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Feasibility of cardiovascular population-based CT screening

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High-pitch versus sequential mode for coronary calcium in individuals with a high heart rate: Potential for dose reduction

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Abstract

Background

To determine the impact of high-pitch spiral mode on radiation dose and cardiovascular disease (CVD) risk stratification in coronary artery calcium (CAC) scanning in participants with a high heart rate.

Methods

Of the ROBINSCA trial, 1,990 participants with regular heart rates and >65 beats per minute (bpm) were included. As reference, 390 participants with regular rate and ≤65 bpm were included. All participants underwent prospectively electrocardiographically (ECG)-triggered CAC scanning with dual-source CT at 120 kVp, 80 ref mAs in high-pitch spiral mode and in sequential mode. Radiation dose, Agatston score, number of positive scores, as well as median absolute Agatston difference were determined or calculated and participants were stratified into CVD risk categories.

Results

Similar numbers of participants had a positive CAC score for high-pitch spiral (57.7%, 55.8%) and sequential mode (58.0%, 54.7%) ($p=n.s.$) for respectively low and high heart rate group. The median absolute difference in Agatston score between scan modes was 14.2% and 9.2%, for respectively high and low heart rate group. Excellent agreement for risk categorization between the two scan modes was found for the high ($\kappa=0.927$) and low ($\kappa=0.946$) heart rate group. Radiation dose was 48% lower for high-pitch spiral versus sequential acquisitions.

Conclusion

Radiation dose for the quantification of coronary calcium can be reduced by 48% when using the high-pitch spiral acquisition mode compared to the sequential mode in participants with a regular high heart rate. CVD risk stratification agreement between the two modes of data acquisition is excellent.

Introduction

Coronary artery calcium (CAC) imaging by computed tomography (CT) is an advanced risk stratification tool for atherosclerotic cardiovascular disease (CVD) [1–4]. The American Heart Association and American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines provide class IIb recommendations for the use of CAC [5,6]. Both societies identified knowledge gaps and raised concerns regarding radiation exposure in CAC imaging [6].

It is of substantial importance to achieve a radiation dose “as low dose as reasonably achievable” when considering any population screening in asymptomatic individuals. The data acquisition mode used for CAC imaging has major implications regarding radiation dose. With dual-source CT (DSCT), next to the spiral acquisition mode, a sequential acquisition mode as well as a high-pitch spiral acquisition mode can be used in combination with prospective electrocardiographic (ECG)-triggering. With the sequential mode, the data set is acquired over several heartbeats, whereas with high-pitch spiral mode, data acquisition is completed within one heartbeat.

Although the high-pitch spiral mode leads to a lower radiation dose than the sequential acquisition mode, the high-pitch spiral mode is not used in all instances. The high-pitch spiral mode is typically not used in participants with high heart rates since the diastolic resting period of the heart may be too short to accommodate the time window required to cover the entire heart. While for screening purposes, medication for heart rate control can not be used, it is possible that some motion artefact, especially of the more caudal scan range, can be tolerated. In fact, prior studies have even suggested that ECG-triggering might not be mandatory to determine CVD risk [7,8]. Therefore, the purpose of this study was to determine the impact of using the high-pitch spiral mode compared to the sequential mode on the percentage of positive CAC scans, the Agatston score, risk stratification and radiation dose of CAC imaging in individuals with a regular, but high heart rate.

Materials and methods

Study population

Participants of the large-scale population-based randomized screening trial ROBINSICA (NTR6471) who had a CT scan in one of the three screening centers were eligible for this study [9]. Informed consent for CT imaging and participation was obtained from all participants. All participants of the ROBINSICA trial are asymptomatic for CVD and have one or more of the following inclusion criteria: age between 45 and 74 (men),

