviations (SD) for normally distributed quantitative data. In the case of skewed data we present the median and the interquartile range (IQR). For comparison of quantitative data between two groups with a normal distribution we used an unpaired *t*-test and for skewed distributions we used the Wilcoxon Rank Sum test. CV risk estimates were positively skewed. Therefore, for correlations of quantitative data including CV risk estimates the Spearman rank correlation coefficient rho was calculated. In order to be able to analyse the CV risk estimates as a dichotomous variable we transformed mSCORE (in RA patients), SCORE (control group), and QRISK2 (RA and control group) into binary variables (with and without increased CV risk). We used the usual thresholds for increased CV risk as cut off points ($\geq$5% for SCORE and $\geq$20% for QRISK2). We also investigated AIx and central PP as ordered categorical data. For these analyses we calculated quartiles (Q1–4) for AIx and for central PP. Furthermore, we calculated receiver operating characteristic (ROC) curves with AIx and central PP as continuous parameter. In the absence of a "gold standard" for CV outcome we used the binary variable described above for SCORE and QRISK2 as outcome variable. The area under the curve (AUC) and 95% confidence interval (CI) was calculated using bootstrap sampling (1000 samples). All tests were two-sided. We considered a p value of <0.05 as statistically significant. For all calculations we used STATA 13 IC.

Table 1 – Demographic and disease related characteristics of RA patients (*n* = 287).

Female (*n* %)	232 (80.8%)
Age (years; mean ± SD)	58.4 ± 12.6
RA disease duration (years; median, IQR)	10.5 (5.0–17.6)
RF positive (*n* %)	218 (76.0%)
Extra-articular manifestation (*n* %)	89 (31.0%)
CRP (mg/dL; median, IQR)	0.45 (0.2–1.2)
ESR (mm/h; median, IQR)	13 (7–29)
DAS28 (median, IQR)	2.54 (1.85–3.82)
Number of current DMARDS	
0 (n %)	15 (5.2%)
1 (n %)	159 (55.40%)
2 (n %)	109 (38.0%)
3 (n %)	4 (1.4%)
DMARDs	
csDMARDs	
Methotrexate (*n* %)	203 (70.7%)
Sulfasalazine (*n* %)	19 (6.6%)
Leflunomide (*n* %)	32 (11.2%)
(Hydroxy-)chloroquine (*n* %)	23 (8.0%)
MMF or azathioprine (*n* %)	3 (1.1%)
bDMARDs	
TNF inhibitor (*n* %)	86 (30.0%)
Abatacept (*n* %)	9 (3.1%)
Rituximab (*n* %)	7 (2.4%)
Tocilizumab (*n* %)	5 (1.7%)
Anakinra (*n* %)	1 (0.4%)
Previous DMARDs (median, IQR)	2 (1–4)

b, biologic; cs, conventional synthetic; CRP, C-reactive protein; DAS28, disease activity score 28; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; MMF, mycophenolate mofetil; RA, rheumatoid arthritis; RF, rheumatoid factor.

