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Cardiac MRI in Young Adults with Sedentary Lifestyle-Related Risks

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Chapter 8

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Summary & general discussion

SUMMARY

Lifestyle is becoming increasingly inactive with unhealthy food intake, leading to growing populations being overweight and obese (1). Obesity affects cellular processes similar to aging, and therefore obesity is considered to accelerate the aging process (2,3). Since young adults are becoming increasingly obese, the aging-related diseases hypertension and type 2 diabetes (T2D) can already have an early onset in the young (4). These risk factors are strongly associated with the development of cardiac and aortic diseases (5,6).

High-risk factors trigger cardiac alterations in mature populations free of symptoms as demonstrated on cardiac magnetic resonance imaging (MRI), however, for young adults this was unknown (7–10). These cardiac alterations can potentially progress to symptomatic heart failure, depending on severity and duration of the underlying risk factors (11–13).

Development of ischemic cardiomyopathy is partly age-related, while progression of risk factor-related cardiac alterations to heart failure depends on duration (14,15). Sudden cardiac death (SCD) in young adults, therefore, often originates from a non-ischemic cardiomyopathy with hereditary components, such as hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM) (16,17). Within these diseases, changes in cardiac function, cardiac morphology, tissue characteristics and myocardial strain are detectable on cardiac MRI (18,19). However, during the early stage, these changes are subtle.

Although risk factor-related alterations are associated with longitudinal adverse outcomes, these alterations can be considered normal within high-risk groups. However, when cardiac MRI outcomes of high-risk populations are evaluated using reference data based on healthy individuals without high-risk factors, this could lead to inaccurate assessment and misdiagnosis of non-ischemic cardiomyopathies, especially in the early stage (20). Since early detection of cardiac diseases is essential for optimal treatment strategy and thus to **prevent the attack** (hence the *Pre-tack* study), the aims of this thesis were to investigate cardiac MRI alterations in young high-risk populations and to improve the diagnostic workflow (21,22).

THESIS RESULTS

Chapter 2 contains a meta-analysis of studies that reported myocardial T_2 and T_2^* mapping values in patients with non-ischemic cardiomyopathies, patients with heart transplantation, and high-risk populations. T_2 mapping is sensitive to the formation of edema, and accordingly, higher T_2 values were reported in diseases with myocardial inflammation, including myocardial infarction, heart transplant rejection, sarcoidosis, lupus and myocarditis. In

amyloidosis, HCM and DCM, T_2 values were also higher relative to controls. Furthermore, changes in T_2^* mapping values are caused by physiological processes that affect the magnetic field. In line with this, lower T_2^* values were found in iron overload patients and in patients with myocardial infarction after percutaneous coronary intervention due to hemorrhage formation. In HCM and DCM patients, lower T_2^* values were also found relative to controls. Although these differences were insignificant on group level, differences were larger when the disease was more advanced, evidenced by late gadolinium enhanced myocardium and severely impaired LV ejection fraction (23,24). Regarding high-risk populations, only one study was found that showed significantly lower T_2^* values in hypertensive individuals relative to controls, especially in presence of left ventricular hypertrophy (LVH) (25). Since studies in high-risk populations were limited, the potential of parametric mapping techniques to differentiate remodeling between risk factors and non-ischemic heart disease could not be demonstrated.

Besides the differences in mapping values between patients and controls, substantial variation was found in mapping values of healthy controls between studies. This variation related to differences in acquisition methods, MRI vendor and population demographics as evidenced by this meta-analysis. For correct interpretation of mapping values in patients, locally generated reference ranges of healthy controls should be available. Without these reference ranges, quantitative mapping results should not be reported clinically (22). Therefore, in the *Pre-tack* study, not only high-risk populations were included, but also healthy controls in the same age group.

