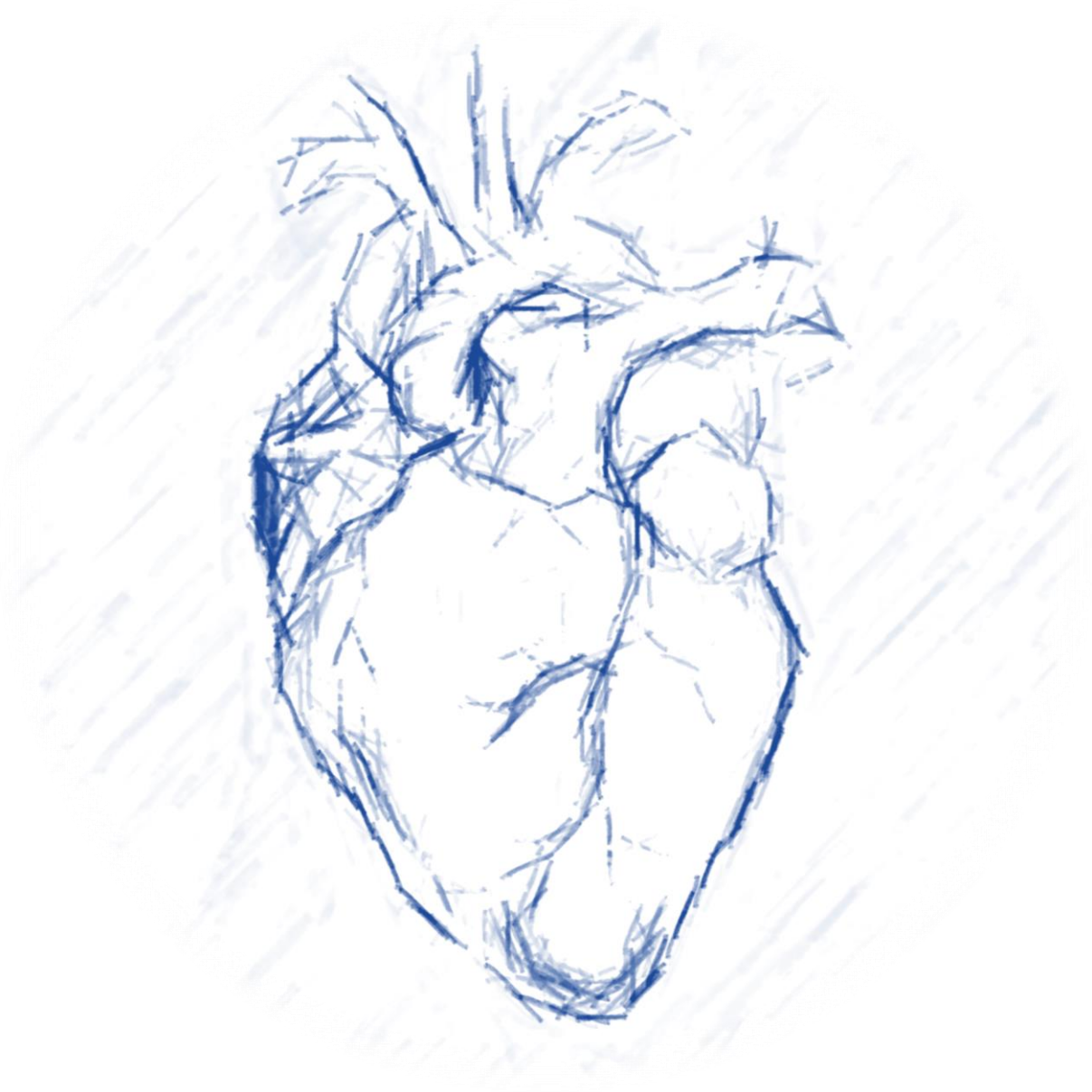

Validation of myocardial infarction diagnostics in adult patients with congenital heart defects in western Sweden

Degree Project in Medicine by Marcus Molinder

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Abstract

Background: At about 1% of live births worldwide, Congenital Heart Defects (CDH) is the most common major congenital defects worldwide. Since the 1950s, survival of these patients into adulthood has increased from 20% to 95%. As a consequence, patients with a CHD are steadily increasing in numbers, age and severity of the CHD but we have limited knowledge regarding the long term consequences and succeptability for risk factors and old age. It has been suggested, for instance, that they are prone to myocardial infarction (MI), but we do not know to what extent our diagnostic criteria applies to these patients. The aim of this study is to validate the diagnostics of MI in adult patients with CHD.

Method: A search was conducted in Elvis, the administative database of Västra Götalandsregionen of Sweden, and all patients with a CHD and an MI diagnosis were included. The medical records were retrieved and used to evaluate the basis for the MI diagnosis. The evaluation was performed using a modified version of a standard questionnaire for validation of potential cases of acute myocardial infarction. The diagnosis was then categorized as either correct, probable, improbable or incorrect.

Results: 32 patients were eligable for this study and accessible for evaluation. 65.6% (n = 21) of MI-diagnoses were classified as correct and 81.3% (n = 26) as either correct or probable, wich is lower than MI in the general population. Cases classified as incorrect or improbable were typically the result of difficulties in evaluating signs of old myocardial infarction or myocardial damage during surgical procedures.

Conclusion: Adult patients with a CHD seems to recieve an incorrect MI-diagnosis more often than in the general population, but not in the setting of the emergency ward. More studies with larger cohorts are needed.

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Abbreviations:

- CHD: Congenital heart disease
- ACHD: Adult with congenital heart disease
- MI: Myocardial infarction
- CAD: Coronary artery disease
- PPV: Positive predictive value
- IPR: Swedish Inpatient register
- PFO: Persistent foramen ovale

Introduction:

The heart

The heart is, quite simply, a pump. Or to be more precise – it is a parallel two-circuit pump where the right system receives deoxygenated blood from the body and pumps it into the lungs where it is filled with oxygen. The left system then recieves the oxygenated blood from the lungs and pumps it out to the body where it is used in the creation of energy and thus – critical for every living cell in the body. As one might expect, the embryonic development of the heart, being so critical for life and function, is a tightly controlled process. Even so – some kind of malfunction in this process occurs in about 1 in 100 babys born worldwide, and it is actually the most common major congenital defect. In order to understand these processes you need some kind of basic understanding of the embryonic development of the heart.

Development of the heart

The formation of the heart starts as two parallel tubes aligned along the axis of the body where the blood flows in a single linear stream from the caudal to the cranial end. These tubes then fuse, enlongates, loops, folds and grows in just the right way to create a primitive heart consisting of an upper chamber, the primitive atria, and lower chamber, the primitive ventricle, as well as an inflow and an outflow region.

But there is still only a linear, single-circuit flow of blood throughout, not the two-circuit system found in a mature heart. This is accomplished by the simultaneus formation of three septa, the atrioventricular, atrial and ventricular septa. By creating the four valves, one for each chamber, and separating the outflow of blood into one pulmonary and one systemic circuit, the heart finally reaches its mature configuration.

Given this complex process, and the essential function of the heart, it is no surprise that it is a tightly controlled process. Even so, each step of the way can go awry, and when it does the

