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EDITORIAL

Night time blood pressure dip

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Abstract

The advent of ambulatory blood pressure monitoring permitted examination of blood pressures during sleep and recognition of the associated circadian fall in pressure during this period. The fall in pressure, called the "dip", is defined as the difference between daytime mean systolic pressure and nighttime mean systolic pressure expressed as a percentage of the day value. Ten percent to 20% is considered normal. Dips less than 10%, referred to as blunted or absent, have been considered as predicting an adverse cardiovascular event. This view and the broader concept that white coat hypertension itself is a forerunner of essential hypertension is disputable. This editorial questions whether mean arterial pressures over many hours accurately represent the systolic load, whether nighttime dipping varies from measure to measure or is a fixed phenomenon, whether the abrupt morning pressure rise is a risk factor or whether none of these issues are as important as the actual night time systolic blood pressure itself. The paper discusses the difference between medicated and nonmedicated white coat hypertensives in regard to the cardiovascular risk and suggests that further work is necessary to consider whether the quality and duration of sleep are important factors.

Key words: Nighttime dip; Ambulatory blood pressure monitor; Blunting; Cardiovascular risk

Core tip: While the blunted or absent nighttime pressure dip in nonmedicated white coat hypertensives is generally believed to be a predictor of adverse cardiovascular events, it does not appear to present the same risk in medicated white coat patients. Of the many measurable pressure issues, including pulse pressure and morning surge, during sleep and with awakening, only the mean systolic pressure appears to be the predictor of risk.

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NIGHT TIME BLOOD PRESSURE DIP

The circadian fall in blood pressure during sleep[1] has been fully examined only since the development of

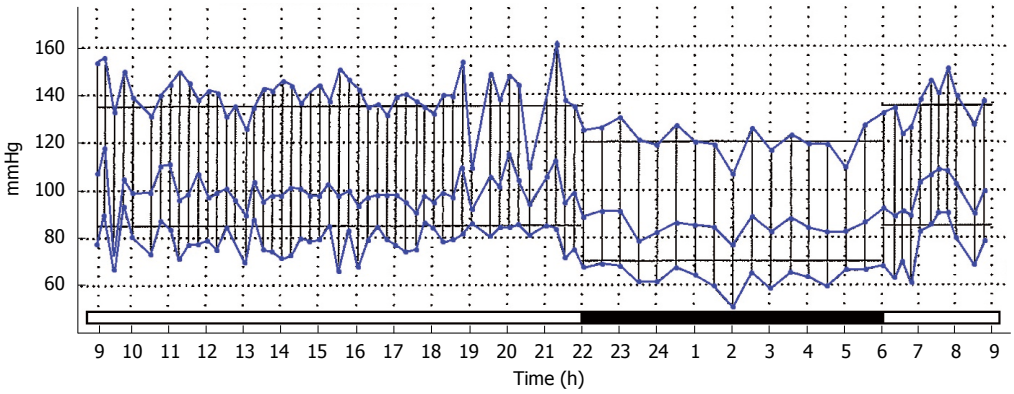

Figure 1 Ambulatory blood pressure recording showing a normal night time dip. In all the ambulatory blood pressure monitoring tracings, the systolic, diastolic, and mean pressures are shown in blue. The pressure scale in mmHg is on the vertical Y-axis on the left and the time scale in hours is on the horizontal X-axis. The duration of sleep corresponding to the night time period is indicated by a heavy black bar.

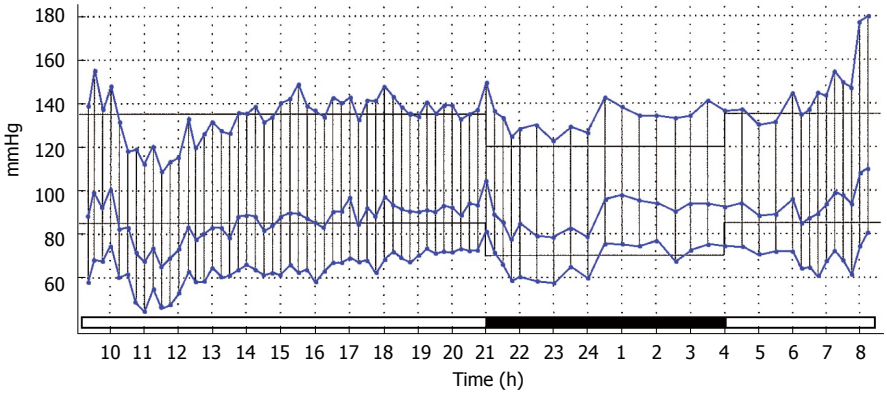

Figure 2 Ambulatory blood pressure recording showing a blunted night time dip.

ambulatory blood pressure monitoring (ABPM) and its occurrence in white coat hypertension (WCH) has not been generally elucidated. First described in 1988, the night time dip has become an accepted measure of cardiovascular risk[1-4]. The dip is defined as the difference between the mean systolic pressure in the day and mean systolic pressure during the night, expressed as a percentage of the day time mean, with the accepted normal between 10% and 20%[5]. A representative ABPM tracing with a normal night time dip is shown in Figure 1.

Dips less than 10% are described as absent or blunted and those in excess of 20% are known as exaggerated or extreme[6]. An example of a blunted dip, such as would be recognized as predicting an adverse cardiovascular event, is shown in Figure 2.

Identification of medical risk factors, particularly cardiovascular ones, carries a couple of requirements. The definition of the conditions must be accepted and unchallengeable and the observations on which this designation is based must be unassailable. These conditions are not met with the night time dip.

The utility of the definition of night time dip is far from practical. It is assumed that the mean systolic pressures are utilized but there is such variation in the actual systolic values during the 24 h that the mean hides much information and bears little relationship to actual daily events. The utilization of average or maximum systolic pressures would be equally inaccurate. In white coat hypertension, mean and average systolic pressures are artificially elevated by the white coat episode.

The ambulatory monitoring data is also soft. It is known that repeated studies do not necessarily provide the same result. Dippers may become non dippers on subsequent testing[7].

Furthermore, the patient-designated "time of sleep" is actually the time of going to bed. The true time of falling asleep clearly cannot be indicated with this methodology. Consequently, the pressures used in the sleep *vs* awake calculations are slightly but inherently inaccurate.

Reported studies in night time dip have almost always been performed in untreated hypertensive patients[8]. In the real world, ABPM is rarely performed in such patients. In our experience, patients are referred for this study to ascertain the effectiveness of the treatment or when progressive medication has failed to control the hypertension. It would be expected that cardiovascular risks would be more evident in the uncontrolled hypertensive patients, however, our studies with medicated patients[8] have

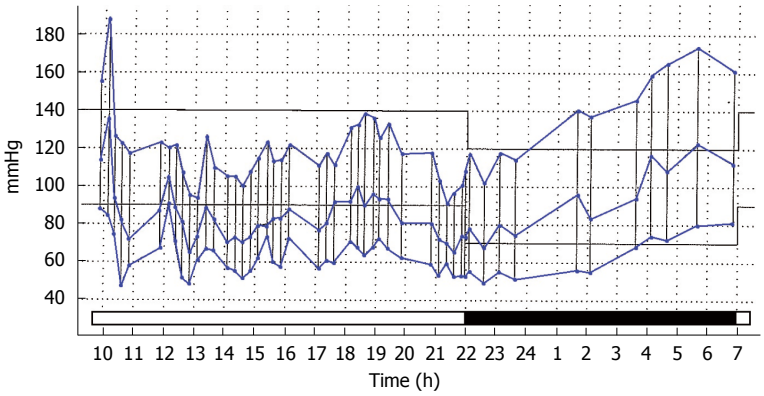

Figure 3 Ambulatory blood pressure recording showing white coat hypertension with a steadily rising pressure of superimposed essential hypertension. The pressure only reaches hypertension levels during sleep when it is likely to be clinically unnoticed.

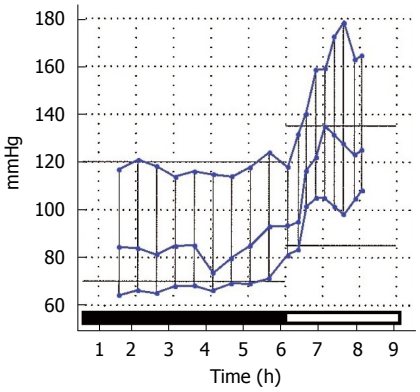

Figure 4 Ambulatory blood pressure recording showing a significantly rapid rise in mean blood pressure upon awakening.

shown no greater incidence of blunted night time dip in uncontrolled hypertensives, controlled hypertensives or white coat hypertensives. Sufficient reduction in the night time pressure may in fact be blunted or negated by protective reflexes if these pressures are already reduced by medication.

Over bridging these considerations is the understanding that the cardiovascular risk associated with the rupture of atheromatous plaques in the coronary and cerebral arteries are essentially systolic issues. They may be related to actual systolic levels or pulse pressure rather than mean pressures or degree of nocturnal dipping.

Masked hypertension, the condition in which the home or the ABPM pressures are significantly higher than the office values must be given considerations here. It is seldom diagnosed in clinical practice as there is little incentive to prescribe ABPM or home pressure devices if the pressure is normal, but occasionally, accidental or incidental incidences of blood pressure measurement may reveal this condition and some explanation is required when masked hypertension is revealed during sleep. This may eliminate the night time dip. Night time narrow peaks of systolic hypertension can occur with dreaming, wider systolic elevations with obstructive sleep apnea and steadily rising pressures are seen with essential hypertension (Figure 3).

A widened pulse pressure has also been recognized as an indicator of cardiovascular risk. White coat hypertensives have a widened pulse pressure during the white-coat episodes but not at night. Analysis of our studies in dippers and non-dippers, hypertensives, white coaters and normal subjects, has found that there is no statistical difference in pulse pressure values between day and night. With the exception of isolated systolic hypertension, a widened pulse pressure occurs in patients who do not have elevated blood pressure as their principle diagnosis and includes those with aortic regurgitation, arteriovenous shunts, thyrotoxicosis and other cardiovascular disorders that, in themselves, increase the risk of death.

Associated with the night time dip, the morning blood pressure surge has been blamed for the increase in cardiovascular events in the morning hours. It is measured as mmHg increase per hour in the mean pressure and it is generally accepted that a rise greater that 10 is significant as a cardiovascular risk factor. Figure 4 shows a typical exaggerated increase in the pressure during the process of awakening.

However, when the rate of rise is continuously calculated during the 24 h ABPM recording, many instances of "significance" are seen to occur at times other than in the morning. Figure 5 adequately depicts this point.

A large study has found that the night time systolic pressure itself, rather than the surge, the dip or the pulse pressure has been shown to correlate more closely with the clinical events[9].

It is clear that the blood pressure at night, in some negative way, impacts the cardiovascular system. What particular element of the pressure, whether it is its depth or its systolic/diastolic width or whether the heart rate or length or quality of sleep is the causative factor remains to be determined.

Unfortunately, the tool to answer these questions, the ambulatory blood pressure monitor, is underutilized in the United States, largely because the study

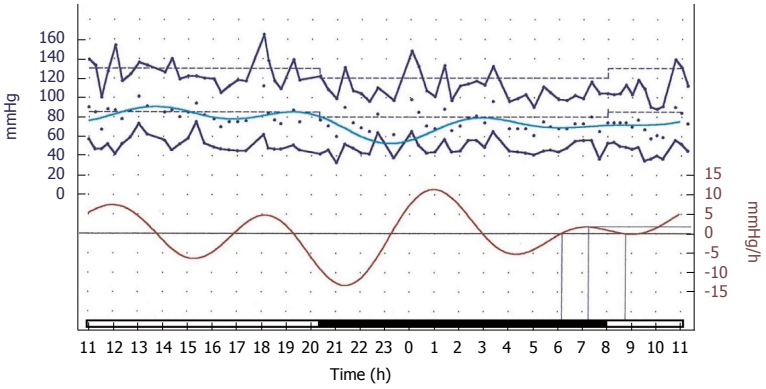

Figure 5 Ambulatory blood pressure recording showing the rate of pressure rise upon awakening at 7 am. At 1 am, the rate of rise reaches cardiac risk significance. The scale in mmHg/h is shown in red on the right.

remains non-reimbursable. As it may hold some basic but unknown secrets of cardiovascular health and disease, the "night time dip" warrants a much more extensive investigation.

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EDITORIAL

Hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery

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Abstract

Although red blood cells (RBCs) transfusion is sometimes associated with adverse reactions, anemia could also lead to increased morbidity and mortality in high-risk patients. For these reasons, the definition of perioperative strategies that aims to detect and treat preoperative anemia, prevent excessive blood loss, and define "optimal" transfusion algorithms is crucial. Although the treatment with preoperative iron and erythropoietin has been recommended in some specific conditions, several controversies exist regarding the benefit-to-risk balance associated with these treatments. Further studies are needed to better define the indications, dosage, and route of administration for preoperative iron with or without erythropoietin supplementation. Although restrictive transfusion strategies in patients undergoing cardiac surgery have been shown to effectively reduce the incidence and the amount of RBCs transfusion without increase in side effects, some high-risk patients (*e.g.*, symptomatic acute coronary syndrome) could benefit from higher hemoglobin concentrations. Despite all efforts made last decade, a significant amount of work remains to be done to improve hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery.

Key words: Cardiac surgery; Blood transfusion; Anemia; Transfusion threshold; Risk factor

Core tip: Anemia and red blood cells transfusion are common during cardiac surgery, and could be associated with adverse reactions. Preoperative hemoglobin optimization through the identification and treatment of anemia and the definition of standardized transfusion algorithm using restrictive transfusion triggers play a central role in the development of Patient Blood Management programs. However, further researches are needed to better define transfusion triggers, based on pathophysiological indices, rather than single hemoglobin thresholds.

Najafi M, Faraoni D. Hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery. *World J Cardiol* 2015; 7(7): 377-382 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i7/377.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i7.377

INTRODUCTION

Patients undergoing cardiac surgery are at increased risk of excessive perioperative bleeding, and increased blood product transfusions[1]. Although blood products are safer than ever, transfusion of allogeneic blood products remains associated with a significant incidence of adverse reactions[2]. Last decades the development of Patient Blood Management (PBM) programs improved perioperative management, and decreased the use to blood products through a better identification of both patient-related and procedure-related risk factors[3].

On the one hand, cardiac surgery is among major procedures that significantly influence the distribution of body fluid through the large volumes of fluid administered during cardiopulmonary bypass (CPB), the volume of cardioplegia, and the amount of fluid administered to optimize cardiac output. In addition, the contact between blood and non-endothelial surfaces will lead to the "activation coagulopathy"[4], and all these mechanisms are part of the CPB-induced coagulopathy that significantly influences the requirement for blood products transfusion[5].

On the other hand, with the progress made in medical therapies and interventional cardiology, patients requiring cardiac surgery become older, and arrive to surgery with a huge number of comorbidities, and medications[6]. Patients are usually treated with antiplatelet agents and/or anticoagulants, which will increase the bleeding risk[7]. Although RBCs transfusion could be associated with adverse events; anemia in high-risk patients could also be associated with increased morbidity and mortality[8]. For these reasons, the definition of perioperative strategies that aims to detect and treat preoperative anemia, prevent excessive blood loss, and define "optimal" transfusion algorithms are crucial.

PHYSIOLOGY

Oxygen is major component of cellular homeostasis; the maintenance of an aerobic metabolism through adequate oxygen supply to cells is crucial. Cardiac output and the arterial oxygen concentration (CaO_2) will allow the maintenance of an adequate oxygen delivery (Do_2).

$Do_2 = CO \times CaO_2$, where $CaO_2 = (Hb \times SaO_2 \times 1.39) + (PaO_2 \times 0.0031)$

With SaO_2 corresponding to the arterial oxygen saturation, PaO_2 is the partial arterial pressure in oxygen, 0.0031 is the amount oxygen diluted in plasma, and 1.39 the amount of oxygen linked to 1 g of hemoglobin. Based on this formula, it appears evident that the hemoglobin concentration will play a central role in oxygen transportation throughout the body, and organs.

The adequacy of tissue oxygenation depends on tissue/organ metabolic needs. Tissue oxygenation is adequate when oxygen delivery (Do_2) is at least equal to the rate of oxygen consumed by the tissues (Vo_2: oxygen consumption). The ratio between Do_2 and Vo_2 allow for the determination of the oxygen extraction (O_2 ER), which in physiologic condition correspond to 25%-30% of the oxygen delivery. Interestingly, adaptive mechanisms allow the maintenance of adequate oxygen consumption in the presence of decreased oxygen delivery through an increase in the amount of oxygen extracted by the tissues[9]. Below a certain Do_2 level, the extraction could not be increased and metabolism will be shift to anaerobic metabolism. This change in metabolic characteristics will be associated with increased lactate plasmatic concentration, if prolonged may cause tissue damage[10].

Although a certain degree of anemia could be tolerated, the "critical" hemoglobin level that will not allow the maintenance of an adequate oxygen delivery will depend on different factors that include physiologic status (*e.g.,* sepsis increases oxygen demand) or condition (*e.g.,* anesthesia decreases oxygen demand)[11]. In case of acute and severe anemia, adaptive mechanisms to optimize the balance between oxygen supply and demand are regulated by hypoxia-inducible factors, and included neuronal nitric oxide synthase, erythropoietin, and hypoxia-inducible factors[12]. Although all these mechanisms improve oxygen delivery, organs with higher baseline oxygen extractions, such as the heart, are usually flow-dependent, which is obtained by vasodilatation of the coronary arteries[13]. This will have an important impact in patients suffering from coronary artery disease, and perioperative management of anemia in patients undergoing coronary artery bypass graft (CABG) surgery is crucial[14].

PREOPERATIVE OPTIMIZATION OF HEMOGLOBIN CONCENTRATION

Based on the World Health Organization (WHO), anemia is defined by hemoglobin levels < 12 g/dL in women, and < 13 g/dL in men[3]. If 25% of the general population is anemic, preoperative anemia is reported in 22% to 30% of patients undergoing cardiac surgery[15] Although preoperative anemia was associated with an increased incidence of acute kidney injury and strokes, both short and long-term mortality increased in anemic patients undergoing CABG surgery[16]. In addition, adverse events associated with

hemorrhage, and blood product transfusion was higher in patients with preoperative anemia compared to non-anemic patients[17]. As a consequence, preoperative detection of anemia, and optimization of hemoglobin level is crucial.

Iron deficiency has been shown to be responsible of 29% of the preoperative anemia, followed by the presence of chronic kidney disease in 10.7%[18]. In case of iron deficiency, preoperative iron supplementation should be recommended. In patients undergoing cardiac surgery, Piednoir *et al*[19] reported that on 100 patients undergoing cardiac surgery, 37% had preoperative iron deficiency, from those one third were anemic. The authors also reported that 62% of patients with iron deficiency received RBC transfusion compared to 35% in controls[19]. No study assessed the efficacy of preoperative iron supplementation in patients undergoing cardiac surgery. So far, our experience is based on studies performed in colorectal[20] or orthopedic surgeries[21] that reported a significant reduction in RBCs transfusion in patients that received preoperative oral iron administration. Other authors reported that iv iron administrated within 3-5 wk before orthopedic surgery could significantly increase hemoglobin level[22]. Although a recent meta-analysis reported a significant increase in hemoglobin level, and reduction of RBCs transfusion following the iv administration of iron, this benefit was balanced by an increased incidence of infection. Based on current evidence, oral iron administration (200-300 mg/d) should be recommended in patients with preoperative iron deficiency, while iv supplementation (1000 mg weekly during 3-5 wk) might only be considered in case of contraindication to oral administration or short delay before a surgery that could not be postponed[23].

If the preoperative administration of erythropoietin stimulating agent could be attractive, the benefit-to-risk balance associated with preoperative administration of erythropoietin (EPO) remains weakly studied. Currently, EPO is approved in anemic patients without nutritional deficiency undergoing orthopedic surgery. However, its administration in patients undergoing cardiac surgery is currently prohibited due to an increased incidence of thromboembolic complication reported in pilot studies[24].

RESTRICTIVE *VS* LIBERAL TRANSFUSION TRIGGERS?

Transfusion has been used for years to increase hemoglobin concentration, and oxygen delivery. However, RBCs transfusion is associated with several side effects, and sometimes, increased mortality[25]. On the other hand, anemia has been associated with adverse outcomes ranging from cardiovascular events, heart failure, renal failure, prolonged recovery, and late mortality. Although the safety of blood products transfusion has been extensively enhanced last decades, there are still concerns over the hazards of transfusion, particularly with respect to the high rate of annual consumption of blood products worldwide (around 85 million units)[26]. With regard to complications associated with blood product transfusion, non-infectious risks such as human errors, acute hemolytic and non-hemolytic reactions have overpassed the risk of infection. Based on large studies performed in cardiac patients, blood product transfusion is associated with negative outcomes such as cardiac, pulmonary, renal, and neurologic complications, as well as increased length of hospital stay and death[27]. In addition, these side effects will have a significant impact on health care resource utilization.

As far as the 1990s, Bracey *et al*[28] reported that restrictive transfusion strategies (Hb threshold = 8 g/dL) led to a 20% reduction of RBCs transfusion without increase in the incidence of side effects[28]. However, it took about 10 years before the publication of a second prospective randomized study that compared a restrictive (hematocrit > 24%) *vs* liberal (hematocrit > 30%) transfusion strategy in patients undergoing cardiac surgery[29]. In this study, Hajjar *et al*[29] reported that although the restrictive transfusion strategy was associated with lower intra-operative hemoglobin levels, no difference was observed in term of morbidity and mortality. A Cochrane systematic review of 17 cardiac and non-cardiac trials published in 2010 concluded that restricted transfusion strategy decreases transfusion without increasing adverse outcomes such as cardiac events, thromboembolic complications, and death[30]. However, this review denotes that patients with "serious heart disease" should not be treated in this way. In a recent systematic review with meta-analysis, Curley *et al*[31] reported that only a few studies (n = 7) adequately compared the efficacy and safety of a restrictive transfusion protocol to a liberal approach in patients undergoing cardiac surgery. Although restrictive transfusion strategies significantly reduced the incidence of RBCs transfusion without side effect, the inter-studies variability was important, and further adequately powered studies are needed to assess the appropriate transfusion threshold in the cardiac population.