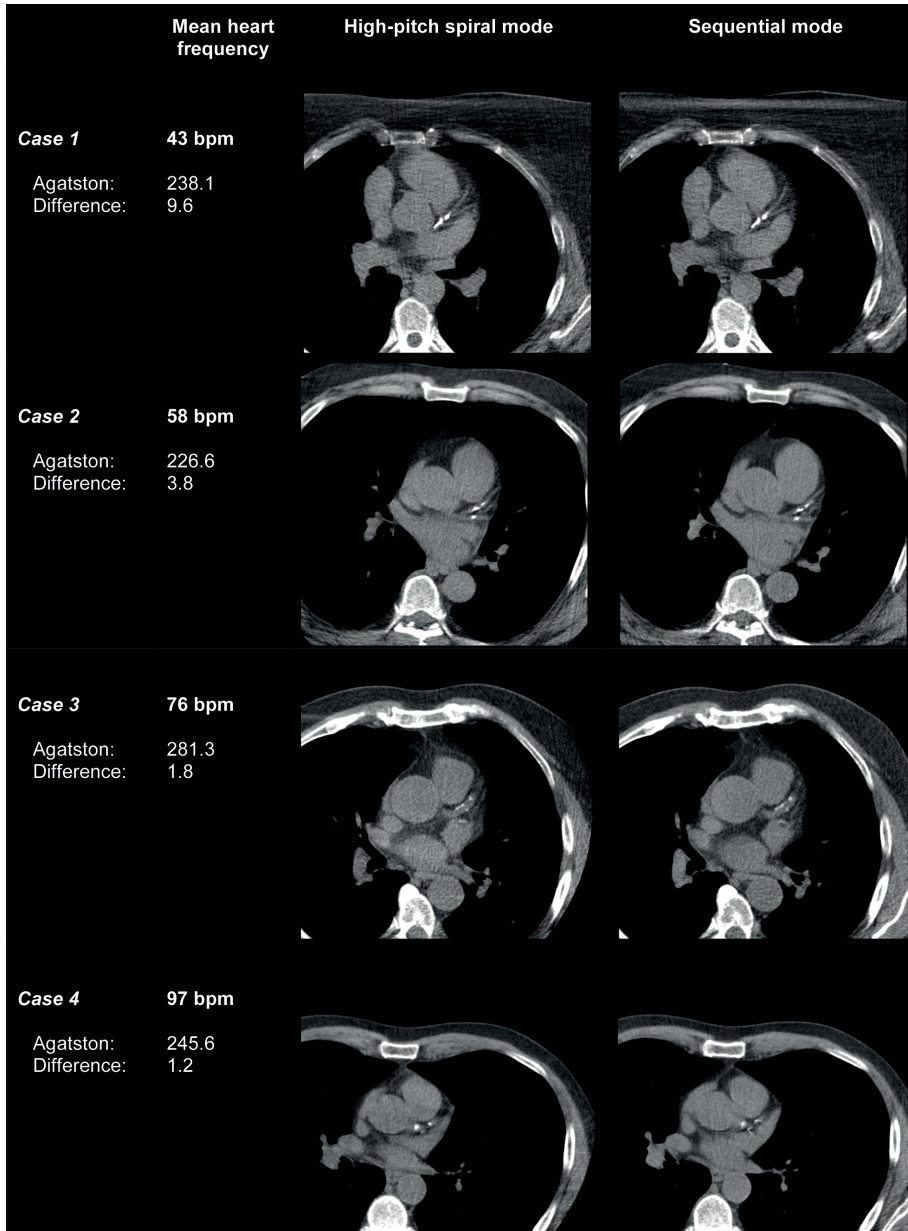


Figure 1 – Case examples high-pitch spiral versus sequential mode. Case-examples of participants with very low (43 bpm) to very high heart rate (97 bpm), showing intra-individually comparable Agatston scores for high-pitch spiral and sequential mode with differences between scan modes ranging from 1.2-9.6 Agatston points. Mean Agatston score of the high-pitch spiral and sequential mode scan is shown.

or 55–74 y (women), BMI ≥ 30 , current smoking, cardiac infarction/cardiac arrest in first degree relative at the age of < 65 y, waist circumference of ≥ 88 cm and ≥ 102 cm for women and men, respectively.

CT image protocol

Participants were scanned with second generation DSCT (Definition Flash, Siemens, Erlangen, Germany). The participants were imaged in sequential mode (as reference), and additionally in high-pitch spiral mode with a pitch of 3.4; for both, collimation was $2 \times 128 \times 0.6$ mm. A tube voltage of 120 kVp was applied and dose modulation was set at a quality reference of 80 mAs. Participants were not repositioned between the sequential and high-pitch spiral acquisition. Prospective ECG-triggering at 60% of the R-R interval was used for both acquisition modes. Z-axis coverage of the scan was from carina to apex of the heart. Images were reconstructed with field-of-view of 250 mm, slice thickness of 3.0 mm and slice increment of 1.5 mm, using filtered back projection (FBP) and a medium-sharp kernel (B35f).