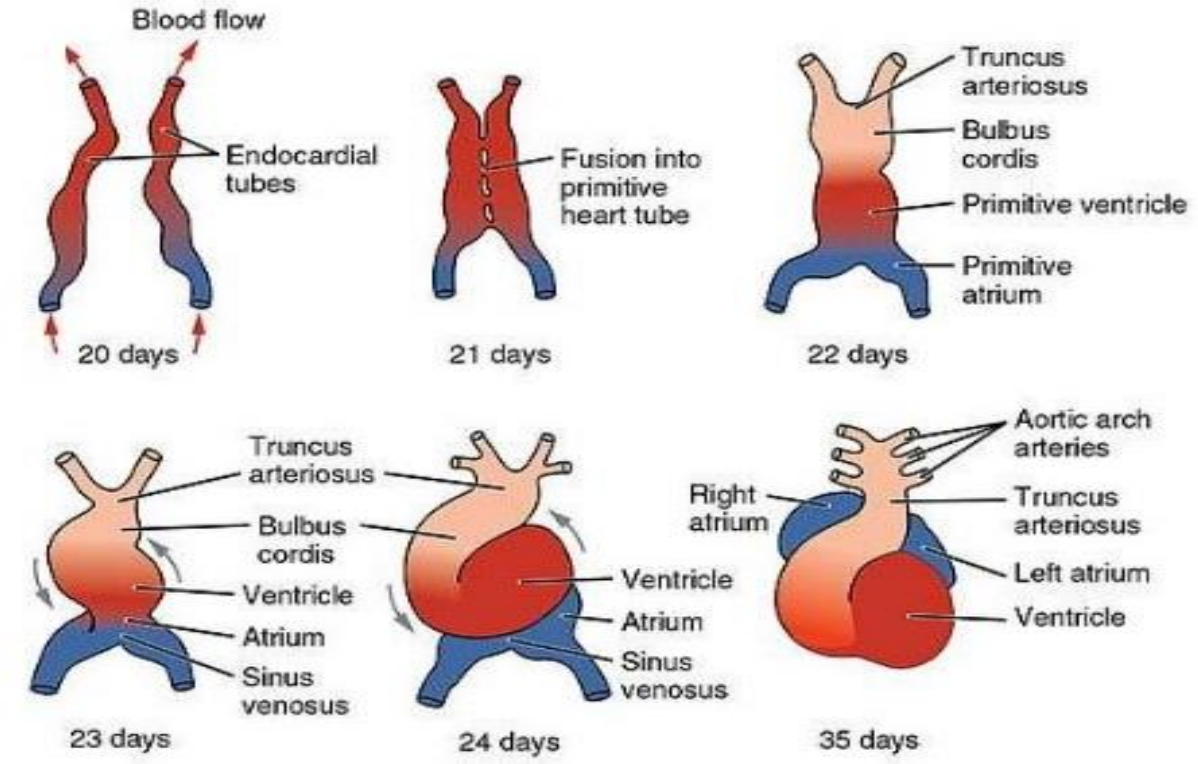

Figure 1 – Featal development of the heart related to number of days from conception

result is a congenital heart defect. If the malformation is severe enough the result is a spontaeus termination of the pregnancy. The malformation may also be so insignificant that the faetus is not only brought to term, but may also live a long and healthy life without becoming aware of it. There is also, of course, everything in between.

Congenital heart defects

As stated above, congenital heart defects (CHD) is present in about 1% of live births worldwide [1, 2, 3], which makes it the most common of all major congenital anomalies [4]. These conditions range substantually in severity - from those who sometimes can be asymtomatic and self-healing, such as atrial septal defects (ASD) and ventricular septal defects (VSD), to more severe conditions such as hypoplastic left heart syndrome, which is not compatible with life beyond 6-12 months of life without several surgical corrective procedures. Other conditions may also require surgery but may still be associated with hypoxia, arrhythmias or heart failure, even after corrective surgury.

During the second half of the last century, the treatment of patients with congenital heart disease has improved dramatically, and today almost 95% of infants born with CHD survive into adulthood [5]. The increase is primarily seen among patients with more severe defects, but the trend is visible in mild and severe defects as well [6]. Even though this is a remarkable development, these patients nevertheless face multiple cardiovascular complications and the healthcare utilization rates of these patients are significantly higher compared to non-CDH adults [7]. They are, for instance, at a higher risk of arrhythmias [8] [9], ischemic stroke [9] [10], endocarditis [11] and congestive heart failure as well as hypertension [11] compared to the general population. And because of the heterogeneity within the group, the risk factors of individuals vary greatly, depending on the nature and severity of the underlying condition.

Overall, the more severe the underlying condition is, the higher the susceptability to the risk factors mentioned above [12].

This development has also lead to dramatic changes in the population with adult congenital heart defect (ACHD), primarily in three aspects:

1. As more and more individuals are surviving into adulthood, the population with an ACHD are steadily increasing in numbers [13].
2. The median age of this patient group is increasing, making them more susceptible to risk factors related to old age**.** Indeed, the main determinants of mortality among this group is no longer attributed to the heart defect, but to acquired general medical conditions [14]. This is examplifyed further by the fact that the mortality rates in congenital heart diseases has shifted from the very young to the old [15]
3. The increased survival rates primarily reflect an improved treatment of patients with more severe and complex heart defects. In other word, many adults now live with a defect which just a couple of decades ago would lead to an early death. As a result these patients, as a group, now have more severe heart defects then before [6], some completely "new" as a diagnosis in adults.

Aspects of Coronary Artery Disease in ACHD

Adults with CHD have an elevated incidence of coronary artery disease (CAD) at a young age (11), and MI is now the leading cause of mortality in these patients [16]. At large, the mechanisms behind this are still unclear, but there are some indications worth noting.

Nature and severity of CHD-diagnosis

The nature and severity of the underlying anomality is surely an important factor regarding the risk of developing CAD. For example, patients with a CHD that entails an obstruction of the left ventricle or the aorta has been found to have coronary intimal hyperplasia more often compared to other CHD-diagnoses. In one study of paediatric patients, 100% of patients with these diagnoses had coronary hyperplasia (thought to represent the first stages of coronary atheroma), compared to 61% in of the patients with other CHD-diagnoses [17]. Also, a number of CHD may give rise to secondary conditions that in turn increases the risk of CAD. These include valvular aortic stenosis, present in about 3 - 6% of patients with ACHD, wich may give rise to left ventricular hypertrofy, an independent risk factor for CAD, [18], as well as aortic coarctation, which may give rise to systemic hypertension [17]. The possibility that more severe heart defects results in a higher rate of CAD is one that needs to be taken all the more seriously given the recent development stated above, namely that the severity of the underlying condition in the population with ACDH is steadily increasing.

So in general, it is supposed that the risk of CAD and MI increases with more severe heart defects. But even anomalities with few structural defects that might seem harmless can increase the incidence of atherosclerotic lesions in the area. Examples of this are the origin of the left circumflex artery from the right coronary artery or an abnormal origin of the left main coronary artery from the right sinus of Valsalva [19].

Another possibility is that what historically has been percieved as an isolated CHD rather is the representation of a more widespread or general cardiovascular disease. This has been proposed regarding the narrowing of the aorta in coarctation, as well as congenital pulmonary stenosis [20]. In this case, it may be that the CHD is not the cause of the CAD, but they are rather both representations of a general cardiovascular disease. In the case of coarctation this

is further implied by the fact that hypertension persists in about 50% of patients with surgically repaired coarcation [21].

Surgeries

It is worth noting that it is difficult to discern to what extent the increased prevalence of CAD is attributable to the nature and severity of the underlying condition or to the heart surgeries these patients undergo. For one thing, the patients with more severe CHD undergo a greater number of heart surgeries. But heart surgeries can range from closing an ASD by transcutaneous catheterization all the way to extremely complex procedures in multiple sessions, such as creating a so called Fontan circulation. So it is also true that the surgeries these patients need are often more advanced and complex then in less severe defect, and perhaps rendering an elevated risk for CAD.

One study of pediatric patients found that the patients with surgically repaired CHD presented higher expression of TGF-β1, a growth factor associated with CAD, in the intimal layer than those who had not undergone surgical repair. They also presented coronary intimal hyperplasia, thought to represent the first stage of coronary atheroma, at a much higher rate than those without surgical repair (80% and 47,3% respectively) [17]. And in the case of coarctation of the aorta, approximately 5% of young adults with repaired coarctation have CAD, and studies have shown that CAD is the main cause of death in patients with corrected coarctation of the aorta [22] [23].

Some of these procedures, like the arterial switch, conducted to correct d-transposition of the great vessels, includes manipulation of the coronary arteries. This may result in turbulent blood flow as well as shear stress on the coronary wall, thus increasing the risk of CAD. One study found that this procedure may result in ostial stenosis, possibly increasing the risk of

atherosclerosis. It also concluded that coronary lesions occurred in 6,8% of patients who underwent this type of surgery [24]. Another study was conducted to assess the morphology of the coronary wall with a long time follow-up in children who had gone through the arterial switch procedure (age 5 to 22 years of age, median 9,5). Of these patients, 89% displayed some type of proximal eccentric intimal proliferation and 50% of these where classified as moderate-to-severe lesions [25].

Lifestyle

A great deal of focus regarding the development of CAD in the general population has to do with lifestyle. Traditionally, the risk factors associated with lifestyle include blood levels of total and high-density lipoprotein (HDL) cholesterol, blood pressure, cigarette use, diet and sedentary lifestyle [26]. It has been reported that patients with ACHD tend to live a sedentary lifestyle [27], a risk factor for CAD [28]. It is the case that having a CHD often leads to reduced exercise capacity, wich is associated with worse prognosis and increased risk of CAD [29] [30]. But even though the exercise capacity often is lowered, there are only a handful ACHD-diagnoses where exercise could be harmful and restrictions regarding exercise are needed. Even so, exercise is frequently not discussed or even cautioned against by as well as relatives as medical professionals [31]. Together, the reduced exercise capacity and obesity contribute to hypertension and diabetes, and several studies has found the prevalence of these diseases to be greater in the ACHD-population compared to age-matched controls without ACHD [32] [33]. Interestingly, one study from Belgium found that even though these patients has a lesser prevalence of smokers and more participation in sports compared to the general population, they more often presented hypertension and diabetes, and only 20% of these patients had a fully heart-healthy lifestyle. [34].