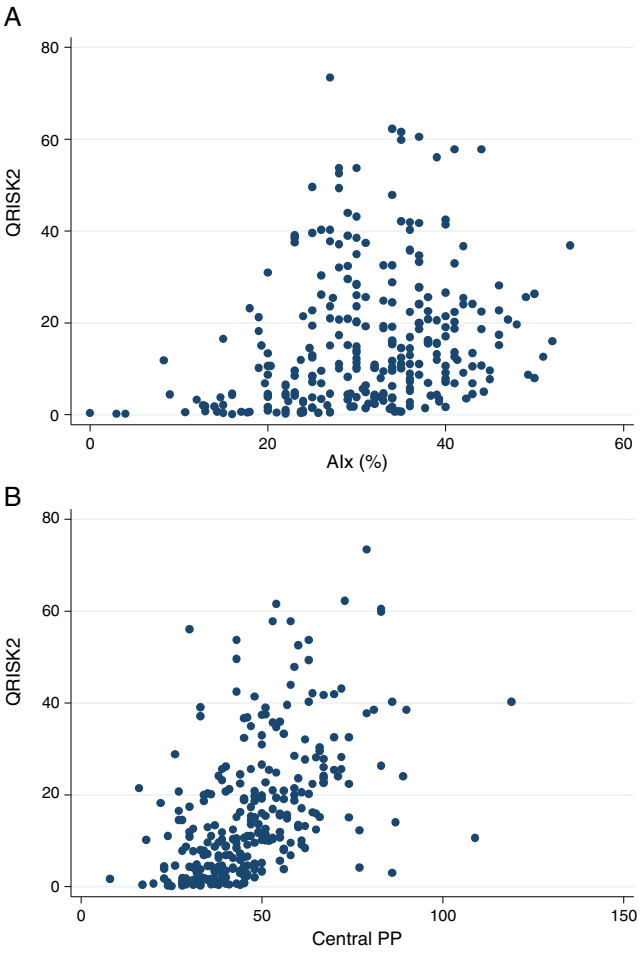

Fig. 1 – Scatterplots for the total RA group (female and male patients) for (A) the correlation of AIx and (B) central PP with QRISK2. Spearman's rho is 0.3307 ($p < 0.0001$) for the correlation with AIx and 0.5828 ($p < 0.0001$) for the correlation with central PP.

Results

In Table 1 we have summarized demographic and disease related characteristics of RA patients. Table 2 gives details for CV risk factors as well as the results of pulse wave analysis in RA patients and controls. AIx was significantly lower in men than in woman in the RA group (26.8 ± 8.7% in men vs 32.1 ± 9.2% in women; $p = 0.0001$) as well as in the control group (15.9 ± 10.2% in men vs 25.5 ± 10.2% in women; $p < 0.0001$). Therefore, we give results of correlations not only for the total group, but also separately for females and males. In total 164 RA patients fulfilled the criteria to allow calculation of SCORE. According to the EULAR recommendations the multiplier for CV risk of 1.5 was applied in 78 cases. In 86 cases the use of the multiplier was not appropriate and SCORE was left unchanged. When in participants younger than 40 years of age the SCORE CV risk was set to 0% the sample consisted of 189 patients (mSCORE (0–65)). 283 patients were eligible for calculation of CV risk using QRISK2. Table 3a shows the details for the correlations of AIx and the CV risk scores in the RA group. The correlation of SCORE ($n = 164$) yielded a rho of 0.1697 ($p = 0.0298$). As can been seen in Table 3a for most of the correlations of AIx we found statistically significant correlations. For men some correlations were not statistically significant, whereby the calculations are based on a much smaller sample size (Table 3a). Overall, correlations of central PP with calculated CV risk tended to correlate better than those including AIx. This was also true for the smaller subgroup of male RA patients. All details for the correlations of central PP and CV risk scores in the RA group are shown in Table 3b. Table 3c and d presents details for the correlations of AIx and central PP with SCORE, SCORE (0–65) and QRISK2 in the control group (mSCORE and mSCORE (0–65) are not applicable in this groups). Fig. 1 shows the scatterplots for the correlations of AIx (Fig. 1A) and central PP (Fig. 1B) with QRISK2 in RA patients.

We further tested the association between central PP and estimated CV risk using ordered categorical data. For this purpose continuous central PP was transformed into quartiles and mSCORE (0–65), which excludes patients aged >65 years (SCORE not applicable), was transformed into a binary variable with increased (mSCORE ≥ 5%) and not increased CV risk (mSCORE 0% to <5%). We found a significant trend of increased odds for high CV risk in RA patients as defined by mSCORE ≥ 5% from Q1 to Q4 (Table 4a). The summary OR was

Table 2 – Characteristics of CV risk factors of RA patients (*n* = 287) and controls (*n* = 232) and results of pulse wave analysis (*n* = 287).