In **chapter 3**, it was demonstrated in patients referred for aortic imaging that electrocardiogram (ECG)-triggered navigator-gated steady-state free precession magnetic resonance angiography (MRA) provides similar thoracic aortic dimensions as the standard contrast-enhanced MRA. Since ECG-triggering minimizes the impact of cardiac motion, this resulted in improved image quality and higher reproducibility of aortic dimensions close to the heart. With ECG-triggered MRA, the use of contrast agents can be avoided and potential health risks can be reduced. This particularly applies to high-risk populations as the renal function is relatively often impaired. Also, risk conditions accelerate vascular aging and therefore these populations are at increased risk for developing aortic diseases. Nevertheless, ECG-triggering is unsuitable for patients with cardiac arrhythmias, and also for unstable patients because of relatively long acquisition times. In conclusion, ECG-triggered MRA is a feasible alternative for assessment of thoracic aortic dimensions in patients who cannot tolerate contrast agents, and also in patients requiring accurate assessment of landmarks close to the aortic root.

For the assessment of cardiac morphology and function, post-processing is performed by manually contour-tracing a stack of short-axis cines (26). Although short-axis cines offer high reproducibility, it may take some learning for beginners to achieve this, especially due to the relatively complex anatomy in basal slices (27–29). Since accurate and reproducible contour-tracing is essential for correct diagnosis, an existing contour-tracing protocol was adjusted and simplified in **chapter 4**, also incorporating post-processing recommendations (26,30). The acquisition parameters of *Pre-tack* study datasets complied with current guidelines and differed from the datasets used for the existing protocol, therefore, adjustments were made to correct for them (31). Further, to reduce operator-induced variability in slices with partial ventricular anatomy, non-ventricular structures were instructed to exclude with straight lines if the border was unclear. Lastly, to avoid large discrepancies in tracing results, LV and right ventricular (RV) stroke volumes were compared as these should be similar in absence of valvular leakage, and also end-diastolic and end-systolic mass were compared. These control mechanisms were also used in the UK Biobank study (32), demonstrating superior reproducibility than other studies. As similar reproducibility was obtained by observers inexperienced in cardiac post-processing in the current study, this suggests that beginners can easily be trained with the new contour-tracing protocol. Nevertheless, manual contour-tracing remains a time-consuming task, limiting clinical workflow.

Studies showed that artificial intelligence could increase speed and improve reproducibility of cardiac function post-processing, however, accurately contour-tracing basal slices remains challenging (33,34). Therefore, in **chapter 4**, two levels of automated post-processing were evaluated in three software packages. Level 1, i.e., fully automated post-processing, was ten times faster and more reproducible than conventional manual contour-tracing, but only few measurements were considered accurate. For Level 2, the automatically generated basal contours were manually corrected using the contour-tracing protocol. In two of the three software packages, the generated contours differed considerably from the real anatomy in several short-axis slices, limiting this semi-automated approach. Nevertheless, one package performed reasonably well and achieved high accuracy after cardiac outcomes were corrected with a factor to overcome the relative difference with manual tracing, i.e., automated contours that are consistently traced too tight or too loose around the region-of-interest. Since these results were still acquired four times faster with superior reproducibility, the semi-automated approach could be a good trade-off between speed and accuracy.

In **chapter 5**, the impact of overweight and hypertension was investigated in age- and gender-matched populations. In populations with these risk-factors, the LV mass was significantly

higher than in normotensive normal-weight controls, and this increase was the highest when both conditions were present. Since overweight and hypertensive populations had normal T_1 values and lower extracellular volume (ECV) relative to controls, this suggested that the increases in LV mass mainly related to myocyte growth instead of fibrosis or fatty infiltration. Further, cardiac volumes were not increased in overweight populations relative to normal-weight populations. However, when considering only the obese subpopulation, higher volumes were showed, though insignificant.

Since cardiac dimensions are strongly correlated with body size, cardiac volumes and LV mass were indexed for body surface area (BSA) as recommended in **chapter 5** (26). However, BSA-indexation in overweight populations resulted in smaller volumes relative to normal-weight groups, and also in normalization of LV mass. These undesired effects in overweight populations can be overcome with indexation for height or height to the power of 2.7.