Data evaluation

Only participants with a regular heart rate were included in this study. A regular heart rate was defined as a heart rate with a difference of less than three beats per minute (bpm) over a time period of 10 s, as determined by software integrated into the CT system. Based on the mean heart rate during acquisition, participants with a regular heart rate were divided into a group with a high heart rate, > 65 bpm, and a reference group with a low heart rate, ≤ 65 bpm. The Agatston score was determined with dedicated software (CaScoring, Syngo.via version VB10A, Siemens, Erlangen, Germany) for all acquisitions. The percentages of positive CAC scores per group and acquisition mode were calculated and participants were categorized into the following cardiovascular risk categories: low risk for Agatston score of 0, intermediate risk for 1–99, high risk for 100–399 and very high risk for ≥ 400 . The thorax diameter (right to left) of each participant was measured on the topogram, halfway between the carina and the apex of the heart. The dose parameter CT Dose Index Volume ($CTDI_{vol}$) was documented for each acquisition and each participant. Differences in calcium prevalence, Agatston score and radiation dose between the high-pitch spiral and sequential acquisitions in the high heart rate group were compared to the respective differences between the high-pitch spiral and sequential mode in the reference group of participants with low heart rates.

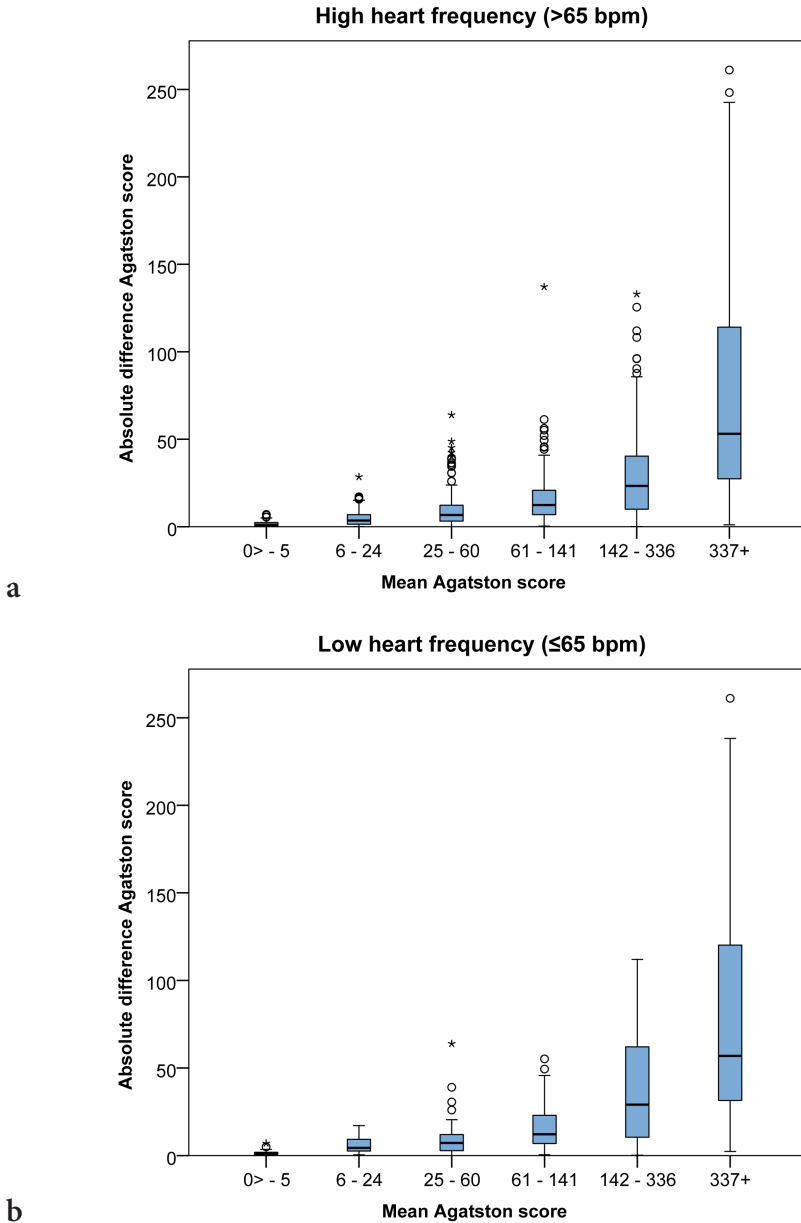


Figure 2 – Impact Agatston score on absolute Agatston difference. Participants were stratified based on the mean Agatston score for the high-pitch spiral and sequential scan into groups of equal size. For the (a) high ($\tau_b=0.60, p<0.001$) and (b) low ($\tau_b=0.59, p<0.001$) heart rate group the absolute difference in Agatston score increases for increasing Agatston scores.

