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ABOUT COVER

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MINIREVIEWS

Sodium glucose cotransporter 2 inhibitors in the management of heart failure: Veni, Vidi, and Vici

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Abstract

Heart failure (HF) is a chronic disease associated with high morbidity and mortality rates. Renin-angiotensin-aldosterone system blockers (including angiotensin receptor/neprilysin inhibitors), beta-blockers, and mineralocorticoid receptor blockers remain the mainstay of pharmacotherapy for HF with reduced ejection fraction (HFrEF). However, despite the use of guideline-directed medical therapy, the mortality from HFrEF remains high. HF with preserved ejection fraction (HFpEF) comprises approximately half of the total incident HF cases; however, unlike HFrEF, there are no proven therapies for this condition. Sodium glucose cotransporter-2 inhibitors (SGLT-2is) represent a new class of pharmacological agents approved for diabetes mellitus (DM) that inhibit SGLT-2 receptors in the kidney. A serendipitous finding from seminal trials of SGLT-2is in DM was the significant improvement in renal and cardiovascular (CV) outcomes. More importantly, the improvement in HF hospitalization (HHF) in the CV outcomes trials of SGLT-2is was striking. Multiple mechanisms have been proposed for the pleiotropic effects of SGLT-2is beyond their glycemic control. However, as patients with HF were not included in any of these trials, it can be considered as a primary intervention. Subsequently, two landmark studies of SGLT-2is in patients with HFrEF, namely, an empagliflozin outcome trial in patients with chronic HF and a reduced ejection fraction (EMPEROR-Reduced) and dapagliflozin and prevention of adverse outcomes in HF (DAPA-HF), demonstrated significant improvement in HHF and CV mortality regardless of the presence of DM. These impressive results pitchforked these drugs as class I indications in patients with HFrEF across major guidelines. Thereafter, empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction (EMPEROR-Preserved) and dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction HF (DELIVER) trials successively confirmed that SGLT-2is also benefit patients with HFpEF with or without DM. These results represent a watershed as they constitute the first clinically meaningful therapy for HFpEF in the past three decades of evolution of HF management. Emerging positive data for the use of

SGLT-2is in acute HF and post-myocardial infarction scenarios have strengthened the pivotal role of these agents in the realm of HF. In a short span of time, these classes of drugs have captivated the entire scenario of HF.

Key Words: Heart failure with preserved ejection fraction; Gliflozins; Diuresis; Natriuresis; N terminal-pro brain natriuretic peptide; Heart failure hospitalization

Core Tip: Heart failure (HF) is associated with high morbidity and mortality rates. Sodium glucose cotransporter-2 inhibitors (SGLT-2is) are approved for diabetes mellitus (DM), and have also demonstrated improvement in renal and cardiovascular (CV) outcomes along with good glycemic control. Two landmark studies of SGLT-2is in patients with HF demonstrated improvement in HF hospitalization and CV mortality, irrespective of DM status. Subsequent clinical trials proved that SGLT-2is also benefit patients with HF with preserved ejection fraction with/without DM. Emerging positive data for SGLT-2is in acute HF and post-myocardial infarction scenarios have bolstered their pivotal role in the full diapason of HF.

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INTRODUCTION

Heart failure (HF) is the chronic outcome of several cardiac illnesses such as coronary artery disease, hypertension, repaired cyanotic congenital defects, and cardiomyopathies. HF is caused by the functional or structural impairment of ventricular filling or ejection[1]. Worldwide, there are approximately 37.7 million cases of HF, and the prevalence of this condition is increasing[2]. The classification of HF includes HF with reduced ejection fraction (HFrEF) (*i.e.* HF with a left ventricular ejection fraction [LVEF] of ≤ 40%), HF with mildly reduced ejection fraction (HFmrEF) (*i.e.* HF with LVEF of 41%-49%), and HF with preserved ejection fraction (HFpEF) (*i.e.* HF with LVEF of ≥ 50%). A new entity recently described in literature is HF with improved ejection fraction (*i.e.* HF with a baseline LVEF of ≤ 40%, a ≥ 10-point increase from baseline LVEF, and a second measurement of LVEF > 40%)[3]. The standard treatment for HFrEF comprises beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers with mineralocorticoid receptor blockers, and diuretics[4]. These medications have offered immense clinical benefits to patients with HFrEF and are supported by evidence from large clinical trials. All of these drugs were introduced into clinical practice in the early 1990s and 2000s. Since then, only angiotensin receptor neprilysin inhibitor (ARNI)-sacubitril-valsartan has shown superiority over angiotensin-converting enzyme (ACE) inhibitors in reducing cardiovascular (CV) mortality and HF hospitalization (HHF) in 2014[5]. Although strong evidence is available for the benefits of these drugs in HFrEF, they have failed to offer comparable benefits in patients with HFpEF. Table 1 depicts the number needed to treat (NNT) of major guideline-approved HF medications derived from the seminal trials. The much anticipated PARAGON-HF trial, which compared ARNI with valsartan, did not report significant benefits in patients with HFpEF. However, certain benefits were observed in women and in those with HFmrEF. Thus, evidence-based therapies to enhance the outcomes of patients with HFpEF are lacking[6].

Sodium glucose cotransporter-2 inhibitors (SGLT-2is), which were initially approved as antidiabetic agents, are now used to treat HF and constitute one of the four pillars of HF pharmacotherapy. The indication for SGLT-2is as major HF medications came after the landmark trial of dapagliflozin in HFrEF, which proved the potential of the drug in reducing CV outcomes irrespective of the presence or absence of diabetes[7,8]. Subsequently, the efficacy of empagliflozin, another SGLT-2i, was confirmed in a major trial on empagliflozin outcome trial in patients with chronic HF and a reduced ejection fraction (EMPEROR-Reduced), which showed that empagliflozin significantly reduced HHF regardless of the presence of diabetes; however, mortality reduction was not noted[9]. Moreover, the most recently published articles on SGLT-2is in HFpEF (Empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction [EMPEROR-Preserved] and dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction HF [DELIVER trial]) have shown promising results. Based on these findings, the latest guidelines recommend their use in HFpEF therapy[10,11].

SGLT-2IS IN HF: MECHANISM OF ACTION

SGLT-2is are a class of drugs that inhibits SGLT-2 receptors in the proximal convoluted tubules of nephrons in the kidney, resulting in the failure of glucose reabsorption in the kidney. However, the benefits in CV outcomes cannot be explained by these simple mechanisms alone. Conventional and direct cardiac mechanisms of action of SGLT-2is can confer CV benefits (Figure 1).

Table 1 Number needed to treat in major heart failure trials

Study	Drug tested	Primary endpoints	Results	NNT	Year	Number of patients	Follow-up
EMPEROR-Reduced trial	Empagliflozin *vs* placebo	CV death or HF hospitalization	19.4% *vs* 24.7% HR: 0.75 (95%CI: 0.65-0.86)	19	2020	3730	16 months
DAPA-HF trial	Dapagliflozin *vs* placebo	CV death or HF hospitalization	16.3% *vs* 21.2% HR: 0.74 (95%CI: 0.65-0.85)	21	2019	4744	18.2 months
SOLOIST-HF trial	Sotagliflozin *vs* placebo	CV death or HF hospitalization	70% *vs* 98% HR: 0.67 (95%CI: 0.52-0.85)	4	2021	1222	9 months
PARADIGM-HF trial	ARNI *vs* enalapril	CV death or HF hospitalization	21.8% *vs* 26.5% HR: 0.80 (95%CI: 0.73-0.87)	21	2014	8442	27 months
RALES trial	Spironolactone *vs* placebo	Death from all causes	35% *vs* 46% HR: 0.70 (95%CI: 0.60-0.82)	9	1999	1663	24 months
EMPHASIS-HF	Eplerenone *vs* placebo	CV death or HF hospitalization	18.3% *vs* 25.9% HR: 0.63 (95%CI: 0.54-0.74)	19	2011	2737	1.8 years
EPHESUS	Eplerenone *vs* placebo	Death any cause CV death or HF hospitalization	HR: 0.85 (95%CI: 0.75-0.96); HR: 0.87 (95%CI: 0.79-0.95)	50 to prevent 1 death; 33 to prevent 1 CV death or HF hospitalization	2003	6642	16 months
MERIT-HF trial	Metoprolol *vs* placebo	All-cause death	7.2% *vs* 11% HR: 0.66 (95%CI: 0.53-0.81)	27	1999	3991	2.4 years
CIBIS II-HF trial	Bisoprolol *vs* placebo	All-cause death HF hospitalization	11.8% *vs* 17.3%; 33% *vs* 39%	18; 17	1999	2647	1.3 years
COPERNICUS trial	Carvedilol *vs* placebo	All-cause death and HF hospitalization	36.8% *vs* 44.7%	13	2001	2289	10 months
CHARM trial	Candesartan *vs* placebo	CV death and HF hospitalization	22% *vs* 24% HR: 0.89 (95%CI: 0.77-1.03)			3023	36.6 months
VA-HEFT Trial	Valsartan *vs* placebo	Mortality plus morbidity	No difference 28.8% *vs* 32.1% HR: 0.87 (95%CI: 0.77-0.97)		2001	5010	23 months
SHIFT trial	Ivabradine *vs* placebo	CV death and HF hospitalization	24% *vs* 29% HR: 0.82 (95%CI: 0.75-0.90)	27	2010	6558	22.9 months
SOLVD trial	Enalapril *vs* placebo	Mortality HF hospitalization			1991	2569	22-55 months

CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; CI: Confidence interval; CIBIS II: The cardiac insufficiency bisoprolol study II; COPERNICUS: Carvedilol prospective randomized cumulative survival; CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; DAPA: Dapagliflozin and prevention of adverse outcomes; EMPEROR: Empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction; EMPHASIS: Eplerenone in mild patients hospitalization and survival study; EPHESUS: Eplerenone post–acute myocardial infarction heart failure efficacy and survival study; MERIT: Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients; NNT: Number needed to treat; PARADIGM: Prospective comparison of angiotensin receptor–neprilysin inhibitor with angiotensin-converting–enzyme inhibitor to determine impact on global mortality and morbidity; RALES: Randomized Aldactone evaluation study; SHIFT: Systolic heart failure treatment with the if inhibitor ivabradine trial; SOLOIST: Effect of Sotagliflozin on cardiovascular events in patients with type 2 diabetes worsening post heart failure; SOLVD: Studies of left ventricular dysfunction; VA-HEFT: The vasodilator-heart failure trial.