In **chapter 6**, it was demonstrated in the entire *Pre-tack* study cohort that cardiac MRI outcomes were not only related with the non-modifiable parameters age, gender and height, but also with risk factor-related parameters. With multivariate linear regression, an increased BMI was associated with larger volumes, increased LV mass, higher native T_1 values and lower ECV, whereas an increased waist–hip ratio was associated with smaller volumes. Further, increased systolic blood pressure was related with increased LV mass, lower ECV and lower T_2 values, whereas systolic and diastolic blood pressure had opposite effects on volumes. The T2D blood marker HbA1c was linked with increased LV mass, a larger right ventricle, and increased ECV. Lastly, increased heart rate was associated with smaller volumes, lower LV mass and lower T_2 values, the latter being a consequence of the MRI sequence. The models explained substantial variation in volumes and LV mass, while for ejection fractions and tissue characteristics less variation was explained. The reported associations were in general similar as demonstrated in mature populations, suggesting cardiac alterations irrespective of age.

In order to better differentiate risk factor-related modifications from early-stage cardiomyopathy, gender-specific reference ranges of cardiac morphology, cardiac function and tissue characteristics were reported for different groups in **chapter 6**. These reference ranges contain mean with standard deviation and the 95th percentile that potentially could be used as cut-off value. Since BSA-indexation is undesired as previously mentioned, height^{2.7}-indexed volumes and LV mass were added. These ranges were only generated for overweight populations, hypertensive populations, hypertensive overweight populations, and healthy controls, as there was insufficient data available for T2D populations.

Chapter 7 showed that myocardial dysfunction is already present in young high-risk populations. This dysfunction was detected using the deep learning post-processing workflow *DeepStrain*, enabling strain analysis in circumferential and radial direction. The global circumferential early-diastolic strain rate was lower in all risk groups relative to controls, with the largest decline in the group with most risk factors, suggesting myocardial dysfunction during the relaxation phase. Also, subtle regional abnormalities in contractility were found in risk groups, as septal systolic strain was reduced, but compensated by the lateral wall, resulting in normal global values. Since these findings, i.e., asymptomatic LV diastolic and systolic dysfunction, are characterized by the risk of progression to symptomatic heart failure, the addition of *DeepStrain* to routine cardiac MRI studies could provide more information on myocardial function than the standard ejection fraction.

GENERAL DISCUSSION

Diagnostic implications

The main goal of this thesis was to investigate the impact of overweight, hypertension and T2D on cardiac MRI outcomes in young asymptomatic adults. In a prospectively recruited study population, it was demonstrated that these high-risk factors cause subclinical alterations in LV mass, cardiac volumes, tissue characteristics and myocardial function.

Body mass index (BMI, in kg/m^2) is often used as a metric to describe the level of body fatness, although it has repeatedly been shown to be a poor determinant of the percentage of body fat (35). According to the World Health Organization, the BMI classification includes underweight (BMI ≤ 18.4), normal-weight (BMI 18.5–24.9), overweight (BMI 25–29.9), class I obesity (BMI 30–34.9), class II obesity (BMI 35–39.9) and class III obesity (BMI ≥ 40) (36). In the Netherlands, 36% of the adults is overweight, 13% has class I or class II obesity, and 1% has class III obesity (37). In the United States, these percentages are substantially higher (31%, 42% and 9%, respectively), showing that normal-weight is not the average among Western populations (38). In the *Pre-tack* study cohort, included subjects with a BMI $\geq 25 \text{ kg}/\text{m}^2$ were mainly overweight (55%) and class I or class II obese (40%), being a good representative across overweight populations. Individuals with a BMI above $40 \text{ kg}/\text{m}^2$ were hardly included (5%), and since especially class III obesity has adverse prognostic impact on the heart, it can be questionable to consider their risk factor-related alterations normal (15).