Closely monitored

Patients with CHD has often from the time of birth been closely monitored regarding their health. They often have a personal doctor´who follows them for long periods. It could be that because these patients are so closely monitored in CHD clinics, CAD is found earlier and more frequently than the general population.

What happens in the emergency ward?

Diagnosis of CAD and MI in this patient group may be difficult; these patients often experience chest pains [35, 36], have abnormal electrocardiograms and elevated levels of Troponin T [37] as a default, effectively muddying the waters for any clinician trying to set a diagnosis of CAD. So what happens when a patient with a known CHD enters the ER? In a way there are, of course, countless scenarios depending on the situation and individuals involved and one might only more or less guess what might happen. But for the purpose of this study, the scenarios can be divided into three major scenarios. One is that the presence of a relatively unusual heart defect might make doctors more prone to suspect and attempt to falsify a MI-diagnosis. In this scenario, it would seem improbable that an experienced clinician would fail to detect an MI. Another scenario is that it might result in a false positive diagnosis, where the manifestation of the CHD is incorrectly interperated as an MI, perhaps leading to lifelong unneccesary medication and anxiety. Since it is unknown to what extent the diagnostic criteria for MI applies to patients with structural heart defect it could even be that the diagnosis is correct considering these criteria, even in the absence of an actual cardiovascular lesion. A third scenario may be that doctors may ascribe symtoms, such as chest pain or tachypnéa, to the CHD when it in reality may be due to an MI. Perhaps the

patient has had elevated TnT-enzymes, abnormal ECG, or chest pains before, and these could be ascribed to the CHD? How does one go about evaluating this kind of patient? The obvious risk of this encounter is that it may result in a false negative diagnosis, where the patient truly has is an myocardial infarction but does not receive the proper diagnosis and treatment.

Myocardial Infarction diagnostics

During the mid 1900, the diagnostic criteria for MI was not something explicit and universally accepted. Rather, clinicians used the criteria for MI used for reaserch by the WHO, comprised of the presence of two out of three criteria: 1. Typical symtoms, like chestpains. 2. Typical ECG-patterns. 3. typical serological markers. This created a blueprint for clinicians around the world when diagnosing MI, but it did leave a lot of room for interpretation. Indeed, the Weinstein report from 1964 [38] found that many published studies on the subject stated no, or highly subjective, criteria for MI. Not only did this mean that sensitivity and specificity for MI varied among different healthcare centers, but it also made large scale research very difficult.

In Gothenburg 1975, acute myocardial infarction was considered to have occurred when at least two of the following three criteria (A, B and C) were fulfilled;

- *"(A) Central chest pain of more than 15 min duration and with debut within the last 48 hr or pulmonary oedema without previously known valvular disorder or shock without suspicion of acute hypovolemia or intoxication.*
- *(B) Transient rise of Serum Glutaminic Oxaloacetic Transaminase to values above the normal limits applied by the laboratory with a maximum approximately 24 hr after the calculated infarction debut, combined with a less pronounced increase or lack of increase of Serum Glutamic-Pyruvic Transaminase.*
- *(C) ECG series with occurrence of pathological Q waves and/or occurrence or disappearance of localized ST elevations in combination with the development of T*

inversion in at least two of the eleven routine standard leads (I, II, III, AVR, AVL, AVF, CR,, CR,, CR,, CR,, CR,)" [39]

As time went by, the accuracy of detecting myocardial infarction improved, largely as a result of the development of more specific biomarkers of myocardial necrosis. From glutamine-oxaloacetic transaminase (GOT, or ASAT, as it is called nowadays) to lactate dehydrogenase (LDH), then creatine kinase (CK), which then could be used for assessing the MB fraction of CK, i.e. CKMB activity and CKMB mass [40]. A major step forward was taken with the discovery of Cardiac Troponin (cTn). Cardiac Troponin I and T are components of the contractile apparatus of myocardial cells, and are almost exclusively expressed in the heart, giving the test a high specificity. These are used as a marker for myocardial cell necrosis [41], and the detection of rise and/or fall of troponins is now a part in the diagnostic criteria accepted worldwide.

Parallel to this development, the imaging techniques for examening potential MI´s has also improved [40, 42]. These delevopments, together with the difficulties facing clinicians and researches, made the need for a universal definition more and more pressing.

There were efforts to reach this goal, and in 1971 WHO revised its criteria and included specific ECG-patterns, but this still required great use of clinical judgement [43]. Eventually, in 2000, the European Society of Cardiology and the American College of Cardiology Consensus group redefined myocardial infarction, with the definition being based on myocyte necrosis as determined by troponins in the clinical setting of ischaemia [42]. It also takes into account the circumstances leading to the infarction (spontaneous or during a coronary artery procedure) and the timing of the myocardial necrosis relative to the time of the observation (evolving, healing or healed MI). In 2007 came the Universal Definition of Myocardial Infarction, which was on the behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the

Redefinition of Myocardial Infarction (40). This work has later been reviewed, latest done in Third Universal Definition of Myocardial Infaction, published in Circulation in 2012 [41]. Since then, MI is defined as follows:

"Detection of rise and/or fall of troponins with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of:

- *Symtoms of ischaemia*
- *ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block)*
- *Development of pathological Q-waves*
- *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality*
- *Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new left bundle branch block, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.*
- *For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.*
- *For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction"* [44].

The Swedish National Inpatient Register (IPR)

The Swedish National Inpatient Register (IPR) was launched in 1964 and has had complete coverage on inpatient care since 1987, although it does not include outpatient care. It is mandatory for all physicians to deliver data to the IPR, and more than 99% of all somatic and psychiatric hospital discharges are now registered. Since all swedish citizens aquire an individual identity number and the IPR has utilized this as identification method since 1991 (as well as retroactively). This allows research to be conducted throughout a multitude of registers, enabeling detailed research across disciplines on a large scale [45, 46]

The IPR has been validated by the National Board of Health and Welfare on several occasions [45] [46-49] and has been validated concerning specific diagnoses numerous times. Current data suggest that the overall positive predictive value (PPV) of diagnoses in the register is about 85-95% [45]. Concerning MI, the PPV has been found to be 98-100% [47, 50] and the sensitivity 77-91,5% [51-54]. And though the PPV for MI is very high, there has, to the best of our knowledge, been no study aimed at varifying the MI-diagnosis for patients with ACHD.

Considering the development seen in the patient group with ACHD, there is great need for further research regarding this patient group. But good research is dependent on good and reliable data, and there are reasons to question the data on CAD in adult patients with CHD. As mentioned above, the clinical charactaristics of these diseases may sometimes overlap, potentially resulting in an incorrect diagnosis. Indeed, it is not known to what extent the standard diagnostic criteria for CAD apply to adults with CHD. The effects on the life of a patient with ACHD given an incorrect MI-diagnosis could be severe. Despite this, there is, to the best of our knowledge, no study which has attempted to validate the diagnosis patients with a CHD-diagnosis and ischemic heart disease.

Summary

The population of adults with CHD are receiving better care than previously and this entails new challenges. They are steadily growing in numbers, they have more severe underlying conditions than previously, and they are getting older and thus being exposed to the cardiac risk factors associated with age. They also have increased risk of CAD and MI, and reasons for this may be aspects regarding the nature and severity of the CHD, high rates of cardiac surgery and an unhealthy lifestyle. Diagnostics of MI in these patients may be difficult, since some of the key aspects of the diagnostic criteria for MI, such as electrocardiograms and biochemichal markers, may also be affected by the CHD. This may make it difficult to discern the CHD from an MI. And since MI is a diagnosis with high risk of adverse effects and high mortality, the importance of ensuring a correct diagnosis cannot be overstated.

Aim

The aim of this study is to validate the myocardial infarction diagnosis among patients with ACHD in the region of Västra Götaland.

Method

A datasearch was conducted in Elvis, the administative database of Västra Götalandregionen, to find patients with a diagnosis of any congenital heart defect (ICD Q200 to Q270) (diagnoses included are found in appendix 1). Among these patients we then conducted a search to find patients who also at some point had been diagnosed with one or more of a range of cardiovascular diseases, including for example acute myocardial infarction, old myocardial infarction, chronic artery disease and stable as well as stable angina (ICD I200 to I259). Because of technical reasons regarding the administrative database in question the search was limited to the years 2000 - 2017. These patients were then used as a ”high-risk pool” used in

order to search for individuals with a diagnosis of MI. Included in the study were patients within the Västra Götalandsregionen who was registered as having a congenital heart defect as well as a diagnose of myocardial infarction at some point.