Conventional effects

Natriuresis and osmotic diuresis occur because of glucosuria. However, the coadministration of loop diuretics and dependence of the degree of osmotic diuresis and glycosuria on blood glucose levels indicate alternative mechanisms of benefit. Similar benefits were observed in patients without diabetes. Studies have suggested that SGLT-2is decrease only interstitial fluid and not plasma volume and thus can act synergistically[12,13]. SGLT-2is reduce blood pressure secondary to improvement in endothelial function, reduction in arterial stiffness, and alterations in sympathetic nervous activity[14,15]. However, these drugs exert only a modest antihypertensive effect. Weight loss occurs because of an

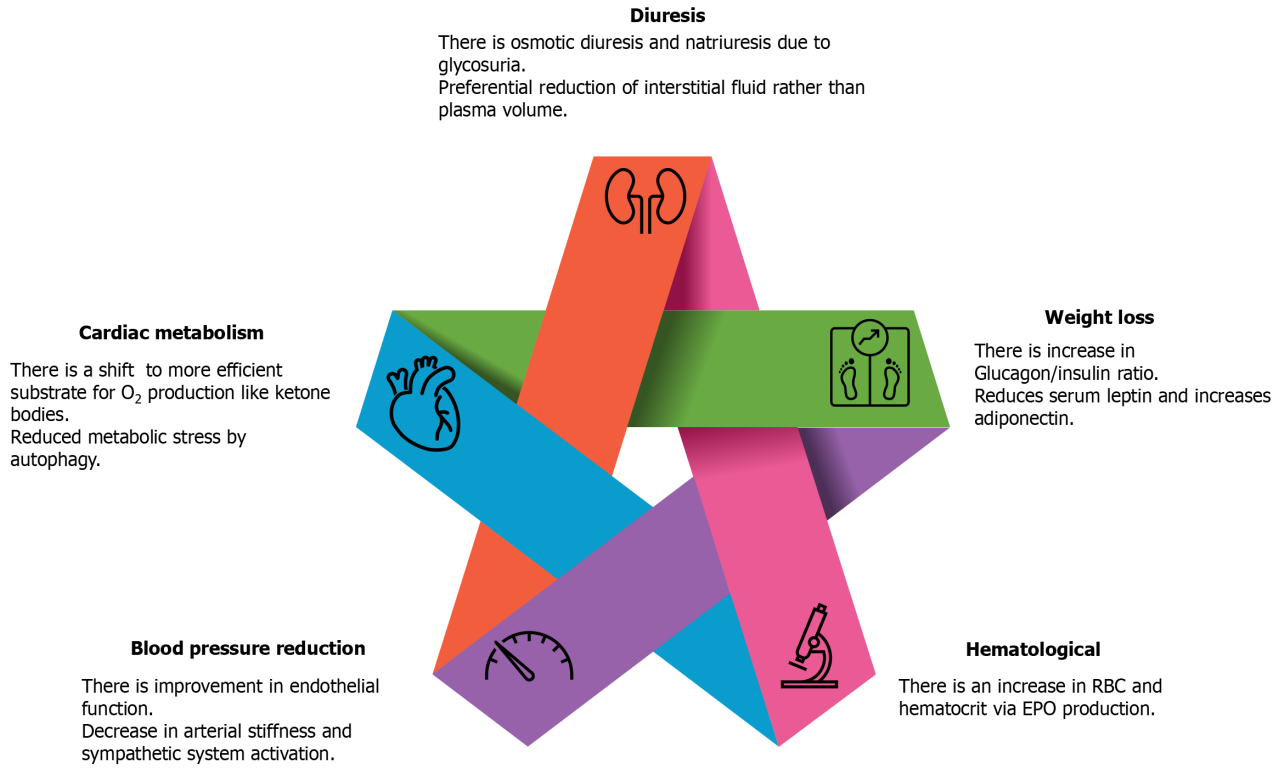

Figure 1 Mechanism of action of sodium glucose cotransporter-2 inhibitors in heart failure. EPO: Erythropoietin; O_2: Oxygen; RBC: Red blood cell.

increased glucagon: insulin ratio, which augments lipid mobilization[16,17]. Hematocrit and red blood cell mass increase with an elevation in erythropoietin production in the kidneys[18].

Direct effects

SGLT-2i therapies reverse adverse cardiac remodeling[19,20]. This effect has been demonstrated in patients with left ventricular hypertrophy and type 2 diabetes mellitus (T2DM) but not in those with HF, and a direct novel cardioprotective effect may be plausible[20,21]. Other effects include changes to more oxygen-efficient ketone bodies, cardiac metabolism of fatty acids, and glucose oxidation, which improve cardiac efficiency[22]. Furthermore, SGLT-2is inhibit sodium-hydrogen exchanger 1 and SGLT-1 transporters and improve the levels of cytosolic sodium[23,24]. Autophagy exerts a favorable effect on HF by alleviating metabolic stress. Continuous glycosuria simulates a state of nutrient depletion and catabolism, which induces autophagy[25,26]. SGLT-2is reduce the serum leptin-to-adiponectin ratio, exerting cardioprotective effects[27,28].

Role in improving cardiac metabolism

SGLT-2is were initially postulated to increase fasting ketone levels, which might act as an additional substrate for myocyte energy production; however, this theory was not supported by experimental data[29,30]. SGLT-2is maintain cytosolic calcium levels by inhibiting the sodium-hydrogen exchanger[23,24]. Certain preclinical studies have suggested that SGLT-2is induce a myocardial substrate switch, thereby improving myocardial energetics. However, in the EMPA-VISION trial (assessment of cardiac energy metabolism, function and physiology in patients with HF taking empagliflozin), treatment with 10 mg empagliflozin once daily for 12 weeks did not enhance cardiac energetics or alter the levels of circulating serum metabolites associated with energy metabolism compared with placebo. Thus, enhanced cardiac energy metabolism is unlikely to mediate the beneficial effects of SGLT-2is in HF[31].

ADVERSE EFFECTS OF SGLT-2IS

The most common adverse effects of SGLT-2is are mycotic genital infections in women, urinary tract infections, nausea, and constipation. Other adverse events include lower limb amputation, which is especially seen with canagliflozin. Predisposing factors to limb amputation with the use of SGLT-2is are preexisting peripheral arterial disease, neuropathy, and diabetic foot ulcers. Hence, in patients with foot ulcers, SGLT-2is should be avoided or discontinued. The risk of euglycemic diabetic ketoacidosis (DKA) is also seen with SGLT-2is, which can be up to three-fold higher, and is again most noted with the use of canagliflozin. This finding could be attributed to noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion. Thus, in patients with suspected DKA, the drug should be discontinued. A modest but reversible decrease in estimated glomerular filtration rate (eGFR) and rise in serum creatinine may also be noted in the initial period with the use of these drugs due to intravascular volume contraction. Therefore, the patient's

volume status should be corrected, especially in the elderly, before initiating treatment. Other rare side effects include bone fractures, bladder cancer (to be avoided in patients with active bladder cancer), and hyperkalemia.

CONTRAINDICATIONS OF SGLT-2IS

The contraindications for therapy include T1DM, dialysis-dependent kidney disease and hypersensitivity reactions, such as anaphylaxis or angioedema, to any of the four agents.

HHF IN PRIMARY PREVENTION STUDIES OF SGLT-2IS

The combined analysis of the canagliflozin cardiovascular assessment study (CANVAS) and CANVAS-renal trials, which compared CV events in patients with T2DM taking the SGLT-2i canagliflozin *vs* those taking placebo, was conducted as a part of the CANVAS program[32]. The findings showed a significant reduction in major adverse cardiac events (26.9 participants per 1000 patient-years in the canagliflozin group *vs* 31.5 per 1000 patient-years in the placebo arm). Equal benefits were observed in patients with HFrEF and those with HFpEF, with greater benefits in those with a history of HF.

The empagliflozin cardiovascular outcome event trial in T2DM patients (EMPA-REG outcome) was conducted to evaluate the CV safety of empagliflozin in patients with T2DM with atherosclerotic CV disease (ASCVD). The trial reported a 14% reduction in major adverse cardiovascular outcomes (MACEs) with empagliflozin compared with placebo, along with a relative risk (RR) reduction of 38% for CV deaths, 32% for all-cause deaths, and 35% for HHF[33].

The dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58 (DECLARE-TIMI 58) study examined the CV safety of dapagliflozin in patients with T2DM having ASCVD or a high risk for the condition. Although dapagliflozin significantly improved glycemic control, it did not significantly reduce MACEs. Nonetheless, in patients with HFrEF, hospitalization and CV death rates significantly decreased[34].

In the effect of sotagliflozin on cardiovascular and renal events in patients with T2DM and moderate renal impairment who are at cardiovascular risk (SCORED) trial, 10584 patients with T2DM (glycated hemoglobin level ≥ 7%), chronic kidney disease (eGFR 25-60 mL/min/1.73 m^2 of body surface area), and CV disease risk were randomly assigned in a 1:1 ratio to receive either sotagliflozin or placebo. The primary endpoint of this study was the composite of CV death, HHF, and urgent HF visits. The rates of primary endpoint events were 5.6 and 7.5 events per 100 patient-years in the sotagliflozin and placebo groups, respectively (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.63-0.88; P = 0.001). Diarrhea, DKA, genitourinary infections, and dehydration occurred more frequently in the sotagliflozin group than in the placebo group. Hence, in patients with diabetic nephropathy with or without albuminuria, sotagliflozin treatment reduced the rates of primary endpoints, especially HHF[35].

META-ANALYSIS OF PRIMARY PREVENTION TRIALS OF SGLT-2IS

The meta-analysis performed by Zelniker *et al*[36] included data from 34322 patients (60.2% with established ASCVD) and three identified trials, namely, EMPA-REG outcomes, CANVAS program, and DECLARE-TIMI-58. A total of 3342 MACEs, 2028 CV deaths and HHF events, and 766 renal composite outcomes were documented. Although the rate of MACEs was reduced to 11% (HR: 0.89; 95%CI: 0.83-0.96; P = 0.0014), the benefit was evident only in patients with ASCVD (HR: 0.86; 95%CI: 0.80-0.93) and not in those without ASCVD (HR: 1.00; 95%CI: 0.87-1.16; P for interaction = 0.0501). However, the risk of CV death or HHF was decreased by 23% (HR: 0.77; 95%CI: 0.71-0.84; P = 0.0001) both in patients with and without established ASCVD and irrespective of the presence or absence of HF. Similarly, SGLT-2is alleviated the risk of renal disease progression by 45% (HR: 0.55; 95%CI: 0.48-0.64; P = 0.0001) regardless of the presence or absence of ASCVD. The extent of benefits offered by SGLT-2is in reducing HHF and the progression of renal impairment was the highest in patients with advanced renal disease[36].

Another meta-analysis of four trials of SGLT-2is in patients with diabetes conducted by Lo *et al*[37] demonstrated benefits in reducing CV events. This meta-analysis examined the results based on renal impairment. The pooled RR (95%CI) for the composite CV outcome was 0.93 (0.87-0.99) in the general study population (NNT: 167 and 0.89 (0.77-1.02) in patients with eGFR 60 mL/min/1.73 m^2; that for all-cause mortality was 0.9 (0.84-0.97) with NNT = 143; that for CV death was 0.89 (0.81-0.99) in the general population and 0.82 (0.62-1.07) in patients with eGFR 60 mL/min/1.73 m^2; and that for HHF was 0.71 (0.63-0.79) with NNT = 91. Regarding renal outcomes, the pooled RR (95%CI) for the composite renal outcome was 0.63 (0.56-0.71) with NNT = 67 in the general population and 0.67 with eGFR 60 mL/min/1.73 m^2. In addition, the risk for albuminuria progression was reduced (RR = 0.80).

These meta-analyses confirm that SGLT-2is are associated with significantly lower MACEs, HHF, and all-cause mortality, with the strongest evidence for HHF reduction. Although the evidence was weaker in the population subset with eGFR 60 mL/min/1.73 m^2, SGLT-2is significantly reduced the number of adverse renal events and also possibly retarded the progression of renal disease, with these effects being obvious even in the population with eGFR 60 mL/min/1.73 m^2[37].

SECONDARY PREVENTION TRIALS OF SGLT-2IS

These trials are shown in Table 2 and Figure 2.

Trials in HFrEF

Dapagliflozin and prevention of adverse outcomes in HF (DAPA-HF): This trial randomized 4744 patients with New York Heart Association (NYHA) class II-IV symptoms and LVEF 40% to either dapagliflozin (10 mg once a day) or placebo along with guideline-directed medical therapy. The primary endpoint was a composite of CV death and hospitalization because of worsening HF symptoms. After a follow-up of 18.2 months, dapagliflozin significantly reduced the primary outcome (16.3% *vs* 21.2%, HR: 0.74, 95%CI: 0.65-0.85; P = 0.001). The first HF event occurred at a significantly lower rate with dapagliflozin than with placebo (10.0% *vs* 13.7%, HR: 0.70, 95%CI: 0.59-0.83). The incidence rate of CV death was 9.6% in the dapagliflozin group and 11.5% in the placebo arm (HR: 0.82, 95%CI: 0.69-0.98), whereas those of non-CV death were 11.6% and 13.9%, respectively (HR: 0.83, 95%CI: 0.71-0.97). These results remained the same irrespective of the patients' diabetes status. The frequency of adverse events was comparable in both treatment groups[7].