	RA group (*n* = 287)	Control-group(*n* = 232)	*p*-value
Female (n %)	232 (80.8%)	186. (802%)	0.849
Age (years; mean ± SD)	58.4 ± 12.6	49.9 ± 13.4	<0.0001
Antihypertensive medication (n %)	90 (31.4%)	75 (32.33%)	0.814
Height (m; mean ± SD)	1.65 ± 0.08	1.67 ± 0.08	0.013
Weight (kg; mean ± SD)	71.7 ± 15.0	72.9 ± 17.3	0.421
BMI (kg/m^2; mean ± SD)	26.3 ± 4.9	26.2 ± 6.0	0.767
Total cholesterol (mg/dL ± SD)	214.8 ± 45.2	193.3 ± 48.6	0.0001
LDL cholesterol (mg/dL ± SD)	127.5 ± 39.2	113.2 ± 37.6	0.0001
HDL cholesterol (mg/dL ± SD)	65.8 ± 19.6	52.9 ± 18.1	<0.0001
Triglycerides (mg/dL; median, IQR)	110.0 (82.0–144.0)	105.5 (68.0–160.0)	0.325
Smoker status			0.046
Never (n %)	167 (58.2%)	130 (56.0%)	
Former (n %)	69 (24.0%)	42 (18.1%)	
Current (n %)	51 (17.8%)	60 (25.9%)	
DM (n %)	21 (7.3%)	69 (29.7%)	<0.0001
DM duration (years; median, IQR)	6. (2–10)	9. (3–15)	0.251
Statin use (n %)	33 (11.5%)	20 (8.6%)	0.282
Brachial systolic BP (mmHg ± SD)	139.3 ± 22.1	135.3 ± 2.4	0.049
Brachial diastolic BP (mmHg ± SD)	82.7 ± 12.0	79.8 ± 13.7	0.012
Pulse rate (bpm ± SD)	71.9 ± 11.6	72.2 ± 12.5	0.830
AIx (%, ±SD)	31.1 ± 9.3	23.6 ± 11.3	<0.0001
Central systolic BP (mmHg ± SD)	130.9 ± 21.7	124.3 ± 23.4	0.0009
Central diastolic BP (mmHg ± SD)	83.9 ± 13.2	81.0 ± 14.1	0.016
Central pulse pressure (mmHg ± SD)	47.5 ± 16.0	43.4 ± 14.6	0.003
SCORE (median, IQR)	2. (1–4)	1. (0–2)	<0.0001
SCORE (0–65) (median, IQR)	1. (1–3)	1. (0–1)	<0.0001
mSCORE (median, IQR)	2. (1–5)	–	–
mSCORE (0–65) (median, IQR)	1.5 (1–4.5)	–	–
QRISK2 (median, IQR)	11.9 (4.3–23.6)	6.1 (1.5–16.6)	<0.0001

BMI, body mass index; DM, diabetes; HDL, high density lipoprotein; LDL, low density lipoprotein; AIx, augmentation index.

2.18 (95% CI 1.58–3.01) per increase of quartile. This OR was not significantly altered after adjustment for sex (OR 2.33; 95% CI 1.67–3.28). We did not find such a trend for AIx and CV risk (data not shown). However, a similar picture was found when we analysed QRISK2 as a binary variable. For QRISK2 we used the proposed 20% threshold to identify patients with a high CV risk (QRISK2 0% to <20% and QRISK2 ≥ 20%). Again, there was a significant trend of increasing odds for high CV risk from Q1 to Q4 of central PP. The summary OR was 2.18 (95% CI 1.75–2.72). The OR remained stable after adjustment for sex (OR 2.20; 95% CI 1.75–2.75). These data are shown in Table 4b. In contrast to mSCORE, we also found a statistically significant trend for AIx quartiles and high CV risk according to QRISK2 (≥20%); (test for trend of odds: $p = 0.0039$). In the control group we used SCORE ≥ 5% as threshold (instead of mSCORE ≥ 5%). We found a significant trend of increased odds for high CV risk as defined by SCORE ≥ 5% from Q1 to Q4 of central PP (summary OR 3.28; 95% CI 1.98–5.41). Again, this OR was not significantly altered after adjustment for sex (OR 3.49; 95% CI 2.10–5.81). For QRISK2 ≥ 20% and central PP (Q1 to Q4) the summary OR was 2.27 (95% CI 1.70–3.03), after adjustment for sex 2.35 (95% CI 1.74–3.15). In the control group we found a trend for increasing odds of being in the SCORE ≥ 5% category for AIx quartiles Q1 to Q4 (summary OR 1.79; 95% CI 1.11–2.87; adjusted for sex 2.50; 95% CI 1.46–4.29) as well as being in the QRISK2 ≥ 20% category (summary OR 1.42; 95% CI 1.07–1.90; adjusted for sex 1.81; 95% CI 1.33–2.48).