Based on a pathophysiologic decrease in anemia tolerance in patients with coronary artery disease, perioperative anemia could be associated with poor outcomes, and a specific transfusion strategy could probably be adopted in this high-risk population[14]. In 2013, Carson *et al*[32] published the preliminary results of a prospective randomized multi-center study that aimed to compare a restrictive (Hb > 8 g/dL) *vs* a liberal (Hb > 10 g/dL) transfusion strategy in patients with symptomatic coronary artery disease. The preliminary analysis reported that higher transfusion thresholds were associated with better outcome in this particular population. Recently, Murphy *et al*[33] published the results of a prospective

Table 1 Practice guidelines for red blood cell transfusion

Guidelines	Release date	Hemoglobin threshold definition	Level of evidence
Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists[33]	2011	6 g/dL preoperative and on CPB	2C
		7 g/dL postoperative and at risk of ischemia on CPB	2C
British Committee for Standards in Haematology[34]	2012	7 g/dL stable, non-bleeding CAD	C
		8-9 g/dL ACS	
The American Association of Blood Banks[35]	2012	7-8 g/dL in stable patients	1A
		8 g/dL in patients with CVD	2B
		No number for ACS	Uncertain recommendation; very low-quality evidence
European Society of Anesthesiology[36]	2013	7-9 g/dL in bleeding patients	1C
American Society of Anesthesiologists[37]	2015	No number	-

1A: Strong recommendation, high quality evidence; 1B: Strong recommendation, moderate quality evidence; 1C: Strong recommendation, low quality evidence; 2A: Weak recommendation, high quality evidence; 2B: Weak recommendation, moderate quality evidence; 2C: Weak recommendation, low quality evidence; CPB: Cardiopulmonary bypass; CAD: Coronary artery disease; CVD: Cardiovascular disease; ACS: Acute coronary syndrome.

multicenter randomized study (TITRe2 study) that randomized more than 2000 patients undergoing cardiac surgery to a restrictive (Hb threshold < 7.5 g/L) or a liberal transfusion strategy (Hb threshold < 9 d/dL). Interestingly, the authors didn't observe any differences in term of postoperative outcome, mortality, and costs between the two transfusion strategies. The authors concluded that restricted strategy was not superior to a liberal transfusion strategy with respect to morbidity and health care costs. These results confirmed that indication for RBCs transfusion in patients undergoing cardiac surgery might not be guided by a single transfusion threshold and that some patients may benefit from higher hemoglobin level, while other may tolerate lower hemoglobin concentrations.

Recent guidelines emphasized that recommendations on blood transfusion in patients with cardiovascular disease are not supported by strong evidence[26,34-37]. (Table 1) Despite their differences, guidelines generally agreed that RBCs transfusion should not be recommended in case of hemoglobin concentration $\geqslant$ 10 g/L and might be useful in case of hemoglobin concentration < 7 g/L[38]. However, transfusion triggers might be reconsidered in critical scenario, and especially in bleeding situations[26,34-36]. Evidence is particularly limited in clinical contexts such as acute coronary syndrome, where the recommendation for higher hemoglobin threshold is still controversial[26]. Patients with acute coronary syndrome (ACS) or patients who were at risk of end organ ischemia were included in different clinical trials over the past years, but the relationship between ACS, RBCs transfusion, and outcome remains to be determined[26,37]. Further results are waited in this context, but this supports the hypothesis that one single transfusion threshold could not fit to all patients, and that RBCs transfusion should be based on more than a single hemoglobin measurement.

CONCLUSION

Both anemia and transfusion are associated with adverse events and increased morbidity in patients undergoing cardiac surgery. Although the "optimal" RBCs transfusion strategy has not yet been defined, RBCs transfusion should be preferred when its benefits outweigh the risks. Patients with cardiac diseases are more vulnerable to anemia-related hypoxia, and recent data suggested that a restrictive transfusion strategy was not superior to a liberal transfusion, that could be associated with "better" outcome in some high-risk patients with symptomatic coronary artery disease. Each cardiac surgical department might develop standardized transfusion algorithm, based on a multidisciplinary approach. This approach should include preoperative identification of anemic patients, preoperative measures to increase hemoglobin concentration (*e.g.,* iron and/or erythropoietin), intraoperative measure to decrease blood loss, and definition of "optimal" transfusion trigger based on patient's characteristics, rather than a single hemoglobin threshold. Because on current knowledge the "ideal" transfusion thresholds to be recommended in cardiac patients is not yet known, further large prospective studies are urgently needed to determine the efficacy and safety of different transfusion strategies in this high-risk population.

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REVIEW

Impairment of aspirin antiplatelet effects by non-opioid analgesic medication

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Abstract

Aspirin is the mainstay in prophylaxis of cardiovascular diseases. Impaired aspirin antiplatelet effects are associated with enhanced incidence of cardiovascular events. Comedication with non-opioid analgesic drugs has been described to interfere with aspirin, resulting in impaired aspirin antiplatelet effects. Additionally, non-opioid analgesic medication has been shown to enhance the risk of cardiovascular events and death. Pain is very frequent and many patients rely on analgesic drugs to control pain. Therefore effective analgesic options without increased risk of cardiovascular events are desirable. This review focuses on commonly used non-opioid analgesics, interactions with aspirin medication and impact on cardiovascular risk.

Key words: Non-steroidal anti-inflammatory drug; Drug-drug interaction; Pharmacodynamic; Dipyrone; Aspirin; Paracetamol; Metamizole

Core tip: Aspirin is the mainstay in prophylaxis of cardiovascular diseases. Impaired aspirin antiplatelet effects are associated with enhanced incidence of cardiovascular events. Comedication with non-opioid analgesic drugs has been described to interfere with aspirin, resulting in impaired aspirin antiplatelet effects. Additionally, non-opioid analgesic medication has been shown to enhance the risk of cardiovascular events and death. Pain is very frequent and many patients rely on analgesic drugs to control pain. Therefore effective analgesic options without increased risk of cardiovascular events are desirable. This review focuses on commonly used non-opioid analgesics, interactions with aspirin medication and impact on cardiovascular risk.

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INTRODUCTION

Approximately 20% of European adults suffer of acute or chronic pain and rely on analgesic drugs[1,2]. The incidence of pain and usage of non-opioid analgesics is even higher in patients with cardiovascular diseases. Forty percent of patients with coronary artery disease reported intake of non-opioid analgesic drugs[3]. This is not surprising, as the incidence of pain correlates with increasing age[4] and cardiovascular diseases are morbidities of middle to older age patients[5].

Aspirin (acetylsalicylic acid; ASA) is essential secondary prevention of cardio-and cerebrovascular events[6]. It inhibits cyclooxygenase (COX)-1 by irreversible acetylating serine 530 near the active site. This hampers conversion of arachidonic acid to thromboxane (TX) A2 for the life span of the affected platelet[7]. Aspirin has been shown to reduce the incidence of death, myocardial infarction and stroke[8-10]. However, during the last decade substantial inter-individual variation in pharmacodynamic response to aspirin has been described. This is called high on-treatment platelet reactivity (HTPR) (formerly known as "aspirin resistance"). Patients with HTPR have an increased incidence of death, myocardial infarction and stroke[11]. Many potential mechanisms including non-compliance[12,13], impaired absorption[14], genetic polymorphisms[15] increased turnover rate, enteric coating of aspirin[16,17] and COX-1 independent pathways may cause this HTPR[18]. Besides that, non-opioid analgesic medication may impair aspirin antiplatelet effects. In contrast to above mentioned internal factors, this drug-drug interaction is avoidable. Therefore special attention should be paid to this interaction leading to impaired aspirin antiplatelet effects. This review focuses on (1) mechanisms-; (2) laboratory-; and (3) clinical evidence of the aspirin drug-drug interaction with commonly used non-opioid analgesics.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in the world[19]. They are available on prescription as well as over the counter. In the United States, 70 million NSAID prescriptions- and 30 billion over the counter sales per year were registered[20]. Approximately 83% of United States - American adults use NSAID to relief pain at least once a year, 29% once a week and 15% daily[21]. In Australia, 55% of people consume NSAIDs at least once per month[22].

The term "NSAID" subsumes a variety of drugs with different chemical structures, pharmacokinetics, pharmacodynamics and mechanism of action but similar effects[23]. The main common feature is prevention of prostaglandin formation by inhibition of COX isoforms. This results in desirable anti-inflammatory and analgesic effects due to COX-2 inhibition in inflamed tissues[24]. On the other hand, inhibition of COX-1 in the gastric mucosa impairs maintenance of the mucosal barrier. This results in an increased risk of gastrointestinal events[25]. Additionally NSAIDs may worsen renal function[26] and affect platelets[27]. Based on the above mentioned differences in pharmacokinetics and pharmacodynamics between different NSAIDs, a considerable variability in analgesic as well as anti-inflammatory and antiplatelet effects is not surprising[23,27]. NSAIDs may also impair cardiovascular prognosis[28,29], possibly by inhibition of prostaglandin synthesis in the vasculature resulting in an increase in blood pressure and disturbed endothelial control of thrombogenesis. This aspect must not be confounded with the pharmacodynamic interaction of non-opioid analgesics with aspirin, which is discussed here. However, it is possible that this interaction contributes to the overall cardiovascular risk of NSAIDs. In the following, we will discuss the most commonly used NSAIDs with respect to their potential to interfere with platelet inhibition by low dose aspirin.

Ibuprofen

Ibuprofen was the first propionic acid derivative NSAID. Worldwide more than 100 million patients consumed ibuprofen and it is available in more than 100 countries[30]. Ibuprofen forms hydrogen bonds to arginine 120 and tyrosine 355 near the active site of the COX[27]. *In-vitro* analysis revealed, that ibuprofen inhibits platelet aggregation of human platelets[27]. In healthy individuals, ibuprofen intake led to inhibition of thromboxane formation[31] and platelet aggregation *ex-vivo*. As ibuprofen inhibited COX transiently, platelet function returned to normal within 4 to 6 h[32]. *In-vitro* coincubation with aspirin completely abrogated platelet inhibition and thromboxane formation by aspirin. This has been shown *ex-vivo* in healthy individuals as well with multiple studies demonstrating hampered aspirin antiplatelet effects in ibuprofen co-treated healthy subjects[33-37]. Catella-Lawson *et al*[33] reported that controlled order of intake with single dose ibuprofen (400 mg) two hours after aspirin intake preserves aspirin antiplatelet effects in healthy individuals. However ibuprofen medication three times per day inhibits aspirin antiplatelet effects independently of the above mentioned order of intake. This finding may be consistent even in lower doses of ibuprofen (150 mg)[36]. None of patients on aspirin for secondary prophylaxis of a cerebrovascular event with ibuprofen co-treatment had adequate aspirin induced inhibition of platelet aggregation. Additionally, 72% of patients experienced recurrent ischemic events. After termination of analgesic medication, aspirin antiplatelet effects restored[32]. In patients with cardiovascular diseases, different studies detected increased incidence of death and recurrent myocardial infarction in aspirin and ibuprofen comedicated patients[38-40]. This finding was confirmed in two meta-analyses, investigating the risk of death

and cardiovascular events in patients at increased risk of vascular disease on ibuprofen medication[29,41].

Naproxen

Naproxen is a propionic acid derivative NSAID like ibuprofen. However, its' pharmacokinetics are different. Plasma half-life of ibuprofen is about two hours, whereas the plasma half-life of naproxen is approximately 12 h[42]. Naproxen forms hydrogen bonds to tyrosine 385 and serine 530 in the active site of COX[27]. This leads to dose-dependent, reversible inhibition of platelet activation *in-vitro*. However, increasing concentrations of arachidonic acid can overcome this COX-inhibition. Additionally, ASA administration after pre-incubation with naproxen prevents ASA antiplatelet effects[43]. In healthy individuals, naproxen co-treatment with aspirin impairs aspirin antiplatelet effects as well[32,35,37]. This effect was consistent in over the counter doses as well as prescription doses[44]. However, data of clinical studies are contradictory. Some studies described an increased incidence of cardiovascular events in naproxen treated patients[32,45]. However others described a beneficial effect on the incidence of adverse events[39,40,46,47]. Two meta-analyses described no significant increase of vascular events and death in naproxen medicated patients[29,41]. The reasons for these inconstant results are unclear. Naproxen inhibits aspirin antiplatelet effects in-vitro similar to ibuprofen[27]. However, Capone *et al*[48] described permanent functionally relevant inhibition of *ex-vivo* platelet function in healthy individuals with 500 mg naproxen twice a day. Therefore, most probably the increased plasma half-life and therefore longer lasting reversible inhibition of platelets by naproxen may be responsible for the protective, respectively less harmful effects of naproxen in patients with cardiovascular diseases. The importance of naproxen's potential to interfere with the antiplatelet action of aspirin is presently not clear. Different authors recommended preferring the use of naproxen in patients with increased cardiovascular risk[49,50].

Diclofenac

Diclofenac is a heteroaryl acetic acid NSAID. It is commonly prescribed to alleviate acute and chronic pain[51]. Like other NSAIDs, diclofenac inhibits COX enzymes (COX-2 > COX-1). There may be additional mechanisms of action inducing its anti-inflammatory, antipyretic and analgesic effects, which are not completely understood. Besides affection of arachidonic acid uptake and release, activation of nitric oxide-cGMP antinociceptive pathway, inhibition of thromboxane prostanoid receptor and lipoxygenase enzymes, it may also inhibit peroxisome proliferator activated receptor gamma, block acid-sensing ion channels, alter interleukin-6 production and inhibit substrate P and N-methyl-D-aspartate receptor hyperalgesia[51].

In-vitro incubation of human platelets with diclofenac inhibited thromboxane formation and platelet aggregation[27]. This was reproducible *ex-vivo* after diclofenac treatment of healthy volunteers[31,52]. Additionally, platelet function was inhibited after diclofenac - treatment in patients[53,54]. However, there seems to be no interaction with aspirin treatment. ASA antiplatelet effects including inhibition of thromboxane formation were preserved *in-vitro* after pre-incubation with diclofenac[27]. Additionally, diclofenac treatment in healthy individuals on aspirin revealed sufficient pharmacodynamic response to aspirin as well[33,34]. This may be explained by molecular docking analyses. Diclofenac did not form any hydrogen bond interactions in the hydrophobic active channel of COX. Therefore it appears not to interfere with the ASA induced acetylation of serine 530, preserving aspirin antiplatelet effects despite of diclofenac co-treatment[27].

In aspirin and analgesic co-treated patients with coronary artery disease, MacDonald *et al*[38] described improved outcome of diclofenac co-treated patients in comparison to ibuprofen comedicated patients. In contrast, in a study including 83667 patients after myocardial infarction, diclofenac co-treatment was associated with the highest risk of recurrent myocardial infarction and death during 90 d[39] as well as in one- and five year follow-up[40]. These findings were confirmed in two meta-analysis investigating death and cardiovascular events in patients with analgesic medication. Both reported an increased risk in diclofenac treated patients as well[29,41].

COX-2 INHIBITORS

Anti-inflammatory and analgesic effects of COX-inhibitors are largely mediated by prevention of COX-2 induced prostaglandin formation in inflamed tissues[24]. Impairment of the gastric mucosal barrier resulting in increased incidence of gastrointestinal events, and affection of platelets are mostly caused by COX-1 inhibition[25,27]. Therefore, during the 90's NSAIDs with COX-2 selectivity were developed[55].

Conflicting data has been reported regarding impairment of aspirin antiplatelet effects by COX-2 inhibitors. Despite COX-2 selectivity, celecoxib was shown to form a hydrogen bond in the hydrophobic channel of COX-1 with tyrosine 355[27]. This goes in line with *in-vitro* experiments, demonstrating inhibition of thromboxane formation and platelet aggregation by celecoxib incubation. In ASA and celecoxib co-incubated platelets, ASA antiplatelet effects were inhibited[27]. Celecoxib administration in dogs interfered with the ability of aspirin to inhibit platelet aggregation[56]. In contrast, no impact on platelet function was observed in healthy individuals on celecoxib treatment[35]. Additionally, different groups reported that COX-2 inhibiting co-treatment in aspirin treated healthy individuals did not impair the pharmacodynamic response to aspirin[33,35,37,57]. Regardless, multiple studies reported increased risk of cardiovascular

events and death in patients receiving COX-2 inhibitors independently of concomitant aspirin intake[28,58-60].

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is an aniline derivative. It is one of the most widely used antipyretic and analgesic drugs worldwide, especially as the risk of gastrointestinal bleeding events are lower in comparison to NSAIDs[61]. It is available over the counter in many countries[62]. However, in supra-therapeutic doses depletion of endogenous glutathione occurs, resulting in paracetamol metabolism shunting to toxic pathways causing severe, even fatal, hepatotoxicity[63,64]. To date, the mechanisms of analgesia by paracetamol remain unclear despite of extensive investigations[65]. A plethora of mechanisms have been postulated including activation of the endocannabinoid pathway[66,67], inhibition of the nitric oxide synthase[68,69], and indirect activation of descending serotonergic pathways[70-72]. Additionally, inhibition of cyclooxygenases in a direct-[73-75], or indirect (by converting to their oxidized, inactive form[76]) way has been described. Current opinion suggests that paracetamol performs its analgesic actions by multiple mechanisms predominantly in the central nervous system[65].

In-vitro addition of paracetamol to human platelets was reported to inhibit collagen, epinephrine and arachidonic acid induced platelet aggregation and TX formation[77]. Accordingly, in healthy individuals a reduced arachidonic acid-induced TX formation one hour after single dose of paracetamol was shown. However an effect on platelet aggregation was observed in only one of five investigated individuals[77]. Munsterhjelm *et al*[78] detected an inhibition of platelet aggregation in healthy individuals 10 min after ingestion of paracetamol. Already 90 min after intake of paracetamol, platelet aggregation was restored. Additionally, a combination of paracetamol and diclofenac exhibits an additive effect on platelet inhibition. In comparison to diclofenac treatment in healthy individuals alone, addition of paracetamol preserves inhibition of platelet aggregation and TX formation 90 min after intake. Nevertheless, platelet function normalized after 24 h[52]. In patients, a single dose of paracetamol reduced arachidonic acid induced TX formation, but did not inhibit platelet aggregation in patients[54]. Molecular modelling and docking analyses revealed that paracetamol forms only one single hydrogen-bond to arginine 120 in the hydrophobic channel of COX-1[27]. No aspirin interaction resulting in inhibition of aspirin antiplatelet effects was seen, suggesting that one hydrogen-bond might not be sufficient to induce impairment of aspirin antiplatelet effects[27]. These findings were supported by the results of Catella-Lawson *et al*[33] and Rao *et al*[79], both did not observe altered aspirin antiplatelet effects in presence of paracetamol, either. However an increased incidence of first cardiovascular event in patients with frequent use of paracetamol was observed[80]. Potential reasons for this observation may be a dose dependent risk of renal insufficiency of paracetamol[81] which is a predictor of cardiovascular events[82]. Secondly, an increased blood pressure in patients with paracetamol usage has been described[83-86]. Also, an impairment of endothelial function by depletion of glutathione is thinkable to induce this enhanced risk of cardiovascular events[87].

DIPYRONE (METAMIZOLE)

Dipyrone is a pyrazolinone analgesic with favorable analgesic, spasmolytic and antipyretic effects. Gastrointestinal complications are rare in comparison to NSAIDs like ibuprofen or diclofenac[88]. Due to the risk of agranulocytosis, it has been withdrawn in many countries including the United States. Nevertheless, it is extensively used in Central- and South America and freely available over the counter in Mexico. Therefore despite of the withdrawal by the Food and Drug Administration, there is a wide spread use in the United States as well[89]. Moreover, it is freely available and the most used analgesic in Eastern European countries like Bulgaria[90]. Guidelines of the European Society of Cardiology do not recommend the use of NSAIDs in patients with cardiovascular diseases[91,92]. This may be one of the reasons why dipyrone daily doses tripled during the last decade in European countries like Germany[93]. The exact mechanism of its analgesic effects is complex and not completely understood, yet. Besides COX inhibition, an activation of opioidergic- and cannabinoid system in combination with inhibition of central COX-3 appears to contribute to its analgesic effects. Comedication with opioids causes superadditive analgesic effects. It inhibits both prostaglandin dependent and - independent pathways of fever and exhibits its spasmolytic effects by inhibition of intracellular calcium release[94]. Dipyrone inhibits all COX isoforms. It reversibly binds near the active site of COX, forming hydrogen bonds to tyrosin 385 and serine 530[27]. Dipyrone sterically hinders aspirin access to the active site and serine 530 of COX-1. Plasma half-life of dipyrone is about 2.5 h. Therefore it is 7.5 fold longer available than aspirin with a plasma half-life of only 20 min[95]. *In-vitro* experiments revealed that dipyrone active metabolite impairs ASA induced inhibition of microsomal platelet COX. The active metabolite of dipyrone in therapeutically relevant (low micromolar) concentrations showed little inhibition of platelet aggregation and TX formation. However, it prevented ASA dependent inhibition of platelet aggregation and thromboxane formation caused by arachidonic acid as well as collagen. The effect was reproducible in terms of microsomal platelet COX activity and p-selectin expression as well[96]. Increasing ASA concentrations *in-vitro* overcame this effect[97]. Additionally, previous incubation with ASA before addition of dipyrone preserves ASA antiplatelet effects[98].