EMPEROR-Reduced: In this trial, patients with NYHA II-IV HF and LVEF 40% were randomized to receive either empagliflozin (10 mg once daily) or placebo. The major endpoint was a composite of hospitalization, worsening HF symptoms, and CV death. After 16 months of follow-up, the primary outcome event occurred at a significantly lower rate with empagliflozin than with placebo (19.4% *vs* 24.7%, HR: 0.75, 95%CI: 0.65-0.86; P = 0.001). These benefits were noted irrespective of the patients' glycemic status. Moreover, the rate of HHF was significantly lower with empagliflozin than with placebo (HR: 0.70, 95%CI: 0.58-0.85; P = 0.001)[8].

Trials of SGLT-2is in HFpEF

EMPEROR-Preserved: In this double-blind trial, 5988 patients with NYHA class II-IV HF and LVEF > 40% were randomized to receive either empagliflozin (10 mg once daily) or placebo in addition to the routine therapy and followed up for 2 years. The primary outcome was a combination of hospitalization for worsening HF symptoms and CV death. The findings indicated that empagliflozin significantly reduced the primary endpoints compared with placebo (13.8% *vs* 17.1%, HR: 0.79, 95%CI: 0.69-0.90; P = 0.001). These outcomes were predominantly driven by a reduction in the rate of HHF with empagliflozin (HR: 0.73, 95%CI: 0.61-0.88; P = 0.001) and were similar in patients with and without diabetes. Uncomplicated genital and urinary tract infections and hypotension were reported more often with empagliflozin than with placebo[10].

DELIVER trial: This trial comprised 6263 stable patients with HF who had LVEF of > 40% with or without diabetes. The patients received dapagliflozin 10 mg once daily or placebo in addition to guideline-directed medical therapy. Those with LVEF 40% and elevated natriuretic peptide levels with structural heart disease were eligible for the study. The time to first CV death or the worsening of HF events (HHF or urgent HF visits) was the primary endpoint. After a median follow-up of 2.3 years, the primary outcome occurred in 16.4% of the patients in the dapagliflozin arm and 19.5% in the placebo group (HR: 0.82, 95%CI: 0.73-0.92; P = 0.001). The rate of HF worsening was 11.8% *vs* 14.5% (HR: 0.79, 95%CI: 0.69-0.91) and that of CV death was 7.4% *vs* 8.3% (HR: 0.88, 95%CI: 0.74-1.05) in the dapagliflozin *vs* placebo group. Comparable results were obtained in the prespecified subgroups, including patients with and without diabetes, and the incidence of adverse events was also similar[11].

Effect of empagliflozin on exercise ability and HF symptoms in patients with chronic HF (EMPERIAL) trial: Patients with HFrEF (EF < 40%) (EMPERIAL-Reduced, n = 312) or HFpEF (EF 40%) (EMPERIAL-Preserved, n = 315), with and without T2DM, were randomized to receive either empagliflozin 10 mg or placebo for 12 weeks. The primary endpoint was a 6-minute walk test distance change at week 12. Key secondary endpoints included the Kansas city cardiomyopathy questionnaire total symptom score (KCCQ-TSS) and Chronic HF questionnaire self-administered standardized format dyspnea score. The 6-minute walk test distance median differences (95%CI) for the empagliflozin and placebo groups at week 12 were -4.0 meters (-16.0 to 6.0; P = 0.42) and 4.0 m (-5.0 to 13.0; P = 0.37) in EMPERIAL-Reduced and EMPERIAL-Preserved, respectively, which were nonsignificant. All secondary endpoints were considered exploratory, indicating an improvement only in the EMPERIAL-Reduced trial[38].

Although HFpEF is not as malignant as HFrEF, considerable morbidity and mortality are associated with it because of comorbidities. In a retrospective study of HFpEF, patients who were admitted for acute or chronic HF exhibited a readmission rate of 21%, which led to increased mortality and resource consumption. Thus, there is a need for better management of these patients, for which SGLT2-is can be helpful[39].

SGLT-2IS IN AHF

Effects of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening HF (SOLOIST-worsening HF) study

Sotagliflozin is a combined of SGLT-2 and SGLT-1 receptor inhibitor. SGLT-1 inhibition reduces postprandial glucose levels by delaying intestinal glucose absorption. In this trial, 1222 patients with HF and recent HF worsening were randomized in a 1:1 ratio to receive either sotagliflozin or placebo, with a median follow-up of 9 months. The patients received either sotagliflozin or placebo before discharge (48.8%) and at a median of 2 days after discharge (51.2%). The

Table 2 Landmark trials of sodium glucose cotransporter-2 inhibitors in heart failure

Trial	Year	Number of patients	SGLT-2i used *vs* placebo	Endpoints		*P* value
				SGLT-2 arm	Placebo arm	
EMPAREG outcomes	2015	7028	Empagliflozin 10 or 25 mg	CV death, non-fatal MI or stroke: 10.5%	CV death, non-fatal MI or stroke: 12.1%	< 0.001
				All-cause mortality: 3.8%	All-cause mortality 5.1%	< 0.01
				HHF: 2.7%	HHF: 4.1%	0.002
DECLARE TIMI 58	2018	17160	Dapagliflozin 10 mg	CV death, MI, stroke: 8.8%	CV death, MI, stroke: 9.4%	0.17
				CV death or HHF: 4.9%	CV death or HHF: 5.8%	0.005
CANVAS	2017	10142	Canagliflozin	Composite of CV death, non-fatal MI or stroke: 26.9%	Composite of CV death, non-fatal MI or stroke: 31.5%	< 0.0001
				CV death or HHF: 16.3%	CV death or HHF: 20.8%	
DAPA-HF	2019	4744	Dapagliflozin 10 mg	CV death or WHF: 16.3%	CV death or WHF: 21.2%	0.001
EMPEROR-Reduced	2020	3730	Empagliflozin 10 mg	CV death or HHF: 19.4%	CV death or HHF: 24.7%	< 0.001
EMPEROR-Preserved	2021	5988	Empagliflozin 10 mg	CV death or HHF: 13.8%	CV death or HHF: 17.1%	< 0.001
DELIVER	2022	6263	Dapagliflozin 10 mg	CV death or WHF: 16.4%	CV death or WHF: 19.5%	< 0.001
SOLOIST WHF	2021	1222	Sotagliflozin	CV death, HHF, urgent visit for HF: 51%	CV death, HHF, urgent visit for HF: 76%	0.001
EMPA RESPONSE	2020	80	Empagliflozin 10 mg	Change in VAS dyspnea score, wt. change, change in NT-proBNP, hospital stay length: 10%	Change in VAS dyspnea score, wt. change, change in NT-pro-BNP, hospital stay length: 13%	0.014
EMPULSE	2022	530	Empagliflozin 10 mg	Net clinical benefit: 53.9%	Net clinical benefit: 39.7%	0.0054
				CV death: 4.2%	CV death: 8.3%	
				HF events: 10.6%	HF events: 14.7%	
				Change in KCCQ-TSS: 4.5	Change in KCCQ-TSS	0.035
				Wt. change: -1.5 Kg	Wt. change	0.014
EMMY	2022	476	Empagliflozin 10 mg	Change in NT-pro-BNP: 15% lower *vs* placebo		0.026
				LVEF: 1.5% *vs* placebo		0.029
				E/e': 6.8% *vs* placebo		0.015
				LVESV: 7.5 mL *vs* placebo		0.0003
				LVEDV: 9.7 mL *vs* placebo		0.0015

CANVAS: Canagliflozin cardiovascular assessment study; CV: Cardiovascular; DAPA: Dapagliflozin and prevention of adverse outcomes; DECLARE TIMI 58: Dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58; DELIVER: Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure; E/e': Mitral inflow E wave velocity/annular tissue' wave velocity; EMMY: Empagliflozin in patients with acute myocardial infarction; EMPAREG: Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients; EMPA-RESPONSE: Effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure; EMPEROR: Empagliflozin outcome trial in patients with chronic heart failure; EMPULSE: Effect on clinical benefit, safety and tolerability of once daily oral empagliflozin 10 mg compared to placebo, initiated in patients hospitalized for acute heart failure who have been stabilized; HF: Heart failure; HHF: Heart failure hospitalization; KCCQ-TSS: Kansa city cardiomyopathy questionnaire total symptom score; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction: NT-pro-BNP: N-terminal pro-B-type natriuretic peptide; SGLT-2is: Sodium glucose cotransporter-2 inhibitors; SOLOIST-WHF: Effect of Sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure; VAS: Visual analogue scale; WHF: Worsening heart failure; Wt.: Weight.

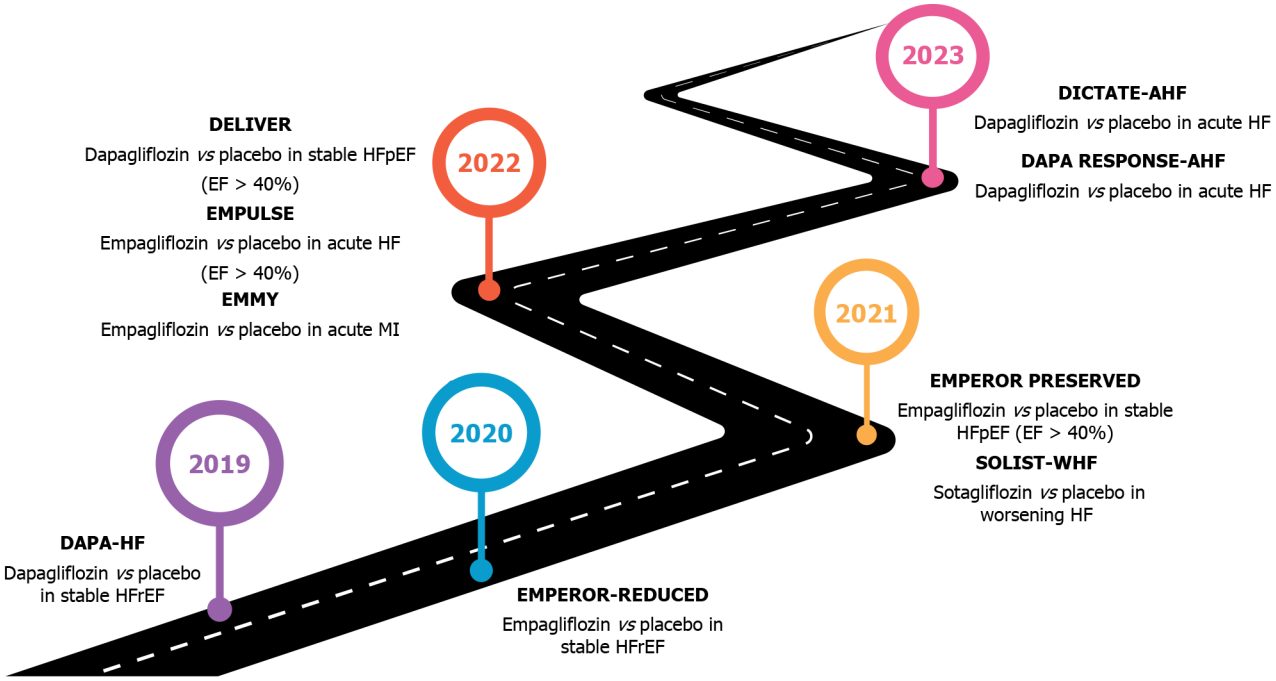

Figure 2 Roadmap of various landmark trials of sodium glucose cotransporter-2 inhibitors in heart failure. HF: Heart failure; MI: Myocardial infarction; EF: Ejection fraction.

primary endpoint was a combination of CV death, hospitalization, and urgent visits for worsening HF (first and subsequent).