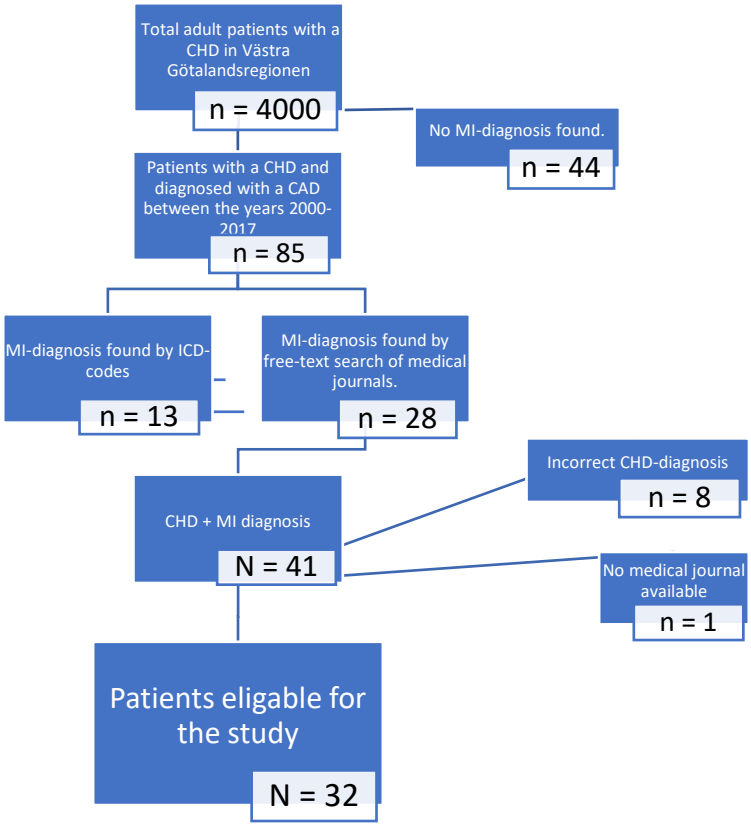

Figure 2 – Flow chart

Total number of adult patients with a CHD is estimated as 4000 patients. Among these, we found 75 patients with a ACHD who at some point had been diagnosed with an MI or a cardiovascular disease of some sort. A simple search for the ICD-codes rendered 13 patients with a diagnosis of MI. In order to increase power and widen the search, making sure that all available infarction diagnoses were being analized, a free text search for ”infarction” was conducted in the medical journals of all patients. This procedure rendered another 28 patients with an MI-diagnosis, making it 41 in total. Out of the 41 patients, there were 1 patient without available medical records, and 8 patients registered as having a ACHD-diagnosis but where closer scrutiny revealed that this was incorrect. These consisted of 2 with PFO (not

classified as a CHD), 2 with infarction VSD and 4 with an incorrect diagnosis all together. That resulted in a total of 32 patients available for evaluation. When a patient was found to have a diagnosis of MI, detected by the ICD-codes or by free-text searching, we searched for the medical journal from the hospitalization when the infarction occurred.

We then used these records to review the basis on which the patient was diagnosed according to the diagnostic criteria for MI. We did not include instances where an individual patient has had a self-stated MI but where no such diagnosis has been set by a clinician. Medical journals from the hospitalization of the event was required in order to evaluate the diagnosis and thus patients where these were unavailable were not accessible for validation. The evaluation was performed using a standard questionnaire for validation of acute myocardial infarction used in Coloma et al [55], modified to include questions regarding ACHD (appendix 2). The modification includes questions regarding the nature of the heart defect, whether it was known prior to the infarction, possible symtoms or complications and heart surgeries. The diagnosis was then categorized as either correct, probable, improbable or incorrect. The primary validation was done by the medical student and validated by one of the other investigators. If disagreement, a third person was involved and a consensus decision was reached. Analysis of patients was performed according to sex and whether the CHD was known prior to the MI. Patients were also analyzed according to the severity of the CHD diagnosis. This was performed by using the hierarchical classification system was described by Liu et al [56] wich also has been used in other published studys [57-59]. Groups were categorized as following:

- Lesion group 1, “conotruncal defects”: common truncus, aortopulmonary septum defect, transposition of great vessels, and tetralogy of Fallot.

- Lesion group 2, “severe nonconotruncal defects”: endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome.
- Lesion group 3, “CoA”: coarctation of the aorta
- lesion group 4, “VSD”: ventricular septal defect and other defects of the cardiac septum.
- Lesion group 5, “ASD”: atrial septal defect
- Lesion group 6: all heart and circulatory system anomalies and all CHD diagnoses not included in the five groups above.

In order to get a representation of the burden of risk factors between these groups, the presence of risk factors in total in the seperate group was identified. This number was then divided by the total number of patients in the group, wich produced a number corresponding to the mean burden of risk factors in this group.

Statistics

Since our study contained a small number of patients it was percieved that more sophisticated statistical methods would not have produced more relevant data. Because of this, only descriptive terms were used.

Ethics

Ethics is an important foundation in all scientific research. Our study, confined to the GUCH-clinic of Västra Götalandsregionen, is a matter of quality control. As such, the ethical approval of the study was performed by the operations manager of the clinic, Maria Taranger.

Results

Age at MI-event ranged from 0 to 90 with a median age of 54.2 years. 53% (n = 17) of the patients were male and 47% (n =15) were female. Results from assessment of the probability of correct MI-diagnosis include 9,4% (n = 3) incorrect, 9.4% (n = 3) improbable, 15.6% (n = 5) probable and 65.6% (n = 21) correct. Divided into two groups, with incorrect and improbable in one and probable and correct in the other, results are 18.8% (n = 6) incorrect or improbable and 87.6 (n = 28) probable or correct. Among males there were 11.8% (n = 2) incorrect, 11.8% (n = 2) improbable, 17.6% (n = 3) probable and 58.8% (n = 10) correct and among females there were 6.7% (n = 1) incorrect, 6.7% (n = 1) improbable, 13.3% (n = 2) probable and 73.3% (n = 11) correct (figure 3). No significant difference could be detected regarding the validity of MI diagnosis between men and women. Number of patients in each group when dividing according to severity of the CHD were as follows: group 1 had 4. Group 2 had 6. Group 3 had 1. Group 4 had 2. Group 5 had 13 and group 6 had 5. Mean age at MI-diagnosis according to severity of the CHD ranged from 36.5 in

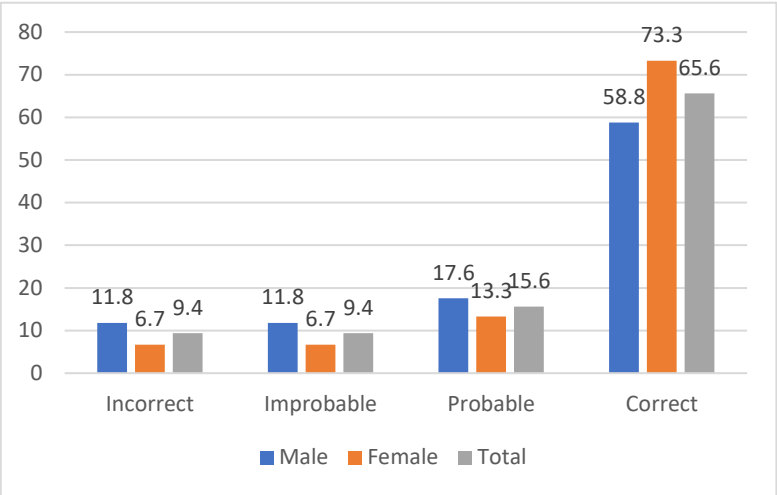

Figure 3 – Distribution of probability of the MI-diagnosis for males, females and total. Expressed in percent

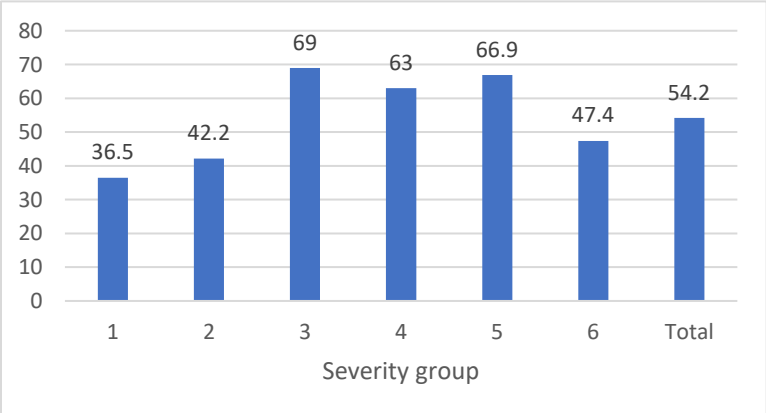

Figure 4 - mean age at MI according to the severity of underlying CHD. 1: conotruncal defects (n = 4). 2: severe nonconotruncal defects (n = 6). 3: CoA (n = 1). 4: VSD (n = 2). 5: ASD (n = 13) 6: Other (n = 5).