In healthy individuals, aspirin intake sufficiently inhibits platelet aggregation, seven days of additional

Table 1 Risk and benefits of non-opioid analgesics

Substance	Platelet inhibition	Aspirin interaction	Benefits	Risks
Aspirin	Irreversible	-	Analgesic, antipyretic, anti-inflammatory Reduction of cardiovascular events and death	Bleeding events
Ibuprofen	Reversible (half-life 1-4 h)	Yes	Analgesic, antipyretic, anti-inflammatory	Death Cardiovascular events Bleeding events
Naproxen	Reversible (half-life 12-24 h)	Yes	Analgesic, antipyretic, anti-inflammatory Reduction of cardiovascular events (?)	Bleeding events
Diclofenac	Reversible (half-life 1-2 h)	No	Analgesic, antipyretic, anti-inflammatory	Death Cardiovascular events Bleeding events
Celecoxib	Reversible (half-life 8-13 h)	Yes	Analgesic, antipyretic, anti-inflammatory Less gastrointestinal events	Death Cardiovascular events
Paracetamol	Reversible (half-life 1-4 h)	No	Analgesic, antipyretic Less gastrointestinal events	Cardiovascular events
Dipyrone	Reversible (half-life 2-4 h)	Yes	Analgesic, antipyretic, anti-inflammatory Less gastrointestinal events	Risk of death and cardiovascular events not investigated

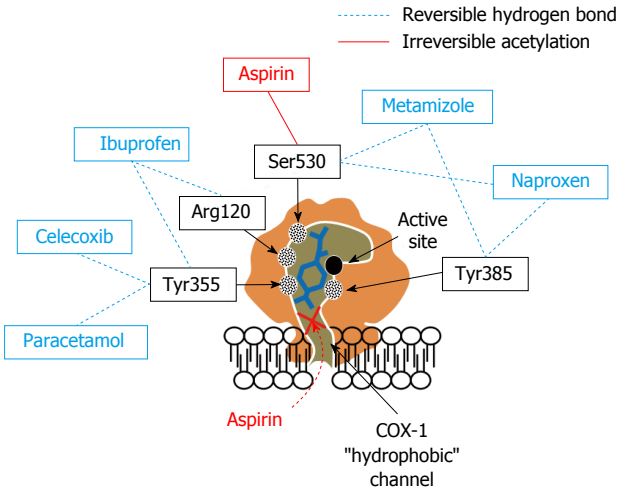

Figure 1 Graphical abstract. Non-opioid analgesics form reversible hydrogen bonds near the active centrum of cyclooxygenase (COX)-1. This prevents (1) aspirin entrance to the hydrophobic channel; (2) irreversible acetylation of Ser530; and (3) platelet inhibition for the remainder of the platelets life-span.

dipyrone intake completely blunts aspirin antiplatelet effects. This effect was reversible within three days of continued aspirin administration after termination of dipyrone intake. However, multiple daily doses of dipyrone were not tested[97]. Interestingly, Börgermann *et al*[99] reported that there was no impaired pharmacodynamic response to aspirin in dipyrone treated healthy individuals. However the duration of aspirin and dipyrone co-treatment was only two days. As aspirin antiplatelet effects are irreversible and persist for the remainder of the affected platelets life-span, it is not surprising, that no relevant differences were observed after two days of additional dipyrone treatment. A partial inhibition of aspirin antiplatelet effects has been described after four days of concomitant intake and complete inhibition after seven days[100]. Furthermore, it has been shown that aspirin intake prior to dipyrone preserves aspirin antiplatelet effects, whereas dipyrone intake prior to aspirin completely blunts aspirin antiplatelet effects measured by platelet aggregation in healthy individuals[97].

In patients with coronary artery disease, residual platelet reactivity despite of aspirin was detected in 50% of dipyrone comedicated patients[101]. Residual platelet TX formation in patients with coronary artery disease correlated with the concentration of dipyrone metabolites. Additionally, in dipyrone treated patients after cardiac surgery, the incidence of HTPR to aspirin nearly tripled postoperatively[99]. The impact of this *in-vitro* and *ex-vivo* effects on clinical outcome has not been investigated yet.

CONCLUSION

The optimal analgesic regimen in patients with pain is challenging. Considering laboratory and clinical data, naproxen and paracetamol seem to display the most favourable benefit/risk ratio. However, increased incidence of adverse events has been described with these analgesics as well. Alternatively, aspirin would be a possible alternative to relieve pain and inhibit platelet function. Yet it is well known, that analgesic doses of aspirin increase the risk of gastrointestinal complications (Figure 1 and Table 1). If medication with non-opioid analgesics is considered indispensable, a strict order of intake, with aspirin medication at least two hours prior to analgesic medication is advisable. However, the optimal analgesic and antiplatelet regimen in patients with increased risk of cardiovascular disease is still unknown and requires further investigation.

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MINIREVIEWS

Peritoneal dialysis for chronic cardiorenal syndrome: Lessons learned from ultrafiltration trials

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Abstract

The current models of cardiorenal syndrome (CRS) are mainly based on a cardiocentric approach; they assume that worsening renal function is an adverse consequence of the decline in cardiac function rather than a separate and independent pathologic phenomenon. If this assumption were true, then mechanical extraction of fluid (*i.e.*, ultrafiltration therapy) would be expected to portend positive impact on renal hemodynamics and function through improvement in cardio-circulatory physiology and reduction in neurohormonal activation. However, currently available ultrafiltration trials, whether in acute heart failure (AHF) or in CRS, have so far failed to show any improvement in renal function; they have reported no impact or even observed adverse renal outcomes in this setting. Moreover, the presence or absence of renal dysfunction seems to affect the overall safety and efficacy of ultrafiltration therapy in AHF. This manuscript briefly reviews cardiorenal physiology in AHF and concludes that therapeutic options for CRS should not only target cardio-circulatory status of the patients, but they need to also have the ability of addressing the adverse homeostatic consequences of the associated decline in renal function. Peritoneal dialysis (PD) can be such an option for the chronic cases of CRS as it has been shown to provide efficient intracorporeal ultrafiltration and sodium extraction in volume overloaded patients while concurrently correcting the metabolic consequences of diminished renal function. Currently available trials on PD in heart failure have shown the safety and efficacy of this therapeutic modality for patients with chronic CRS and suggest that it could represent a pathophysiologically and conceptually relevant option in this setting.

Key words: Cardiorenal syndrome; Peritoneal dialysis; Heart failure; Ultrafiltration

Core tip: This article briefly reviews the clinical significance of renal dysfunction in heart failure and evaluates the results of the ultrafiltration studies in acute heart failure and cardiorenal syndrome (CRS). It concludes that peritoneal dialysis could represent an

efficacious option for chronic CRS due to its ability to simultaneously address renal and cardiac dysfunction in these patients. Recent technical advances such as possibility of initiating peritoneal dialysis (PD) in the acute setting and placement of the PD catheter by interventional radiology could make this home-based therapeutic option even more accessible and intriguing.

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INTRODUCTION

Renal dysfunction is a prevalent feature of heart failure (HF) and portends adverse impact on its potential management options, course, and outcomes. Although several therapeutic strategies have so far been evaluated for patients who present with simultaneous dysfunction of the heart and the kidney [*i.e.,* cardiorenal syndrome (CRS)], the optimal therapy for "chronic" CRS remains largely unknown. This could reflect the paucity of data on the precise mechanisms underlying this syndrome, which is unfortunately unlikely to resolve soon due to its complexity. The contemporary question for clinicians providing care for patients with chronic CRS is whether there exists a safe management strategy that could provide this group of patients with improved outcomes and quality of life compared with conventional therapies. The answer might paradoxically lie in the lessons learned from trials on "acute heart failure" (AHF).

ULTRAFILTRATION FOR HF AND CRS

In the last decade a multitude of attempts have been aimed at finding more efficacious and safer therapies for AHF[1]. While trials on pharmacologic agents such as endothelin receptor antagonists and adenosine receptor antagonists have mostly been disappointing, extracorporeal ultrafiltration has shown promising results that ranged from more efficient fluid and sodium removal to reduction in the rate of re-admission[2,3]. Indeed, ultrafiltration has been recognized as an emerging therapy for patients with AHF which can be used either as an alternative to conventional diuretic-based strategies or as an adjuvant therapy. However, it is noteworthy that patients with significant renal dysfunction have often been excluded from the ultrafiltration trials and as such their favorable results can hardly be extrapolated to common clinical scenarios in which the decline in renal function parallels deterioration in cardiac status[3,4].

In contrast to most previous AHF studies, the recently published Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) trial examined the role of ultrafiltration in management of patients with AHF who also presented with worsening renal function (WRF)[5]. In this randomized controlled trial that included 188 patients, ultrafiltration was compared to a diuretic-based pharmacologic therapy in patients who were admitted with a primary diagnosis of AHF and experienced acute CRS. Surprisingly, once the renal component was added to the clinical picture, the favorable findings of the previous trials were not observed anymore; ultrafiltration was found to be inferior to pharmacologic therapy with regards to its impact on both renal function and development of serious adverse events, and the recruitment of the patients had to be stopped. Although considered a trial of AHF, the unprecedented design of CARRESS-HF (*e.g.*, inclusion of patients with an increase in serum creatinine level as small as 0.3 mg/dL up to 3 mo prior to admission to the hospital) made it possible for the trial to also recruit and follow patients with cardiorenal physiology of less acuity.

CARDIO-RENAL PHYSIOLOGY AND ULTRAFILTRATION

Renal dysfunction is an established predictor of adverse outcomes in patients with HF. Until recently, the traditional model of therapy for HF mainly focused on low cardiac output (*i.e.*, low forward flow) being the trigger for a cascade of pathologic events ultimately leading to deterioration in renal function. Even though most patients admitted for AHF present with normal blood pressure, a significant subset still experience concomitant WRF and CRS. Therefore, the decrease in renal perfusion pressure secondary to reduced stroke volume, which was once considered the major mechanism, cannot fully explain renal dysfunction of all these patients. Indeed, more recent data suggested that WRF in the setting of AHF would correlate better with the degree of renal venous congestion rather than cardiac output (*i.e.*, high backward pressure)[6]. In this model, alteration in renal function is more related to right atrial and central venous pressure than cardiac index or left ventricular ejection fraction, hence proposing the hypothesis of backward rather than forward failure.

Does ultrafiltration therapy affect cardiac physiology and hemodynamic status? A number of studies including those using invasive methods have reported several beneficial effects on cardio-circulatory parameters such as cardiac index and systemic vascular resistance following ultrafiltration therapy. While the precise mechanisms remain to be determined, these positive results could still be explained to some extent by the aforementioned models of CRS. On the arterial side, efficient fluid removal by ultrafiltration therapy reduces left ventricular end-diastolic volume and pushes the heart towards the left side of the Frank-Starling curve.

Table 1 Proposed benefits of peritoneal dialysis therapy for heart failure

Continuous gentle ultrafiltration with minimal impact on hemodynamic status
Improvement in functional status and symptoms of volume overload
Reduction in number of days of heart failure-related hospitalizations
Restoration of diuretic responsiveness
Reduction in weight and improvement in volume status
Improvement in left ventricular ejection fraction
Sodium sieving effect and possibility of better control of natremia
Removal of pro-inflammatory mediators (medium-sized molecules)
Reduction in intra-abdominal pressure in patients with severe ascites
Improvement in quality of life
Improved atherogenic lipid serum profile
Lack of impact on neurohormonal activity (renin-angiotensin-aldosterone system and sympathetic nervous system)
Improved control of serum potassium level (hence providing the opportunity to use medications such as aldosterone receptor blockers)
Reduction in healthcare cost

Adapted from Courivaud *et al*[9], with permission.

This effect can hinder the intermediary pathways such as activation of renin-angiotensin-aldosterone and sympathetic nervous systems and their downstream adverse effects such as ventricular remodeling and perturbation in renal hemodynamics. On the right side, ultrafiltration extracts fluid directly and exclusively from the venous side of the circulation leading to immediate reduction in preload, ventricular wall stress, and capillary hydrostatic pressure. Decongestion of the venous side of the circulation has also been reported to improve renal vein engorgement without affecting counteracting intermediate pathways such as adenosine receptors and tubuloglomerular feedback that result in a decrease in glomerular filtration rate. We have previously reviewed the currently available data on the interactions between the cardiocirculatory system and the kidney in the setting of AHF, and the potential role of ultrafiltration in modifying these mechanisms[7].

RENAL IMPLICATIONS OF ULTRAFILTRATION TRIALS

The common theme in the above-mentioned models of CRS is the dependence of the renal component on the cardiac status (*i.e.*, a cardiocentric approach). They both assume that WRF is an adverse consequence of the decline in cardiac function rather than a separate and independent phenomenon. If this assumption were true, then ultrafiltration therapy would be expected to portend positive impact on renal hemodynamics and function as it is capable of improving cardio-circulatory physiology and reducing neurohormonal activation. However, available ultrafiltration trials, whether in AHF alone or in CRS, have so far failed to show any improvement in the associated WRF; they have either reported no impact or even observed adverse renal outcomes in this setting[3,5]. This important observation questions the accuracy of the above-mentioned cardiocentric models of WRF in AHF, and suggests that renal component of acute CRS is not merely a consequence of deterioration in cardio-circulatory status or the use of conventional therapies in a subset of patients; it can reflect an independent but related phenomenon that needs to be regarded and managed separately. In this model, a number of maladaptive mechanisms (*e.g.*, inflammation and endothelial cell dysfunction) are shared by the kidney and the heart resulting in a decline in the function of both organs and development of CRS. As such, any therapeutic option for this syndrome should not only target cardio-circulatory status, but it also needs to have the ability of addressing the adverse homeostatic consequences of the decline in renal function. In this respect, ultrafiltration might not be the optimal option for management of all cases of acute CRS, as supported by recent trials such as CARRESS-HF, simply due to the fact that it lacks any clearance property and cannot address the diverse metabolic and homeostatic derangements associated with concomitant renal dysfunction.

PERITONEAL DIALYSIS AND CHRONIC CRS

In the chronic setting, where patients present with various degrees of HF and slowly declining renal function, a therapy with the ability of simultaneously addressing both organs will be conceptually attractive and mechanistically relevant. Peritoneal dialysis (PD) can be such an option. PD has been shown to provide efficient intracorporeal ultrafiltration and sodium extraction in volume overloaded patients (especially through the use of icodextrin solution), while concurrently correcting the metabolic consequences of diminished renal function. It has also been reported to portend less well-characterized benefits such as removal of myocardial depressant factors and improvement in endothelial dysfunction (Table 1). It is noteworthy that not all proposed beneficial mechanisms are exclusive to PD; while many can be the direct consequences of using this specific therapeutic modality (*e.g.*, reduction in intra-abdominal pressure in patients with severe ascites), some can also be achieved through other methods of renal replacement therapy such as hemodialysis (*e.g.*, reduction in weight and improvement in volume status).

Several uncontrolled PD studies have so far reported favorable results for patients with chronic CRS despite the fact that they often used PD as "the last resort" for very sick patient populations who were refractory to alternative options and were not candidates for heart transplant[8-10]. For instance, in a study on 126 patients with refractory heart failure and various degrees of renal dysfunction, Courivaud *et al*[10] reported a 90% reduction in the number of days of hospitalization after initiation of PD (3.3 d/patient per month *vs* 0.3 d/patient per month; $P < 0.0001$).

Table 2 Selected studies on the role of peritoneal dialysis in heart failure

Ref.	Study design	No. of patients	Mean age (yr)	Male gender	NYHA class	EF	Renal function	Main findings	Comment
Koch *et al*[11]	Prospective	118	73.2	60.2%	Ⅲ (49.2%) Ⅳ (50.8%)	43.5%	Creatinine clearance 19.2 mL/min	Significant improvement in body Weight and NYHA class	Negligible incidence of peritonitis and catheter dysfunction
Núñez *et al*[8]	Prospective	25	75.1	72%	Ⅲ or Ⅳ (100%)	40%	eGFR 33 mL/min per 1.73 m^2	Significant improvement in patients' clinical status and NYHA class	Marked reduction in the number of days hospitalized for acute heart failure
Bertoli *et al*[12]	Multicenter retrospective	48	74	81%	Ⅱ (6%) Ⅲ (48%) Ⅳ (46%)	30%	eGFR 21 mL/min per 1.73 m^2	Significant improvement in NYHA class and reduction in the number of days hospitalized	Significant reduction in pulmonary artery pressure and improvement in EF
Courivaud *et al*[10]	Retrospective	126	72	69%	N/A	38%	eGFR 33.5 mL/min per 1.73 m^2	Significant reduction in the number of days hospitalized for acute heart failure	Improvement in cardiac function in patients with a an EF of 30% or less

NYHA: New York Heart Association.

The results of selected studies on the role of PD in HF are summarized in Table 2. Since HF is the single most common reason for hospitalization of patients over 65 and the majority of its cost is related to the in-hospital care, use of this home-based therapy for chronic CRS could potentially lead to significant savings in healthcare expenditure while providing a better quality of life for patients. The advantages, potential mechanisms, safety, and efficacy of this therapeutic modality for patients with HF has been discussed elsewhere[9]. In patients with significant residual renal function who do not require dialytic support, nocturnal automated PD or a single night time exchange with icodextrin solution could be sufficient to maintain euvolemia. Depending on the severity of HF, degree of volume overload, symptoms, and comorbidities, the PD therapy can be customized and some patients could use it only a few nights a week rather than every night. In patients with more severe renal dysfunction who require dialytic support for clearance, continuous ambulatory PD or automated PD with day time icodextrin exchange could have the greatest promise to generate the needed gentle continuous ultrafiltration while providing adequate clearance.

A major concern regarding the use of PD in this patient population has been that its morbidity might replace the morbidity from HF. This issue seems to be less compelling nowadays with reasonably low incidence of PD-related complications such as peritonitis, catheter dysfunction, and hernias as reported by most studies as well as the reports on the reduction in HF-related hospitalization after initiation of PD. Moreover, although the data are not consistent, it appears that PD does not alter the natural history of the disease and as such is unlikely to have a significant effect on survival of these patients. Finally, it should be noted that the current literature on the use of PD in the setting of HF still suffers from significant limitations which could hamper its more widespread use (*e.g.*, lack of an appropriately matched control group and relatively short follow-up periods). This could explain the fact that despite aforementioned advantages of this modality, PD is not yet considered by the professional cardiology societies as a therapeutic option for HF. Future prospective randomized studies with longer follow-up periods could address the knowledge gap and prove helpful in this regard.

In summary, based on the currently available data, PD represents one of the few options for patients with chronic CRS that not only is pathophysiologically and conceptually relevant, but is also reported to be safe and effective in several clinical trials. Recent technical advances such as possibility of initiating PD in the acute setting and placement of the PD catheter by interventional radiology could make this home-based therapeutic option even more accessible and intriguing[13].

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Prognostic impact of atrial fibrillation on clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease

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Abstract

Atrial fibrillation (AF) is the most common type of sustained arrhythmia, which is now on course to reach

epidemic proportions in the elderly population. AF is a commonly encountered comorbidity in patients with cardiac and major non-cardiac diseases. Morbidity and mortality associated with AF makes it a major healthcare burden. The objective of our article is to determine the prognostic impact of AF on acute coronary syndromes, heart failure and chronic kidney disease. Multiple studies have been conducted to determine if AF has an independent role in the overall mortality of such patients. Our review suggests that AF has an independent adverse prognostic impact on the clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease.

Key words: Atrial fibrillation; Heart failure; Chronic kidney disease; Acute coronary syndromes; Prognostic impact

Core tip: Atrial fibrillation (AF), the most common type of arrhythmia, is on course to reach epidemic proportions in the elderly. AF is a commonly encountered comorbidity in patients with acute coronary syndromes, heart failure and chronic kidney disease. Multiple studies have been conducted to determine if AF has an independent role in the overall mortality of such patients. Our review suggests that atrial fibrillation has an independent adverse prognostic impact on the clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease.

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INTRODUCTION

Atrial fibrillation (AF) is a commonly encountered arrhythmia in clinical practice[1] with an increased prevalence being reported with advanced age[2]. It is estimated that more than 8 million patients over the age of 80 will be affected by the year 2050[1,3]. Consequently, the associated healthcare expenses are also rising and have reached an all-time high of 16 to 26 billion dollars annually[4]. The major contributors to the burgeoning healthcare costs of AF include outpatient care and testing which accounted for nearly $1.5 billion of the total costs, prescription drugs that cost an approximate of $235 million, and also high costs associated with inpatient interventional procedures[4-6].

With a rising prevalence and economic burden, there is concern in the medical community regarding the temporal effect of cardiovascular conditions including atrial fibrillation on the clinical outcomes of associated comorbidities. In addition to its deleterious health consequences, cardiovascular disease is the number one cause of death in the United States and globally[7]. It is important to understand the role of other comorbidities in cardiovascular disease to prevent and reduce this mortality. In this article we focus on atrial fibrillation and commonly associated comorbidities. Atrial fibrillation is commonly encountered in the setting of acute coronary syndromes, heart failure and chronic kidney disease. The purpose of this article is to review the prognostic impact of atrial fibrillation on these comorbid conditions.

ACUTE CORONARY SYNDROMES

Acute coronary syndrome (ACS) is commonly associated with concomitant or incident AF. Most of the studies conducted have noted that the incidence of AF in ACS ranges from 2.3% to 23%[8]. Multiple factors explain this wide range of variation. The Cooperative Cardiovascular Project by Rathore *et al*[9] reported a higher incidence of AF in ACS patients, as the subjects were primarily elderly patients. Eldar *et al*[10] reported a lower incidence as they studied only paroxysmal AF. Some randomized controlled trials like TRACE and OPTIMAAL which studied the efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in acute myocardial infarction (AMI) have also reported lower incidences; the efficacy of these drugs in preventing atrial fibrillation had however been proven in earlier studies[11,12].

Broadly there has been a downward trend in the incidence of AF in AMI in studies done over time. This can be explained possibly by more widespread use of thrombolytic therapy and percutaneous coronary interventions (PCI) over the years. Advanced age, tachycardia at the time of admission, and advanced stage of heart failure were found to be the major clinical predictors of atrial fibrillation in patients with AMI[9,13,14].