In total, 600 primary endpoint events were reported (245 in the sotagliflozin group and 355 in the placebo group). The rate of primary endpoint events was significantly reduced in the sotagliflozin group compared with the placebo group (51.0 *vs* 76.3, HR: 0.67, 95%CI: 0.52-0.85; P = 0.001). Moreover, the rates of CV death were 10.6% with sotagliflozin and 12.5% with placebo (HR: 0.84, 95%CI: 0.58-1.22) and those of non-CV death were 13.5% in the sotagliflozin group and 16.3% in the placebo group (HR: 0.82, 95%CI: 0.59-1.14). However, more episodes of diarrhea (6.1% *vs* 3.4%) and severe hypoglycemia (1.5% *vs* 3.0%) were reported in the sotagliflozin group than in the placebo group. Furthermore, the percentages of patients with hypotension (6.0% *vs* 4.6%) and acute renal injury (4.1% *vs* 4.6%) were slightly higher in the sotagliflozin group[40].

Effects of empagliflozin on clinical outcomes in patients with acute decompensated HF (EMPA-RESPONSE-AHF) trial: In this randomized, placebo-controlled, double-blind, parallel-group, multicenter pilot study, 80 patients with AHF with and without diabetes were randomized to receive either empagliflozin 10 mg/day or placebo for 30 days. The primary endpoints were alterations in the visual analog scale (VAS) dyspnea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and the length of stay. The secondary outcomes comprised safety and clinical endpoints. The mean age was 76 years, 33% were women, 47% had *de novo* HF, and the median NT-proBNP level was 5236 pg/mL. Differences were not observed in the primary endpoints between the empagliflozin and placebo groups. Nevertheless, empagliflozin decreased the combined endpoint of in-hospital HF worsening, rehospitalization for HF, or death at 60 days compared with placebo (4 [10%] *vs* 13 [33%]; P = 0.014). Moreover, urinary output was higher in the empagliflozin group than in the placebo group. Empagliflozin was well tolerated, safe, and did not exert any adverse effects on the patients' blood pressure or renal function[41].

Effects on clinical benefit, safety, and tolerability of once daily oral empagliflozin 10 mg compared to placebo, initiated in patients hospitalized for acute heart failure who have been stabilized (EMPULSE) trial: In this trial, patients with AHF who exhibited a systolic blood pressure of 100 mmHg and did not receive inotropic support during the last 24 hours were randomized to receive either empagliflozin 10 mg (n = 265) or placebo (n = 265). Any intravenous (IV) diuretic or vasodilator use was discontinued within the last 6 hours of randomization. Patients with NT-proBNP of ≥ 1600 pg/mL or BNP of ≥ 400 pg/mL during hospitalization or within 72 hours prior to admission were included. The median LVEF was 31%. The primary endpoints were the composite of death, number of HF events, time to first HF event, and the KCCQ-TSS score from baseline to 90 days (P = 0.0054). In patients with acute decompensated HF (ADHF), empagliflozin was linked to a significant clinical benefit at 90 days and resulted in improved weight loss (decongestion) compared with placebo[42].

Efficacy and safety of dapagliflozin in AHF (DICTATE-AHF): The DICTATE-AHF trial investigated the efficacy and safety of dapagliflozin initiated within 24 hours of hospital admission on the diuretic response in patients with hypervolemic ADHF. Adult patients with T2DM admitted to the hospital with ADHF and underwent current or planned treatment with IV loop diuretics were included in this study. The findings were presented at the European Society of Cardiology (ESC) congress 2023. Early initiation of dapagliflozin did not significantly improve the diuretic efficiency

compared with structured routine care in patients with ADHF. However, it did not worsen any prespecified safety outcomes. Exploratory analyses revealed that the drug alleviated decongestion and resulted in early discharge from the hospital[43].

Effect of adjuvant dapagliflozin on improving the treatment of congestion in patients with AHF (DAPA-RESPONSE AHF): This randomized double-blind study included 87 patients with ADHF who presented with dyspnea. The patients were randomized to receive either dapagliflozin (10 mg/day, n = 45) or placebo (n = 42) for 30 days within 24 hours of admission. The primary outcome was the difference in the area under the curve (AUC) of the VAS dyspnea score between the groups over the first 4 days. The secondary endpoints were urinary sodium concentration 2 hours after randomization, percent change in NT-proBNP, cumulative urine output (UOP), and differences in mortality and hospital readmission rates. The results revealed that dapagliflozin significantly reduced the AUC of the VAS dyspnea score compared with placebo (3192.2 ± 1631.9 mm × hr *vs* 4713.1 ± 1714.9 mm × hr; P < 0.001). Moreover, the relative change in NT-proBNP compared with baseline was larger with dapagliflozin than with placebo (-34.89% *vs* -10.085%; P = 0.001). In addition, a higher cumulative UOP was observed with dapagliflozin on day 4 (18600 mL *vs* 13700 mL; P = 0.031). Dapagliflozin also reduced the rehospitalization rates within 30 days after discharge; however, it did not affect spot urinary sodium concentration, incidence of HF worsening, or mortality rates[44].

SGLT-2is in acute myocardial infarction

Empagliflozin in patients with acute myocardial infarction (EMMY) trial: In this randomized, double-blind trial, 476 patients with acute myocardial infarction (MI) were randomly assigned to receive either empagliflozin 10 mg or a matching placebo once daily within 72 hours of percutaneous coronary intervention (PCI). The primary endpoint was the change in NT-proBNP level over 26 weeks, and the secondary endpoint was alterations in echocardiographic parameters. The baseline median (interquartile range) NT-proBNP level was 1294 (757-2246) pg/mL. NT-proBNP reduction was significantly higher in the empagliflozin group than in the placebo group, which was 15% lower (95%CI: -4.4 to -23.6) after adjusting for baseline NT-proBNP level, sex, and diabetes status (P = 0.026). In addition, significant improvements were noted in LVEF, E/e', and left ventricle volume. Seven patients (three in the empagliflozin group) were hospitalized for HF[45].

EFFECT OF SGLT-2IS ON INTRACARDIAC DEFIBRILLATOR DEVICE IMPLANTATIONS

Sudden cardiac death (SCD) is the most devastating complication of HF. Current guidelines recommend intracardiac defibrillator device implantation in patients with HFrEF who have LVEF of ≤ 35% even after receiving optimized HF treatment for at least 3 months. ACE inhibitors/angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and ARNIs prevent adverse cardiac remodeling and thus reduce the risk of SCD. Moreover, SGLT-2is also reduce the risk of ventricular arrhythmia, thereby preventing SCD.

In a population-based cohort study involving 399810 patients with recently diagnosed T2DM, SGLT-2is decreased the risk of all-cause mortality and new-onset arrhythmias (17% lower risk of new-onset arrhythmia) compared with placebo [46]. Furthermore, the EMPA-REG outcome study reported a significant reduction in CV deaths, including SCD, with empagliflozin[47].

Moreover, post-hoc analysis of the DAPA-HF (dapagliflozin and prevention of adverse outcomes in HF) study indicated that patients on dapagliflozin [140/2373 patients (5.9%)] exhibited significantly fewer arrhythmic events and SCD than those on placebo [175/2371 patients (7.4%); HR: 0.79; 95%CI: 0.63-0.99; P = 0.037)[48]. The mechanism was, in this case too, a reduction in wall stress and adverse remodeling.

In a recent meta-analysis of 22 trials that comprised 52115 patients, SGLT-2is were found to alleviate the risks of atrial fibrillation and ventricular tachyarrhythmia by 18% and 28%, respectively[49].

HYPERURICEMIA AND GOUT REDUCTION BY SGLT-2IS

The pathogenesis of hyperuricemia and gout is intricately linked to that of T2DM and HF. Visceral obesity, diabetes, and HF increase the incidence of hyperuricemia, which in turn exacerbates the risk of diabetes and HF. Hyperuricemia worsens glucose tolerance in patients with diabetes and causes ventricular dysfunction in those with HF. Nutrient surplus and signal deprivation are deranged, which leads to urate overproduction and underexcretion. SGLT-2is induce starvation mimicry in a state of nutrient surplus and decrease flux *via* the pentose phosphate pathway. These changes attenuate purine and urate synthesis and promote renal urate excretion, thus alleviating hyperuricemia and gout. Hence, the use of SGLT-2is may reduce the need for gout medications in patients with HF[50].

FUTURE STUDIES

EMPA-AHF (NCT05392764) study

A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of empagliflozin in ADHF.

EMPA (NCT05556044) study

To evaluate the efficacy and safety of in-hospital initiation of empagliflozin in patients hospitalized for new-onset AHF, regardless of LVEF, for up to 90 days of follow-up.

Empagliflozin for patients with acutely decompensated congestive HF, diuretic resistance, and moderate to advanced chronic kidney disease (DRIP-AHF, NCT05305495)

A prospective, single arm, cohort study to evaluate the synergistic empagliflozin and furosemide in acutely decompensated HF patients complicated by hypovolemia and diuretic resistance.

Peri-treatment of SGLT-2is on myocardial infarct size and remodeling index measured by cardiac magnetic resonance imaging in patients with acute myocardial infarction and high risk of HF undergoing percutaneous coronary intervention (PRESTIGE AMI; NCT04899479)

To evaluate whether SGLT-2is is effective in reducing the size of infarction and myocardial remodeling in patients with AMI and at high risk of heart failure. SGLT-2is will be administered before PCI in patients with ST-elevation MI (STEMI) or non-STEMI, and infract size as well as LV end systolic volume will be assessed using cardiac magnetic resonance imaging.

Acute reno-cardiac action of dapagliflozin in advanced HF patients on heart transplant waiting list (ARCADIA AHF; NCT04782245)

To examine whether dapagliflozin use in patients waiting for heart transplant has any effect on soluble urokinase type plasminogen activation receptor-a biomarker useful both in acute kidney injury and HF.

Dapagliflozin on volume vascular outcomes (DAPA VOLVO; NCT04869124)

To investigate the effects of dapagliflozin on volume status (assessed by change in relative plasma volume and blood volume) and vascular function (flow mediated dilatation and pulse wave velocity) in patients with congestive HF.

GUIDELINES

Although SGLT-2is were initially recommended for HFrEF, latest guidelines have extended their use to HFpEF. The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines for HF provide SGLT-2i class IA indications for HFrEF treatment. In patients with HFmrEF (41%-49%) and HFpEF, SGLT-2is are given a class 2A indication, which is also supported by the 2023 American College of Cardiology expert consensus decision pathway for the management of HFpEF. This guideline recommends that SGLT-2is should be started in all patients in the absence of any contraindications[51,52]. The 2023 Focused Update of ESC provides SGLT-2is a class IA indication in patients with HFrEF and HFmrEF to alleviate the risk of HHF or CV death. In addition, ESC provides a strong class IA indication for SGLT-2is in patients for HFpEF in this recent update[53].

CONCLUSION

SGLT-2is are a class of drugs that were initially introduced as antidiabetic medications but have recently become one of the four essential pillars of HF management. The efficacy of these inhibitors has been proven in the entire HF spectrum, irrespective of LVEF and diabetic status. The mechanisms underlying these benefits, although not well established, are believed to involve various cardiometabolic and biomolecular targets, in addition to the diuretic effects. These inhibitors offer early and sustained benefits without substantial side effects and should therefore be initiated at the earliest in HF management to reduce morbidity and mortality.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Carotid *versus* axillary artery cannulation for descending aorta remodeling in type A acute aortic dissection

Qin Jiang, Tao Yu, Ke-Li Huang, Ke Liu, Xi Li, Sheng-Shou Hu

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Abstract

BACKGROUND

Arterial cannulation sites for the surgical repair of type A aortic dissection (AAD) have evolved from right axillary artery (AA) cannulation to bilateral carotid artery (CA) based of femoral artery (FA) cannulation. Postoperative descending aorta remodeling is closely linked to the false lumen area ratio (FLAR), defined as false lumen area/aortic area, as well as to the incidence of renal replacement therapy (RRT).