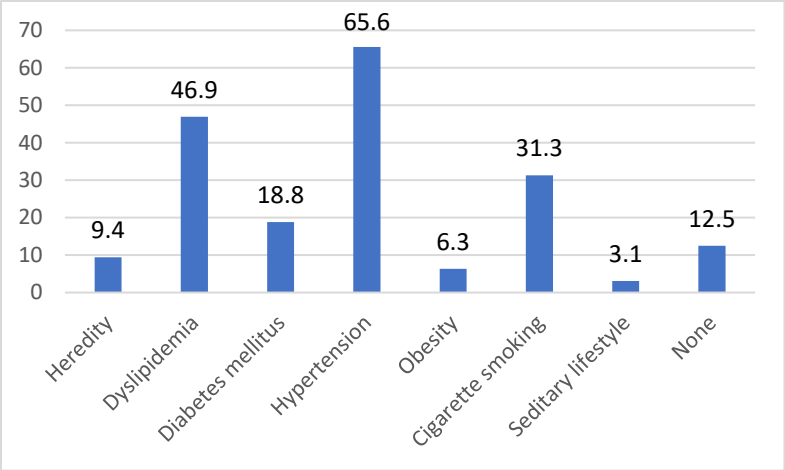

Figure 5 - Risk factors for CAD, total. Expressed in percent.

group 1 to 69 in group 3 (figure 4). There were no significant difference regarding probability of diagnosis when categorizing cases according to the severity of the CHD. Risk factors: The most prominent risk factors where hypertension with 65.6% (n = 21) and dyslipidemia at 46.9% (n = 15) and 12.5% (n = 4) of patients did not have any risk factors on record (figure 5). The distribution of risk factors according to the severity of the CHD is presented in figure 7. Mean burden of risk factors for all patients was 1.81. Calculation of mean burden of risk factors for each severity group resulted in the following results: Group 1 - 1.75. Group 2 – 1.66. Group 3 – 1.00. Group 4 – 2.50. Group 5 – 1.92 and group 6 – 2.00. The most common CHD diagnosis was ASD (37.5% n=12 patients), followed by VSD and Ebsteins anomaly with 6.25% (n = 2) patients each. The age at diagnosis of a CHD varied from infant to 81 years old, with a mean age of 47.5 years. With the patients diagnosed as

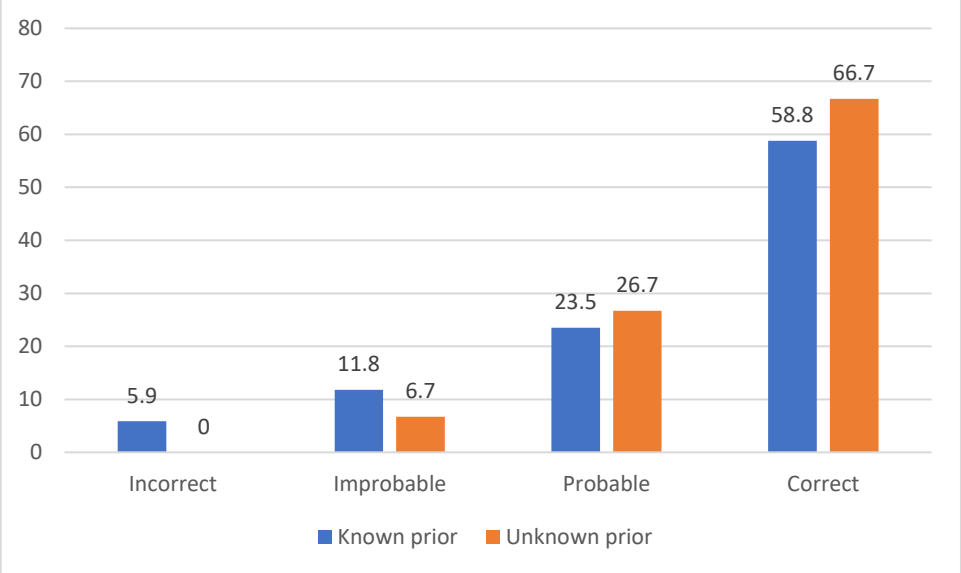

Figure 6 - Probability of correct diagnosis of myocardial infarction, according to wether the CHD was known prior to the myocardial infarction or discovered as a result of it. Expressed in percent

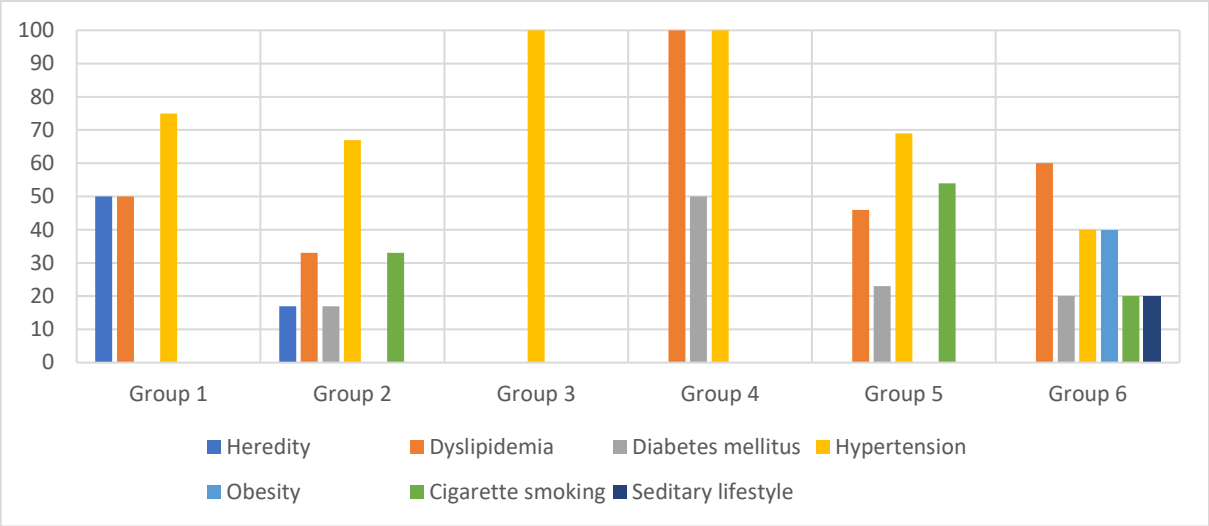

Figure 7 - Risk factors distributed according to severity of the CHD. Expressed in percent. 1: conotruncal defects (n = 4). 2: severe nonconotruncal defects (n = 6). 3: CoA (n = 1). 4: VSD (n = 2). 5: ASD (n = 13) 6: Other (n = 5)

infants excluded mean age was 57 years. In 46.9% (n=15) of cases the ACDH was discovered as a result of diagnostics following the MI, the most prominent was ASD at 66.7% (n=10) of the previously unknown diagnoses. When focusing on ASD alone, 76.9% (n=10) of cases was diagnosed after the MI and when excluding ASD, mean age for getting i CHD diagnosis was 22.4 years. A comparison regarding the probability a correct MI-diagnosis between those who already had a CHD-diagnosis at the event and those who´s CHD was diagnosed as a result of the MI (figure 6). A comparison regarding risk factors for CAD revealed that the distribution was quite even. The exception was for cigarette smoking (53.3% among undiagnosed and