For the diagnosis of HCM, a maximum wall thickness of $\geq 15 \text{ mm}$ should be found in absence of conditions leading to secondary hypertrophy such as hypertension or athletic conditioning (39). For relatives of HCM patients, an unexplained wall thickness of $\geq 13 \text{ mm}$ is already sufficient for its diagnosis (40). In the *Pre-tack* study cohort, few participants had a wall thickness of 13.5 mm , potentially suggestive for HCM. However, these were all diagnosed with hypertension, showing that considering pressure-overload conditions is indeed essential. Although none of the participants with only overweight or obesity exceeded cut-off values for HCM diagnosis (maximum 12.5 mm), the wall thickness in these groups was higher relative to controls. Despite obesity being associated with concentric remodeling, this factor was not mentioned as potential overlapping factor in the guideline, whereas especially severe obesity could influence decision-making and may lead to false positive diagnosis (41). Also, for the assessment of other cardiac diseases in which a thickened wall is a suggestive manifestation such as amyloidosis and Anderson-Fabry disease, considering risk-related adaptation is important (42,43).

Enlargement of ventricles is an important finding on MRI for some cardiac diseases (18). For the diagnosis of DCM, one of the two major diagnostic criteria is a LV end-diastolic volume that is two standard deviations above the normal after correction for BSA (44). Similarly, for arrhythmogenic RV dysplasia, one of the three major criteria is a BSA-indexed RV end-diastolic volume above gender-specific cut-off values (45). Correction for BSA is recommended since cardiac volumes are strongly correlated with body size (26). Indeed, with multivariate linear regression, significant positive associations of volumes were found with both height and BMI. Nevertheless, based on generated reference ranges, cardiac volumes were similar between overweight and normal-weight groups, whereas for the obese subpopulation volumes seemed somewhat larger. After BSA-indexation, however, cardiac volumes were smaller in overweight populations relative to normal-weight. Consequently, in overweight populations, this could potentially lead to underdiagnosis of cardiac diseases that rely on BSA-indexed volumes. With indexation for height or by using the normal of overweight populations instead of healthy populations, this could be circumvented.

In the studied high-risk groups, native T_1 and T_2 values were comparable to controls. The reported effect of overweight was consistent with findings in a bit older population that also used a BMI of 25 kg/m² to differentiate between normal-weight and overweight (46). In general, increased native T_1 and T_2 values in young populations in a clinical setting are therefore unlikely to be a consequence of risk-related remodeling, and more suggestive for any cardiac disease, for instance HCM or amyloidosis (47,48). Nevertheless, previous studies reported higher native T_1 values in hypertensive populations with compensated LVH, i.e., a higher LV mass than found in the *Pre-tack* study population (49). However, these native T_1 values were still substantially lower relative to HCM patients, and also lower than reported in relatives of HCM patients with gene mutations but without LVH. Furthermore, the ECV was decreased within the risk-populations overweight and hypertension, whereas in cardiac diseases the ECV is mainly increased (50). Similar to athletes, ECV could therefore help differentiate between risk-related adaptation and cardiac diseases (51). Although some studies reported increased ECV in older hypertensive subjects relative to controls (52), this increase was still smaller than reported in cardiac diseases (49).

Furthermore, the demonstrated subclinical myocardial dysfunction in high-risk populations could overlap findings in early non-ischemic cardiomyopathy (53). For instance, in patients with HCM, the diastolic function is significantly impaired caused by LVH and myocardial stiffness, while the systolic function is affected less (54). As carriers of HCM disease mutations without LVH already have subtle dysfunction relative to controls, strain is suggested to be an

early marker (55). Further, in DCM patients, the systolic function is impaired, sometimes accompanied by diastolic dysfunction (19). Recently, strain was proposed as screening method for subclinical disease within asymptomatic relatives of DCM patients (56). For correct interpretation of strain outcomes in high-risk populations with suspected heart disease, considering risk factor-related myocardial dysfunction is essential.