AIM

To investigate the effect of the updated arterial cannulation strategy on descending aortic remodeling.

METHODS

A total of 443 AAD patients who received FA combined cannulation between March 2015 and March 2023 were included in the study. Of these, 209 received right AA cannulation and 234 received bilateral CA cannulation. The primary outcome was the change in FLAR, as calculated from computed tomography angiography in three segments of the descending aorta: Thoracic (S1), upper abdominal (S2), and lower abdominal (S3). Secondary outcomes were the incidence of RRT and the serum inflammation response, as observed by the levels of high sensitivity C reaction protein (hs-CRP) and Interleukin-6 (IL-6).

RESULTS

The postoperative/preoperative ratio of FLAR in S2 and S3 was higher in the AA

group compared to the CA group (S2: 0.80 ± 0.08 *vs* 0.75 ± 0.07, $P < 0.001$; S3: 0.57 ± 0.12 *vs* 0.50 ± 0.12, $P < 0.001$, respectively). The AA group also had a significantly higher incidence of RRT (19.1% *vs* 8.5%, $P = 0.001$; odds ratio: 2.533, 95%CI: 1.427-4.493) and higher levels of inflammation cytokines 24 h after the procedure [hr-CRP: 117 ± 17 *vs* 104 ± 15 mg/L; IL-6: 129 (103, 166) *vs* 83 (69, 101) pg/mL; both $P < 0.001$] compared to the CA group.

CONCLUSION

The CA cannulation strategy was associated with better abdominal aorta remodeling after AAD repair compared to AA cannulation, as observed by a greater change in FLAR and lower incidence of RRT.

Key Words: Acute type A aortic dissection; Bilateral carotid arterial cannulation; Descending aortic remodeling; False lumen area ratio; Prognosis

Core Tip: Arterial cannulation sites for the surgical repair of type A acute aortic dissection have gradually evolved from right axillary artery cannulation to bilateral carotid artery cannulation based on femoral artery cannulation. This retrospective observational study found the carotid artery cannulation strategy was associated with better postoperative abdominal aorta remodeling with a higher false lumen area ratio, a lower incidence of renal replacement therapy, and lower levels of inflammation cytokines compared with the axillary artery cannulation mode.

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INTRODUCTION

With the improved survival rate following surgery for acute type A aortic dissection (AAD), the therapeutic focus amongst cardiac surgeons has switched from mortality to morbidity[1]. It is now widely accepted that total aortic arch replacement concomitant with the frozen elephant trunk technique is the standard procedure for eliminating the risk of rupture of the proximal segment of AAD[2]. In theory, the perfect repair of AAD should result in elimination of the false lumen throughout the entire aorta and its branches. However, the aortic remodeling that is characteristic of a completely thrombosed false lumen is usually incomplete, especially in the distal descending aorta[3].

The onset and progression of AAD endangers blood perfusion of the involved branches in the descending aorta, leading to poor organ perfusion and triggering systemic inflammation responses[4]. The anatomical morphology of the descending aorta continues to change following repair of the proximal aorta, and poor aortic remodeling increases the risk of unfavorable events and the need for aortic reintervention[5]. Computed tomography angiography (CTA) is the standard imaging tool used to evaluate the preoperative and postoperative morphology of the whole aorta. The false lumen area ratio (FLAR), defined as false lumen area/aortic area, is an important quantitative index for determining the extent of aortic remodeling. The FLAR is evaluated using auxiliary software[6].

Different cannulation sites used to establish the cardiopulmonary bypass (CPB) have distinct hemodynamic characteristics, including the velocity, stress, and shear stress at the tear site[7]. Although the triple artery cannulation mode is used in clinical practice, few studies have used medical imaging results to explore the hemodynamic effects of more recent arterial cannulation modes. A study on AAD patients who received total arch replacement in addition to the frozen elephant trunk implantation technique compared bilateral carotid artery (CA) cannulation and right axillary artery (AA) cannulation in terms of neurologic protection[8]. However, the effect of using bilateral CA cannulation on descending aorta modeling was not examined, nor was it compared with AA cannulation in combination with femoral artery (FA) cannulation. Hence, the aim of the present study was to compare CA cannulation and AA cannulation in terms of changes in FLAR in the descending aorta.

MATERIALS AND METHODS

This retrospective observational study was carried out on AAD patients treated between March, 2015 and March, 2023 in the Cardiac Surgery Department of one tertiary hospital (Figure 1). Patients who received total aortic arch replacement and intraoperative frozen-trunk stent implantation surgery using femoral and right axillary/bilateral carotid artery cannulation were reviewed. The inclusion criteria included the availability of preoperative and postoperative CTA data on the entire aorta in the imaging system. The exclusion criteria were preoperative kidney disease or deformity, other surgical or cannulation type, and unqualified images or datasets. Patients were assigned to the AA or CA groups

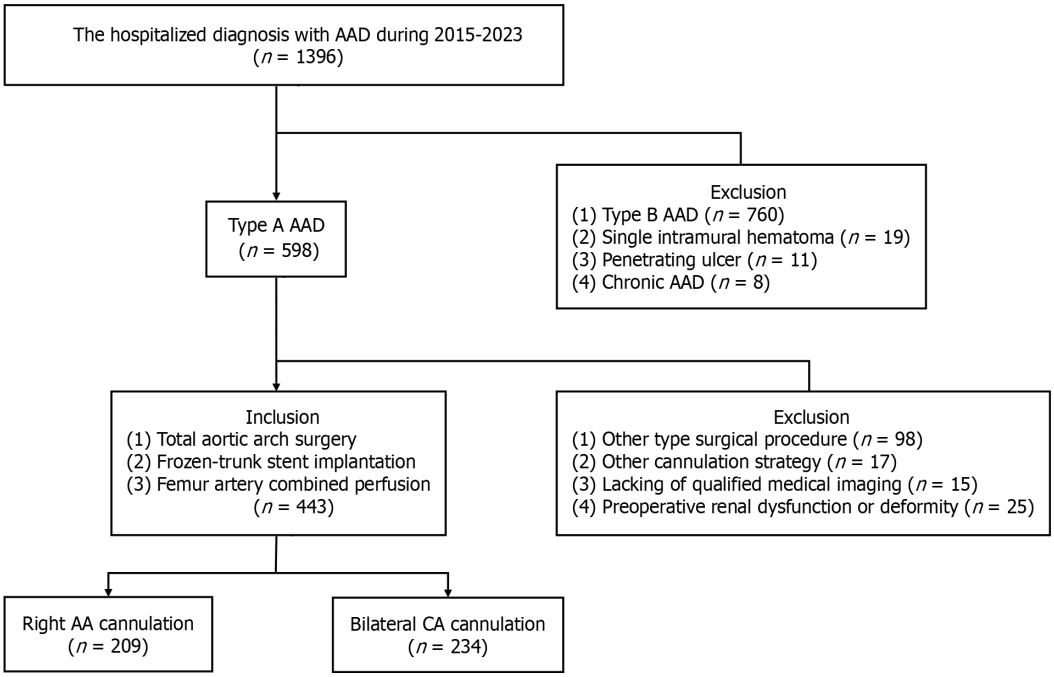

Figure 1 Study protocol. AA: Axillary artery; AAD: A aortic dissection; CA: Carotid artery.

according to the primary arterial cannulation mode. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Medical Ethics Committee of our institute (Approval number: 2021-215; March 1, 2021). Patient consent was waived due to the retrospective nature of the study. The primary endpoint of the study was the postoperative/preoperative FLAR, as calculated by CTA software. Secondary outcomes were the incidence of renal replacement treatment (RRT), and the levels of two serum inflammation response markers: high sensitivity C reaction protein (hs-CRP), and interleukin-6 (IL-6)[9].

Surgical approach and cannulation strategies

All procedures were carried out by the same surgeon under intravenous and inhaled anesthesia. Arterial cannulation was administered with the "Seldinger" technique on the normal region in order to enter into the true lumen[10]. The use of bilateral CA cannulation was updated from right AA cannulation due to the high incidence of stroke and mortality with the latter[8]. In the AA group, right AA cannulation and FA cannulation jointly provided perfusion for the entire body during the CPB. Cerebral perfusion was achieved *via* right AA cannulation by blocking the proximal end of the innominate artery. In the CA group, right and left CA cannulation in addition to FA cannulation was used to sustain systemic circulation during the CPB. The aortic arch was replaced by a tetra-furcated graft (Maquet, Rastatt, Baden-Württemberg, Germany), and an endovascular frozen-trunk stent with a soft edge (CRONUS, MicroPort Scientifc Corporation, Shanghai, China) was implanted into the descending aorta during the hypothermia circulatory arrest (HCA) period.

CTA follow-up

Aortic CTA extending from the CA to FA was routinely prescribed at hospital admission and before discharge[11]. FLAR was calculated from the preoperative and postoperative CTA results using an area measurement tool (Neusoft PACS/RIS Version 5.5 Workstation) on three segments of the descending aorta: thoracic segment (S1), upper abdominal segment (S2), and lower abdominal segment below the ostium of the renal artery(S3)[12]. The aortic area (mm^2) was quantified along the inside contours of the aortic wall in the axial plane. To ensure objectivity and consistency, FLAR was determined at the maximum false lumen cross-section by a single radiologist who was not directly involved in the study. In addition, the condition of the ostium of abdominal aortic branches was recorded preoperatively and postoperatively.

Inflammatory response cytokines

Venous blood samples for laboratory tests were drawn at the time of admission and 12 hours, 24 hours and 48 hours after the procedure. Inflammatory response markers such as white blood cells, neutrophils, and hs-CRP were evaluated[13]. Human cytokines including IL-6 were also measured by flow cytometry at 24 hours postoperatively.

Criteria for the initiation of renal replacement treatment (RRT)

Blood gas analysis was performed regularly during stay in the intensive care unit (ICU) to inform the pulmonary ventilation function and electrolyte balance. The plasma creatinine level was monitored each day and the urine output each hour during the ICU stay. The indications for RRT included an increase in the creatinine level to > 26.5 μmol/L within 48 hours after surgery, a urine output of < 0.5 mL/kg/h and lasting for 6 hours, a serum potassium concentration

of > 6.0 mmol/L, or a serum HCO_3^- concentration of < 10 mmol/L[14].

Statistical analysis

Continuous variables were expressed as the mean ± SD, and categorical values as a number (frequency). Continuous parameters with a non-normal distribution as determined by the Kolmogorov-Smirnov test were expressed as the median (1st quartile, 3rd quartile). Statistical differences between two groups were assessed using the Student independent samples *t* test for normally distributed continuous variables, the Mann-Whitney *U* non-parametric test for non-normally distributed variables, and Fisher's χ^2 test for categorical variables. The likelihood of RRT in the two groups was determined by binary logistic regression analysis. Receiver Operating Characteristic (ROC) curve analysis was used to determine the ability of FLAR to predict the incidence of RRT. The cutoff value was determined as the maximum value of sensitivity and specificity, minus one. Statistical analyses were performed using SPSS software (version 25.0 SPSS, Inc, Chicago, IL, United States) and a *P* value of < 0.05 was set for statistical significance.

RESULTS

Patient demographics and clinical characteristics

A total of 1396 patients were identified in the medical records as being admitted with a diagnosis of AAD. Amongst these were 598 cases of type A AAD. Patients who underwent other types of surgical procedures, such as hemiarch replacement (*n* = 98), or other cannulation strategies (*n* = 17) were excluded. Also excluded were patients with incomplete preoperative or postoperative CTA images (*n* = 15), or with preoperative kidney injury or deformity (*n* = 25). A total of 209 cases with AA cannulation and 234 cases with CA cannulation were included in the final study cohort (Figure 1). The baseline characteristics of the two groups were not significantly different (Table 1).