Statistical analysis

A power analysis was performed (Stata/SE 14.0, StataCorp College Station, USA) to calculate the sample size needed to demonstrate non-inferiority of high-pitch spiral acquisition versus the sequential acquisition for participants with a regular high heart rate. An acceptable difference was set at 2% to demonstrate non-inferiority of the high-pitch spiral mode compared to the sequential mode. With a power of 0.95 and estimated correlation of 0.9 between the two scan modes, this resulted in a required sample size of $n=1553$.

Results were expressed as median and interquartile ranges (IQR) for Agatston scores, thorax size and $CTDI_{vol}$ per heart rate group and acquisition mode. McNemar testing was used to determine any difference in positive CAC scores between high-pitch spiral and sequential mode. Wilcoxon signed rank test was used to determine differences in Agatston score between the acquisition modes. Independent samples Median test was used to determine differences between the high and low heart rate group for difference in Agatston score between the scan-modes. Kendall's tau-b (τ_b) was used to determine trends between absolute difference in Agatston score and the mean Agatston score of the high-pitch and sequential acquisition. Besides, τ_b was used to determine trends in absolute difference in Agatston score and heart rate and thorax diameter. To determine trends for the continuous parameters mean Agatston score, heart rate and thorax diameter, the data of these parameters were binned into categorical data with each category containing equal number of participants. The percentage of reclassification of cardiovascular risk as a result of the high-pitch spiral mode compared to sequential mode was determined. Cohen's kappa (κ) was used to determine agreement of risk categorization between the scan modes. The statistical analyses were performed with a software package (SPSS, release 23.0.0.3, IBM, New York, USA) and level of significance was defined as $\alpha=0.05$.

Results

Study population

In total, 2380 out of 3105 participants of the ROBINSCA trial, who underwent CT between April 2015 and February 2017, had a regular heart rate and were included in this study. The group with a high heart rate comprised 1990 participants of whom 47.1% were male. Mean age was 61.5 (standard deviation (SD): ± 7.2) y, mean heart rate was 77.2 (SD: ± 9.2) bpm and mean thorax diameter was 40.1 (SD: ± 4.7) cm. The reference group with a low heart rate included 390 participants of whom 57.0% were

Table 1 – Cardiovascular risk stratification based on scan mode for participants with a high heart rate (>65 bpm)

		Sequential mode				Total
		0	1-99.9	100-399.9	≥400	
High-pitch spiral mode	0	821	13	0	0	834
	1-99.9	25	661	29	0	715
	100-399.9	0	11	277	12	300
	≥400	0	0	7	134	141
	Total	846	685	313	146	1,990

Table 2 – Cardiovascular risk stratification based on scan mode for participants with a low heart rate (≤65 bpm)

		Sequential mode				Total
		0	1-99.9	100-399.9	≥400	
High-pitch spiral mode	0	171	5	0	0	176
	1-99.9	2	119	4	0	125
	100-399.9	0	2	52	1	55
	≥400	0	0	0	34	34
	Total	173	126	313	35	390

male. Their mean age was 59.7 (SD: ± 7.6) y, mean heart rate was 58.8 (SD: ± 4.7) bpm and mean thorax diameter was 40.6 (SD: ± 4.9) cm.

Positive CAC score

For the group with a high heart rate, no difference in the number of participants with a positive CAC score was found between high-pitch spiral (57.7%) and sequential acquisition (58.0%, $p=0.360$). Likewise, for the reference group of individuals with low heart rates, no difference in number of participants with a positive CAC score was found between the high-pitch spiral (55.8%) and sequential mode (54.7%, $p=0.289$). Participants shifted from a zero score based on sequential mode to a positive score based on the high-pitch spiral acquisition in 1.3% and 1.3% ($p=0.175$) of the cases and from a positive score to a zero score in 0.7% and 0.5% ($p=0.103$) of the cases for the high and low heart rate group, respectively. *Figure 1* shows case examples of CAC scoring with high-pitch spiral and sequential acquisition mode in participants with low and high heart rates.