Early studies done to assess the independent prognostic impact of atrial fibrillation on ACS outcomes were found to have contrasting results. A number of studies after multivariate analyses found atrial fibrillation to have no independent impact and concluded that it was more the coexisting comorbidities that contributed to the mortality[10,14-19]. However, a greater number of studies have reported that atrial fibrillation in the setting of AMI, results in a worse prognostic outcome[9,11-13,19-22].

However, two major meta-analyses done by Jabre *et al*[23] and Angeli *et al*[24] proved conclusively the independent impact atrial fibrillation had on AMI. In the analysis of 43 studies by Jabre *et al*[23] where 278854 patients were studied, it was observed that AF was associated with a 40% increase in risk mortality as compared to patients with normal sinus rhythm. While the impact of atrial fibrillation on both in hospital

mortality and long term mortality was noted, the timing of atrial fibrillation development, *i.e.*, new onset or pre-existing AF was not a contributor to the poor outcome as per this meta-analysis. Angeli *et al*[24], on the other hand, found that new onset atrial fibrillation had worse outcomes with an 87% higher risk compared to pre-existing atrial fibrillation. The study however only assessed in hospital mortality and not long-term outcomes.

Atrial fibrillation leads to a number of hemodynamic effects such as loss of atrial contraction, rapid ventricular rates, loss of atrio-ventricular synchrony and an irregular RR interval. All of these factors lead to a decreased cardiac output, which in turn explain the higher mortality rates[25,26].

Many mechanisms have been proposed to explain how AF is commonly encountered in the setting of ACS. Although many theories exist, the pathophysiological mechanism of the onset of AF after ACS is still not clearly understood. Conclusions drawn from experimental models and clinical investigations have shown different factors accounting for new-onset AF in ACS; it can be explained either by myocardial infarction causing atrial ischemia or atrial stretch[27]. Role of inflammation, autonomic nervous system activity, BNP and other hormone activation cannot be excluded as possible mechanisms for AF development in this patient subset[28,29]. Thus, proper understanding of the role of new onset AF complicating ACS can provide us with a new approach in formulating therapeutic guidelines.

Consensus has been reached on the independent role of AF on mortality in ACS. Treatment targeting the pathophysiological mechanism of AF development in ACS remains an area that needs to be explored. It therefore remains imperative to develop strategies to prevent AF onset and initiate aggressive treatment in case of a new onset AF in ACS.

HEART FAILURE

Heart failure (HF) and AF are closely linked cardiovascular diseases that often coexist and share a complex pathophysiological relationship. Both have continuously increasing prevalence, and the presence of AF in HF patients has been reported as being anywhere between 10% and 50%[30]. The difference in coexistence of this two-disease condition can be attributed to the different study settings, study design, severity of heart failure and other factors[30,31]. The prevalence of AF correlates directly with the severity of HF, as about 5% of patients with New York Heart Association (NYHA) class Ⅰ HF have AF and this prevalence increases to about 50% in NYHA class IV HF[32,33]. Regardless of the study design, a few factors like hypertension, prior history of ACS, diabetes, and obesity were commonly observed to be associated with an increasing prevalence of AF and HF.

Recent large heart failure trials have demonstrated the adverse prognostic influence of AF on HF[34]. A study conducted by Dries *et al*[35], in which data was obtained from SOLVD trial, showed AF was associated with an increased risk of all cause mortality in patients with symptomatic and asymptomatic left ventricular systolic dysfunction[35]. On the other hand, the COMET trial analysis by Swedberg *et al*[36] showed AF did increase mortality risk and HF hospitalizations but it was not identified as an independent risk factor for mortality when adjustment for other prognostic indicators was made[36].

AF also increases re-hospitalization rates, hospital stays, and has an overall adverse prognosis in HF patients that is very clearly evident in many studies. Mountantonakis *et al*[37] analyzed data obtained from 99810 patients enrolled in the Get with the guidelines - Heart failure Registry and concluded that AF independently was associated with adverse hospital outcomes and a longer length of in-hospital stay. Mentz *et al*[38] showed presence of AF on initial electrocardiogram in patients hospitalized with HF was associated with higher readmission, higher mortality and lower use of evidence-based therapies.

Corell *et al*[39] proved an adverse prognostic impact of AF in HF patients. Olsson *et al*[40] reviewed results from Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program and showed that AF is associated with an increased risk of poor cardiovascular outcomes. In the meta-analysis by Mamas *et al*[41] which included 16 studies involving 53969 patients; the conclusion was that irrespective of left ventricular systolic function, AF has an overall adverse prognosis in HF patients.

Pathophysiological changes that explain the increased prevalence of AF in HF patients are not very well understood. It is difficult to ascertain in most cases if HF leads to AF or changes due to AF leads to worsening of the underlying HF. Studies have different conclusions on the cause - effect process but there is a general agreement about the vicious cycle of deterioration when both conditions co-exist. According to one thought process, HF results in specific electrophysiological changes in the atrium like prolonging the atrial refractory period or increasing heterogeneity of repolarization that leads to the development of AF[42]. On the other hand, HF also plays a part in concurrent worsening of AF through mechanical and hemodynamic changes. Atrial tissue stretching occurs as a result of the increased pressure and volume in HF patients, which in turn triggers AF by increasing automaticity and altering atrial repolarization[43]. Activation of the renin-angiotensin system secondary to HF and other neurohormonal changes also promotes the development of AF[43]. Further studies need to be conducted to understand the impact AF has on HF, especially in regards to the dynamic pathophysiological interplay and therapy should be aimed at correcting the predisposing factors.

Although beyond the scope of this article, the op-

timal management approach of AF in HF remains unclear. Pharmacological therapy remains the mainstay of choice in AF, and includes rate control and rhythm control. A recent meta-analysis involving 2486 patients suggested no significant difference in terms of mortality and thromboembolic events between both modes of pharmacological management. However, hospitalizations appear to be less frequent with rate control than with rhythm control[44]. Also there are data that suggest role of cardiac resynchronization therapy (CRT) in non-ischemic dilated cardiomyopathy and severe heart failure, which has favorable outcome on incidence of AF[45,46]. Further studies are warranted to determine the optimal management approach for AF in patients with HF.

CHRONIC KIDNEY DISEASE

It is a well-established fact that there is a high occurrence of cardiovascular disease in patients with chronic renal insufficiency. The overall prevalence of AF is higher among patients with end-stage renal disease (ESRD)[47]. Studies examining the prevalence of AF in cohorts pooled from the Dialysis Outcomes and Practice Patterns Study (DOPPS) and the United States Renal Data System (USRDS) estimated the occurrence of AF to range from 6% to 27% among patients with ESRD on dialysis[48-50]. This high rate of occurrence in ESRD patients is nearly two times higher than that reported in the general population[49]. Dissimilarity of the individual study pattern, study population, sample size, disease definition and diagnostic methods of AF can account for the difference between the prevalence of AF in this population.

Wetmore *et al*[50] and Wizemann *et al*[48] concluded that a significantly higher prevalence of AF exists in ESRD patients on dialysis. On the other hand, recent studies have found a higher incidence and prevalence of AF among patients with chronic kidney disease (CKD) who have not been started on dialysis, as is clearly evident in the ARIC study and CRIC study done by Alonso *et al*[51] and Soliman *et al*[52]. In the latter study by Soliman *et al*[52] where a multicenter cohort with a wide range of kidney function was studied, it was estimated that the prevalence of AF was at 18%.

Moreover, AF is an independent risk factor for ischemic stroke and death among patients with ESRD on dialysis[53]. A large cross sectional cohort study conducted by Winkelmayer *et al*[49], analyzed data from 1992 to 2006 for the prevalence of AF in hemodialysis patients from the United States Renal Data System (USRDS). According to this study, the prevalence of AF increased 3 fold from 3.5% in 1992 to 10.7% in 2006. A one-year mortality rate among patients with AF was twice that of those without AF and was as high as 72% after demographic variant adjustment was made.

Several mechanisms have been proposed to explain the increased risk of death in CKD patients with AF. Systemic inflammation could be responsible for the fibrotic changes seen in the kidney and myocardium and by could worsen cardiovascular outcomes such as heart failure, thromboembolic risk and stroke which in turn increases the risk of morbidity and mortality[35,54-57].

A large cohort study on adults with AF by Go *et al*[58] concluded that a lower level of GFR was associated with an increased risk of thromboembolism independent of the known AF risk factors. A higher rate of thromboembolic events was observed among individuals with a lower estimated GFR.

The cumulative effect of AF and CKD together has been shown to not only increase mortality but also the rate of cardiovascular events, as has been observed in two separate studies done by Nakagawa *et al*[59] in Japan and Genovesi *et al*[60] in Italy. From the findings of the study by Nakagawa *et al*[59], it was determined that a lower eGFR (< 60 mL/min per 1.73 m^2) with CHADS2 score > 2 was associated with a higher all-cause (12.9% *vs* 1.4% per year, $P < 0.001$) and cardiovascular (6.5% *vs* 0.2% per year, $P < 0.001$) mortalities compared to preserved eGFR (> 60 mL/min per 1.73 m^2) combined with CHADS2 score < 2. Also cardiovascular events, which include cardiac death, nonfatal myocardial infarction, or hospitalization for worsening of heart failure and ischemic stroke risk, were much higher in the same group (13.6% *vs* 1.5% per year, $P < 0.001$). The study concluded that a combined eGFR and CHADS2 score could be an independent powerful predictor of cardiovascular events and mortality in patients with nonvalvular AF[59].

Although there is a substantially increased risk of thromboembolism in patients with CKD and AF, there are no distinct guidelines to follow for thromboembolism prophylaxis in AF patients with CKD when compared to patients without CKD. Patients with severe renal impairment have been excluded from a vast majority of trials studying stroke prevention in AF, including trials that have formed the landmark for risk factor scoring schemes and guidelines. It therefore, poses a huge challenge to healthcare providers to treat this subset of patients. The available data suggests that the benefit from warfarin in terms of stroke reduction in CKD patients is not as clear as in the general population, and there is also an increased risk of bleeding complications[61].

One of the few studies that show a favorable outcome of anticoagulation for prevention of stroke in renal failure patients is the study by Hart *et al*[62]. Efficacy of adjusted-dose warfarin in prevention of stroke in atrial fibrillation patients with stage 3 CKD was demonstrated by this study. The study by Chan *et al*[63], a large retrospective cohort study of patients with AF on hemodialysis, suggests that warfarin use is associated with an increased risk for ischemic (HR = 1.81; 95%CI: 1.12-2.92) and hemorrhagic (HR = 2.22; 95%CI: 1.01-4.91) stroke. The data however is influenced by lack of appropriate monitoring and

difficulties in maintaining the international normalized ratio (INR) target[63].

Thus, it remains a dilemma to refer to the benefits of warfarin administration as has been determined by anticoagulation guidelines in the general population, to a group of people that have been actively excluded from clinical trials; the prediction rules for bleeding risk would be inaccurate and oversimplified and probably not suitable for clinical practice. In reality, there appears to be no large randomized controlled trials that evaluate the real risk *vs* benefit of full intensity anticoagulation including newer novel anticoagulants in patients with severe renal impairment. Information about management is limited and in the future there might be an opportunity to look into these patients and form risk stratification guidelines that can be followed.

LIMITATIONS

Although we have searched a wide range of appropriate literature from online data sources for our article, sometimes such studies are potentially susceptible to vary in conclusion due to different populations, settings, interventions, or outcome measures. All the studies we included have different limitations. Despite the limitations, the present article has important strengths, including a real-world large sample size from different studies and the absence of selection bias associated with clinical trials.

CONCLUSION

In conclusion, atrial fibrillation is a commonly encountered arrhythmia in clinical practice that has a rising prevalence and significant adverse prognostic implications on other comorbidities. In this article we concluded that AF, with its rising prevalence increases the economic burden on healthcare, and has an independent adverse prognostic impact on comorbidities like ACS, HF and CKD. A thorough understanding of AF prevalence and its pathophysiology, including the role of genetics, can serve as a potential biomarker for the prevention and treatment of AF[64,65]. Along with it, factors associated with AF and its increased association with other comorbidities, outcomes of these comorbidities in the setting of AF, prospective data and appropriate guidelines are needed to define more precisely how to treat these patients. Individual risk stratification may represent the best possible approach and provide opportunities for improvement in the future. Further studies need to be conducted to determine risk stratification for decision making and to develop an optimal management approach.

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MINIREVIEWS

Cholesterol confusion and statin controversy

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Abstract

The role of blood cholesterol levels in coronary heart disease (CHD) and the true effect of cholesterol-lowering statin drugs are debatable. In particular, whether statins actually decrease cardiac mortality and increase life expectancy is controversial. Concurrently, the Mediterranean diet model has been shown to prolong life and reduce the risk of diabetes, cancer, and CHD. We herein review current data related to both statins and the Mediterranean diet. We conclude that the expectation that CHD could be prevented or eliminated by simply reducing cholesterol appears unfounded. On the contrary, we should acknowledge the inconsistencies of the cholesterol theory and recognize the proven benefits of a healthy lifestyle incorporating a Mediterranean diet to prevent CHD.

Key words: Cholesterol; Statins; Coronary heart disease; Mediterranean diet; Cardiovascular disease; Mortality

Core tip: Traditional efforts to prevent cardiovascular disease have emphasized the benefits of cholesterol lowering and statin drugs. Often overlooked is the fact that numerous studies of cholesterol lowering have failed to demonstrate a mortality benefit and the benefits of statins may have been overstated. The Mediterranean diet has consistently lowered cardiovascular events and mortality in numerous studies and does not typically lower cholesterol levels. Alternative theories of atherosclerosis are independent of cholesterol metabolism and may provide the key to future preventive strategies.

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INTRODUCTION

Nearly twenty years ago two landmark randomized clinical trials appeared in *The Lancet* which forever changed the course of medicine for patients with coronary heart disease (CHD). The 4S study employed a cholesterol-lowering statin drug and reported a 30% mortality reduction[1]. The Lyon Diet Heart Study utilized the Mediterranean diet and reported a 70% mortality reduction[2]. Subsequent studies of the Mediterranean diet have confirmed these findings and also shown a reduced risk of cancer, diabetes, and Alzheimer's disease[3-6]. Subsequent statin studies have led the United States Food and Drug Administration to issue warnings regarding the increased risk of diabetes and decreased cognition with statin drugs. Paradoxically, statins have gone on to become a multi-billion dollar industry and the foundation of many cardiovascular disease prevention guidelines while the Mediterranean diet has often been ignored. We believe this statin-centric cholesterol-lowering approach to preventing CHD may be misguided.

ASSOCIATION DOES NOT EQUAL CAUSATION

The cholesterol hypothesis links cholesterol intake and blood levels to cardiovascular disease. Because cholesterol is considered a risk factor for atherosclerosis many believe that lowering cholesterol in the blood is the best way to prevent CHD. Ideally, risk factors should help us distinguish those who will develop a disease from those who will not. However, if one examines the original Framingham Heart Study data (as an example) it is clear that the cholesterol levels of those who developed CHD and those who did not overlap except when the total cholesterol level exceeded 380 mg/dL or was less than 150 mg/dL (Figure 1). Moreover, cholesterol may be associated with CHD but that does not prove causation. Despite the fact that high triglycerides and low HDL have long been associated with CHD, studies designed to raise HDL or lower triglycerides have failed to reduce CHD mortality. Similarly, cholesterol should not automatically become a treatment target. It may be a leap of faith to assume that lowering cholesterol is the best way to prevent CHD.

LOWERING CHOLESTEROL MAY NOT LOWER CARDIOVASCULAR MORTALITY

The rare occurrence of CHD in isolated, rural societies such as Tukisenta, New Guinea has been attributed to low cholesterol levels[7]. However, it is equally plausible that the diets and lifestyles of these individuals may protect them from CHD. While we may never be certain if low cholesterol or a healthy lifestyle (or both) are responsible for preventing CHD in these societies, there is ample evidence that lowering cholesterol does not consistently lower CHD mortality. Reducing

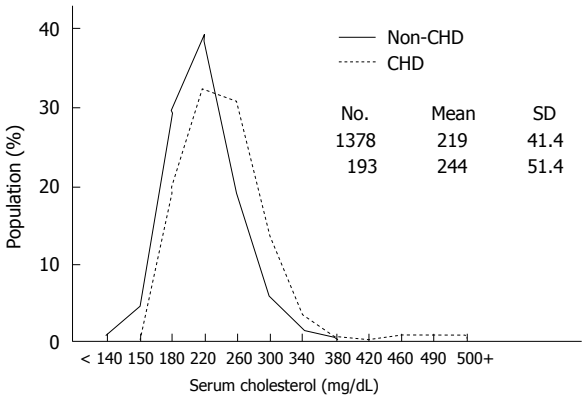

Figure 1 Serum cholesterol distribution among coronary heart disease and non-coronary heart disease patients in the Framingham Heart Study[43]. Reprinted with permission of the publisher. CHD: Coronary heart disease.

cholesterol blood levels by reducing dietary saturated fats is commonly recommended, but an exhaustive review and meta-analysis of 72 dietary studies concluded that reduced consumption of saturated fat does not reduce cardiovascular mortality[8]. Many drugs such as niacin, fibrates, and bile acid sequestrants can lower cholesterol levels, but the recent AHA/ACC guidelines on cholesterol concluded that these drugs do not lower CHD mortality rates[9]. Moreover, the results of cholesterol-lowering statin trials, as will be discussed and analyzed later, do not consistently lower mortality rates[10]. Consider also the dramatic mortality benefit of the Mediterranean diet in the Lyon Diet Heart Study which was achieved without a reduction in cholesterol levels[2-4]. Thus, the hypothesis that lowering cholesterol lowers mortality from CHD is not supported by many clinical research studies.

EARLY STATIN TRIALS MAY HAVE BEEN FLAWED

Early statin trials reported significant mortality benefits, yet serious concerns have been raised in some studies regarding biased results, premature trial terminations, under reporting of adverse events, high numbers of patients lost to follow-up and oversight by the pharmaceutical company sponsor[10]. Heightened awareness within the scientific community regarding problems in clinical trial conduct and analysis - exemplified by the unreported risk of heart attacks in patients taking the pain killers Vioxx and Celebrex - led to new regulatory rules for clinical trials in 2005[11]. Curiously, statin trials conducted after 2005 have failed to demonstrate a consistent mortality benefit[10].

MORTALITY RESULTS ARE MORE IMPORTANT THAN COMBINED CLINICAL ENDPOINTS

Cholesterol-lowering statin trials are often viewed as supporting the cholesterol hypothesis by reporting

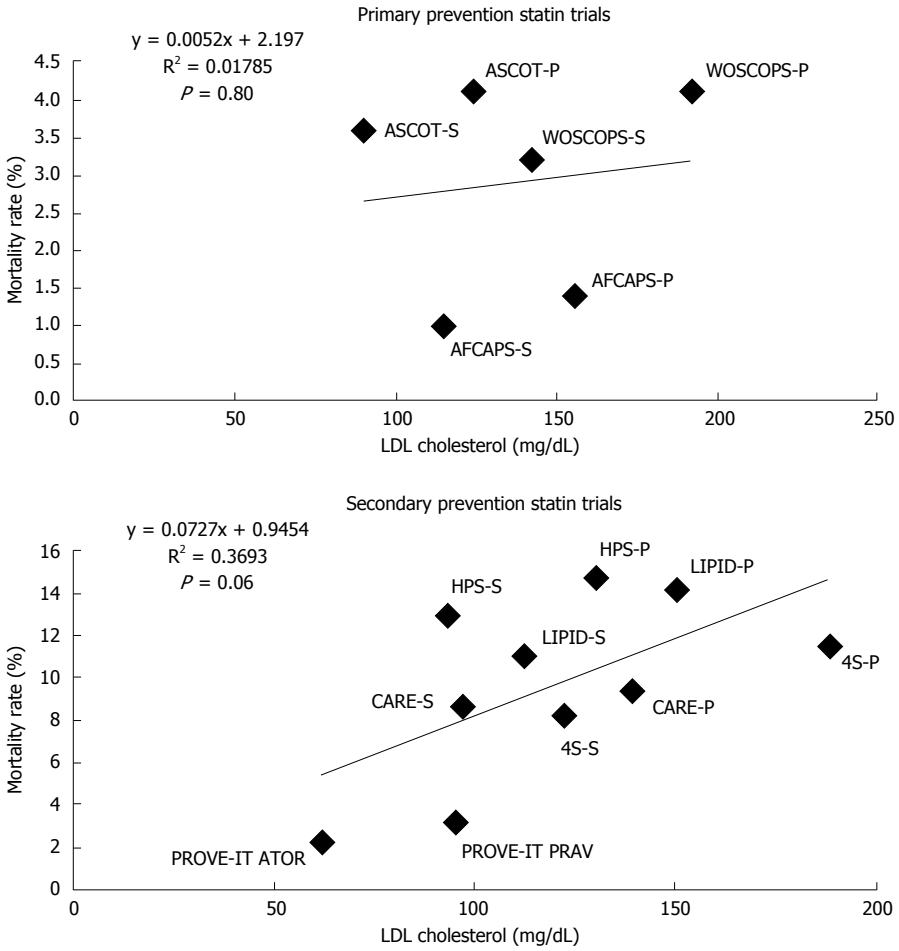

Figure 2 Comparison of mortality rates to low-density lipoprotein cholesterol levels using the randomized clinical trials cited in reference 14 (taken as an example).

significant reductions in combined clinical endpoints. Clinical endpoints are valuable and should not be ignored, but the ultimate measure of efficacy is total mortality that reflects both the treatment effect and potentially fatal side effects. Utilizing combined endpoints may lead to an exaggeration of perceived benefit by assigning equal importance to disparate clinical events such as a hospital admission for angina and death from a heart attack[12,13]. Some have argued that there is a linear relation between low-density lipoprotein (LDL) levels and CHD events[14]. This analysis may be inaccurate because it combines different types of CHD events from diverse studies into one endpoint even though each study defines CHD events differently. A more meaningful analysis compares total mortality rates to LDL cholesterol levels. When we performed such an analysis on these same statin trials - those analyzed in reference 14 - we found no statistically significant relationship (Figure 2).