Serum levels of inflammatory response indexes

The operative characteristics (operative type, duration, blood product use) between the two groups were not significantly different (Table 2). However, the serum hs-CRP level at 12, 24, and 48 hours after the procedure was significantly higher in the AA group than in the CA group (all $P < 0.01$). The serum IL-6 level at 24 hours after the procedure was also significantly higher in the AA group than in the CA group [129 (103, 166) pg/mL *vs* 83 (69, 100) pg/mL, $P < 0.001$]. In addition, the AA group had a higher APACHE II score (18 ± 6 *vs* 17 ± 5, $P = 0.028$; Table 3).

Comparison of FLAR in three segments of the descending aorta

Preoperative CTA revealed no significant differences in FLAR between the AA and CA groups in three segments of the descending aorta (S1: 0.71 ± 0.12 *vs* 0.73 ± 0.11; S2: 0.75 ± 0.10 *vs* 0.76 ± 0.08; S3: 0.78 ± 0.10 *vs* 0.77 ± 0.10; all $P > 0.05$). However, a significant difference between the two groups was observed in S2 and S3 of the descending aorta (S2: 0.60 ± 0.10 *vs* 0.57 ± 0.08, $P = 0.002$; S3: 0.44 ± 0.11 *vs* 0.39 ± 0.10; $P < 0.001$; Figure 2 and Figure 3). The postoperative/preoperative ratio of FLAR in the S2 and S3 segments was higher in the AA group compared to the CA group (S2: 0.80 ± 0.08 *vs* 0.75 ± 0.07, $P < 0.001$; S3: 0.57 ± 0.12 *vs* 0.50 ± 0.12, $P < 0.001$; Figure 2 and Figure 3). The percentage of postoperative involvement of the coeliac trunk artery, superior mesenteric artery, and renal artery was markedly lower in the CA group compared to the AA group (Table 3).

ROC analysis of FLAR for the prediction of RRT

The incidence of RRT was 19.1% in the AA group and 8.5% in the CA group ($P = 0.001$), with an odds ratio of 2.533 (95%CI: 1.427-4.493). ROC analysis showed that postoperative/preoperative FLAR in S1, S2 and S3 was significantly better at predicting RRT than both the preoperative and postoperative FLAR. The ROC curve results for postoperative/preoperative FLAR in S1, S2 and S3 were 0.668 (95%CI: 0.595-0.741, $P < 0.001$), 0.693 (95%CI: 0.615-0.771, $P < 0.001$), and 0.535 (95%CI: 0.459-0.610, $P > 0.05$), respectively, for the prediction of RRT (Figure 4). The postoperative/preoperative FLAR cutoff value for the prediction of RRT was 0.712 for S1 (sensitivity of 0.650, specificity of 0.616), and 0.775 for S2 (sensitivity of 0.70, specificity of 0.514).

DISCUSSION

The three major findings of this study were: (1) Following surgical repair of AAD, the CA cannulation strategy resulted in a significantly lower FLAR in S2 and S3 of the descending aorta compared with AA cannulation in combination with FA cannulation; (2) The CA cannulation strategy also showed a lower incidence of RRT and inflammation response compared with AA cannulation in combination with FA cannulation; and (3) the change in FLAR in the upper abdominal aorta was predictive of postoperative RRT in patients who underwent total arch replacement and the frozen elephant trunk technique.

For the repair of AAD, it is widely accepted that the frozen elephant trunk technique gives superior results for descending aortic remodeling than total arch replacement alone. Tochii *et al*[15] reported that the ratio of the true lumen area and false lumen complete thrombosis rate in the segment of thoracic descending aorta were significantly higher in patients who underwent the frozen elephant trunk technique. For type A aortic dissection in Marfan syndrome, the frozen elephant trunk technique can also induce favorable remodeling in the distal aorta by expanding the true lumen

Table 1 Baseline characteristics, *n* (%)

Characteristics	AA group (*n* = 209)	CA group (*n* = 234)
Age (years)	53 ± 9	53 ± 9
Male	147 (70.3)	163 (69.7)
BMI (kg/m^2)	23.3 ± 2.2	23.1 ± 2.3
Previous medical history		
Hypertension	158(75.6)	183 (78.2)
Dyslipidemia	46 (22.0)	47 (20.0)
Involved branch arteries		
Coronary artery	20 (10.0)	25 (10.7)
Brachiocephalic artery	43 (20.6)	51 (21.8)
Coeliac trunk artery	80 (38.3)	92 (39.3)
Superior mesenteric artery	73 (34.9)	83 (35.5)
Renal artery	156 (74.6)	169 (72.2)
Cardiac function		
LAD (mm)	37 [35,43]	36 [34,40]
LVEDD (mm)	51.6 ± 6.0	51.5 ± 5.8
LVEF (%)	55.6 ± 7.0	56.2 ± 7.1
Laboratory findings		
hs-CRP (mg/L)	27.0 ± 12.4	27.0 ± 10.9
hs-troponin I (ug/L)	0.09 [0.04, 0.25]	0.11 [0.06, 0.18]
Lactate (mmol/L)	0.34 ± 0.13	0.32 ± 0.19
Hb (g/L)	134.2 ± 18.3	132.1 ± 17.1
WBC (10^9/L)	10.6 ± 2.2	10.9 ± 2.6
Neutrophil (10^9/L)	8.7 [7.5, 10.2]	8.6 [7.8, 10.4]

AA group: Right axillary artery in combination with femoral artery cannulation; CA group: Bilateral carotid artery in combination with femoral artery cannulation; BMI: Body mass index; LAD: Left atrium diameter; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; hs-CRP: High sensitivity C reaction protein; Hb: Hemoglobin; WBC: White blood count. The data are presented as mean ± SD, median [interquartile range], or number (frequency).

[16]. However, a decreasing trend of aortic remodeling was observed in the descending aorta, with 85% at the middle of the frozen elephant trunk, 70% at the distal end of the frozen elephant trunk, 50% at the unstented thoracic aorta, and 35% proximal to the renal artery[17]. Failure to reduce the false lumen volume after endovascular repair of type B AAD predicted the likelihood of aortic distention and re-do surgery[18]. Therefore, modification of the arterial cannulation mode was one of the strategies used by the cardiovascular surgery community to enhance postoperative aortic remodeling.

The most commonly used arterial cannulation strategies used for type A aortic dissection are right AA, FA and both. In a previous study, combined cannulation with AA and FA provided advantages over a single cannulation strategy in terms of vascular wall injury, organ perfusion, and rapid cooling[19]. Patients undergoing unilateral cerebral perfusion have a higher risk of permanent cerebral dysfunction. This procedure is usually performed *via* right AA cannulation and by blocking the origin of the innominate artery after HCA. In a previous study, we suggested bilateral cerebral perfusion *via* bilateral CA cannulation[8]. This cannulation mode not only provides sufficient cerebral blood perfusion, particularly for patients without an intact Willis artery circuit, but also allows good blood supply of the branches in the descending aorta from FA, resulting in a lower incidence of RRT and low inflammation response indexes. Single FA perfusion in the descending aorta using this combined cannulation mode can eliminate the collision effect downward from AA perfusion by reducing the blood supply to the brachiocephalic trunk artery. Using an *in vitro* model, Heo *et al*[20] demonstrated that FA perfusion could compensate for the partial blood to the celiac and renal arteries when the intimal flap motion blocked the ostium of these branches in the descending aorta only in the axillary cannulation mode.

By monitoring the maximal cross-section diameter and false lumen area, CTA is the main imaging tool used to follow aortic modeling. Yamashita *et al*[21] found the predischarge maximal aortic diameter was a predictor of late aortic dilation in patients with residual dissected aorta after aortic replacement for AAD. Squizzato *et al*[22] demonstrated that

Table 2 Operative and postoperative characteristics, *n* (%)

Characteristics	AA group (*n* = 209)	CA group (*n* = 234)
Surgical type on the root of aorta		
Sinus repair (commissure suspension)	113 (54.1)	118 (50.4)
Bentall	36 (17.2)	38 (16.2)
Wheat	18 (8.6)	21 (9.0)
Carbrol (modified)	42 (20.1)	57 (24.4)
operative duration (min)		
PT	403 ± 25	402 ± 26
CPB	189 ± 20	186 ± 20
ACC	89 [79,102]	88 [79,95]
HCA	20 [18,22]	20 [18,22]
Intraoperative allogenic transfusion		
RBC (U)	4 [4,6]	4 [4,6]
PLT (U)	0.6 ± 0.6	0.5 ± 0.6
FFP (ml)	621 ± 222	610 ± 196
Cryoprecipitation (U)	1.4 ± 1.9	1.2 ± 1.9

AA: Axillary artery; CA: Carotid artery; PT: Procedure time; CPB: Cardiopulmonary bypass; ACC: Aortic cross clamp; HCA: Hypothermia circulatory arrest; RBC: Red blood cell; PLT: Platelet; FFP: Fresh frozen plasma. The data are presented as mean ± SD or number (frequency).

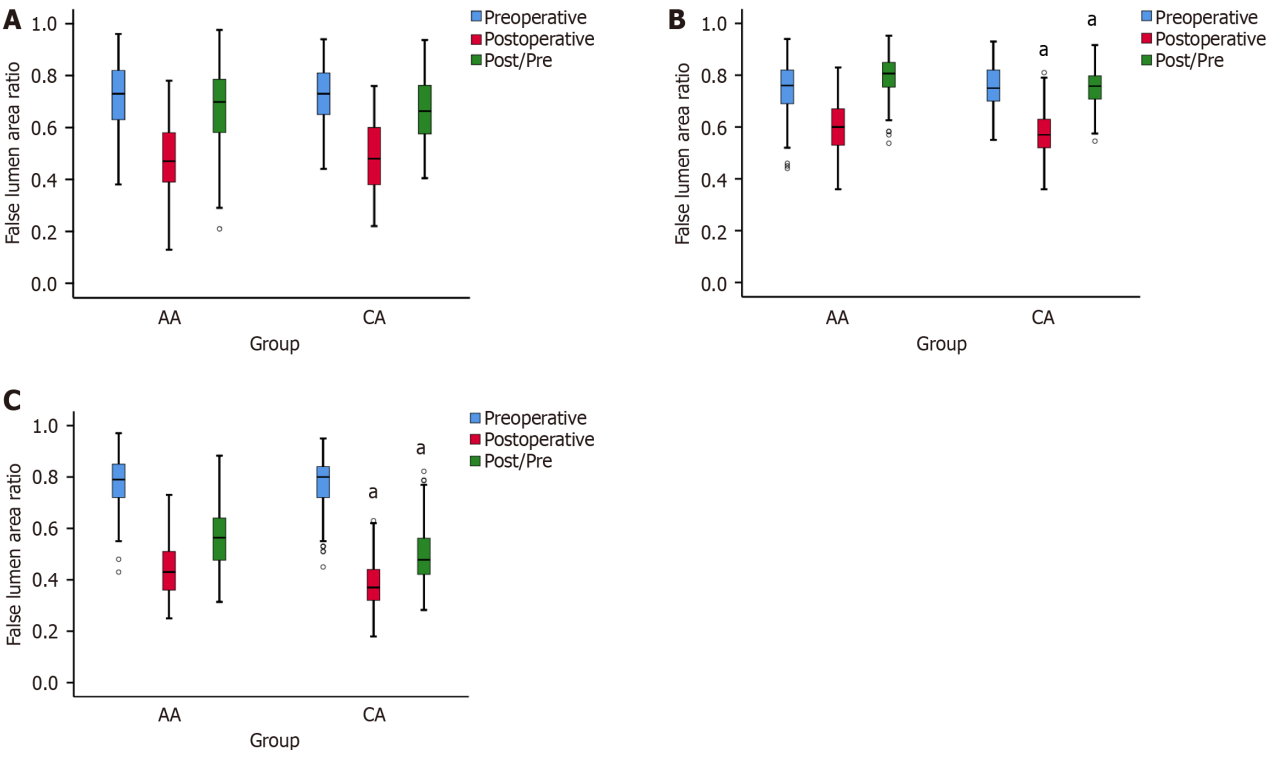

Figure 2 Segment changes in the false lumen area ratio in the descending aorta of the axillary artery and carotid artery groups calculated by computed tomography angiography. A: The preoperative (left), postoperative (middle), and postoperative/preoperative (right) false lumen area ratio (FLAR) of the S1; B and C: S2 and S3 segments in the AA and CA groups. S1: Thoracic segment; S2: Upper abdominal segment; S3: Lower abdominal segment. [a] Indicates a significant difference between the two groups ($P < 0.01$).