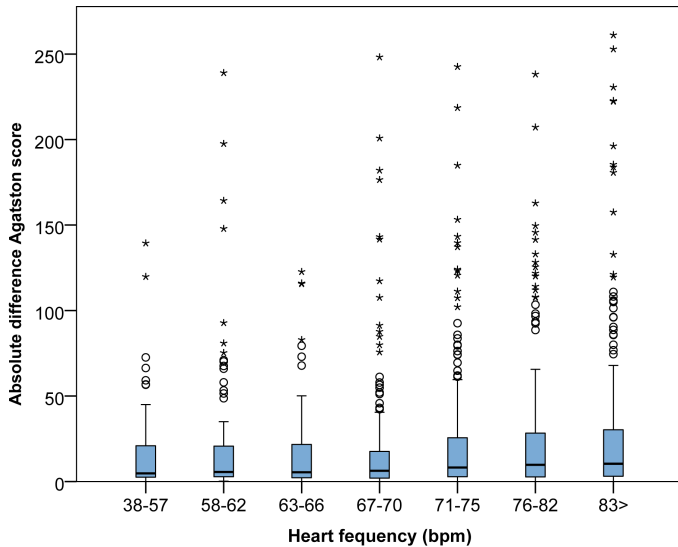


Figure 3 – Impact of heart rate on absolute Agatston difference. Participants were stratified based on mean heart rate during the scan into groups of equal size. The absolute difference in Agatston score between high-pitch spiral and sequential mode scans showed a very weak correlation with heart rate ($\tau_b=0.074$, $p<0.001$).

Participants with a positive CAC score in both data sets were selected and included for comparison of the median Agatston score between acquisition modes. For the group with a high heart rate, the median Agatston score was 59.5 (IQR: 13.4–198.4) and 59.1 (IQR: 13.8–205.9) for high-pitch spiral and sequential mode respectively ($p=0.002$). Also, for the low heart rate group, a significant difference in CAC score was found between the acquisition modes, with median Agatston scores of 54.6 (IQR: 11.3–219.1) for the high-pitch spiral mode and 60.1 (IQR: 13.0–216.0) for the sequential mode ($p=0.042$). The median difference of Agatston scores between the high-pitch and sequential mode was -1.6 and -4.8 for the high and low heart rate group, respectively ($p=0.08$). The absolute difference in Agatston scores increased for increasing mean Agatston scores (of the two scan modes), both for the high heart rate group ($\tau_b=0.60$, $p<0.001$) and for the low heart rate group ($\tau_b=0.59$, $p<0.001$, see *Figure 2*). The median absolute difference in Agatston scores was 14.2% and 9.2% for the high and low heart rate group, respectively. For the Agatston score, absolute differences score showed a very weak correlation with heart rate ($\tau_b=0.074$, $p<0.001$, see *Figure 3*). No trend was found for the relationship between thorax diameter and absolute differences of Agatston scores ($\tau_b=0.034$, $p=0.06$).

Cardiovascular risk categorization

The CVD risk categorization was determined for each acquisition mode in each heart rate group (*Table 1* and *Table 2*). In the high heart rate group, reclassification occurred in 4.9% of the cases. In 2.2% of all cases, participants shifted to a higher risk category and in 2.7% of all cases, participants shifted to a lower risk category for the high-pitch spiral acquisition compared to the categorization based on the sequential acquisition. No participants shifted more than one risk category upward or downward, and agreement was high between the two acquisition modes for the high heart rate group ($\kappa=0.927$).

In the reference group of individuals with low heart rates, reclassification occurred in 3.6% of the cases. In 1.0% of all cases, participants shifted to a higher risk category and in 2.6% of all cases, participants shifted to a lower risk category for the high-pitch spiral acquisition compared to the categorization based on the sequential acquisition. No participants shifted more than one risk category upward or downward, and agreement between the two scan acquisition modes was high for individuals in the low heart rate group ($\kappa=0.946$).

Radiation dose

The mean $CTDI_{vol}$ of the high-pitch spiral acquisition, including both the high and low heart rate group, was 1.75 (SD: ± 0.60) mGy. This was significantly lower than the mean dose of the sequential acquisition with 3.37 (SD: ± 1.23) mGy, $p < 0.001$. With a mean scan length of 19.1 (SD: ± 1.2) cm and using the conversion coefficient of 0.017 mSv/mGy \times cm, the mean effective radiation dose was 0.57 (SD: ± 0.19) mSv for high-pitch spiral acquisition and 1.09 (SD: ± 0.39) mSv for sequential acquisition. This corresponds to a potential dose reduction of 48% when high-pitch spiral imaging is used instead of the sequential scan mode.

Discussion

In this study, we have shown that high-pitch spiral mode instead of sequential mode can be used for CAC risk stratification in individuals with a regular high heart rate, resulting in 48% radiation dose reduction. A similar percentage of data sets without detectable calcium was found for high-pitch spiral and sequential acquisitions regardless of the heart rate. The Agatston score was slightly lower based on high-pitch spiral acquisition compared to sequential acquisition both for the low and high heart rate group. However, the difference in Agatston scores between high-pitch spiral and

sequential acquisitions was similar for the high heart rate group and the reference group of patients with a heart rate ≤ 65 bpm. Moreover, risk categorization based on the Agatston score showed almost perfect agreement for both acquisition modes in both heart rate groups. Thus, radiation dose can potentially be halved when the high-pitch spiral mode is used instead of the sequential mode in patients with a high, but regular heart rate.