MORTALITY BENEFITS OF STATINS ARE INCONSISTENT

Although a number of statin trials have reported a mortality benefit, quite a few have not. A corollary to the cholesterol hypothesis posits that patients at highest risk should derive the greatest benefit from cholesterol lowering. However, statin trials in the elderly (PROSPER), in patients with heart failure (CORONA, GISSI-HF), and in patients with renal failure (4D, AURORA, SHARP) have all failed to demonstrate a mortality benefit[10,15]. A Cochrane meta-analysis of 18 cholesterol-lowering trials (some with statins) in patients with peripheral arterial disease also failed to demonstrate a mortality benefit[16]. A separate meta-analysis of 11 statin trials for high-risk primary prevention similarly failed to demonstrate a mortality benefit[17]. Another Cochrane meta-analysis of statin usage after acute coronary syndromes concluded there was no mortality benefit[18]. The Cholesterol Treatment Trialists (CTT) performed a meta-analysis of 27 statin trials and concluded that statins were clearly beneficial in reducing cardiovascular events[19]. However, when the same 27 trials were assessed for mortality outcomes, no benefit was seen[20]. The coronary calcium score is considered to be one of the best predictors of cardiovascular risk, yet the St. Francis Heart Study showed no clinical benefit in asymptomatic patients with coronary calcium scores > 80th percentile randomized to statin therapy[21]. Finally,

diabetes mellitus is considered a CHD risk equivalent, but the three randomized controlled trials specifically designed and powered to assess the effect of statins in diabetes all failed to demonstrate a mortality benefit (CARDS, 4D, ASPEN)[22-24].

ALTERNATIVE THEORIES OF ATHEROSCLEROSIS AND CHD COMPLICATIONS ARE CHOLESTEROL INDEPENDENT

The dramatic benefits of the Mediterranean diet are likely due to multiple mechanisms which do not directly involve cholesterol. Independent of cholesterol metabolism are the true fatal complications of coronary atherosclerosis - thrombotic coronary occlusion, acute myocardial ischemia, left ventricular dysfunction, and malignant arrhythmias. The hemostatic system appears to be a principal modulator of atherosclerotic plaque formation and progression and the Mediterranean diet can favorably alter elements of the coagulation cascade[25,26]. Plaque rupture and intra-plaque hemorrhage leads to progressive atherosclerosis, thrombosis causes acute coronary syndromes, and sudden cardiac death is the main cause of cardiac mortality. At the genetic level large scale, genome-wide association studies have identified 46 loci directly linked to CHD, yet a majority of these loci have no apparent relation to cholesterol or traditional risk factors[27]. Although we can't change our genes, epigenetic studies have shown that the Mediterranean diet can favorably alter the expression of atherogenic genes[28], whereas a recent cholesterol-lowering statin trial failed to demonstrate a similar effect[29]. At the cellular level we now know that atherosclerosis is an inflammatory disease where macrophages and T lymphocytes likely play a dominant role. Whether or not specific anti-inflammatory therapies will be successful remains to be determined, but prior experience with Vioxx and Celebrex, which unexpectedly increased cardiovascular deaths, emphasizes the importance of proceeding cautiously. Recent studies have demonstrated that the Mediterranean diet can reduce markers of inflammation[26]. Accumulating evidence also implicates sugar in the pathogenesis of atherosclerosis. Diabetes is considered a coronary artery disease equivalent yet diabetics typically have average cholesterol levels. Other studies indicate that those who drink sugar-sweetened beverages are at much higher risk for CHD[30]. How elevated levels of blood glucose lead to atherosclerosis and why cholesterol lowering statins increase the risk of diabetes remains enigmatic, yet the totality of evidence suggests molecular mechanisms of atherosclerosis that are independent of cholesterol metabolism. The Mediterranean diet has been shown to reduce the risk of developing diabetes and the metabolic syndrome[31,32]. Elegant research into the gut microbiota is also providing an alternative theory of atherosclerosis[33]. Consider that L-carnitine, a component of red meat, is metabolized by the gut microbiota into trimethylamine oxide (TMAO). TMAO, in turn, promotes atherosclerosis and has been associated with a higher risk of cardiovascular events independent of traditional risk factors such as cholesterol. The gut microbiota can also adapt to changes in diet, which may explain why some vegans do not produce any TMAO after an L-carnitine challenge and how the Mediterranean diet may exert its anti-inflammatory and anti-atherosclerotic effects[34].

STATIN DRUGS HAVE UNINTENDED CONSEQUENCES

If statins have failed to consistently reduce mortality one must ask if statins improve the quality of life. Serious or fatal statin adverse events are rare, but side effects are not. The incidence of muscular aches and weakness in statin trials is highly variable, and real world experiences may differ from clinical trial reports. Consider that the adherence rates for statins in the elderly are poor with nearly 75% of primary prevention patients stopping the drug within the first two years[35]. More recently a cohort study of statin users reported a 53% discontinuation rate although a very high percentage were able to continue statin therapy after being rechallenged[36]. In the largest statin survey ever conducted, the National Lipid Association observed that roughly 30% of statin patients reported experiencing muscle pain and weakness and 57% of surveyed patients reported stopping the drug due to side effects[37]. One may debate the relationship of statins to diabetes and dementia, but the fact remains that the FDA now requires disclosure of these warnings. Most distressing is the recent report of gluttonous behavior among statin users who mistakenly believe they are "protected" by taking statins and can eat whatever they want[38].

CONCLUSION

The debate over the cholesterol hypothesis and statins has raged for decades. Some may point to the recent decline in cardiovascular deaths in the United States as proof of statin effectiveness, but this view fails to incorporate the impact of smoking cessation, lifestyle changes, and dramatic improvements in heart attack survival rates due to timely reperfusion and the availability of external and implantable defibrillators. Others may argue that statins are started too late in life to be effective (the horse may already be out of the barn) and reference Mendelian randomization studies which show that rare individuals with genetically low cholesterol levels have a much lower incidence of CHD[39].

However, this concept should not be extrapolated to the 99.99% of us who lack these genes and also fails to explain how the Mediterranean diet reduces mortality within months of initiation[2-4]. In 1996 Nobel laureates Brown and Goldstein anticipated the eradication of coronary disease in their *Science* editorial, "Exploitation of recent breakthroughs - proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors - may well end coronary disease as a major public health problem early in the next century"[40]. History has proven otherwise, and the global prevalence of CHD, despite worldwide statin usage and cholesterol lowering campaigns, has reached pandemic proportions. Coronary heart disease is an extremely complex malady and the expectation that it could be prevented or eliminated by simply reducing cholesterol appears unfounded. After twenty years we should concede the anomalies of the cholesterol hypothesis and refocus our efforts on the proven benefits of a healthy lifestyle incorporating a Mediterranean diet to prevent CHD[2-4,41,42].

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MINIREVIEWS

Cardiac involvement in Duchenne and Becker muscular dystrophy

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Abstract

Duchenne and Becker muscular dystrophy (DMD/BMD) are X-linked muscular diseases responsible for over 80% of all muscular dystrophies. Cardiac disease is a common manifestation, not necessarily related to the degree of skeletal myopathy; it may be the predominant manifestation with or without any other evidence of muscular disease. Death is usually due to ventricular dysfunction, heart block or malignant arrhythmias. Not only DMD/BMD patients, but also female carriers may present cardiac involvement. Clinically overt heart failure in dystrophinopathies may be delayed or absent, due to relative physical inactivity. The commonest electrocardiographic findings include conduction defects, arrhythmias (supraventricular or ventricular), hypertrophy and evidence of myocardial necrosis. Echocardiography can assess a marked variability of left ventricular dysfunction, independently of age of onset or mutation groups. Cardiovascular magnetic resonance (CMR) has documented a pattern of epicardial fibrosis in both dystrophinopathies' patients and carriers that can be observed even if overt muscular disease is absent. Recently, new CMR techniques, such as postcontrast myocardial T1 mapping, have been used in Duchenne muscular dystrophy to detect diffuse myocardial fibrosis. A combined approach using clinical assessment and CMR evaluation may motivate early cardioprotective treatment in both patients and asymptomatic carriers and delay the development of serious cardiac complications.

Key words: Muscular dystrophies; Electrocardiography; Heart failure; Echocardiography; Cardiovascular magnetic resonance imaging

Core tip: Duchenne and Becker muscular dystrophy are the commonest X-linked muscular diseases. Death is usually due to cardiac disease including ventricular dysfunction, heart block or malignant arrhythmias. Female carriers may also present cardiac involvement. Overt heart failure may be delayed or absent. Electrocardiography findings include conduction defects, arrhythmias and myocardial necrosis. Echocardiography assesses a marked

variability of left ventricular dysfunction. Epicardial fibrosis in both patients and carriers has been documented by Cardiovascular Magnetic Resonance (CMR), even if overt muscular disease is absent. A combined approach using clinical and CMR assessment may motivate early cardioprotective treatment and delay serious cardiac complications.

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INTRODUCTION

Duchenne and Becker muscular dystrophy (DMD/BMD) includes a group of X-linked muscular diseases responsible for over 80% of all cases of muscular dystrophy[1]. The incidence of DMD is 1 in 3500 male newborns with a prevalence of 6 in 100000 males[1] and is characterized by weakness of leg, pelvic and shoulder girdle muscles starting in early childhood. BMD is a milder variant of dystro-phinopathy with a better prognosis. The incidence of BMD is 1 in 18450 males and prevalence 2.4 per 100000 in the general population[2,3]. First symptoms appear between ages of 3-21 years with a mean age of onset at 11 years. Age at death is at 21-89 years with an average age of about 45 years[4-7].

In DMD, boys are diagnosed as toddlers and most are wheelchair bound by age 15. Death usually occurs at the age of 20 years, due to respiratory complications or cardiomyopathy. Currently more patients survive until the age of 30 years, due to home ventilation and corticosteroids, which can prolong ambulation by 2-3 years, reduce risk of scoliosis and postpone pulmonary and heart failure after the age of 20 years[1]. Despite this documented efficacy, more than 25% of DMD boys are not treated with corticosteroids, either due to side-effects or lack of response[1]. In BMD, the disease is milder and more heterogenous, compared to DMD. Muscle weakness often is first noticed in adolescence or young adulthood. Cardiac involvement in BMD may precede the skeletal muscle decline, with death due to cardiomyopathy often occurring before the age 60 years[1].

Mutations leading in the absence of a functional dystrophin protein cause DMD, whereas mutations leading in a reduced amount or shortened dystrophin protein cause BMD[8,9]. Dystrophin is a large (427 kDa) subsarcolemmal protein that represents a physical link between the intracellular actin cytoskeleton and the extracellular matrix[10]. Loss or abnormal dystrophin destabilizes the sarcolemma, making the muscle fibers susceptible to contraction injury[11]. The repeated episodes of necrosis followed by regeneration finally lead to replacement of muscles by fat and connective tissue that is clinically manifested as progressive muscle weakness[10]. Dystrophin is also a scaffold protein that localizes other proteins to the sarcolemma and forms a highly organized multimeric dystrophin-associated glycoprotein complex (DGC)[10]. Dystrophin deficiency disrupts the DGC, resulting in downregulation and/or mislocalization of the dystrophin-associated proteins.

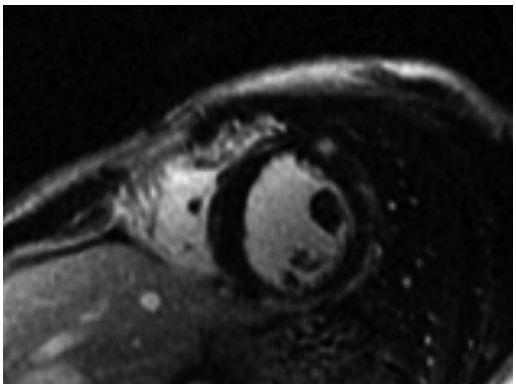

Figure 1 Fibrosis of the left ventricle in ecker muscular dystrophy patient, presented as late gadolinium enhancement in the inferolateral wall of left ventricular.

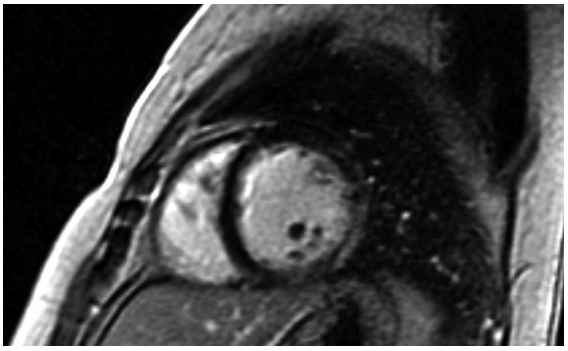

Figure 2 Fibrosis of the left ventricle in a mother Duchenne muscular dystrophy carrier, presented as late gadolinium enhancement in the lateral wall of left ventricular.

CARDIAC DISEASE IN DMD/BMD

Cardiac disease in DMD is progressive and finally leads to ventricular dysfunction, usually accompanied by ventricular dilation[12]. Pathology examination during the late stages of the disease shows cardiomyocytes' hypertrophy, atrophy and fibrosis[13-15]. Fibrosis of the left ventricle in DMD, BMD and DMD/BMD carriers has been observed at autopsy[13-15] and after evaluation with cardiovascular magnetic resonance (CMR) using late gadolinium enhancement (LGE)[16-19] (Figures 1 and 2).

The majority of DMD after the third decade of their age have established cardiomyopathy[20]. Although clinically overt heart failure may be delayed or absent, due to relative physical inactivity, cardiomyopathy is

the leading cause of death in DMD and myocardial damage precedes decline in left ventricular systolic function. Neither the age of onset nor the severity of cardiomyopathy was correlated with the type of mutation[21]. It was recently documented that in DMD with pre-served ejection fraction, the addition of eplerenone to background ACE inhibitors or ARB attenuates the progressive decline in left ventricular systolic function[22].

Cardiomyopathy is the main clinical complication in patients affected by subclinical or mild BMD. The clinical presentation is usually characterized by early right ventricular dysfunction and is later associated with left ventricular impairment. In mild BMD, myocardial damage may develop because the patients, who are unaware of a possible cardiac disease, can still perform strenuous muscle exercise and, through pressure or volume overload, may induce mechanical stress, which is harmful for dystrophin-deficient myocardial cells[23].

Cardiac disease in female carriers of dystrophinopathies may present with hypertrophy, arrhythmias or dilated cardiomyopathy[24]. The percentage of clinically overt cardiac involvement increases significantly with age, from 15% in carriers < 16 years to 45% in carriers > 16 years. By contrast, significant cardiac disease is unlikely in female carriers < 16 years[25]. In a cross-sectional study of 85 DMD and 44 BMD carriers aged 18-58 years, left ventricular dilatation and dilated cardiomyopathy were assessed in 18% and 8%, respectively[26]. Electrocardiography (ECG) abnormalities were found only in 47% of this population[27]. Another series of 56 adult, female carriers did not present any ECG abnormalities, but ventricular dilatation or hypertrophy was documented in 14% and dilated cardiomyopathy in 7% of them[28]. Nevertheless, severe heart failure may develop in some women necessitating heart transplantation to survive[29,30]. Exercise may unmask left ventricular (LV) systolic dysfunction in female carriers[31]. In a study by our group, CMR documented myocardial fibrosis in the majority of DMD and BMD mother-carriers, although the clinical presentation and the usual noninvasive assessment were mildly abnormal[19]. Therefore, detailed cardiac evaluation, at least once after the teenage years, should be recommended in all female carriers in order to start early cardiac treatment[32].

DMD is associated with increased R/S ratio in the right precordial leads, deep Q waves in the lateral leads, conduction abnormalities and arrhythmias (mainly supraventricular but also ventricular). In a study of 131 DMD, ECG was abnormal in 78.6%. All were in sinus rhythm and the following percentages were found for the main variables studied: short PR interval = 18.3%; abnormal R waves in V1 = 29.7%; abnormal Q waves in V6 = 21.3%; abnormal ventricular repolarization = 54.9%; abnormal QS waves in inferior and/or upper lateral wall = 37.4%; conduction disturbances in right bundle branch = 55.7%; prolonged QTc = 35.8% and wide QRS = 23.6%[33]. According to the study by Petri *et al*[34], ECG abnormalities were non-progressive in BMD and asymptomatic SVT and NSVT were present in 21% and 14%, respectively. Both ECG and Holter monitoring are necessary for DMD/BMD assessment. Serial clinical evaluation, including routine monitoring of electrocardiograms may detect early cardiomyopathy in DMD/BMD, even if left ventricular function is still preserved[35].

Echocardiography has already documented marked differences in LV function of DMD patients, independently of age of onset or mutation groups[21]. It has also proved a high prevalence of LV dysfunction in DMD, with frequent evidence of systolic ventricular asynchrony, particularly in patients with EF < 35%[36]. New echocardiographic techniques, using transmural strain profile (TMSP), can detect subclinical LV dysfunction in patients with DMD without wall motion abnormalities by conventional echocardiography[37]. The application of myocardial strain imaging in DMD patients was characterized by decreased peak systolic strain of the posterior wall, despite normal standard echocardiographic findings[38]. However, these studies were not universally accepted for the routine assessment of DMD/BMD.

Cardiovascular magnetic resonance (CMR) a non-invasive, non-radiating technique has been proved the most robust tool for detection of early myocardial fibrosis in DMD, BMD and female carriers, using late gadolinium enhancement (LGE). The pathology of cardiomyopathy in dystrophinopathies includes the presence of subepicardial fibrosis in the inferolateral wall[39], similar to that observed in viral myocarditis. The application of CMR in DMD/BMD and female carriers, in addition to the standard monitoring is of great value because: (1) Early start of heart failure treatment may delay the progression of LV dysfunction[22,40]; (2) Myocardial fibrosis, assessed by LGE, may be observed, even if the echocardiographic evaluation remains normal[16-18,40] and can potentially be used as an early sensitive index to start cardioprotective treatment; (3) It can be also applied as a screening tool to detect patients at high risk for ventricular arrhythmias, more advanced disease, adverse LV remodelling and death[41]. An impaired LV systolic function (LV-EF $\leqslant$ 45%) and a "transmural" pattern of myocardial fibrosis independently predict the occurrence of adverse cardiac events in DMD/BMD patients. Even in DMD/BMD patients with relatively preserved LV-EF (> 45%), the simple and visually assessable parameter "transmural LGE" is of additive prognostic value[42]; (4) in mutation carriers, CMR revealed a pattern of fibrosis similar to that observed in DMD[36], but without any correlation with genotype-phenotype[43], even in the absence of overt muscular disease; and (5) new CMR techniques, such as postcontrast myocardial T1 mapping, have been used in DMD to detect diffuse myocardial fibrosis. It was documented that post-contrast T1 obtained from the Look-Locker sequences (T1LL) ratio is abnormally shortened in DMD compared

with controls, even in DMD patients with otherwise normal CMR study. It is assumed that the application of more aggressive therapy for DMD with shorter T1LL may improve morbidity and mortality in DMD cardiomyopathy[44].

CONCLUSION

To conclude, heart involvement is common in both DMD/BMD and female carriers. Serial cardiac evaluation, including clinical examination, ECG, Holter monitoring, echocardiographic and CMR study, is the "sine qua non" for this population. Early detection of heart involvement should motivate early cardiac treatment with ACE inhibitors and b-blockers to delay serious cardiac complications.

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ORIGINAL ARTICLE

Basic Study

Feasibility of real-time magnetic resonance imaging-guided endomyocardial biopsies: An *in-vitro* study

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Author contributions: Lossnitzer D, Seitz SA, Krautz B and André F performed the research; Lossnitzer D, Seitz SA and Steen H designed the research and wrote the paper; Schnackenburg B, Korosoglou G and Katus HA contributed to the new analytic tools and reviewing the paper.

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Institutional review board statement: The study was not reviewed by the University of Heidelberg Institutional Review Board since there were no patients enrolled and only phantoms and explanted pig hearts which were bought by a regional butcher were used.

Institutional animal care and use committee: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Regierungspräsidium Karlsruhe Case Number 35-9185.81/G-79/12.

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Data sharing statement: No additional data are available.

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Abstract

AIM: To investigate if magnetic resonance (MR)-guided biopsy can improve the performance and safety of such procedures.

METHODS: A novel MR-compatible bioptome was evaluated in a series of *in-vitro* experiments in a 1.5T magnetic resonance imaging (MRI) system. The bioptome was inserted into explanted porcine and bovine hearts under real-time MR-guidance employing a steady state free precession sequence. The artifact produced by the metal element at the tip and the signal voids caused by the bioptome were visually tracked for navigation and allowed its constant and precise localization.

RESULTS: Cardiac structural elements and the target regions for the biopsy were clearly visible. Our method allowed a significantly better spatial visualization of the bioptoms tip compared to conventional X-ray guidance. The specific device design of the bioptome avoided inducible currents and therefore subsequent heating. The novel MR-compatible bioptome provided a superior cardiovascular magnetic resonance (imaging) soft-tissue visualization for MR-guided myocardial

biopsies. Not at least the use of MRI guidance for endomyocardial biopsies completely avoided radiation exposure for both patients and interventionalists.

CONCLUSION: MRI-guided endomyocardial biopsies provide a better than conventional X-ray guided navigation and could therefore improve the specificity and reproducibility of cardiac biopsies in future studies.