In the absence of a "gold standard" for CV outcome we used the thresholds of mSCORE (≥5%) and QRISK2 (≥20%) as outcome variable for ROC curves. In the RA group AIx performed poorly in the discrimination of the mSCORE ≥ 5% threshold (AUC 0.55; 95% CI 0.45–0.66) and only marginally better for the QRISK2 ≥ 20% threshold (AUC 0.59; 95% CI 0.53–0.66). Central PP performed much better for both, mSCORE (AUC 0.77; 95% CI 0.68–0.86; tests of equality of ROC areas compared to AIx: $p = 0.0009$) and QRISK2 (AUC 0.77; 95% CI 0.71–0.83; tests of equality of ROC areas compared to AIx: $p = 0.0001$) (Fig. 2A and B). In the control group the AUC for AIx predicting SCORE ≥ 5% was 0.72 (95% CI 0.61–0.84) and for QRISK2 ≥ 20% 0.63 (95% CI 0.56–0.72). For central PP the corresponding values were 0.86 (95% CI 0.80–0.9) for SCORE ≥ 5% and 0.76 (95% CI 0.68–0.84) for QRISK2. Again, central PP performed better than AIx in the prediction of SCORE ≥ 5% (tests of equality of ROC areas compared to AIx: $p = 0.01$) as well as for QRISK ≥ 20% (tests of equality of ROC areas compared to AIx: $p = 0.005$).

Discussion

In RA patients AIx and central PP, two measures of central haemodynamics predicting CV outcome, are correlated with

Table 3 – Correlations of (a) AIx and (b) central PP and calculated CV risk in the RA group and correlations of (c) AIx and (d) central PP and calculated CV risk in the control group.

	Observations (*n*)	rho	*p*-value
(a) Correlations of AIx and calculated CV risk in the RA group			
SCORE – total group	164	0.1697	0.0298
SCORE – female	128	0.3468	0.0001
SCORE – male	36	0.2578	0.1290
SCORE (0–65) – total group	189	0.3314	<0.0001
SCORE (0–65) – female	152	0.4992	<0.0001
SCORE (0–65) – male	37	0.3170	0.0560
mSCORE – total group	164	0.1812	0.0203
mSCORE – female	128	0.3740	<0.0001
mSCORE – male	36	0.2047	0.2310
mSCORE (0–65) – total group	189	0.3374	<0.0001
mSCORE (0–65) – female	152	0.5146	<0.0001
mSCORE (0–65) – male	37	0.2680	0.1088
QRISK – total group	283	0.3307	<0.0001
QRISK – female	229	0.4046	<0.0001
QRISK – male	54	0.4956	0.0001
(b) Correlations of central PP and calculated CV risk in the RA group			
SCORE – total group	164	0.3919	<0.0001
SCORE – female	128	0.4116	<0.0001
SCORE – male	36	0.5803	0.0002
SCORE (0–65) – total group	189	0.4863	<0.0001
SCORE (0–65) – female	152	0.5292	<0.0001
SCORE (0–65) – male	37	0.5547	0.0004
mSCORE – total group	164	0.3704	<0.0001
mSCORE – female	128	0.3949	<0.0001
mSCORE – male	36	0.5494	0.0005
mSCORE (0–65) – total group	189	0.4692	<0.0001
mSCORE (0–65) – female	152	0.5164	<0.0001
mSCORE (0–65) – male	37	0.5259	0.0008
QRISK – total group	283	0.5828	<0.0001
QRISK – female	229	0.5975	<0.0001
QRISK – male	54	0.5813	<0.0001
(c) Correlations of AIx and calculated CV risk in the control group			
SCORE – total group	151	0.2104	0.0095
SCORE – female	133	0.3498	<0.0001
SCORE – male	18	0.3703	0.1304
SCORE (0–65) – total group	201	0.4241	<0.0001
SCORE (0–65) – female	169	0.4734	<0.0001
SCORE (0–65) – male	32	0.7071	<0.0001
QRISK – total group	219	0.3919	<0.0001
QRISK – female	178	0.4695	<0.0001
QRISK – male	41	0.7568	<0.0001
(d) Correlations of central PP and calculated CV risk in the control group			
SCORE – total group	151	0.3616	<0.0001
SCORE – female	133	0.4450	<0.0001
SCORE – male	18	0.3003	0.2260
SCORE (0–65) – total group	201	0.4521	<0.0001
SCORE (0–65) – female	169	0.5437	<0.0001
SCORE (0–65) – male	32	0.0401	0.8276
QRISK – total group	219	0.5442	<0.0001
QRISK – female group	178	0.6117	<0.0001
QRISK – male group	41	0.3746	0.0158