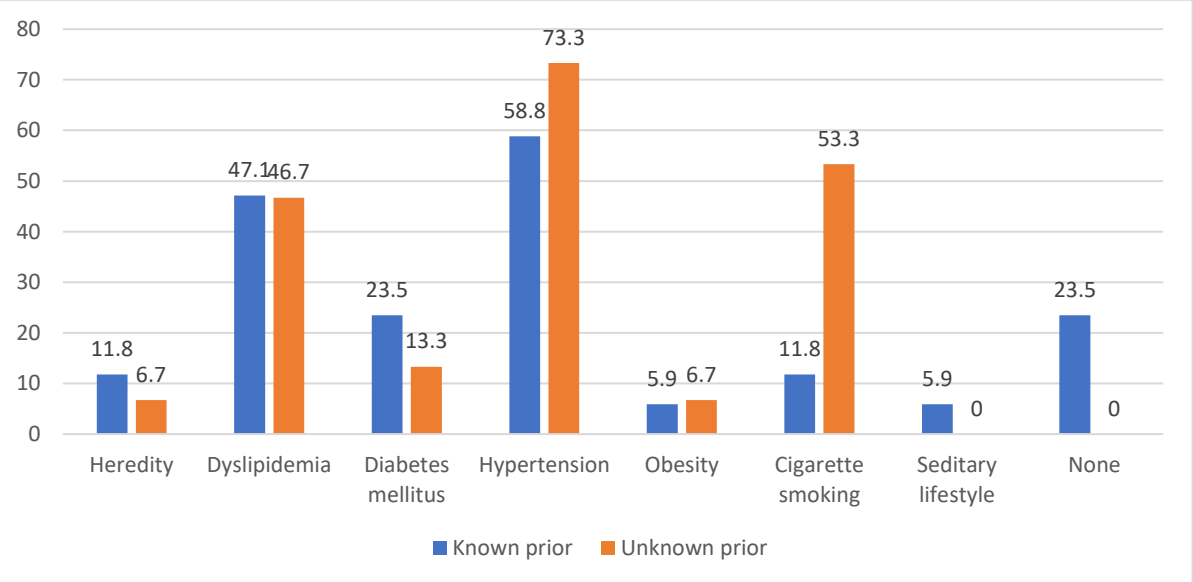

Figure 8 - Risk factors present according to whether the CHD diagnosis was known prior to the MI or not. Expressed in percent.

11.8% among diagnosed) and no risk factors present (0% among undiagnosed and 23.5% among diagnosed) (figure 8). The most prominent previous sign or symtom of CHD which might affect the MI-diagnostics was abnormal EKG patterns, present in 7 patients and one patient with a pacemaker. There was one patient who was reported to experience chest pains before the MI. There were no patients who was reported to present elevated levels of troponins before the MI. There were 8 patients who had underwent open heart surgery for their CHD, and 10 who had underwent catheterization.

Discussion

MI-diagnosis

Our results show that an incorrect diagnosis was present in 9.4% (n = 3) of all cases and 9.4% (n = 3) were categorized as improbable. A probable diagnosis was present in 15.6% (n = 5) of cases and correct diagnosis represented 65.6% (n = 21) of cases. While this manor of presenting data, as four categories instead of a binary choice of correct or incorrect, does give a more nuanced image it also creates some difficulties when comparing our findings to the findings of other studys. For this purpose, it is worth seperating these into two categories, correct + probable (CP) and improbable + incorrect (II). When presented in this manor, the results are 81.3% (n = 26) in the CP-group, and 18.8% (n = 6) in the II-group.

This is the first study to attempt to validate the MI diagnosis in adults with a CHD. This makes us unable to compare our findings with similar studys. At 81.3%, our result is lower than found by several studies conducted on a general population, including Lindblad et al who could confirm 96% of MI diagnoses [60] as well as Emily S. et al who found a specificity of 0.979 to 0.993, depending on wich method that was used [61]. Another study by Coloma et al, conducted in Denmark, compared the PPV of codes from the International Classification of Primary Care (ICPC), International Classification of Diseases 9th revision-clinical

modification (ICD9-CM) and ICD-10th revision (ICD10) and found that the ICD-10 codes had a PPV of 100%, and ICD9-CM and ICPC had 96.6% and 75% respectively [55]. Since ICD-10 is the system used in Sweden, and Denmark has as a society and medical system in specific close to swedish conditions, the results from the Danish study might be the ones most valid for our study. So in general, studies have found PPV´s that vary from 95 - 100%. In light of these numbers, our results suggests that adult patients with a CHD indeed does recieve an incorrect or improbable MI diagnosis at higher rates compared to the general population, or at least that their MI diagnosis are more disputable. It is important, though, to take into account that our study has a small sample size compared to other studies, a reality facing most studies concerning patients with a CHD. In the *Euro Heart Survey on adults with congenital heart disease* conducted by Engelfreit et al (11) wich included 4 168 patients they found only 1% (n=34) who had had either an MI, Coronary Artery Bypass Graft (CABG) or a Percutaneous transluminal coronary angioplasty (PTCA) at baseline.

In this study, we could not find a significant difference between male and female patients regarding the validity of the MI diagnosis.

Regarding risk factors, our findings are at consistently higher rates compared to studies conducted on general CHD-patients. Hypertension, for instance, were present in 65.6%. Other studies have found rates at eg. 4% or 13% in a general CHD-population (11, 34), and in a study conducted on an older population (>65 years) they found that 47% were hypertensive (14). This is also true regarding the prevalence of diabetes, wich in our study was found to be 18.8%. A study conducted in the Netherlands by Zomer et al (62) did report a significantly higher prevalence of diabetes in a CHD-population (3.4%) compared to the control group (2.3%). The finding of this study, being conducted on patients with an MI-diagnosis, confirms the notion that it is the commonly known risk factors for CAD that predicts the incidence of MI, found in several studies (14, 16, 34, 36)

We found no cases in the setting of the emergency ward where a patient presented symtoms of an acute MI and recieved an incorrect or improbable diagnosis. To return to the question regarding what happens in the emergency ward when a patient with a CHD enters with symtoms of acute MI, the typical cases evaluated in this study can be divided into two major scenarios.

1. The CHD has not been diagnosed previously and thus, the patient is treated just like any other and undergoes the standardized procedures, and is diagnosed using troponins, electrocardiogram.
2. The patient has a previously known CHD, in wich case they do go through the standard procedures using troponins, electrocardiograms and most often a percutaneus coronary intervention (PCI). The major difference seems to be that the presence of a CHD lowered the bar for taking these tests and proceeding in the MI diagnostics. And thus, there does not seem to be a significant risk that an MI is missed in patients with CHD.

It is also worth noting that we found few cases with previous signs or symtoms of the CHD, and in cases were these were present, they do not seem to have played any significant role. Indeed, all of the cases were these were present were either classified as correct or probable. When scrutinizing an individual case classified as incorrect, this revealed that this was due to the patient not showing signs of an acute MI. Instead it had to do with findings of hypoperfusion in some areas during an scintigraphic heart examination wich at first hand was interperated as signs of an old infarction, but later was interperated as effects of an eisenmangers syndrome. There were also cases where it was believed that the myocarida had been damaged during a procedure, but where it was unclear whether it should be classified as an MI or not. The same trends can be seen among the cases that was classified as improbable.

Patients who´s CHD diagnosis was unknown prior to the MI

15 of the 32 patients included in this study were cases where the CHD was discovered as a result of the MI. After being diagnosed with an MI, all patients in Sweden undergo an examination to determine the extent of the damage caused by the MI, typically using ultrasound. This ”MI-driven diagnostics” of CHD phenomena was not something that we expected to find when initiating this study and it somewhat disrupts our initial question, since a part of it had to do with how the presence of an CHD effects the doctor at the emergency ward. If the CHD is unknown then the patient is probably managed just like any other patient presenting these symtoms. When comparing the validity of the MI-diagnose in those with a previosly diagnosed CHD to the ones who recieved the CHD diagnose as a result of the MI, no significant differences could be found (figure 6). A broader comparison between the two groups showed that there were some differences. For one thing, one might suspect that patients with a previously undiagnosed CHD would have less severe lesions, and it is true that 10 out of the 15 patients did have ASD. In light of that, one might expect that there would be lower rates of hypertension in this group, when in reality it was actually higher (73.3% compared to 58.5%). This might be due to the fact that the patients with less severe CHD diagnoses, such as ASD, had a higher mean age at the time of the infarction. (Another aspect of the same phenomena could account for the fact that all patients who was reported to have no risk factors were cases where the CHD-diagnose was known before the infarction, namely that they would have more severe CHD diagnoses and therefore be younger at MI diagnosis). The observation that the risk factors are distributed quite evenly dispite the fact that patients in group 5 are older than patients in group 1 indicates that the patients with more severe lesions develop risk factors for CAD earlier than those with less severe diagnoses. In the case of diabetes, the rates are even slightly higher than in group 5 (23.5% compared to 13.3%). Lastly, the patients who were undiagnosed before the MI had cigarette smoking as a risk

factor at much higher rates compared to the other group (53.3% compared to 11.8%). This is in line with a study by, Moons P et al, who not only found that 80% of adults with a CHD diagnosis had at least 1 or more cardiovascular risk factor, but they also had fewer smokers, and even though they participated in sports activities at a higher rate then the general population, they had a higher prevalence of hypertension and diabetes [34].