Prognostic implications

BMI is the widely accepted measure to classify overweight and obesity, however, it does not provide information about body fat distribution (35,57). In peripheral obesity, fat is mostly stored around the hips and thighs, and this is the so-called pear body shape (58). In abdominal obesity, fat is mostly concentrated around the abdomen, known as the apple body shape (59). As especially abdominal obesity is associated with incident cardiovascular events, considering the fat distribution is important, and this was measured in this thesis with the ratio between waist and hip circumference (60). Also, particularly in abdominal obesity, the excessive amount of adipose tissue releases inflammatory adipocytokines, leading to hypertension and T2D (61–63).

In absence of coronary artery disease or any primary cardiomyopathy, presence of high-risk factors can still lead to symptomatic heart failure. In obesity, increased central blood volume can result in ventricular dilation and LVH (64). Adequate LVH could result in diastolic dysfunction, while inadequate LVH can cause systolic dysfunction (11). Also, accumulation of myocardial fat or formation of myocardial fibrosis can occur, potentially resulting in diastolic and eventually systolic dysfunction. The risk of developing heart failure, i.e., obesity cardiomyopathy, grows with increasing BMI and also with longer duration of obesity (15). In hypertension, elevated blood pressure leads to increased ventricular wall stress. After compensatory mechanisms take place to minimize wall stress, this could evolve to hypertensive heart disease. The progression of hypertensive heart disease can be divided among four degrees based on pathophysiological and clinical impact (12): (I) LV diastolic dysfunction without LVH; (II) LV diastolic dysfunction with concentric LVH; (III) symptomatic heart failure with preserved ejection fraction; and (IV) symptomatic heart failure with dilated cardiomyopathy and reduced ejection fraction. In T2D, pathophysiological pathways are triggered by hyperglycemia, insulin resistance and hyperinsulinemia, leading to subclinical changes, including myocardial fibrosis, and eventually LVH (13). These cardiac abnormalities can lead to symptomatic heart failure with preserved ejection fraction, and ultimately result in systolic dysfunction with reduced ejection fraction, also known as diabetic cardiomyopathy.

Since progression of (uncontrolled) high-risk factors towards symptomatic heart failure is a long-term process, these cardiomyopathies are uncommon in younger populations (11–13).

The American Heart Association uses four stages to classify the evolution and progression of heart failure: stage A includes asymptomatic patients at risk for developing heart failure, such as obesity, hypertension and T2D; stage B includes asymptomatic patients with structural heart disease; stage C includes symptomatic patients with underlying structural disorders; and stage D includes symptomatic patients with end-stage heart failure requiring specialized treatment (65,66). Patients in stage A or stage B are classified as being at risk, while patients in stage C or stage D are classified as having heart failure (67). In reality, onset of heart failure symptoms is gradual, and patients might remain symptom-free by unconsciously reducing activity levels to compensate for worsening cardiac function, and therefore differentiating between stage B and stage C could be challenging. Since none of the included subjects had signs of structural heart disease, such as LVH, low ejection fraction or myocardial fibrosis, the asymptomatic high-risk study population is in stage A (68). Deterioration of diastolic or systolic function was not incorporated in the current staging system (66). However, recently it has been suggested to include this as stage B heart failure, because it is linked with heart failure in absence of structural remodeling or impaired ejection fraction (69).

Although there was no evidence of structural heart disease, some of the demonstrated subclinical cardiac alterations are related with longitudinal adverse events. Increased LV mass is strongly associated with SCD, even in asymptomatic populations, though the increases in LV mass in the *Pre-tack* study population were relatively small (70,71). Further, the accumulation of especially abdominal fat was associated with smaller volumes and concentric remodeling, the latter being linked to heart failure with preserved ejection fraction (72,73). Lastly, the reported subtle asymptomatic LV global diastolic and regional systolic dysfunction are characterized by the risk of progression to symptomatic heart failure (74,75). As populations with risk conditions are growing around the world, this forecasts an epidemic of heart failure and a huge burden for health care (76).