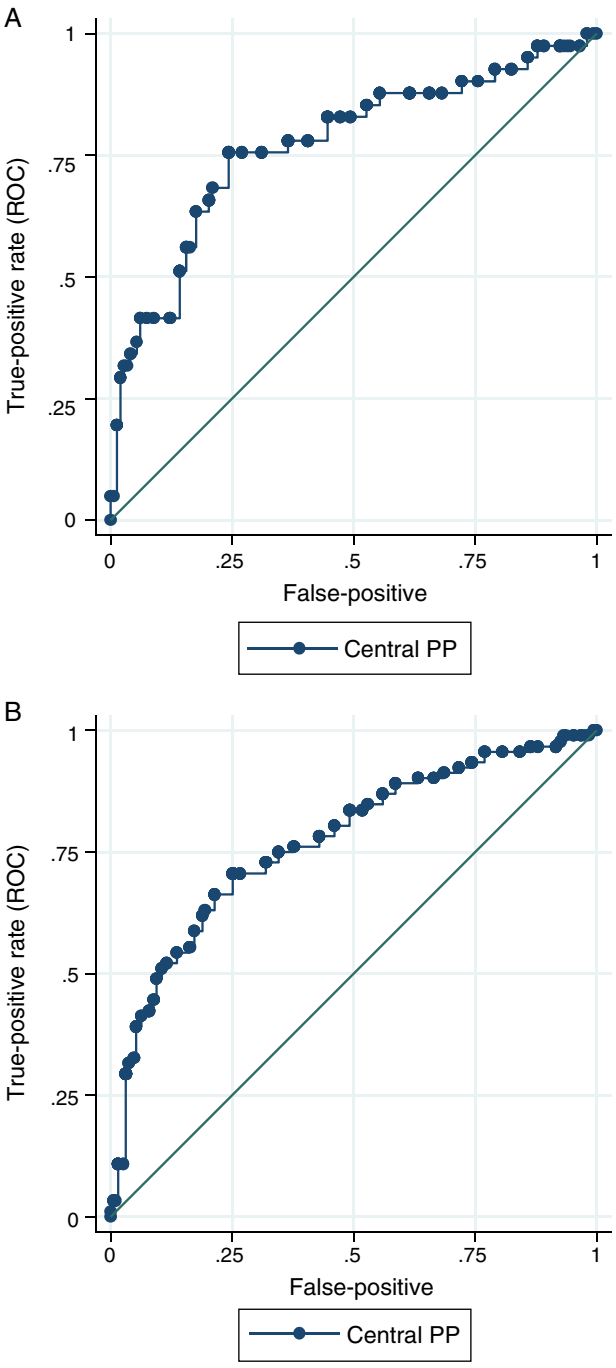

Fig. 2 – ROC curves for central PP as continuous variable and (A) mSCORE (0–65) (≥5%) and (B) QRISK2 (≥20%) as binary outcome variable in the RA group.

the CV risk estimated by SCORE and QRISK2. A similar picture was found in the control group. This was true when AIx and central PP as well as CV risk estimates were used as continuous data. In addition, a trend of increased CV risk was found when quartiles of central PP were used. In the RA group, for AIx this was only true for QRISK2 as an outcome, but not for mSCORE (0–65). Using established thresholds of mSCORE and QRISK2 for high CV risk central PP showed better discriminatory

Table 4 – With increasing quartile of central PP there is an increased OR (Q1 as baseline) of having high CV risk as determined by (a) mSCORE (0–65) and (b) QRISK2 in the RA group.

(a)

Quartile (central PP)	*n*	mSCORE (0–65)		
		0% to <5%	≥5%	OR (95% CI)
Q1 (8 to <36 mmHg)	52	47 (90.4%)	5 (9.6%)	1.0 (ref)
Q2 (36 to <45 mmHg)	51	47 (92.2%)	4 (7.8%)	0.80 (0.20–3.19)
Q3 (45 to <56 mmHg)	51	36 (70.6%)	15 (29.4%)	3.92 (1.25–12.28)
Q4 (≥56 mmHg)	35	18 (51.4%)	17 (48.6%)	8.88 (2.49–31.66)
Total	189	148 (78.3%)	41 (21.7%)	

(b)

Quartile (central PP)	*n*	QRISK2		
		0% to <20%	≥20%	OR (95% CI)
Q1 (8 to <36 mmHg)	68	60 (88.2%)	8 (11.2%)	1.0 (ref)
Q2 (36 to <45 mmHg)	61	49 (80.3%)	12 (19.7%)	1.84 (0.69–4.90)
Q3 (45 to <56 mmHg)	78	56 (71.8%)	22 (28.2%)	2.95 (1.19–7.32)
Q4 (≥56 mmHg)	76	26 (34.2%)	50 (65.8%)	14.42 (5.03–41.36)
Total	283	191 (67.5%)	92 (32.5%)	