Dose reduction

In the last decade, many publications have addressed dose reduction for coronary calcium imaging by computed tomography. To the best of our knowledge, no studies have yet compared different acquisition modes for CAC imaging by DSCT. Several studies focused on iterative reconstruction in combination with a low tube current and/or the use of a low tube voltage to reduce the radiation dose of CAC imaging [10–15]. It has been shown that the radiation dose for CAC imaging with iterative reconstruction can be reduced by 40–80%, resulting in radiation doses in the range of 0.8–6.3 mGy [10–15]. These studies included CT systems of different vendors used in today's clinical practice. The results of our study reveal that a dose reduction of 48% is feasible, resulting in a median dose in vivo of 1.75 mGy using FBP. In literature, some studies showed no significant difference in CAC scores when iterative reconstruction was applied compared to the reference scan with FBP [11,14]. On the other hand, other studies did report significantly lower CAC scores when iterative reconstruction was applied [10,12,15]. Nevertheless, a combination of high-pitch spiral acquisition with iterative reconstruction and a lower tube current may potentially result in even lower radiation dose for CAC imaging with similar CAC scores and/or CVD risk stratification. However, future clinical studies should confirm this.

Agatston score differences and risk categorization agreement

In our study, we could show that use of high-pitch spiral acquisitions did not affect the number of participants with a zero score compared to the sequential mode, regardless of the heart rate. This is of major importance, since the absence of detectable calcification is associated with very low risk of developing CVD [16]. Nevertheless, a small number of participants did shift from a zero score to a positive score and vice versa. However the percentage of individuals who shifted was similar in the high heart rate group compared to the reference group of individuals with low heart rates.

The difference in Agatston scores between acquisition modes increased for increasing

Agatston scores. Heart rate had only minor impact on this difference, and thorax diameter did not influence the difference in Agatston scores at all. In studies of Sabour et al. and Budoff et al., repeated imaging of patients with identical acquisition parameters or with different CT systems also showed that the difference in Agatston scores increased for increasing Agatston scores [17,18]. Therefore, comparison of absolute differences in Agatston scores between different studies is not possible. Studies reporting Agatston score differences/variability for inter- and intra-scanner comparison showed mean and median differences with a wide range: 1.8–29% [17,19–22]. In our study, similar absolute median differences were found, i.e. from 9-14%.

Although positive Agatston scores were higher based on sequential acquisitions than high-pitch spiral acquisitions - for both heart rate groups - CVD risk categorization showed excellent agreement ($\kappa \geq 0.972$) between acquisition modes, both for the high and low heart rate groups. Besides, reclassification occurred in 4.9% of the cases when the high-pitch spiral mode was used in participants with a high heart rate, and also occurred in 3.6% of the participants with low heart rates. Other studies have reported reclassification up to 2–9% for inter- and intra-scanner comparisons, and up to 11% for iterative reconstruction versus standard FBP reconstructions [13,22–24]. This shows that reclassification remains within routine limits when using a different data acquisition mode even in patients with high heart rates, minimizing any potential impact of the reclassification. Besides, both up- and downward reclassification were present in nearly similar percentages in both heart rate groups, further minimizing a potential impact of reclassification due to the acquisition mode on a population level.

Study limitations

In this multi-center study, a large sample size was used to show non-inferiority of data acquisition modes for CAC imaging in participants with a regular, but high heart rate. The fact that all acquisitions were triggered at 60% of the R-R interval regardless of the heart rate is a limitation of this study. In literature, it is shown that the cardiac phase with least motion and measurement variability is mid-diastolic (60–75%) for heart rates ≤ 70 bpm and end-systolic (40–45% of the R-R interval) for heart rates > 70 bpm [25,26]. However, ECG-triggering in mid diastole in patients with high heart rate has also revealed favorable results, suggesting that mid-diastolic ECG-triggering should be possible in all individuals, regardless of heart rate [26]. Moreover, we included a reference group of participants with low heart rates, which showed that the magnitude of differences between data acquisition modes is mainly related to the magnitude of the score and not to the heart rate.

In this study, we excluded participants with an irregular heart rates (23% of the scanned population). In these participants, no mean heart rate could be determined and the sample-size of this group was too low to determine non-inferiority of the high-pitch spiral mode versus the reference sequential mode.