Key words: Endomyocardial biopsy; Cardiovascular magnetic resonance (imaging); Magnetic resonance imaging-guided interventions; Real-time imaging

Core tip: Myocardial biopsy is the method of choice for assessing tissue pathologies. Cardiac magnetic resonance imaging (MRI) provides a 3D visualization and discrimination of soft-tissue and could therefore enable a targeted specimen sampling. We developed a novel MR-compatible bioptome which was evaluated by *in-vitro* experiments in a 1.5T MRI system under real-time MR-guidance. MRI-guided endomyocardial biopsies provide a superior soft-tissue visualization, a better than conventional X-ray guided navigation and could therefore improve the specificity and reproducibility of cardiac biopsies in future studies. Not at least the use of MRI guidance for endomyocardial biopsies completely avoided radiation exposure for both patients and interventionalists.

Lossnitzer D, Seitz SA, Krautz B, Schnackenburg B, André F, Korosoglou G, Katus HA, Steen H. Feasibility of real-time magnetic resonance imaging-guided endomyocardial biopsies: An *in-vitro* study. *World J Cardiol* 2015; 7(7): 415-422 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i7/415.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i7.415

INTRODUCTION

Endomyocardial biopsy (EMB) is the "gold" standard diagnostic tool in the detection and classification of myocardial pathologies. It is recommended in the management and diagnosis of cardiomyopathies and inflammatory myocardial diseases[1-4].

Despite the benefits, EMB indications and their procedural management are controversially discussed. Reasons include EMB's low sensitivity when conducted under fluoroscopic guidance[5,6] as well as its potential complications. Thus, EMB may cause pericardial tamponade, severe arrhythmias or structural damages of the tricuspid valve[1]. Since sensitivity of EMB is low, clinicians are forced to increase the amount of samples (> 6, according to the AHA/ACCF/ESC scientific statement[1]) while focal pathologies like fibrosis in different forms of myocarditis may remain undetected.

In the clinical routine, fluoroscopy is used to guide the EMB procedure, offering a high frame rate (⩽ 30 fps) and high spatial resolution (2-3 line pairs/mm). However, this technique provides only two-dimensional projection images containing overlays of all anatomic structures in the X-ray beam in combination with a low soft-tissue contrast. Furthermore, it exposes both patient and interventionalist to a substantial radiation burden[7].

Cardiac magnetic resonance imaging (CMR) is a non-invasive modality which offers superior soft-tissue contrast, enables tissue characterization and allows the capture of specific slices with any required spatial orientations. Furthermore, contrast-enhanced CMR itself is able to visualize distinct pathologies like myocardial fibrosis, necrosis or inflammation and additionally provides macroscopic information, which may be complementary to that acquired by EMB[8]. Consequently, targeted myocardial biopsies under CMR guidance could reduce the number of required samples, increase specificity and sensitivity of the retrieved tissue samples and obviate radiation exposure. However, due to the very high static magnetic and radiofrequency (RF) electromagnetic fields, conventional metal bioptomes cannot be used in the MRI environment. First, the RF signals induce significant heating, mainly at the tip of metal wires leading to the necrosis of tissue[9,10], and secondly, metal devices lead to massive CMR image disturbance that could impair visualization of target areas. However, such problems can be overcome by MRI-compatible needles, which are already in use for real-time MR-guided tissue biopsies in static organs like breast, brain, liver, kidney or the prostate[11-14].

The localization and navigation of an invasive interventional instrument in the MRI system can be achieved with either active or passive tracking. While active tracking is more precise and faster since the bioptome's position is always known, it requires substantial modifications and cost-intensive miniaturized electrical extensions within the instrument. Conversely, passive tracking requires only minor modifications of the device to assure an appropriate visualization because it is implemented solely on the MRI system or additional computer systems and uses only the acquired real-time images to determine the instrument's position. This can be carried out manually by the operator, possibly supported by a software solution, but it requires a significant amount of operator training.

Therefore, we sought to develop and assess the feasibility of a novel MR-compatible bioptome for passive tracking in an *in-vitro* model to address these technical issues. Subsequently, we applied this method and performed endomyocardial biopsies in explanted animal heart models.

Table 1 Magnetic resonance imaging imaging sequences used during the real-time guidance procedures

Name	Type	SAR (W/kg)	Frame rate (fps)	Flip angle (degrees)	TR/TE (ms)	Resolution (mm)
Interactive	Balanced SSFP	0.765	8	45	3.10/1.55	1.79 × 1.79 × 6

SSFP: Steady state free precession.

MATERIALS AND METHODS

MRI system

All experiments were carried out in a cylindrical 1.5T MRI system (Achieva 1.5T, Philips Medical Systems, Best, The Netherlands) using the built-in birdcage coils for excitation and a cardiac 32-channel receive coil. The images were obtained with standard real-time sequences which provides continuous scanning and tracking of the bioptome's position in every possible angulation of three imaging planes within space (Table 1).

Bioptome

The major safety concern when using conventional metallic instruments that have dimensions in the range of the RF field's wave length is the possibility of tissue heating. The B_0-field of a 1.5T system correlates with a RF frequency of 64 MHz that corresponds then to a wavelength λ_{Air} of approx. 0.78 m in saline (0.9% NaCl), which is comparable to human body conditions. Therefore, characteristic RF wave lengths like $\lambda/2$ and $\lambda/4$ are well in the range of an outstretched bioptome, which could then lead to significant heating at the forceps of conventional endomyocardial bioptomes.

The shaft and the tip of the distal end of bioptome were constructed by using non ferromagnetic metals, synthetics and ceramic. The mechanical properties of the sample extraction mechanism at the tip of the MR bioptome were identical to a conventional device. It consisted of two spoon-shaped parts with sharp edges that could be pressed together and opened with a handle at the grip part. The spoons were coated with an MRI-visible marker to help determining the opening state. The device was engineered in close collaboration with H. + H. Maslanka GmbH, Tuttlingen, Germany.

The MR bioptome in the tested version did not have the capability of deflecting the tip for navigation purposes, which was compensated with a separate deflectable sheath (see below).

Deflectable sheath

The sheath prototype we used was a guiding catheter developed for electrophysiology applications and provided by Imricor (Burnsville, MN). It had the ability to deflect and steer the MR bioptome during the procedure and was fully MR-compatible causing neither heating nor disturbing imaging artifacts[15]. It was open at the distal end and a port prevented the outflow of blood at the proximal side. Its inner lumen provided a tight fit of the MR bioptome, effectively preventing a reverse flow of blood. The level of deflection (up to 150 degrees) at the tip could be adjusted and maintained in two directions with a mechanism at the grip. The diameter was approximately 3.7 mm.

Tracking and visualization of the instrument

In this study, we focused on a passive tracking approach with MRI visible markers at the spoons and the distal end of the device but without the need of an additional coil at the bioptome's tip and electronics inside the bioptome to evaluate the possibility of an affordable, easily available biopsy system as established in conventional EMB while benefiting from the imaging capabilities of MRI.

The necessary procedural adjustments of the corresponding image plane were conducted by the technician at the console while an MRI in-room monitor allowed the interventionalist to instruct the technician and navigate the bioptome. The MRI-control software provided an interface for real-time image visualization and parameter manipulation to allow a real time tracking of the bioptome within the phantom or heart.

Heart model

All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Regierungspräsidium Karlsruhe Case Number 35-9185.81/G-79/12.

The most beneficial aspect of the MR-guided myocardial biopsy was the targeted and specific retrieval of tissue samples. To reproduce the complex anatomical structures present in a human heart, explanted porcine and bovine hearts were employed. With their anatomical properties being comparable to human hearts, they provided an appropriate test environment to evaluate the navigation features and the new MR biopsy system.

When a catheter is pushed forward in a living heart, crossing the valve plane can normally be achieved in ventricular diastole (right ventricular biopsy) or systole (left ventricular biopsy). In an explanted, *ex-vivo* heart, the valves are static and might permanently obstruct the anatomic path of the instrument. Since their presence was not of primary concern for the actual experiment, the valve cups were removed during the preparation of the models.

A transparent plastic tube was attached at the orifice of the superior vena cava (SVC) into the right atrium (ostium venae cavae superioris) to mimic the venous vasculature normally guiding the instrument *in-vivo* into the right atrium and ventricle (Figure 1). The blood flow was not simulated.

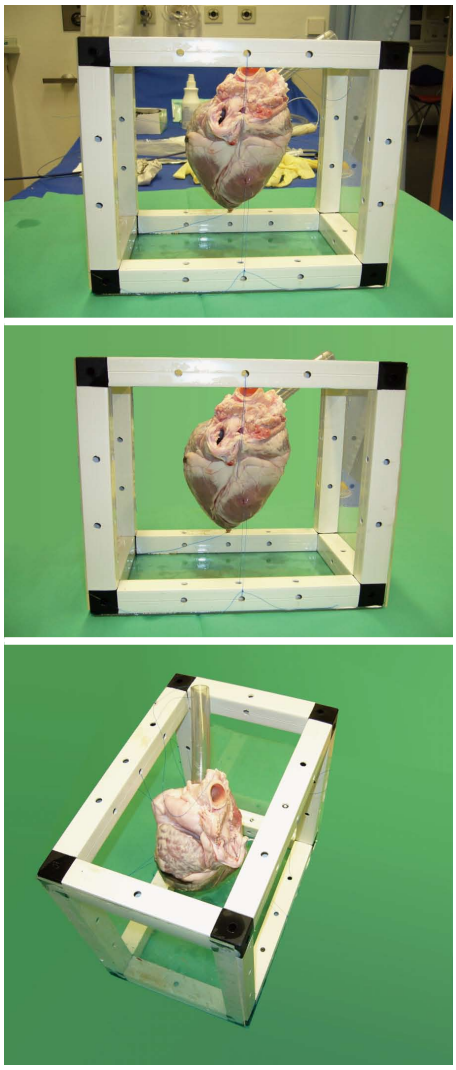

Figure 1 Model of swine heart with plastic tube attached to the trunk of the vena cava. The heart is fixated in a plastic frame to maintain form and position when submerged into the saline filled phantom.

To be able to evaluate the success of the biopsy later, several target areas of the endocardium were marked with an injection of a mixture of india ink and gadolinium. The first served as a visual marker in the specimen, the latter mimicked the elevated levels of gadolinium deposition in scar or fibrotic tissue areas eligible for an EMB. In the employed interactive sequences, a gadolinium marked area would appear as slightly brighter spot compared to the surrounding tissue.

Monitoring of heating

Due to the design and material composition of the MR bioptome, a heating problem was not expected. Nevertheless, the temperature was constantly monitored with a fiber optic-based thermometer (Fotemp, Optocon, Dresden, Germany) during the first experiment. One sensor was placed in the vicinity of the tip of the MR bioptome[16,17], the second recorded the overall temperature of the phantom filling.

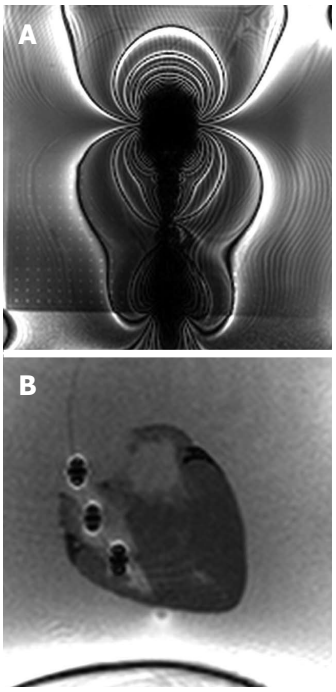

Figure 2 Cardiac magnetic resonance imaging-Images of conventional bioptome for endomyocardial applications (A), novel bioptome with three metal markers at the distal end inserted into a swine heart model (B).

RESULTS

Safety aspects/heating

During the course of the *in-vitro* experiments, the metal parts of the MR bioptome induced no heating. Only a general heating (< 1 ℃) of the phantom due to the constant exposure to the RF field and the heat dissipated by the MRI system during operation was detected.

Imaging and tracking

The new design of the MR bioptome effectively prevented the device from a negative interaction with the RF fields present during the MRI examination in terms of excessive artifacts. Only the coating of the sample cutting mechanism caused a small artifact at the tip (size approx. 2 mm × 2 mm, Figure 2), but this did not overlay the target structures in the heart (Figure 3). The shaft of the MR bioptome and the sheath caused a signal void compared to the surrounding tissue. At the same time signal voids supported the visual tracking of the tip of the MR bioptome when being pushed forward inside the sheath. The size of the artifact slightly increased when the tip left the isolating sheath and was exposed directly to the saline (Figure 3).

The opening and closing states of the sample cutter were slightly visible on the MRI images (Figures 4 and 5) when the bioptome was not moving. All maneuvers were carried out (1) in a saline (0.9% NaCl) filled but otherwise empty plastic container; and (2) in a porcine

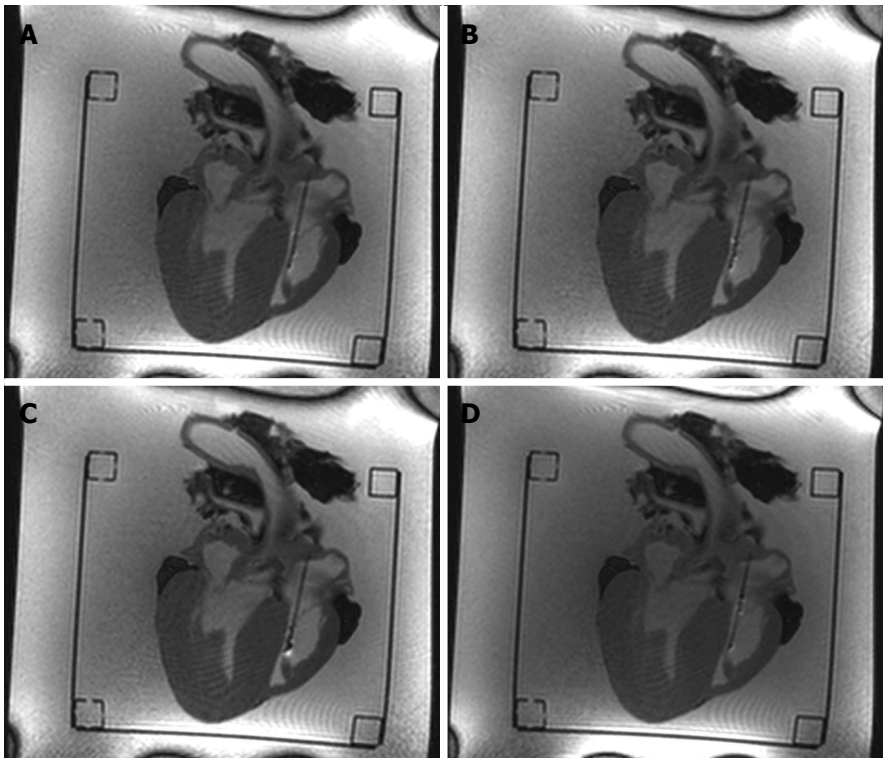

Figure 3 Real-time magnetic resonance image frames showing bioptome inside bovine heart. The bioptome is pushed forward through a plastic tube (A, B), is bare in the heart model (C) and then pulled back (D).

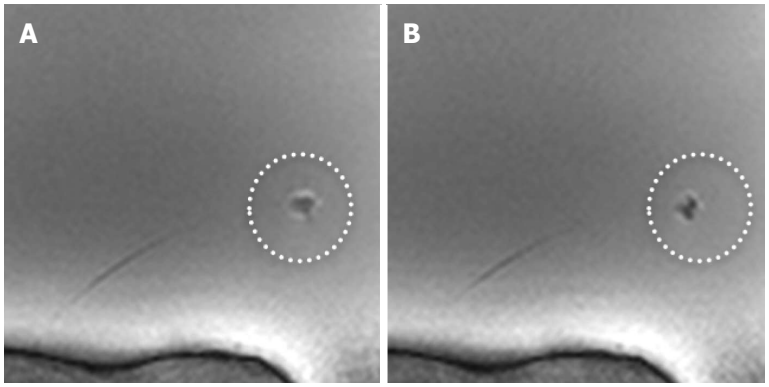

Figure 4 Real-time magnetic resonance imaging image frames with closed (A) and opened (B) cutter.

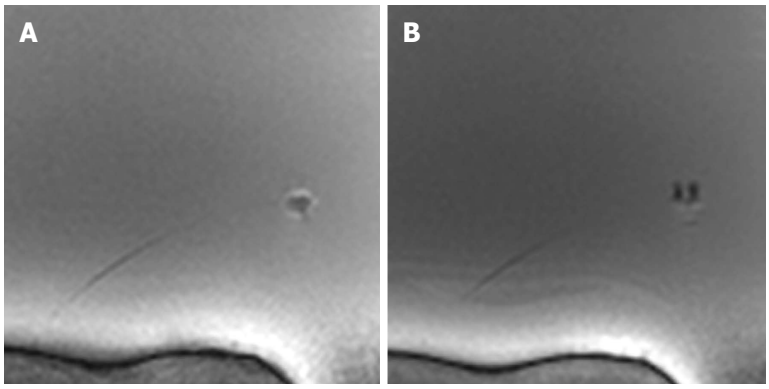

Figure 5 Real-time magnetic resonance imaging image frames with opened (A) and moving (B) tip.

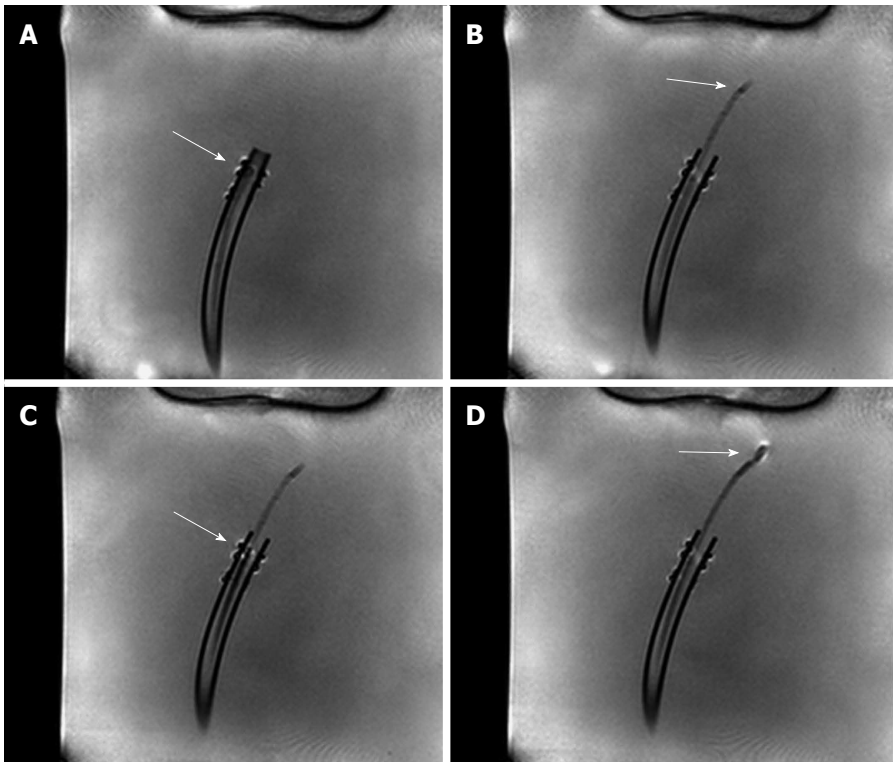

Figure 6 Real-time magnetic resonance imaging image frames showing bioptome and sheath inside saline filled phantom. The empty sheath is pushed forward in a plastic tube (A, B), later the bioptome is guided inside the sheath (C) until the tip is bare in the phantom (D).

heart (Figure 6) submerged in the saline.

The passive, visual tracking of the MR bioptome/sheath system and especially the tip was easily feasible due to the static design of the experiment. As shown in Figure 5, a moving tip caused turbulences in its vicinity which resulted in an artifact similar to the opened sample cutting mechanism. As a consequence, only for a non-moving tip, the opening/closing state could be reliably determined.

The control interface of the scanner supported a quick re-adjustment of the current imaging plane into parallel and orthogonal planes to follow the bioptome's movement. The achieved frame rate was approx. 4 fps for one slice when using an automatic continuous imaging mode. The visualization of orthogonal slices was only manually possible with manual plane re-adjustment causing the frame rate to decrease to approx. 0.3 fps to 0.25 fps.

Handling

In case of a jugular venous insertion, the interventionalist's access to the MR bioptome would be realized from the rear end of the scanner bore. Even the limited inner bore diameter of the MRI system (60 cm) left enough space to maneuver the bioptome. The handling was acceptable, but required a leaned-forward position of the interventionalist that was less comfortable than when carrying out a fluoroscopy.

When an access into the femoral venous system was simulated, the interventionalist stood in front of the CMR system. Here, the handling was better because it allowed a more upright position during the procedure.

Biopsy

The new MR bioptome retrieved tissue samples of appropriate size and quality (Figure 7). As with a conventional X-ray bioptome, the samples were derived from the endocardium and a visual inspection of the lesion area showed no irregular defects of the tissue. The samples were all taken at the targeted areas (Figure 8) and no rupture or substantial damage to the free lateral wall of the right ventricle was induced. Histological examinations of the specimen were abandoned because of the expected tissue degradation due to the time delay of about 12 h between the slaughter of the animals and the actual experiments.

DISCUSSION

To our knowledge, this is the first *in-vitro* study using MR-guided endomyocardial biopsy. The main findings of this study are as follows: (1) The visualization of the anatomical soft-tissue structures inside the heart is superior compared to fluoroscopy and allowed a good localization of the MR bioptome; (2) The biopsies could be performed successfully without any unintended damages to the endomyocardial tissue; and (3) No dangerous heating of the introduced instruments and surrounding environment was observed.