Table 3 Postoperative results, *n* (%)

Characteristics	AA group (*n* = 209)	CA group (*n* = 234)	*P* value
Inflammation response indexes			
hs-CRP (12 hours, mg/L)	70 ± 16	65 ± 15	0.001
hs-CRP (24 hours, mg/L)	117 ± 17	104 ± 15	< 0.001
hs-CRP (48 hours, mg/L)	190 ± 16	183 ± 18	< 0.001
IL-6 (24 hours, pg/mL)	129 [103,166]	83 [69,101]	< 0.001
Cardiac injury indexes			
TnI (12 hours, ng/mL)	10.6 ± 2.8	10.5 ± 2.5	0.606
TnI (24 hours, ng/mL)	5.7 [4.8, 6.7]	5.7 [5.0, 6.9]	0.612
TnI (48 hours, ng/mL)	3.0 ± 1.2	3.2 ± 1.0	0.227
Anaerobic metabolism			
Lactate (12 hours, mmol/L)	9.0 ± 1.7	8.5 ± 1.6	0.003
Lactate (24 hours, mmol/L)	3.5 ± 0.8	3.2 ± 0.9	0.001
Lactate (48 hours, mmol/L)	2.1 ± 0.7	1.8 ± 0.6	< 0.001
ICU recovery			
APACHE II score (24 hours)	18 ± 6	17 ± 5	0.028
Ventilation time (hour)	49 ± 20	36 ± 18	< 0.001
Duration in ICU stay (day)	4 [3,5]	3 [2,3]	< 0.001
Chest tube drainage (mL)	906 ± 168	836 ± 163	< 0.001
Involved branch arteries			
Coeliac trunk artery	51 (24.4)	37 (15.8)	0.014
Superior mesenteric artery	56 (26.8)	42 (17.9)	0.025
Renal artery	121 (57.9)	105 (44.9)	0.006
30-day recovery			
Death	25 (12.0)	13 (5.6)	0.018
Stroke	35 (16.7)	22 (9.4)	0.023
RRT	40 (19.1)	20 (8.5)	0.001
Duration in hospital stay (d)	16 [14,19]	14 [12,15]	< 0.001

hs-CRP: Highly sensitive C-reactive protein; IL: Interleukin; TnI: Troponin I; ICU: Intensive care unit; APACHE II score: Acute physiology, age and chronic health evaluation (APACHE) II score; RRT: Renal replacement treatment; other abbreviations as in Figure 1 The data are presented as mean ± SD, median (interquartile range), or number (frequency).

aortic branch involvement and dilatation were associated with the patency of aortic false lumen and poor perfusion in patients with aortic dissection. Volume measurement was a much more sensitive indicator for identifying lumen expansion/shrinkage in the distal stented region[23]. However, specialized software is required to quantify the geometric area of the false lumen along the length of the aorta. The circumferential ratio of dissection at the cross-section was also associated with positive remodeling of the descending thoracic aorta following tear-oriented replacement for acute type I aortic dissection[24].

A previous study reported that the postoperative false lumen presented as an olive shape in the descending aorta during FA and AA cannulation mode, indicating the postoperative change in FLAR in S2 was less than that in S1 and S3 [12]. In the present study, FLAR in S1 was not obviously different between the AA and CA cannulation modes. Moreover, the postoperative/preoperative FLAR values in S2 and S3 were lower with CA cannulation compared to the AA mode. Accordingly, the percentage involvement of the abdominal aorta branch ostium was also lower with CA cannulation. Furthermore, ROC analysis showed that postoperative/preoperative FLAR in S1 and S2 was predictive of RRT, with the strongest predictive ability found for S2. Other critical care indexes such as the APACHEIIscore, duration of ICU stay, inflammation response[25] and anaerobic metabolism[26] were also lower with the bilateral CA and FA cannulation approach. We speculate that the sufficient bloodstream resulting from isolated FA perfusion in the descending aorta exerts a higher radially outward expanding force on the vessel wall compared with bilateral face-to-face perfusion in the

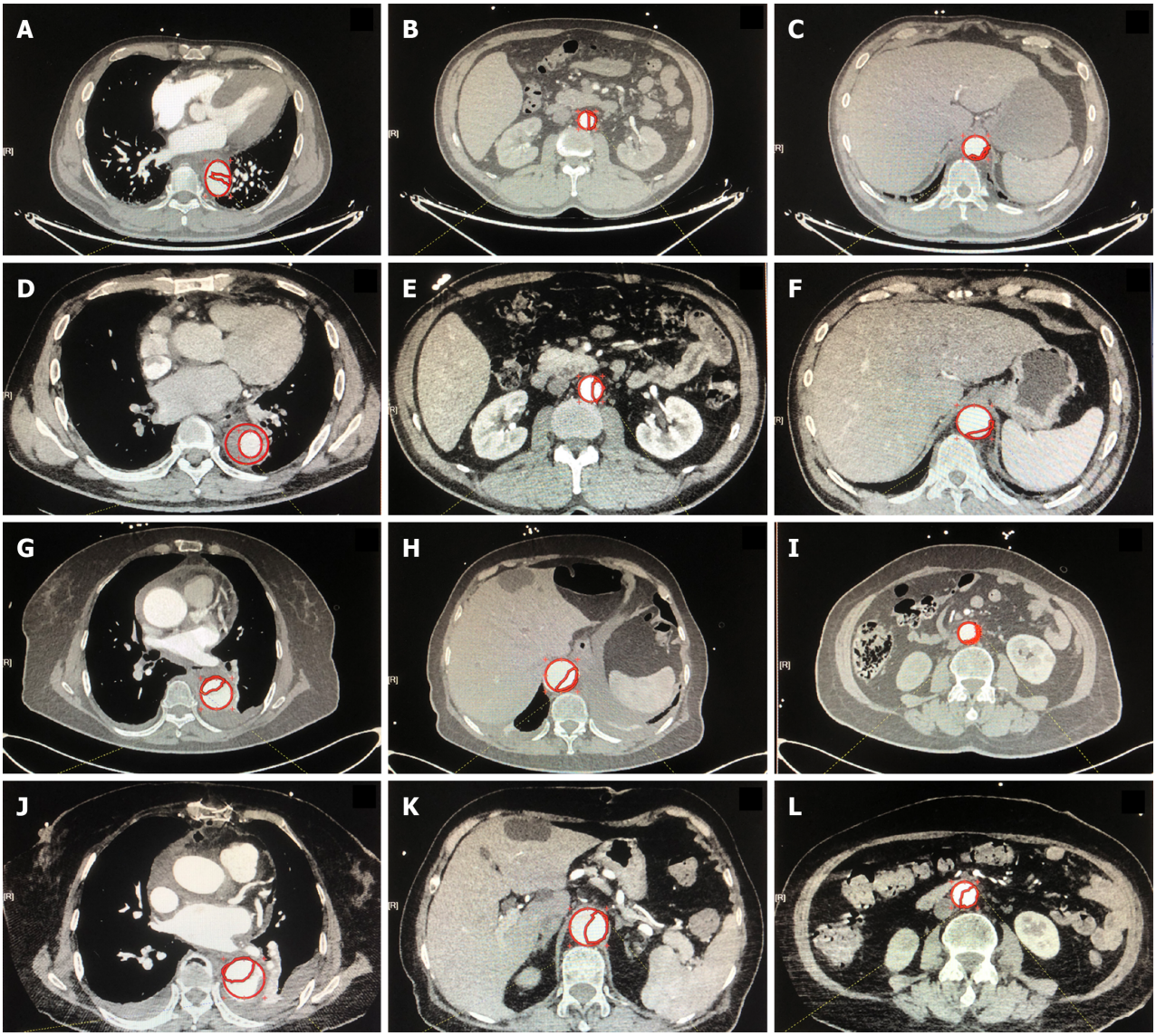

Figure 3 Typical preoperative and postoperative imaging for the false lumen area ratio in the descending aorta of the axillary artery and carotid artery groups by computed tomography angiography. A-F: Typical preoperative and postoperative imaging of the false lumen area ratio (FLAR) in S1 (A and D), S2 (B and E) and S3 (C and F) in the CA group; G-L: Typical preoperative and postoperative imaging of FLAR in S1 (G and J), S2 (H and K) and S3 (I and L) in the AA group. False lumen area was defined as the traced area of the whole aorta (full line) minus the traced area of the true lumen (dotted line). S1: Thoracic segment; S2: Upper abdominal segment; S3: Lower abdominal segment.

AA and FA mode. This occurs especially at the abdominal aortic segment, which usually experiences inferior remodeling after surgical repair of AAD.

Limitations

The main limitation of this study is its statistical reliability due to the single-center, retrospective study design. The CA approach was mostly utilized in the last four years, giving rise to selection bias. Another limitation was the lack of long-term follow-up for FLAR as a predictor of aortic remodeling. A longer follow-up period is therefore required to accumulate more meaningful data. Finally, FLAR was calculated based on CTA and was an independent predictor of hospitalized RRT events. This quantitative result was derived from the work of an experienced expert who gave a relatively precise evaluation after browsing the entire aorta. Calculation of the false lumen using deep learning-based reconstruction, or specialized software analysis of the irregular dissected aorta, may prove to be more accurate than manual analysis.

CONCLUSION

In patients undergoing AAD repair based on the FA cannulation strategy, we conclude the CA cannulation mode results in greater changes in FLAR in the S2 and S3 segments and a lower incidence of RRT compared with AA cannulation.

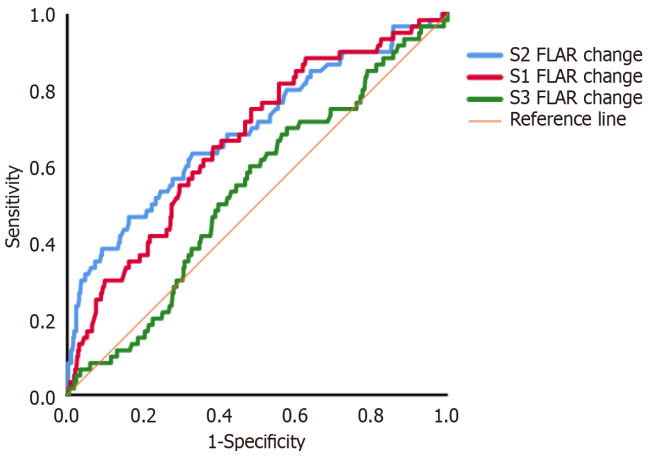

Figure 4 Receiver operating characteristic curve analysis of changes in the false lumen area ratio in segments of the descending aorta and the prediction of renal replacement therapy. The results of receiver operating characteristic curve analysis of the postoperative/preoperative false lumen area ratio (FLAR) for the prediction of renal replacement therapy were: S1, 0.668 (95%CI: 0.595-0.741, $P < 0.001$); S2, 0.693 (95%CI: 0.615-0.771, $P < 0.001$); and S3, 0.535 (95%CI: 0.459-0.610, $P = 0.387$). S1: Thoracic segment; S2: Upper abdominal segment; S3: Lower abdominal segment.

Computational fluid dynamics should be used in future research to investigate how FLAR improvement is associated with the beneficial outcomes associated with bilateral CA and FA cannulation.