Our study focused on two data acquisition modes, of which the high-pitch spiral mode is only available in the latest (2nd and 3rd) generations of DSCT. CAC imaging on multi-detector CT (single source) systems can be performed with a prospectively ECG-triggered sequential mode or a retrospectively ECG-gated spiral mode. Dose reduction by use of the high-pitch spiral acquisition mode is thus possible only in a limited number of CT system types.

Conclusion

In conclusion, CVD risk stratification based on coronary calcium imaging in high-pitch spiral mode shows excellent agreement with risk stratification based on sequential mode, both in individuals with low and high heart rates. If heart rate is high, but regular, radiation dose of coronary calcium imaging can be reduced by 48% through use of a high-pitch spiral mode compared to the sequential mode.

References

- [1] M.J. Blaha, K. Matsushita, Coronary Artery Calcium, Need for More Clarity in Guidelines, *JACC Cardiovasc. Imaging*. 10 (2017) 154–156. doi:10.1016/j.jcmg.2016.05.017.
- [2] A.A. Mahabadi, S. Möhlenkamp, N. Lehmann, et al., CAC Score Improves Coronary and CV Risk Assessment Above Statin Indication by ESC and AHA/ACC Primary Prevention Guidelines, *JACC Cardiovasc. Imaging*. 10 (2017) 143–153. doi:10.1016/j.jcmg.2016.03.022.
- [3] V. Sathiyakumar, R.S. Blumenthal, K. Nasir, S.S. Martin, Addressing Knowledge Gaps in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Review of Recent Coronary Artery Calcium Literature, *Curr. Atheroscler. Rep.* 19 (2017) 7. doi:10.1007/s11883-017-0643-4.
- [4] M.J. Blaha, M.G. Silverman, M.J. Budoff, Is There a Role for Coronary Artery Calcium Scoring for Management of Asymptomatic Patients at Risk for Coronary Artery Disease?: Clinical Risk Scores Are Not Sufficient To Define Primary Prevention Treatment Strategies Among Asymptomatic Patients, *Circ. Cardiovasc. Imaging*. 7 (2014) 398–408. doi:10.1161/CIRCIMAGING.113.000341.
- [5] D.C. Goff, D.M. Lloyd-Jones, G. Bennett, et al., 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *Circulation*. 129 (2014) S49-73. doi:10.1161/01.cir.0000437741.48606.98.
- [6] M.F. Piepoli, A.W. Hoes, S. Agewall, et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice, *Atherosclerosis*. 37 (2016) 2315–2381. doi:10.1093/eurheartj/ehw106.
- [7] R.A.P. Takx, I. Išgum, M.J. Willeminck, et al., Quantification of coronary artery calcium in nongated CT to predict cardiovascular events in male lung cancer screening participants: Results of the NELSON study, *J. Cardiovasc. Comput. Tomogr.* 9 (2015) 50–57. doi:10.1016/j.jcct.2014.11.006.
- [8] J.M. Hughes-Austin, A. Dominguez, M.A. Allison, et al., Relationship of Coronary Calcium on Standard Chest CT Scans With Mortality, *JACC Cardiovasc. Imaging*. 9 (2016) 152–159. doi:10.1016/j.jcmg.2015.06.030.
- [9] M. Vonder, C.M. van der Aalst, R. Vliegenthart, et al., Coronary Artery Calcium Imaging in the ROBINSCA Trial, *Acad. Radiol.* 25 (2018) 118–128. doi:10.1016/j.acra.2017.07.010.
- [10] S. Oda, D. Utsunomiya, T. Nakaura, et al., The Influence of Iterative Reconstruction on Coronary Artery Calcium Scoring—Phantom and Clinical Studies, *Acad. Radiol.* 24 (2016) 1–7. doi:10.1016/j.acra.2016.11.003.
- [11] N.R. van der Werf, M.J. Willeminck, T.P. Willems, M.J.W. Greuter, T. Leiner, Influence of dose reduction and iterative reconstruction on CT calcium scores: a multi-manufacturer dynamic phantom study, *Int. J. Cardiovasc. Imaging*. 33 (2017) 899–914. doi:10.1007/s10554-017-1061-y.
- [12] M.J. Willeminck, A.M. den Harder, W. Foppen, et al., Finding the optimal dose reduction and iterative reconstruction level for coronary calcium scoring, *J. Cardiovasc. Comput. Tomogr.* 10 (2015) 69–75. doi:10.1016/j.jcct.2015.08.004.