As individuals in stage A are at risk, this provides an early opportunity to minimize the future burden of heart failure (65). In this group, therapy is aimed at modification of the underlying risk factor to stop progression to advanced stages. Indeed, it is known that intentional weight loss in obesity is associated with a reduction in LV mass, and an improvement in LV diastolic function (77). Furthermore, antihypertensive medication in hypertensive patients can regress LV mass, and the use of antidiabetic drugs in T2D patients could prevent diabetic

cardiomyopathy (78,79). These therapies should be initiated early to minimize the impact of high-risk conditions, and to prevent irreversible adverse myocardial alterations (11,80).

Future perspectives

The additional inclusion of high-risk populations diagnosed with non-ischemic cardiomyopathy could provide more insights in the differentiation between risk factor-related adaptation and heart diseases. These non-ischemic cardiomyopathies should not be caused by risk factors, i.e., obesity cardiomyopathy, hypertensive heart disease or diabetic cardiomyopathy, but should include other heart disease etiologies, such as HCM, DCM or arrhythmogenic right ventricular cardiomyopathy. Therefore, future studies including healthy controls, asymptomatic high-risk populations, and high-risk populations diagnosed with non-ischemic cardiomyopathy could be the next step in unraveling the grey zone of cardiac alterations in young high-risk populations.

In absence of heart disease, the presence of high-risk factors can eventually still result in symptomatic heart failure (13,81,82). This raises the question, to what extent remain risk-related cardiac alterations non-harmful, and when are these alterations becoming suggestive for potential adverse events in the long-term. Ideally, subjects in the latter group should be recognized early to provide optimal treatment. For this purpose, future studies on young high-risk populations with long-term follow-up could help to link cardiac alterations with adverse events.

Inclusion of subjects with even higher BMI could provide more insights in obesity-related cardiac alterations. Nevertheless, it is known that especially severe obesity is associated with long-term adverse events, making it debatable to consider these normal (15). Further, with *DeepStrain*, only circumferential and radial strain were calculated, whereas longitudinal strain is usually reduced first in the early stage of cardiac diseases (83). Therefore, future analyses on longitudinal strain in high-risk populations would be of interest. Lastly, including more young adults with T2D would help to generate reference ranges of several cardiac MRI parameters for this group.

Individuals with obesity, hypertension and T2D are in stage A of the heart failure classification (65). With increasing severity and duration of these conditions, the likelihood of individuals progressing to advanced stages rises (81). Treatment of high-risk factors provides the earliest opportunity to prevent heart failure progression, emphasizing the importance of early recognition. Although overweight is easily identifiable, there is low awareness of having hypertension or T2D (84), and therefore health checks can be performed. In the United States,

adults aged 18 years and above are recommended to regularly visit health care providers for screening of hypertension, and additionally for diabetes when having risk-factors (85). In the United Kingdom, individuals aged 40 years and above are invited for health checks (86). In the Netherlands, health checks are less common, albeit the Dutch Heart Association recommended individuals aged 40 years and above to check their blood pressure on regular basis (87). Nevertheless, health checks in younger age groups seem not redundant, as hypertension and T2D can already have an early onset, especially in the growing overweight population. Ultimately, the phrase ‘prevention is better than cure’ also applies here, as healthy lifestyle from a young age on reduces the chance of developing high-risk conditions, and consequently reduces the future burden of heart failure.

Conclusion

In the prospectively recruited asymptomatic young adult study cohort, it was demonstrated that presence of overweight, hypertension and T2D already trigger cardiac alterations. Since duration of these high-risk factors was short, and severity of especially overweight was relatively mild, these subclinical alterations were not overlapping with current diagnostic criteria of non-ischemic cardiomyopathies. Nevertheless, for early detection of cardiac diseases, risk-related cardiac alterations need to be considered in clinical decision-making, and the generated reference ranges could be used to this end. With longer duration and increasing severity of high-risk factors, the associated cardiac alterations become more apparent as demonstrated in previous studies. Since these are associated with long-term adverse outcomes, this emphasizes the importance of a healthy lifestyle.

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