In the study presented here, we could show the feasibility of MRI-guided myocardial biopsies. During

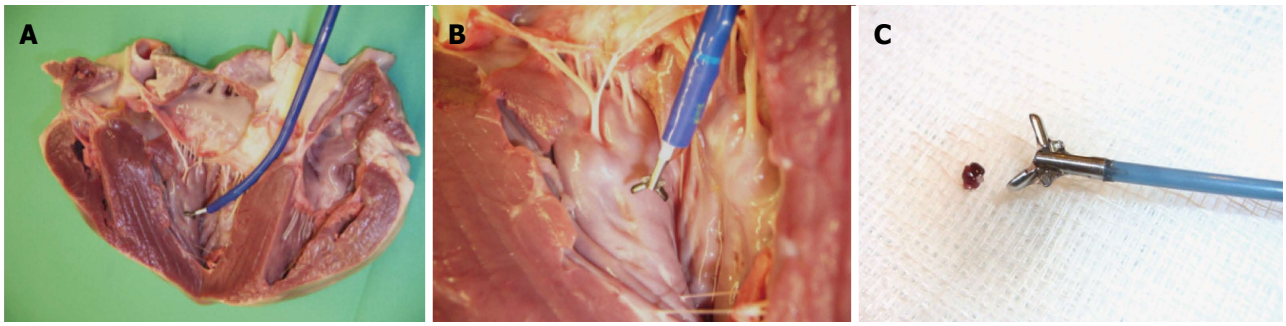

Figure 7 Close-up images of experimental *in-vitro* setup as shown in Figure 1: Opened porcine heart model with magnetic resonance bioptome (white) advanced through sheath (blue) (A), opened magnetic resonance bioptome forceps (B), magnetic resonance bioptome with tissue sample retrieved from endocardium (C).

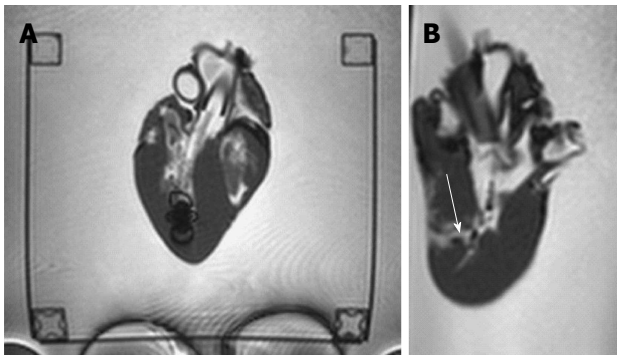

Figure 8 Side by side comparison of initial (A) and improved (B) version of magnetic resonance imaging compatible bioptome. Note the huge artifact in (A). The tip is highlighted in the circle. The targeted region is marked by previous Gadolinium injection (arrow).

the development of the novel device, we were able to reduce the size and the amount of artifacts to a level where no relevant areas in the vicinity of the instrument where obstructed. The visualization by MRI imaging allowed a clear and reliable distinction of the myocardial structures and therefore a safe and precise navigation to the targeted location previously marked with gadolinium injections. This targeted approach can potentially provide a higher sensitivity and specificity of each individual biopsy tissue sample and therefore reduce the number of required biopsy samples as well as the likelihood of complications.

The decision to use a separate bioptome and sheath system, as opposed to an all-in-one design provided substantial advantages. It allowed the maintenance of the position of the sheath while retrieving the individual samples from the myocardium. This could reduce the risk of valvular damage caused by repeated passages for sample acquisitions.

In conclusion, the complete absence of ionizing radiation is an important benefit of MRI based procedures, especially in younger patients with the need of repeated biopsies or multiple interventional procedures, *i.e.*, in cardiac transplant recipients.

Despite the significant advantages of MR-guided compared to fluoroscopically guided endomyocardial biopsies, MRI guidance also provides a number of challenges: (1) An overestimation of the image quality might be caused by the absence of motion artifacts of the static *ex-vivo* heart models. Further *in-vivo* experiments are required to evaluate the imaging capabilities when the heart as well as the instrument are constantly shifting and twisting during a cardiac cycle. Additionally, blood flow artifacts around the instrument could further impair the tracking performance; and (2) Since only one spatial slice is scanned, the operator can lose the tip's location of a passively tracked object when the instrument leaves the actual slice, whereas fluoroscopy with its projected image will always display the instrument as long as it is in the X-ray beam. This issue was successfully compensated by adding multiple passive markers at the distal end of the device. It could be further compensated with an active tracking system.

COMMENTS

Background

The aim of this study was to demonstrate the feasibility of magnetic resonance imaging (MRI)-guided endomyocardial biopsy in an *in-vitro* study. The motivation to use MRI was its superior soft tissue visualization and three-dimensional imaging capabilities when compared to the traditionally used fluoroscopy providing only two-dimensional projection images. Furthermore, the complete absence of ionizing radiation.

Research frontiers

As conventional bioptoms comprise multiple metallic components that prevent their use in an MRI environment. Furthermore, the navigation is more complex in MRI as this modality can only visualize objects in the imaging plane, whereas fluoroscopy creates projection images containing all objects in the X-ray beam.

Innovations and breakthroughs

In this study, a novel and fully MRI compatible instrument was developed. It could be successfully evaluated in a cylindrical 1.5T MRI system using bovine heart models. The bioptome was well visible and allowed precise discrimination from the surrounding tissue.

Applications

The new instrument allowed us to show the feasibility of MRI-guided interventional procedures, enabling radiation free procedures while benefitting from the widely accepted soft-tissue visualization and characterization capabilities of cardiac MRI.

Peer-review

The article under review represents the authors to present an *in-vitro* study to explore the feasibility of real-time MRI-guided endomyocardial biopsies. They found that MRI-guided endomyocardial biopsies provide a better than conventional X-ray guided navigation and could therefore improve the specificity and reproducibility of cardiac biopsies in future studies. The issue is interesting.

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ORIGINAL ARTICLE

Observational Study

Electrocardiographic changes during induced therapeutic hypothermia in comatose survivors after cardiac arrest

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Author contributions: All the authors contributed to this manuscript.

Institutional review board statement: The institutional ethics review committee approved the retrospective anonymous analysis of the patients, in accordance with European guidelines for good clinical practice.

Informed consent statement: All patient's relatives signed informed consents for the clinical procedures performed during admission. No special tests were done for the realization of this study, nor there was any follow-up. Therefore, no specific informed consent was obtained for this the retrospective anonymous observational study.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at estebanlopezdesa@secardiologia.es. Consent was not obtained but the presented data are anonymized and risk of identification is very low or absent.

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Abstract

AIM: To assess the safety of therapeutic hypothermia (TH) concerning arrhythmias we analyzed serial electrocardiograms (ECG) during TH.

METHODS: All patients recovered from a cardiac arrest with Glasgow < 9 at admission were treated with induced mild TH to 32-34 ℃. TH was obtained with cool fluid infusion or a specific intravascular device. Twelve-lead ECG before, during, and after TH, as well as ECG telemetry data was recorded in all patients. From a total of 54 patients admitted with cardiac arrest during the study period, 47 patients had the 3 ECG and telemetry data available. ECG analysis was blinded and performed with manual caliper by two independent cardiologists from blinded copies of original ECG, recorded at 25 mm/s and 10 mm/mV. Coronary care unit staff analyzed ECG telemetry for rhythm disturbances. Variables measured in ECG were rhythm, RR, PR, QT and corrected QT (QTc by Bazett formula, measured in lead v2) intervals, QRS duration, presence of Osborn's J wave and U wave, as

well as ST segment displacement and T wave amplitude in leads Ⅱ, v2 and v5.

RESULTS: Heart rate went down an average of 19 bpm during hypothermia and increased again 16 bpm with rewarming (P < 0.0005, both). There was a non-significant prolongation of the PR interval during TH and a significant decrease with rewarming (P = 0.041). QRS duration significantly prolonged (P = 0.041) with TH and shortened back (P < 0.005) with rewarming. QTc interval presented a mean prolongation of 58 ms (P < 0.005) during TH and a significant shortening with rewarming of 22.2 ms (P = 0.017). Osborn or J wave was found in 21.3% of the patients. New arrhythmias occurred in 38.3% of the patients. Most frequent arrhythmia was non-sustained ventricular tachycardia (19.1%), followed by severe bradycardia or paced rhythm (10.6%), accelerated nodal rhythm (8.5%) and atrial fibrillation (6.4%). No life threatening arrhythmias (sustained ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation) occurred during TH.

CONCLUSION: A 38.3% of patients had cardiac arrhythmias during TH but without life-threatening arrhythmias. A concern may rise when inducing TH to patients with long QT syndrome.

Key words: Cardiac arrest; Therapeutic hypothermia; Post-cardiac arrest síndrome; Cardiac arrythmias; QT interval

Core tip: Induced, therapeutic hypothermia is a treatment for post-cardiac arrest syndrome with a potential survival benefit; however it is not widely used. We aimed to assess the safety of this therapy regarding cardiac arrhythmias through a systematical evaluation of electrocardiograms (ECG) changes during hypothermia and telemetry data. Our conclusions are that therapeutic hypothermia according to current practice is safe with arrhythmias in one third of the patients (38.3%) but no life-threatening arrhythmias. Bradycardia and reversible prolongation of ECG intervals are common findings. A concern may rise when inducing hypothermia to patients with arrhythmias related to long QT syndrome.

Salinas P, Lopez-de-Sa E, Pena-Conde L, Viana-Tejedor A, Rey-Blas JR, Armada E, Lopez-Sendon JL. Electrocardiographic changes during induced therapeutic hypothermia in comatose survivors after cardiac arrest. *World J Cardiol* 2015; 7(7): 423-430 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i7/423.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i7.423

INTRODUCTION

In 2002, two randomized clinical trials demonstrated that inducing mild therapeutic hypothermia (TH) between 32 ℃ and 34 ℃ Celsius during 12 to 24 h improve survival and neurologic outcome in comatose adults recovered from ventricular fibrillation (VF) cardiac arrest (CA)[1,2]. Thenceforth, the recommendation to induce TH has been extended to non-VF cardiac arrest, and in-hospital CA[3-6]. Today, TH is the only in-hospital treatment that improves survival in comatose patients recovered from a CA[7]. Despite the evidence, TH is still underused nowadays. Some causes have been proposed: technical difficulties, lack of experience with cooling methods, safety concerns and the many gaps on various issues such as optimal target temperature, duration of TH or rewarming rate[8,9].

While there are reports about complications and side effects of hypothermia from more than 50 years ago[10-12], the vast majority of the information on cardiovascular and side effects comes from case reports, accidental deep hypothermia or induced deep hypothermia in cardiac surgery. Known side effects of TH are shivering[13], increased risk of infection[2,14], increased diuresis, electrolyte abnormalities such as hypokalemia, hypophosphatemia and hypomagnesaemia[15], hyperglycemia, coagulopathy with increased risk of bleeding, bradycardia and complex effects in hemodynamics, with small reduction in cardiac output that balances with the decrease of metabolic rate[16]. The randomized clinical trials of TH did not show any differences in arrhythmias between patients assigned to TH or normothermia, but there is paucity of data regarding electrocardiographic abnormalities in humans recovered from a cardiac arrest under controlled mild hypothermia.

In this prospective, observational study we performed a systematic analysis on serial electrocardiograms (ECG) and arrhythmias during TH, in order to describe changes and assess the safety of TH concerning ECG alterations and rhythm disturbances.

MATERIALS AND METHODS

We prospectively collected data about every CA admission in the Coronary Care Unit of a Spanish tertiary hospital during a period of 3 years. TH was performed according to current guidelines to those patients recovered from CA with any initial rhythm and Glasgow ⩽ 8 at admission. Sedation was obtained with midazolam, fentanyl and muscular relaxation with cisatracurium. All drugs adjusted to body weight and administered by intravenous infusion through a central venous line. Patients where cooled to a target temperature of 32 ℃ to 34 ℃, as soon as possible, with cold fluid infusion. TH was maintained with physical measures (ice packs, isolating blankets) during 24 h in the first 20 patients. The rewarming process was passive, withdrawing cooling measures, during 12 to 24 h. In the last 34 patients an intravascular cooling device (Coolgard 3000®, Zoll medical Corp, Chelmsford, MA) was used to induce, maintain (33 ℃ for 24 h) and withdraw TH, set to fastest cooling speed at induction

Table 1 Baseline characteristics of study population

Patients	47
Age (median, range)	65.9 (19-85)
Male	40 (85.1%)
Cardiogenic shock at admission	15 (31.9%)
Urgent coronary angiography	28 (59.6%)
Left ventricular ejection fraction	43.2 (15.3%)
Initial Rhythm, *n* (%)	
Ventricular Fibrillation	30 (63.8)
Asystole	14 (29.8)
Pulseless Electrical Activity	3 (6.4)
Rhythm at admission, *n* (%)	
Sinus rhythm	31 (66)
Atrial fibrillation	8 (17)
AV block/nodal rhythm/paced rhythm	8 (17)
TH protocol	
Temperature at admission	35.7 (0.7)
Induction time (from admission to TH, h)	4.8 (2.6)
Time in TH (median, range, h)	20.8 (5-28.5)
Temperature during TH	32.8 (0.5)
Rewarming time (from TH to 36 ℃, h)	11.3 (7.4)
Cause of CA, *n* (%)	
Acute coronary syndrome	21 (44.7)
Chronic coronary disease[1]	8 (17.0)
Chronic heart failure	4 (8.5)
Others/unknown[2]	14 (29.8)

[1]This group represents those patients with known preexisting coronary disease but without an acute coronary syndrome diagnosis at admission. Presumed cause were ventricular arrhythmias secondary to chronic coronary disease; [2]No final diagnosis of the cardiac arrest could be made for this group, all of these patients died during admission. TH: Therapeutic hypothermia. Data are number (percentage) or mean (standard deviation).

and slow rewarming at a rate of 0.08-0.17 ℃/h, to slowly rewarm the patient in 12-24 h. Core temperature was measured with a Swan-Ganz catheter or urinary catheter.

During TH, all patients were under mechanical ventilation, muscular relaxation and sedation. Inotropics or vasodilators were used if necessary to maintain a target mean arterial pressure of 80-90 mmHg. Patients underwent urgent coronary angiogram (and percutaneous coronary intervention if necessary) if ST elevation acute coronary syndrome (ACS) or clinical indication. Echocardiogram was performed at admission. Complete 12 lead ECG were recorded at admission (ECG A), during peak hypothermia or minimum stable temperature (ECG B) and after rewarming (but before sedation was withdrawn, ECG C). Continuous ECG telemetry was recorded during TH. The ethical board of the hospital approved TH protocol.

For the present study we selected all consecutive patients (n = 54) that underwent TH. Baseline characteristics of the patients, cooling rates and temperatures of TH protocol, clinical outcome data, ECG telemetry data and original ECG were recorded. ECG analysis was blinded and performed with manual caliper by two independent cardiologists from blinded copies of original ECG, recorded at 25 mm/s and 10 mm/mV. Coronary care unit staff analyzed ECG telemetry for rhythm disturbances. Variables measured in ECG were rhythm, RR, PR, QT and corrected QT (QTc by Bazett formula, measured in lead v2) intervals, QRS duration, presence of Osborn's J wave and U wave, as well as ST segment displacement and T wave amplitude in leads II, v2 and v5. Quantitative data was obtained through arithmetical mean of 2 measured values. If there was any discordance in rhythm analysis or categorical variables, a final joint decision was reached with a third cardiologist.

Statistical analysis of measured intervals was performed with paired t-tests for related samples. Statistical significance was considered at $P < 0.05$ (two sided). Continuous variables are represented as means and standard deviation in brackets and categorical variables as percentages. Statistical analysis was performed with SPSS 15 (SPSS Inc, Chicago, IL).

The statistical methods of this study were reviewed by Pablo Salinas, MD, PhD, and bachelor degree in biostatistics.

RESULTS

A total 54 post-CA patients were included in the TH protocol. Of this 54 patients, 7 had one ECG missing (4 of them died before rewarming, 3 had unsatisfactory quality or were missing), therefore a total of 47 patients make the study population. PR interval changes were only considered when the 3 ECG were in sinus rhythm, 29 patients (61.7%).

Baseline characteristics of study population are shown in Table 1. Twenty one percent of the patients were under intraaortic balloon counterpulsation and 10% had a temporary transvenous pacemaker implanted, all of them during coronary angiogram. Two patients (4%) received continuous veno-venous hemofiltration therapy. Three patients (6.4%), already at TH target temperature, required premature protocol termination because of clinical indication, two because of hemodynamical instability and one because of emergent surgery of intraperitoneal hemorrhage, spleen and hepatic lacerations due to traumatic resuscitation. Median hospital stay was 11.5 d, ranging from 2 to 71 d. Mechanical ventilation was maintained for a median of 5.1 d. In-hospital survival rate was 53.2%. Implantable defibrillator was implanted in 23% of survivors.

Comparison of heart rate, QRS duration and RR, PR, and QTc intervals among ECG at admission (ECG A), during hypothermia (ECG B) and in normothermia after rewarming (ECG C) are shown in Table 2 and Figure 1. Changes form ECG A to ECG B were a statistically significant increase in RR interval (decrease of heart rate of 19.5 bpm, $P < 0.0005$); a non-significative prolongation in PR interval; a minor significant prolongation of QRS duration of 9.9 ms, $P = 0.041$; and a significant increase in QTc interval of 57.5 ms ($P < 0.0005$). Changes from ECG B to ECG C were a statistically significant decrease in RR interval (increase of heart rate of 15.9 bpm, $P < 0.0005$); a small

Table 2 Changes in electrocardiograms intervals, represented as means, standard deviation (in brackets) and *P* for difference

	Admission (ECG A)	During MTH (ECG B)	After MTH (ECG C)	*P* for difference (A to B)	*P* for difference (B to C)	*P* for difference (A to C)
RR interval (ms)	653.8 (174.6)	818.1 (222.6)	656.9 (114.4)	< 0.0005[a]	< 0.0005[a]	0.9
Heart rate (bpm)	97.9 (24.9)	78.3 (19.8)	94.2 (17.4)	< 0.0005[a]	< 0.0005[a]	0.3
PR interval (ms)	169.2 (42.7)	179.3 (37.5)	161.2 (37.0)	0.090	0.003[a]	0.2
QRS duration (ms)	108.8 (23.2)	118.7 (37.9)	102.0 (22.9)	0.041[a]	< 0.0005[a]	0.029[a]
QT interval (ms)	353.8 (58.1)	448.1 (106.1)	374.9 (72.0)	< 0.0005[a]	< 0.0005[a]	0.042[a]
QTc interval (ms)	441.7 (50.7)	499.2 (95.5)	463.9 (76.4)	< 0.0005[a]	0.017[a]	0.046[a]

Indicates statistical significance ([a]*P* < 0.05); ms: Milliseconds; ECG: Electrocardiograms.

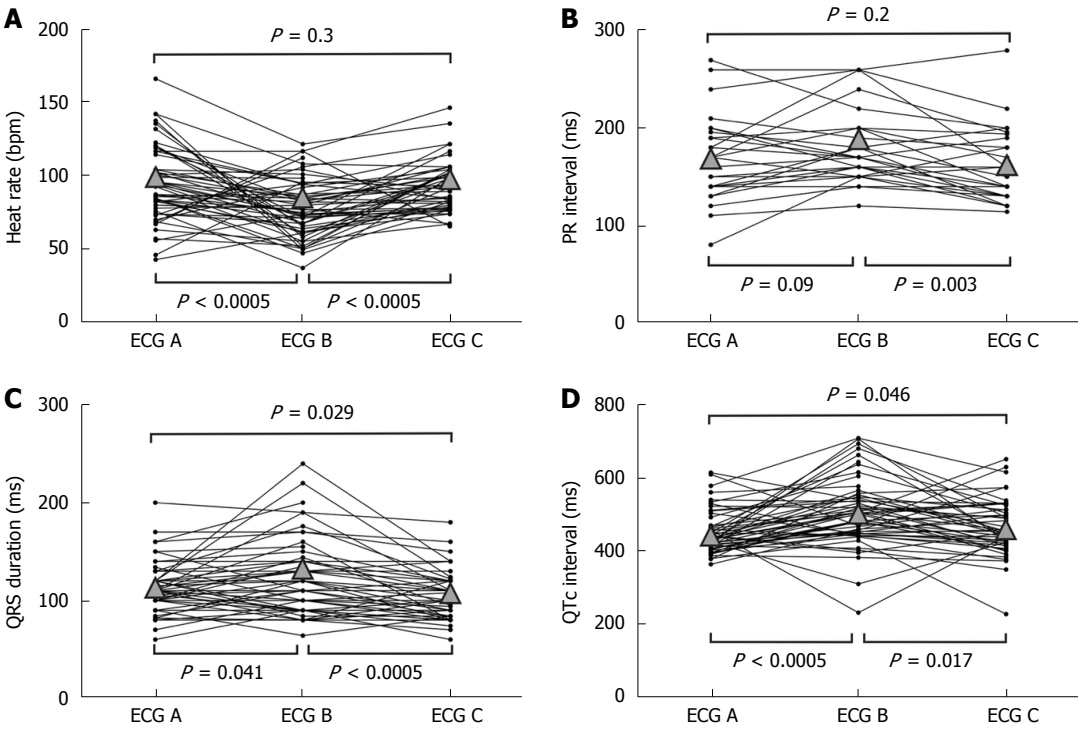

Figure 1 Graphics and statistical significance for paired *t*-test analyses for related samples. A: Heart rate (bpm); B: PR interval (ms); C: QRS duration (ms); D: QTc interval (ms). The dark dots are individual values of each single patient. Triangles represent mean values, shown in Table 2. Electrocardiograms (ECG) A represents ECG at admission; ECG B was performed at peak hypothermia and ECG C was recorded after rewarming.

significant decrease in PR interval of 18.1 ms (*P* = 0.003); a significant but small shortening of QRS duration of 16.7 ms, *P* < 0.0005; and a significant shortening of QTc interval of 35.3 ms (*P* = 0.017). Comparing basal ECG (A) with post-TH ECG (C), there were no significant difference in heart rate or PR interval; but we found a slight significant shortening in QRS duration of 6.8 (*P* = 0.029) and a significant increase in QTc of 22.2 ms (*P* = 0.046), with a final mean QTc interval above the upper limit of normal QTc interval (463.9 ms).