- [13] A.D. Choi, E.S. Leifer, J. Yu, et al., Prospective evaluation of the influence of iterative reconstruction on the reproducibility of coronary calcium quantification in reduced radiation dose 320 detector row CT, *J. Cardiovasc. Comput. Tomogr.* 10 (2016) 359–363. doi:10.1016/j.jcct.2016.07.016.
- [14] A.M. den Harder, J.M. Wolterink, M.J. Willeminck, et al., Submillisievert coronary calcium quantification using model-based iterative reconstruction: A within-patient analysis, *Eur. J. Radiol.* 85 (2016) 2152–2159. doi:10.1016/j.ejrad.2016.09.028.
- [15] J. Blobel, J. Mews, J.D. Schuijff, W. Overlaet, Determining the Radiation Dose Reduction Potential for Coronary Calcium Scanning With Computed Tomography the Adaptive Iterative Dose Reduction Algorithm for Image Reconstruction, *Invest. Radiol.* 48 (2013) 857–862.
- [16] A. Sarwar, L.J. Shaw, M.D. Shapiro, et al., Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification, *JACC Cardiovasc. Imaging.* 2 (2009) 675–688. doi:10.1016/j.jcmg.2008.12.031.
- [17] S. Sabour, A. Rutten, Y.T. Van Der Schouw, et al., Inter-scan reproducibility of coronary calcium measurement using Multi Detector-Row Computed Tomography (MDCT), *Eur. J. Epidemiol.* 22 (2007) 235–243. doi:10.1007/s10654-007-9123-4.
- [18] M.J. Budoff, R.L. McClelland, H. Chung, et al., Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: The multi-ethnic study of atherosclerosis, *Am. J. Roentgenol.* 192 (2009) 613–617. doi:10.2214/AJR.08.1242.
- [19] J.R. Ghadri, R. Goetti, M. Fiechter, et al., Inter-scan variability of coronary artery calcium scoring assessed on 64-multidetector computed tomography vs. dual-source computed tomography: A head-to-head comparison, *Eur. Heart J.* 32 (2011) 1865–1874. doi:10.1093/eurheartj/ehr157.
- [20] J. Horiguchi, N. Matsuura, H. Yamamoto, et al., Coronary Artery Calcium Scoring on Low-dose Prospective Electrocardiographically-triggered 64-Slice CT, *Acad. Radiol.* 16 (2009) 187–193. doi:10.1016/j.acra.2008.05.017.
- [21] J. Horiguchi, M. Kiguchi, C. Fujioka, et al., Variability of Repeated Coronary Artery Calcium Scoring and Radiation Dose on 64- and 16-Slice Computed Tomography by Prospective Electrocardiographically-triggered Axial and Retrospective Electrocardiographically-gated Spiral Computed Tomography, *Acad. Radiol.* 15 (2008) 958–965. doi:10.1016/j.acra.2008.03.007.
- [22] M.J. Willeminck, R. Vliegthart, R.A.P. Takx, et al., Coronary Artery Calcification Scoring with State-of-the-Art CT Scanners from Different Vendors Has Substantial Effect on Risk, *Radiology.* 273 (2014) 695–702.
- [23] A. Hutt, A. Duhamel, V. Deken, et al., Coronary calcium screening with dual-source CT: reliability of ungated, high-pitch chest CT in comparison with dedicated calcium-scoring CT, *Eur. Radiol.* 26 (2016) 1521–1528. doi:10.1007/s00330-015-3978-7.
- [24] A. Rutten, I. Isgum, M. Prokop, Coronary Calcification: Effect of Small Variation of Scan Starting Position on Agatston, Volume, and Mass Scores, *Radiology.* 246 (2008) 90–98. doi:10.1148/radiol.2461070006.
- [25] A. Rutten, S.P.J. Krul, M.F.L. Meijs, A.M. de Vos, M.-J.M. Cramer, M. Prokop, Variability of coronary

calcium scores throughout the cardiac cycle: implications for the appropriate use of electrocardiogram-dose modulation with retrospectively gated computed tomography, *Invest. Radiol.* 43 (2008) 187–94. doi:10.1097/RLI.0b013e31815cdd56.

- [26] N. Matsuura, J. Horiguchi, H. Yamamoto, et al., Optimal cardiac phase for coronary artery calcium scoring on single-source 64-MDCT scanner: Least interscan variability and least motion artifacts, *Am. J. Roentgenol.* 190 (2008) 1561–1568. doi:10.2214/AJR.07.3120.





Part II

Dose reduction as a function of imaging biomarker validity