Test of homogeneity: $p < 0.0001$; test for trend of odds: $p < 0.0001$.

capacity in ROC curves than AIx. In summary, pulse wave analysis provides information on central haemodynamics, which are associated with estimated CV risk. However, as expected "measured" (i.e., PWA) and calculated CV risk do not provide exactly the same information. To date it is not clear whether the combination of both types of risk determination – measurement of vascular function and calculation – would result in a better prediction of CV events in RA patients. Up to now it was even unclear whether the results obtained by PWA and CV risk models would correlate in any way. Previous research indicated that risk prediction models in general lack precision of CV risk estimation in RA patients.[6] A cohort study in which CV risk would be measured and calculated in RA patients and in which study participants would be followed over several years could probably answer the question, whether a combination of both methods would result in better risk prediction.

Previously it was demonstrated that central haemodynamic indices are independent predictors of future CV events and all-cause mortality. For a 10% absolute increase of central AIx the relative risk (RR) of total CV events increases to 1.318 (95% CI 1.093–1.588). For all-cause mortality the RR increases to 1.384 (95% CI 1.192–1.606). In addition, for a 10 mmHg increase of central PP the RR of total CV events increases to 1.137 (95% CI 1.063–1.215).[10] Previously it could be shown that AIx is increased in RA patients compared to controls.[13–15] Therefore, it is very likely that the increased CV risk found in RA patients is represented in parameters of central haemodynamics. As parameters of central haemodynamics correlate with calculated CV risk, but do not give exactly the same information, the question arises whether a combination of both concepts would result in an improved CV risk prediction.[7]

Our study has some limitations. As its design is cross-sectional we were not able to analyse CV events as an outcome. However, we demonstrated that parameters of central haemodynamics and calculated CV risk yield similar, but not identical information with regard to CV risk in RA patients. As discussed above, to date we are unable to answer the question, which of the two concepts can better predict CV events in RA patients. This question should be answered in a prospective cohort study. This would be especially of interest with regard to AIx: AIx does not seem to correlate as well as central PP with calculated CV risk. However, this could also mean that AIx could offer additional – functional – information with regard to CV risk, which might not be incorporated in CV risk models. The lack of having CV events as an outcome also limits the analysis with regard to ROC curves. In the absence of a gold standard we used the proposed thresholds for high CV risk of SCORE and QRISK2 as outcome. A further limitation seems to be the proposed use of SCORE: SCORE is applicable for people aged 40–65 years. Therefore, the CV risk estimation is not possible for a substantial proportion of RA patients. This results in a reduced sample size and makes statistical estimates less precise. The latter is especially true for the subgroup of male RA patients. We have tried to compensate for this limitation in part. Therefore, we determined the CV risk in patients <40 years of age with 0%, as according to SCORE it is extremely unlikely that patients younger than 40 years of age would have a CV risk higher than 0%. QRISK2 is applicable to a much broader age range, yielding a much larger sample size. While QRISK2 has the important advantage of specifically including the diagnosis of RA in the risk algorithm, QRISK2 was developed in the UK. Today, it is not clear whether QRISK2 is valid in a non-UK population. However, it is common practise to apply CV risk calculators which have been developed in other countries on a wide range of populations. For instance, the Framingham score was used in

European patients,[6,24] despite the fact that it was developed in a North-American population.[25] QRISK2 was previously used in non-UK RA patients.[6] Our primary endpoint was the association of AIx and mSCORE (0–65). In addition, we performed a number of further statistical analyses with AIx as well as central PP and different versions of estimated CV risk. It should be underlined that these further tests cannot be considered confirmatory but rather exploratory. This study was performed in an outpatient clinic of a tertiary referral centre. Therefore, patients with more sever RA or more multi-morbid and older patients may be overrepresented in our sample. So, the CV risk in our sample could be higher compared to, for instance, RA patients managed by office-based rheumatologists. Therefore, it might be that our results are not generalizable to RA patients with lower CV risk.

Conclusions

We could demonstrate that results of two concepts of CV risk determination in RA patients – PWA and CV risk calculators – correlate with each other. However, obviously both do not give the same information. This raises the question whether a combination of both concepts might result in more accurate risk prediction in RA patients.

Conflicts of interest

The authors declare no conflicts of interest.

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