Comparing according to severity of underlying CHD

When dividing cases into 6 different categories according to the severity of the underlying CHD diagnose several implications can be found, but there are two aspects that needs to be accounted for when attempting to draw any conclusions from this analizes. First of all that group 6 is quite different from the other 5 groups. While these are ordered as a falling scale of severity of the CHD, group 6 is categorized as any CHD which does not fall under any of the other categories. As a result, this group should not be viewed as the mildest on a continous scale of severity of the CHD. In fact, this group includes patients with abnormal coronary arteries, wich in one case led to a fatal MI in the patients 20´s. Secondly, this study has quite a small sample to start with and dividing these into even smaller groups creates challenges. Group 3 (coarctation), for instance, merely consist of 1 patient, and group 4 (VSD) consists of 2 patients. With groups so small it is impossible to draw any conclusions, so this needs to be taken into account when analyzing the data. The low number of patients with a VSD in our study might seem surprising, considering how common these patients are compared to other CHD. Studies conducted on a general CHD-population report a higher prevalence of VSD, such as Engelfreit et al (11) at 15.3%. But this is in line with findings by Fedchenko et al. (12), in part conducted on the same cohort, where these patients constituted 19.9% of the study population but had the lowest incidence of ischemic heart disease (IHD) at 31.2 cases per 100 000 person-years compared to 71.1 cases per 100 000 person-years among patients

with conotruncal defects. The same is true for coarctation of the aorta, at 44.6 cases of IHD per 100 000 person-years. As the presence of an MI is required for inclusion into our study, this leads to a low prevalence of VSD and coarctation of the aorta, confirming the findings of said article.

For one thing, mean age at MI diagnosis seems to decrease with more severe CHD diagnoses. Group 1, the most severe CHD diagnoses, have the lowest mean age at 36.5 years while group 5 has the highest, at 66.9. The exception to this trend is group 3 at 69 years, but since this group 3 actually is only one individual it is difficult to know how to evaluate its significance. This is in line with findings of Mandakenakis et al (5) and Engelfreit et al (11). These findings are also in line with findings in Fedchenko et al (12), which uses the same classification system for CHD according to severity. In the study, the highest rates of ischemic heart disease could be found among patient in the two most severe lesion groups (conotruncal defects and nonconotruncal defects), and they could identify a rapidly increased incidence of IHD from around 20 years of age in the CHD-group, not found in the control group. The distribution of risk factors were quite even across the different groups with two exceptions. First is the fact that group 5 (ASD) scores high in dyslipidemia, diabetes, hypertension and especially cigarette smoking. This finding is in line with Moons P et al, mentioned above [34]. The exception is, once again, group 3 and 4, but it is difficult to know what conclusions could be drawn from this because of the reasons stated above regarding these groups.

Limitations

One obvious limitation to this study is the small sample size. Part of this has to do with the quite narrow focus of the study. Although heart defects are the most common major congenital defect, there are often not enough patients to conduct large scale quantitave studies. Even more so when focusing on those with myocardial infaction as well. It also has to

do with problems we have faced when trying to retrieve data for the study. Originally, the study was designed to be a national study, including all patients with any ACHD-diagnosis as well as heart infarction in all of Sweden. The application for ethical approval for such a study has been approved. When applying to retrieve this data from the Swedish Health Registery, though, there was a 6 month waiting period for getting this data, making it accessable to us in the beginning of fall 2017. Since the study was to be conducted during the first half of 2017, there was simply no time to wait for this data. Therefore, we decided to use local data instead, which inevitably led to a smaller sample size.

Furthermore, the study was originally designed to include patients as early as 1975, but as the work to extract local data was initiated it became clear that we did not have access to records predating 2000. This further reduced our sample size.

Another limitation is the focus solely on myocardial infarction. One could argue that myocardial infarction as the last stage on a continuous scale of Coronary Artery Disease. In that perspective, a study on the diagnostics of myocardial infaction without adressing its precursors is insufficiant. Our study initially aimed to take these aspects into account as well, but was once again forced to narrow the focus to myocardial infarction due to lack of time, since the final data became available in mid april. When faced with this problem, instead of including the diagnostics of CAD-diagnoses in the study, we decided to use the patients in our dataset with these diagnoses as a kind of concentrated group of ”high risk” patients for myocardial infarction, and thus performe a free-text search for ”infarction” in order to make sure that no stones were left unturned. This revealed that, among the 62 patients not on record as having myocardial infarction in our dataset, 28 of these actually had the diagnosis. Why our dataset was unable to detect these patients is unclear, but it begs the question if there are more patients who do meet the inclusion criteria but that our dataset was unable to detect and

therefore not included in this study. In order to perform quality research in the future, this problem needs to be adressed.

And lastly there are limitations related to the study design. For one thing, the design of this study does not allow evaluation of cases where a patient has recieved a false negative diagnosis, that is when there truly is an MI but they are not diagnosed as such. Furthermore, the way this study was designed, as a retrospective study based on reviewing medical records, makes it entirely dependent on the clinician at the time and how thorough he or she has been intervjuing the patient and in the journal. This in turn makes it difficult to evaluate the extent and accuracy of some of the data retrieved. The presence of risk factors, for example, is one area particularly affected by this. It is only when there has been a mention of heredity or obesity, for example, that this data has been able to be included. But to what extent the various risk factors has been asked about specifically is unknown and it is quite probable that the focus from the various clinicians is variable. One implication of this is the fact that there are only 1 patient registered as having a sedentary lifestile, while associated conditions such as obesity, diabetes mellitus, hypertension and dyslipidemia where much more common in this dataset. And it is important to note that the ones registered as having none of the risk factors could indeed have risk factors, only that they were never mentioned in their medical records. This uncertainty is also important to keep in mind in the case of previous signs and symtoms. Still, a part of the aim of this study is how the diagnostics of these patients are affected by symtoms of their ACHD-diagnosis and one might argue that the fact that these are mentioned so little in the medical journals might suggests that they do not play any significant role.

Conclusions

In this study we found that adult patients with a CHD are more likely to recieve an incorrect or improbable diagnosis of MI than the general population, and only 65.6% of the diagnoses evaluated considered to fully conform to the diagnostic criteria. When dividing these into two groups, correct/probable and improbable/incorrect, the results are 81.3% and 18.8% respectively. But this differance does not seem to be valid in the setting of a patient presenting symtoms of an MI in the emergency ward. The reduced rates of correct diagnostics seems to mainly stem from difficulties of evaluating signs of an old MI, or how to classify myocardial damage during a surgical procedure. How do you evaluate, for instance, whether a hypoperfusioned area on a scintigraphic exam or an abnormal electrochardiogram originates from an silent MI or from the patients CHD? In these instances there can truly be an overlap between the manifestations of an MI and the CHD, making the diagnostics troublesome. In order to resolve these issues, more specific and informative methods of examening the heart may be required, such as MRI with gadolinium contrast in order to identify scarring of the heart muscle tissue and old MI´s. Considering the recent and ongoing development in the population with CHD, further research is needed. The trends visible in this study is based on a small cohort, and further studies on larger cohorts is needed.

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Populärvetenskaplig sammanfattning

Medfödda hjärtfel är den vanligaste formen av allvarliga medfödda strukturella missbildningar. 1 barn av 100 drabbas, eller ca 1,35 miljoner barn per år världen över. Missbildningarnas svårighetsgrad varierar stort, från de som lever långa liv utan att ens upptäcka sitt hjärtfel till de som dör bara timmar efter födseln utan större kirurgiska och medicinska insatser. Det finns även allt där emellan.

Framtidsutsikterna för dessa barn har i västvärlden förbättrats enormt de senaste årtiondena. Sedan 1950-talet har överlevnaden till vuxen ålder ökat från cirka 20% till dagens 95%. Men de har i genomsnitt lägre livskvalitet och ökad sjuklighet samt dödlighet jämfört med övriga befolkningen, nyare forskning har bland annat visat en ökad risk för hjärtinfarkt i unga åldrar. Hand i hand med ökad överlevnad följer även att dessa patienter, som grupp, blir fler och äldre. Dessutom - i takt med att vården klarar av att rädda personer med allt allvarligare hjärtfel gör detta att patientgruppen som helhet får en ökad allvarlighetsgrad i sin grundsjukdom, vilket är associerat med lägre livskvalitet och ökad sjuklighet samt dödlighet. Vi har mycket begränsad kunskap om hur dessa patienter svarar på ökande ålder.