Comparison of T wave amplitude and ST segment deviation are shown in Table 3. On the whole there were no significant changes, except for a progressive decrease in amplitude of T wave in lead v5 through the TH process, a minor descent in ST from ECG B to ECG C in lead v5, and a slight decrease in amplitude of T wave in lead II. Osborn or J wave was observed in 21.3% of the patients in ECG B (Figure 2, arrow) with average amplitude of 0.2 millivolts. All of them appeared with cooling and reverted when patient was rewarmed. No U wave was detected in any ECG.

Arrhythmia analysis is shown in Table 4. Any new arrhythmia occurred in 38.3% of the patients during TH. The most frequent arrhythmia (50% of the patients with arrhythmias) was non-sustained monomorphic ventricular tachycardia (VT), 55% of them in patients with ACS. A 10.6% had severe bradycardia (< 50 bpm) or paced rhythms. An 8.5% had rapid nodal rhythms and 6.4% atrial fibrillation. Neither polymorphic VT, nor sustained VT, nor VF (considered as life-threatening arrhythmias) happened during TH. Twelve percent of the population changed to sinus rhythm after TH induction: half of them were in atrial fibrillation and the other half in accelerated nodal rhythm. Two patients (4.2%) had a reversible change of rhythm with TH: one in sinus rhythm developed an atrial fibrillation during TH and then relapsed to sinus rhythm and the other with an atrial fibrillation at admission had an accelerated nodal

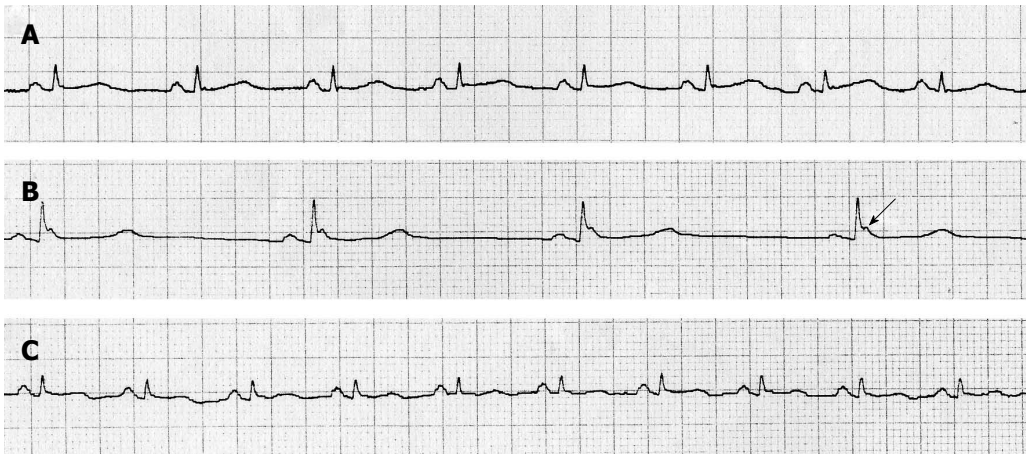

Figure 2 Electrocardiograms in lead Ⅱ from the same patient. Reversible prolongation of all electrocardiograms (ECG) intervals may be observed. A: ECG at admission, core temperature was 35.9 ℃; B: ECG at peak hypothermia, 33 ℃. Osborn or J wave is marked with a black arrow; C: ECG after rewarming, core temperature was 36.4 ℃.

Table 3 Changes in ST segment and T wave, represented as means, standard deviation (in brackets) and *P* for difference

	Admission (ECG A)	During MTH (ECG B)	After MTH (ECG C)	*P* for difference (A to B)	*P* for difference (B to C)	*P* for difference (A to C)
ST deviation lead II	+ 0.05 (1.4)	- 0.20 (1.4)	- 0.12 (0.7)	0.2	0.3	0.4
ST deviation lead v2	+ 0.39 (3.2)	+ 0.08 (0.6)	+ 0.32 (1.0)	0.4	0.06	0.9
ST deviation lead v5	- 0.25 (1.9)	- 0.38 (0.8)	- 0.16 (0.8)	0.6	0.036[a]	0.7
T wave lead II	+ 1.0 (1.8)	+ 0.63 (1.1)	+ 0.38 (1.2)	0.2	0.1	0.036[a]
T wave lead v2	+ 2.0 (3.6)	+ 2.10 (3.2)	+ 1.62 (2.4)	0.8	0.3	0.5
T wave lead v5	+ 1.60 (2.9)	+ 0.84 (2.3)	+ 0.04 (2.4)	0.1	0.013[a]	< 0.0005[a]

Indicates statistical significance ([a]$P < 0.05$). Units are millivolts. +: ST segment elevation or T-wave positive deflection; -: Descent in ST segment or T-wave negative deflection.

Table 4 Incidence of arrhythmias or rhythm changes during hypothermia

New arrhythmias during TH	38.3%
Non sustained monomorphic VT	19.1%
Bradycardia < 50 bpm/paced rhythm	10.6%
Accelerated nodal rhythm	8.5%
Atrial fibrillation	6.4%
Sustained VT	0%
Polymorphic VT or VF	0%
Change to sinus rhythm with TH	12.8%
Atrial fibrillation to sinus rhythm	6.4%
Accelerated nodal rhythm to sinus rhythm	6.4%

TH: Therapeutic hypothermia; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

rhythm in TH and then reverted to atrial fibrillation with rewarming. No patient needed pacemaker implantation or chronotropic drugs as a result of bradycardia during TH. Supraventricular tachycardias were treated following current guidelines if considered necessary. No treatment was given to non-sustained VT.

DISCUSSION

In the 1950's there was a growing interest in hypothermia as a protective measure in the beginnings of open-heart surgery. Some reports from intraoperative ECG obtained during circulatory occlusion and profound hypothermia (reaching 21-23 ℃), described a decrease in heart rate and a prolongation in PR, QRS and QT intervals. Arrhythmias were common and were related to core temperature. During mild hypothermia most frequent arrhythmias were ectopic atrial rhythms and nodal rhythms. A remarkable incidence of atrial fibrillation occurred below 30-32 ℃[10,11]. VF appeared associated with circulatory occlusion. Other studies in dogs suggested temperature thresholds for VF below 26 ℃ and asystole below 18 ℃[10,11,17]. Changes in ECG and arrhythmias in these reports are subject to multiple confounding factors: very low temperatures, myocardial ischemia, circulatory occlusion, cardioplegic solutions and the open-heart surgery itself. Because of those factors, previously described changes can hardly be applicable to current mild controlled TH.

Since the beginning of our decade, and after a gap in the literature of 40 years, hypothermia has regained interest, partly because the mechanism involved in its therapeutic effect were progressively clarified. Most information about complications and side effects come from old reports, animal experimentation and case reports. In the present study we provide a systematized analysis of cardiac arrhythmias and

temperature-dependent, sequential ECG changes during TH performed to an unselected post-CA population.

According to our findings, during TH to a target temperature of 32-34 ℃ in post-CA patients, some ECG changes may be expected: a considerable decrease in heart rate, a minimum prolongation of PR interval, a slight prolongation of QRS duration and a significant prolongation in QTc interval. All of these changes were reversible, except the prolongation of QTc interval (at least in the first 24 h after rewarming). Temperature-related changes in ST segment and T wave were not conclusive, but there was a trend towards flattening of T waves through TH process. ST segment and T wave changes may be interfered by previous cardiac disease and cause of CA, as almost half of the patients had an ACS.

The Osborn wave, or J wave, first observed in 1938 and fully described in 1953[18], is a frequent ECG feature in deep hypothermia. It can be seen as a notch or hump-like deflection in the terminal forces of QRS or between QRS and ST segment, more visible in precordial leads[19]. The amplitude and duration correlates with temperature, and although literature rarely describes it in mild hypothermia, we found a J wave in 21.3% of the patients (Figure 2, arrow). It is caused by a temperature dependent, transmural voltage gradient of a transient potassium current, more intense in epicardium than endocardium.

On the whole, ECG changes found in our study are concordant with those described previously in deep hypothermia[20-23]. Medical staff as well as nurses working with patients treated with induced TH should be aware of the possible arrhythmias and ECG changes that may occur. An example of ECG changes is shown in Figure 2. These changes are secondary to low body temperature and should not be considered pathological. Prolongation of action potential and decrease of myocardial conduction velocity has been proposed as physiopathological explanations for these phenomena[16]. These changes were reversible with rewarming and did not deteriorate hemodynamic status or clinical situation.

Bradycardia is one of the most disturbing effects of hypothermia because CA-recovered patients are often in cardiogenic shock and cardiac output decreases along with heart rate. In our series, patients with low initial heart rates did not decrease further, but maintained or increased their heart rates (Figure 1A). Besides, some studies suggest that the relation between heart rate and cardiac output inverses with hypothermia and that allowing mild TH to reduce heart rate could actually improve myocardial contractility. This is explained because hypothermia worsens diastolic function in the myocardium, and this is partially balanced by bradycardia[24,25]. External pacing or administration of chronotropic drugs is not recommended during TH to increase cardiac output[16].

The use of TH in post CA patients was safe with no life-threatening arrhythmias that worsened hemodynamic stability or required withdrawing the TH protocol. Non life-threatening arrhythmias were found in less than a half of the patients (38.3%).

The behavior of QTc interval in our TH series was remarkable (Figure 1D). We found a mean baseline QTc interval in the upper normal limits (mean 441 ms), it increased with TH (mean 499 ms), and partially reverted with rewarming, but final QTc interval was still lengthened when compared to initial QTc interval (463 ms) and was above upper normal limits. In spite of that, we had no arrhythmias related to prolongation of QT interval, like polymorphic ventricular tachycardia. We presumably (some patients died before a cause of the CA could be elucidated) did not have any patient with arrhythmic CA caused by long QT, but as QT and QTc intervals lengthen with TH, and remain lengthened afterwards, a concern may raise about safety of hypothermia in patients with long QT CA. Further investigation about this issue is warranted.

There is a concern about whether TH may increase the risk for arrhythmias and that the hypothermic myocardium can be somewhat resistant to antiarrhythmic drugs during hypothermia. It is well known that deep hypothermia under 30° increments the risk for atrial fibrillation and progressively with cooling under 28° the risk for life-threatening arrhythmias as VT and VF is increased[26]. Conversely, controlled mild TH is associated with higher rates of ROSC in animal CA models and is successfully used as a treatment for junctional ectopic tachycardia in infants[27-29]. Our study supports all previous reports that controlled, mild TH, is a safe technique with no increased risk for malignant arrhythmias and a relatively small number of minor arrhythmias that on the other hand can not only be attributed to TH but also to post-CA situation and previous cardiac disease.

Our study has some limitations. Accuracy of manual calipers is limited but represents day-by-day clinical practice. Arrhythmias and ECG changes could be interfered by several confounding factors like electrolyte disturbances. We had no control group, so this point cannot be ruled out in our study. However, our findings are congruent with those previously described in hypothermia and the fact that the changes were reversible with rewarming supports that TH was the cause of these changes. Recent trials show conflicting evidence regarding optimal target temperature, one of them suggests a benefit from deeper hypothermia (32 ℃ *vs* 34 ℃), while other found no benefit of 33 ℃ over normothermia (36 ℃)[30,31]. It would be relevant to know the "arrythmical" safety of different temperature levels, however our study did not analyzed different target temperatures.

In summary, therapeutic hypothermia according to current practice is safe with a 38.3% of patients having cardiac arrhythmias during TH but without life-threatening arrhythmias. Main ECG changes were bradycardia and prolongation of PR, QRS and QT

intervals. A concern may rise when inducing TH to patients with long QT syndrome.

COMMENTS

Background

Induced therapeutic hypothermia is currently recommended by most cardiac arrest guidelines, to improve the prognosis of the so-called post-cardiac arrest syndrome. However it is not widely used and has some controversies. Some of the main concerns that prevent intensive care physicians from inducing therapeutic hypothermia are the potential pro-arrhythmic effects of hypothermia. A study regarding cardiac arrhythmias is relevant to reassure patient's safety, especially for patients with heart disease.

Research frontiers

The influence of hypothermia over cardiac rhythm and cardiac conduction system is unknown and main data comes from case reports of accidental deep hypothermia.

Innovations and breakthroughs

This study allows a more comprehensive understanding of the influence of mild hypothermia in cardiac conduction. It shows a reversible prolongation of all cardiac intervals measured by electrocardiograms, suggesting that mild hypothermia slows cardiac conduction speed. The absence of life-threatening arrhythmias is reassuring for using this therapy in cardiac patients.

Applications

This study must be interpreted with caution due to the relatively small sample and its observational nature. However, it supports the "electrical" safety of therapeutic hypothermia for cardiac patients. Future lines of research suggested by the study are the potential influence of QT prolongation by hypothermia in long-QT syndromes, and the need for experimental (most probably in animal models) studies on the influence of hypothermia and cardiac conduction speed.

Terminology

Hypothermia: any temperature below 35.5-36 ℃. It may be accidental (cold exposure in winter) or induced (cold fluid or specific devices); Target temperature: The desired temperature in induced hypothermia. Usually 32-34 ℃. Some groups are investigating 32 ℃ *vs* 34 ℃, while others advocate for only preventing hyperthermia (≤ 36 ℃).

Peer-review

It is an important topic and well written and well presented.

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CASE REPORT

Giant and thrombosed left ventricular aneurysm

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Institutional review board statement: The case report was reviewed and approved by the Hospital Clinico San Carlos Institutional Review Board.

Informed consent statement: The patient provided informed written consent to publish the case report.

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Abstract

Left ventricular aneurysms are a frequent complication of acute extensive myocardial infarction and are most commonly located at the ventricular apex. A timely diagnosis is vital due to the serious complications that can occur, including heart failure, thromboembolism, or tachyarrhythmias. We report the case of a 78-year-old male with history of previous anterior myocardial infarction and currently under evaluation by chronic heart failure. Transthoracic echocardiogram revealed a huge thrombosed and calcified anteroapical left ventricular aneurysm. Coronary angiography demonstrated that the left anterior descending artery was chronically occluded, and revealed a big and spherical mass with calcified borders in the left hemithorax. Left ventriculogram confirmed that this spherical mass was a giant calcified left ventricular aneurysm, causing very severe left ventricular systolic dysfunction. The patient underwent cardioverter-defibrillator implantation for primary prevention.

Key words: Myocardial infarction; Echocardiography; Coronary artery disease; Left ventricular aneurysm; Coronary angiography

Core tip: Early diagnosis of ventricular aneurysms following acute transmural myocardial infarction is vital due to the serious complications that can occur. We report the case of a 78-year-old male with history of previous anterior myocardial infarction and currently under evaluation by chronic decompensated heart failure. Subsequent investigation revealed a huge thrombosed and calcified anteroapical left ventricular aneurysm. The peculiar findings of echocardiography, fluoroscopy and left ventriculography are shown with demonstrative images.

de Agustin JA, Gomez de Diego JJ, Marcos-Alberca P, Rodrigo JL, Almeria C, Mahia P, Luaces M, Garcia-Fernandez MA, Macaya C, Perez de Isla L. Giant and thrombosed left ventricular aneurysm. *World J Cardiol* 2015; 7(7): 431-433 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i7/431.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i7.431

INTRODUCTION

True left ventricular aneurysms are a frequent complication following acute extensive myocardial infarction. Early diagnosis is crucial due to the serious complications that can potentially occur, including heart failure, thromboembolism, or tachyarrhythmias.

CASE REPORT

A 78-year-old male with history of previous anterior myocardial infarction and currently under evaluation by chronic decompensated heart failure (NYHA functional class Ⅲ), underwent transthoracic echocardiogram revealing the presence of a huge and peripherally calcified anteroapical left ventricular aneurysm with a giant mural thrombus (Figures 1-3). Elective coronary angiography was performed which demonstrated that the left anterior descending artery was chronically occluded (Figure 4) and nonsignificant lesions in the other coronary arteries. Fluoroscopic imaging revealed a complete oval calcified image enclosed within an abnormal cardiac silhouette (Figure 5). Left ventriculogram confirmed that this image corresponded of a giant calcified and thrombosed left ventricular aneurysm, causing severe left ventricular systolic dysfunction (Figure 6). The calculated left ventricular ejection fraction was only 7%. The patient underwent cardioverter-defibrillator implantation for primary prevention.

DISCUSSION

Left ventricular aneurysms are a frequent complication of acute extensive myocardial infarction and are most commonly located at the ventricular apex[1,2]. A timely diagnosis is vital due to the serious complications that can occur, including heart failure, thromboembolism, or tachyarrhythmias. The benefits of surgical repair of left ventricular aneurysm have long been debated. Although a large amount of studies have showed that aneurysmectomy might improve the outcome[3], the results from the STICH trial have questioned the benefit of this treatment[4]. Therefore, indication for aneurysmectomy depends on the decision of individual surgeons, and should be based on the assessment of the left ventricular dimensions, mitral valve regurgitation severity, extent of myocardial scar tissue and viability of the other regions of the left ventricle, and surgery should be performed in centers with a high surgical experience.

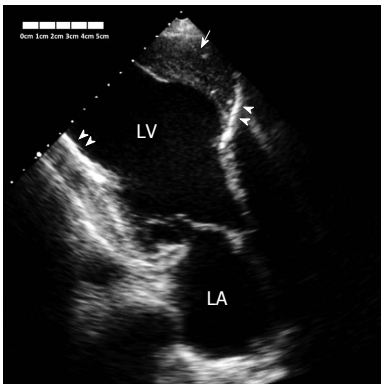

Figure 1 Transthoracic echocardiogram using apical three chamber view showing the big anterior left ventricular aneurysm (arrow). The wall of the aneurysm was calcified (arrowheads), and the aneurysm was covered with thrombus (arrow). LA: Left atrium; LV: Left ventricle.

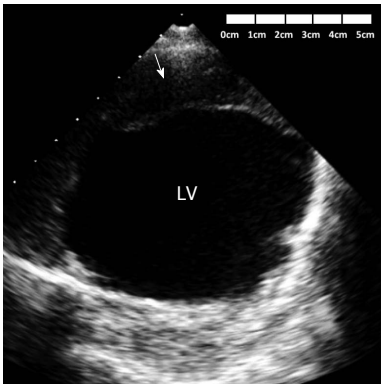

Figure 2 Transthoracic echocardiogram using parasternal short axis view at the midventricular level showing the thrombus (arrow) covering the anterior wall aneurysm. LV: Left ventricle.

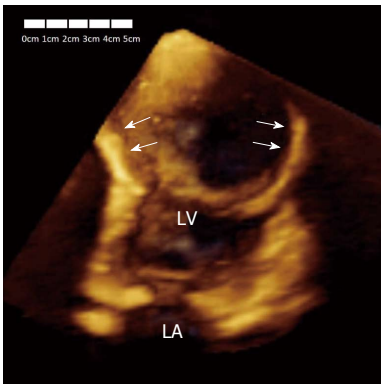

Figure 3 Three-dimensional echocardiography in apical four chamber view showing the big size of the aneurysm (arrows). LA: Left atrium; LV: Left ventricle.

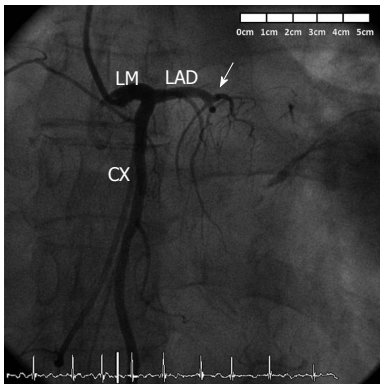

Figure 4 Left coronary angiography demonstrating a proximal occlusion of the left anterior descending artery (arrow). CX: Circumflex coronary artery; LAD: Left anterior descending coronary; LM: Left main coronary artery.

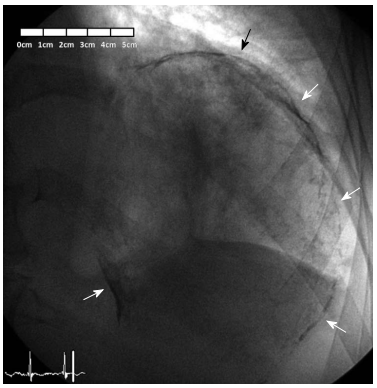

Figure 5 Fluoroscopic imaging in right anterior oblique projection showing a complete oval calcified mass (arrows), corresponding with the left ventricular aneurysm.

COMMENTS

Case characteristics

A 78-year-old male with history of previous anterior myocardial infarction and currently under evaluation by chronic decompensated heart failure.

Clinical diagnosis

Giant thrombosed left ventricular aneurysm.

Differential diagnosis

Intrathoracic mass.

Imaging diagnosis

Echocardiography and coronary angiography were used for the diagnosis of left ventricular aneurysm.

Treatment

The patient received an implantable cardioverter-defibrillator for primary prevention and was referred for consideration of cardiac transplantation.

Related reports

True left ventricular aneurysms are widely recognized as a common and serious complication following acute transmural myocardial infarction. However, this case is particular because of the huge size of the aneurysm.

Experiences and lessons

The recognition of ventricular aneurysms is of great importance due to the numerous complications that can potentially occur. Echocardiography and catheterism are fundamental tests for diagnosis.

Peer-review

It is a interesting case and well described.

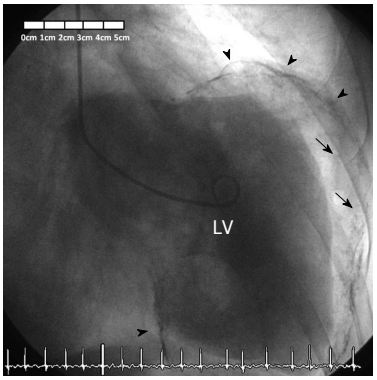

Figure 6 Left ventriculogram confirming diagnosis of a giant calcified and partially thrombosed left ventricular aneurysm, with severe left ventricular systolic dysfunction. The wall of the aneurysm is calcified (arrowheads), and the aneurysm is covered with thrombus (arrows). LV: Left ventricle.

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