Denna utveckling utmanar sjukvården och ställer krav på bra forskning. Men forskning kan aldrig vara bättre än den data som ligger till grund, och när det gäller risken för hjärtinfarkt är det svårt att veta hur tillförlitlig vår data är. Detta eftersom flera av symptomen på hjärtinfarkt även kan orsakas av ett medfött hjärtfel och det kan därför vara svårt för en läkare att avgöra vad som orsakar en patients tillstånd. Vi vet därför inte om vi kan lita på de hjärtinfarktdiagnoser som läkare har satt, och därmed dras forskningen alltid med osäkerhet. Denna studie syftar till att utvärdera de hjärtinfarktdiagnoser som har satts på vuxna patienter med medfödda hjärtfel i Västra Götalandsregionen.

Vi fann 32 vuxna patienter med medfött hjärtfel under perioden 2000 - 2017 fått en hjärtinfarktdiagnos. Vi granskade deras journaler och utvärderade hjärtinfarktdiagnosen utifrån de internationella diagnoskriterierna för hjärtinfarkt. Vi fann 66.6% (21 st) korrekta, 15.6% (5 st) sannolika, 9.4% (3 st) osannolika och 9.4% (3 st) inkorrekta.

Även om detta är en liten studie så är 66,6% korrekta är ett resultat som är mycket lägre jämfört med patienter utan medfött hjärtfel. Nordiska studier på området visar en korrekt diagnos i 95 - 100% av fallen. Samtliga diagnoser som klassats som inkorrekta rörde sig om fall där man hittat tecken på en redan genomgången hjärtinfarkt, men där det fanns svårigheter att avgöra huruvida det bör klassas som hjärtinfarkt eller som orsakat av hjärtmissbildningen. Fynden ställer vissa frågetecken kring tillförlitligheten i forskningen på området, men de pekar också åt att då dessa patienter söker akuten för en pågående hjärtinfarkt kan de lita på att de diagnostiska metoder som används fungerar.

För att få bukt med detta bör man finna nya sätt att utvärdera tecken till en redan genomgången infarkt, t.ex. med hjälp av nya bildtekniker såsom magnetkamera med kontrastmedel. För att utvärdera dessa resultat krävs även mer forskning.

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Appendix 1, the ICD-10 codes used for identifying cases

- CHD
  - Q203 – Diskordant ventrikulo-arteriell förbindelse D-TGA
  - Q205 – Diskordant ventrikulo-arteriell förbindelse L -TGA
  - Q210 – Kammarseptumdefekt
  - Q211 – Förmaksseptumdefekt
  - Q213 – Fallots tetrad
  - Q220 – Atresi av pulmonalisklaff
  - Q224 – Medfödd tricuspidalisstenos
  - Q225 – Ebsteins anomali
  - Q230 – Medfödd aortaklaffstenos
  - Q231 – Medfödd aortaklaffsinsufficiens
  - Q232 – Medfödd mitralisstenos
  - Q233 – Medfödd mitralisinsufficiens
  - Q234 – Hypoplastiskt vänsterkammarsyndrom
  - Q241 – Levokardi
  - Q245 – Kranskärlsmissbildning
  - Q249 – Medfödd hjärtmissbildning, ospec
  - Q250 – Öppetstående ductus arteriosus
  - Q251 – Coarctatio aortae
  - Q253 – Stenos av aorta
  - Q254 – Andra medfödda missbildningar av aorta
  - Q257 – Andra medfödda missbildningar av lungartären
  - Q261 – Kvarstående vänstersidig övre hålven
  - Q263 – Partiellt anomailt mynnande lungvener
  - Q269 – Medödd missbildning av de stora venerna, ospec.
- CAD
  - I200 – Instabil angina pectoris
  - I208 – Andra former av angina pectoris
  - I209 – Angina pectoris, ospec
  - I210 – Akut transmural framväggsinfarkt
  - I212 – Akut transmural hjärtinfarkt med andra lokalisationer
  - I213 – Akut transmural hjärtinfarkt med icke specificerad lokalisation
  - I214 – Akut subendokardiell infarkt i framvägg
  - I219 – Akut hjärtinfarkt, ospec
  - I230 – Hemoperikardium som komplikation till akut hjärtinfarkt
  - I231 – Förmaksseptumdefekt som komplikation till akut hjärtifarkt
  - I248 – Andra specificerade former av akut ischemisk hjärtsjukdom
  - I250 – Aterosklerotisk kardiovaskulär sjukdom
  - I252 – Gammal hjärtinfarkt
  - I251 – Andra hjärtsjukdomar vid andra infektionssjukdomar och parasitsjukdomar som klassificeras annorstädes
  - I259 – kronisk ischemisk hjärtsjukdom, ospec

Appendix 2, questionnaire used to evaluate the MI diagnosis:

Questionnaire for assessors

- Database: _____
- ID Patient: _____
- Sex: M/W
- Birthdate: ___/__/__
- Diagnosis: _____
- Date of event/diagnosis: ____/__/__
- Age at event/diagnosis: ___ years
- **Is there a medical record available for this patient?**
  - Yes/No
- Is there sufficient information in order to validate the diagnosis?
  - Yes/No
- Diagnosed by senior doctor in cardiology or GUCH
  - Yes/No
- **A) Information on characteristics and detection of AMI**
  - 1. Was there any mention of the presence of '**acute myocardial infarction**' in the records reviewed?
    - Yes/No
  - 2. If (*Answer to 1 is*) YES, was the myocardial infarction referred to as '**old myocardial infarction**' or '**history of myocardial infarction**'?
    - Yes/No
  - 3. Was there an explicit mention of '**acute myocardial infarction**' as a cause of death?
    - Yes/No
  - *For Questions 4-6, evaluate within 30 days of presumed index date [i.e., date of diagnosis]*
  - 4. Were any of the following interventions done? Multiple answers are possible:
    - Coronary artery bypass graft (CABG)
    - Percutaneous coronary intervention (PCI)
    - Thrombolysis (rTPA/streptokinase, others)
    - Initiation of long-term pharmacotherapy
    - None of the above
  - 5. Were any of the following examinations done to confirm a suspicion of acute myocardial infarction? Multiple answers are possible:
    - Coronary angiography (specify findings if possible)
      - coronary occlusion
      - coronary obstruction
      - vessel narrowing
      - ruptured plaque
      - other, please specify _____
    - Electrocardiography (ECG) (specify findings if possible)
      - ST-segment elevation>1mm in 2 anatomically contiguous leads
      - new Q waves
      - new left bundle branch block (LBBB)
      - T wave inversion
      - Other, please specify _____
    - Cardiac enzymes (specify values and units, if given)
      - Elevated levels of Troponin T_____
      - Other, specify if possible_____
      - None of the above
  - 6. Were any of these signs or symptoms of myocardial ischemia recorded shortly on or before the date of diagnosis? Multiple answers are possible:
    - chest, jaw or upper extremity pain at rest or with exertion
    - difficulty breathing (dyspnea)
    - excessive sweating (diaphoresis)
    - fatigue/weakness

- epigastric pain
- none of the above
- other, please specify _____

- **B) Information about cardiovascular risk factors**
  - 1. Was there mention/evidence in the records of any of the following risk factors for acute myocardial infarction? Multiple answers are possible.
    - Family history of myocardial infarction/cardiovascular disease
    - Dyslipidemia
    - Diabetes mellitus
    - Hypertension
    - Obesity
    - Cigarette smoking
    - Sedentary lifestyle
    - None of the above
  - Were these risk factors detected as a result of the myocardial infarction?
    - Yes/No
    - If yes, please specify_____
- **C) Information about congenital heart defect, previous signs/symptoms/complication.**
  - CHD diagnosis _____
  - Age at diagnosis _____
  - Was the CHD-diagnosis known prior to the myocardial infarction?
    - Yes/No
    - If no, was is detected as a result of the myocardial infarction?
      - Yes/No
  - Previous signs/symtoms/complications
    - Abnormal ECG-patterns
      - Please specify_____
      - _____
    - Elevated levels of troponin
      - From___ to ___ Median_____
    - Chest pains
    - Number of cardiac surgeries
      - Open_____
      - Catherization_____
      - Involving manipulation of coronary arteries
        - Yes/No
    - Other_____
- **D) Information about potential alternative explanations for the signs/symptoms/ laboratory findings**
  - 1. Was there mention/evidence in the records of any of the following diseases at the time of/before the diagnosis? Multiple answers are possible.
    - Pericarditis and/or Cardiac Tamponade _____
    - Myocarditis _____
    - Aortic dissection _____
    - Cardiac contusion _____
    - Pneumothorax _____
    - Pulmonary embolism _____
    - Stable angina _____
    - Unstable angina _____
    - Gastroesophageal reflux disease (GERD) _____
    - None of the above
- **E) Estimated probability of diagnosis**
  - Correct
  - Probable
  - Inprobable
  - Incorrect

Other comments

_____

_____