FOOTNOTES

Author contributions: Jiang Q, Huang KL, and Hu SS designed the research study; Yu T, Liu K, and Li X preformed the research; all authors analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript

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ORIGINAL ARTICLE

Retrospective Cohort Study

Percutaneous decannulation of extracorporeal membrane oxygenation using MANTA device: A real-world single-center experience

Ioannis Milioglou, Alice Qian, Pedro Rafael Vieira de Oliveira Salerno, Gabriel Tensol Rodrigues Pereira, Luis Augusto Palma Dallan, Kelsey E Gray, Michael Morrison, Yasir Abu-Omar, Mohammad Eldiasty, Cristian Baeza

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Abstract

BACKGROUND

The MANTA vascular closure device (VCD) represents a novel approach to achieving hemostasis after large-bore femoral access procedures. Numerous clinical studies have evaluated the efficacy of the MANTA device across a range of patient populations undergoing different procedures. However, there is still a paucity of data available concerning the use of MANTA devices in aiding the decannulation of venoarterial extracorporeal membrane oxygenation (VA-ECMO).

AIM

To present our single-center experience of utilizing the MANTA VCD in patients undergoing this procedure.

METHODS

This single-center study included all patients undergoing percutaneous decannulation of femoral VA-ECMO using the MANTA plug-based VCD between January 2021 and October 2023 at University Hospitals Cleveland Medical Center. Inclusion criteria were adult patients who required prolonged (> 24 hours) hemodynamic support with VA-ECMO. Outcomes included all-cause mortality, hemostasis, bleeding, limb ischemia, and site infection.

RESULTS

This is a retrospective cohort study of 19 patients with a mean age of 56.8 years. Twelve of them were males with a mean body mass index of 29. The most common extracorporeal membrane oxygenation indication was acute coronary syndrome complicated by cardiogenic shock at 36.8%. The mean length of intensive care unit stay for these patients was 18.8 ± 8.42 days. Seventeen out of 19 patients survived to discharge. The MANTA device was successfully deployed in 19 patients, with 10 procedures conducted at the bedside and 9 in an operating room setting. Complete hemostasis was achieved within 5 minutes of MANTA deployment in 17 out of 19 patients. In 2 patients manual compression after Manta deployment was required to achieve adequate hemostasis. Additionally, acute lower extremity ischemia was noted in two patients, necessitating endovascular interventions. No infections were reported at the site of MANTA deployment.

CONCLUSION

Overall, based on our experience and that of other centers, the MANTA VCD has proven to be a simple, safe, and effective percutaneous technique for facilitating in the OR, but most of all it opens the opportunity for bedside VA-ECMO decannulation. Post-decannulation ischemic complications are higher in this series of sick patients when compared with elective procedures like transcatheter aortic valve replacement and endovascular aneurysm repair. Additionally, operators should be mindful of the incidence of ischemic complications. Distal Doppler pulse signals should always be checked, to indicate bailout options when this occurs.

Key Words: Extracorporeal membrane oxygenation; MANTA; Decannulation; Hemostasis; Ischemia

Core Tip: The MANTA vascular closure device offers a novel approach to achieving hemostasis after large-bore femoral access procedures, particularly in complex interventions like transcatheter aortic valve replacement and endovascular aneurysm repair. This single-center study assessed the use of MANTA for percutaneous decannulation in 19 patients undergoing venoarterial extracorporeal membrane oxygenation. The device achieved rapid hemostasis in most cases, though some patients experienced late bleeding or ischemic complications. Despite these challenges, MANTA allowed for bedside decannulation, reducing the need for operating room resources. While promising, the study's small size and lack of a comparison group suggest that further research is needed to validate these findings.

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INTRODUCTION

The MANTA vascular closure device (VCD) represents a novel approach to achieving hemostasis after large-bore femoral access procedures. Its development addresses the need for effective closure devices in the era of complex percutaneous interventions, such as transcatheter aortic valve replacement (TAVR) and endovascular aneurysm repair (EVAR). The MANTA VCD is designed to achieve rapid and reliable closure of large arteriotomies, up to 24 French. Numerous clinical studies have evaluated the efficacy of the MANTA device across a range of patient populations undergoing different procedures[1,2].

However, there is still a paucity of data available concerning the use of MANTA devices in aiding the decannulation of venoarterial extracorporeal membrane oxygenation (VA-ECMO). This is particularly important because VA-ECMO standard cut-down decannulation is often troubled due to vascular injury, including significant, hard-to-control bleeding due to further vessel damage. There is also a significant risk of post-decannulation complications like groin hematomas, infection, lymphoceles, and others. In a recent study, major vascular complications were seen in 72/432 patients (16.7%) undergoing VA-ECMO decannulation with a conventional technique[3]. Therefore, considering the potential advantages of using the MANTA VCD and the limited data available regarding its application in VA-ECMO decannulation, our study aims to present our single-center experience of utilizing the MANTA VCD in patients undergoing this procedure.

MATERIALS AND METHODS

This single-center study included all patients undergoing percutaneous decannulation of femoral VA-ECMO using the MANTA plug-based VCD between January 2021 and October 2023 at University Hospitals Cleveland Medical Center in

Cleveland, Ohio, United States. Inclusion criteria were adult patients who required prolonged (> 24 hours) hemodynamic support with VA-ECMO. Demographics, preprocedural, procedural, and postprocedural data with a focus on femoral artery complications were retrospectively collected from medical charts using RedCap software. All statistical analyses were performed on R platform. IRB approval was obtained for the conduction of this study.

Decannulation and vessel closure technique: Once the ECMO circuit was disconnected, the arterial cannula was clamped and cut leaving about 5 centimeters length distal to the clamp. Using 3 medium size tegaderms at the distal end of the cannula, a water-sealed membrane was created. The clamp was removed and then an 18 G needle was used to perforate the tegaderm membrane to push the guide wire inside the artery. To avoid complications and follow the device instructions for use, a pre-deployment depth measurement is necessary to ensure the plate is inside the vessel but not too deep into the vessel lumen so other complications are avoided. For obvious reasons, in this situation, this cannot be achieved so we used a standard 8 centimeters depth. This was decided based on our own experience using Manta on elective cases. None of those cases were above 8 centimeters in depth. Once the wire was secured inside the artery, the cannula was removed holding manual compression while the Manta sheath was pushed over the wire. Subsequently, the insert piece was removed from the sheath and the closure unit was inserted. The toggle was then released, the assembly component was withdrawn, and the collagen pad was secured onto the anterior arterial wall using the stainless-steel lock.

RESULTS

This is a retrospective cohort study of 19 patients in which the MANTA device was utilized during decannulation from VA-ECMO. The mean age of these patients was 56.8 years (± 13.6), 12 were male (63.2%) and the body mass index was 29.0 (± 5.43). Baseline characteristics and pre-decannulation labs are shown in Table 1. The most common ECMO indication was acute coronary syndrome complicated by cardiogenic shock at 36.8%, followed by cardiac arrest and decompensated heart failure with reduced ejection fraction complicated by cardiogenic shock, each at 21.1%. The mean length of intensive care unit (ICU) stay for these patients was 18.8 (± 8.42) days. The 18 Fr MANTA device was used for most of the patients, especially given the larger size of the arterial cannulas as shown in Table 1. All patients received distal perfusion catheters at initial VA-ECMO cannulation. Seventeen out of 19 patients survived to discharge. The MANTA device was successfully deployed in 19 patients, with 10 procedures conducted at the bedside and 9 in an operating room setting. Complete hemostasis was achieved within 5 minutes of MANTA deployment in 17 out of 19 patients (Table 2). In 2 patients, manual compression after Manta deployment was required to achieve adequate hemostasis. We had 2 patients with late bleeding after 24 hours post-decannulation and before discharge; both were managed conservatively. There were no significant post-deployment bleeding events observed until discharge. Additionally, acute lower extremity ischemia was noted in two patients, necessitating endovascular interventions. No infections were reported at the site of MANTA deployment.

DISCUSSION

This is a single-center, retrospective review of the results using a MANTA VCD closure device for trans-femoral VA-ECMO decannulation. The initial findings are consistent with other retrospective studies and meta-analyses regarding its use in VA-ECMO decannulation. Most of the current data on MANTA's use in VA-ECMO decannulation come from observational studies, as the major randomized controlled trials (RCTs) reporting outcomes on MANTA's safety and efficacy are focused on transcatheter aortic valve intervention (TAVI) and EVAR procedures[4]. These results cannot be extrapolated to our results since this is an entirely different patient population, situation, and scenario. The patients are sicker and the groins are considered as “hostiles” since the vessels have been cannulated for more than a week. Regarding hemostasis, the MANTA device has demonstrated a similarly safe profile regardless of the indication for its use (TAVI *vs* VA-ECMO). VA-ECMO decannulation with MANTA has resulted in a higher incidence of ischemic complications, necessitating endovascular limb salvage procedures which is consistent with the literature, however, these complications can be easily related to the previous vessel damage than the actual use of the closure device[5]. Our results show that when a patient is ready to be decannulated, they have been in the ICU sedated and connected to mechanical ventilation for a week or more. On top of that, they are usually fluid-overloaded with some degree of edema and hematoma around the cannulation area. This scenario makes a standard cut-down decannulation extremely difficult, it requires patient transportation and mobilization which always represent a major risk. It also requires an operating room setting. Essentially, this is a group of extremely sick patients; many of them were cannulated in very suboptimal conditions due to acute decompensation or definitely in the middle of cardiopulmonary ressuscitation maneuvers. It is crucial to note that all ischemic complications are usually associated with this kind of very challenging cannulation situation. Using the MANTA closure device for a bedside procedure becomes very useful when it comes to mobilizing these patients and requires a very limited resource like an operating room. Additionally, Manta device deployment requires an accurate depth measurement which was not possible to be performed in this series. We do not think this played a role in our results, but it is a factor to be considered. In theory, prolonged VA-ECMO cannula stays in critically ill ICU patients can also make the arteriotomy edges less elastic and more prone to complications[6]. While studies have compared other VCDs (*e.g.*, Proglide) with MANTA for VA-ECMO decannulation without significant differences in complication rates and hemostasis success, operators must consider the potential future need for re-accessing the same vessel since suture-based VCDs demonstrate a better profile in this regard, as the MANTA plug requires approximately 6 months to be fully reabsorbed[7].

Table 1 Baseline and per-procedural characteristics of patients undergoing venoarterial extracorporeal membrane oxygenation decannulation with MANTA vascular closure device

Items	Overall (*n* = 19)
Age (years)	
Mean (SD)	56.8 (13.6)
Median (Min, Max)	56.0 (31.0, 83.0)
Sex, *n* (%)	
Male	12 (63.2)
Female	7 (36.8)
BMI	
Mean (SD)	29.0 (5.43)
Median (Min, Max)	29.0 (19.1, 42.6)
Smoking, *n* (%)	
Never	11 (57.9)
Former	4 (21.1)
Active	4 (21.1)
HTN, *n* (%)	
Yes	11 (57.9)
No	8 (42.1)
Diabetes, *n* (%)	
Yes	8 (42.1)
No	11 (57.9)
CAD, *n* (%)	
Yes	15 (78.9)
No	4 (21.1)
Total duration of ECMO (days)	
Mean (SD)	6.79 (4.20)
Median (Min, Max)	5.00 (2.00, 20.0)
ECMO indication, *n* (%)	
ACS	7 (36.8)
Cardiac arrest	4 (21.1)
Cardiogenic shock	4 (21.1)
Postcardiotomy	2 (10.5)
TAVI	2 (10.5)
Length of ICU stay (days)	
Mean (SD)	18.8 (8.42)
Median (Min, Max)	19.0 (5.00, 43.0)
Arterial cannula size (Fr), *n* (%)	
17	9 (47.4)
18	1 (5.3)
19	8 (42.1)
21	1 (5.3)
Manta size (Fr), *n* (%)	

14	2 (10.5)
18	17 (89.5)
Hb prior to decanulation	
Mean (SD)	8.85 (1.12)
Median (Min, Max)	8.50 (7.50, 12.5)
Platelets prior to decanualtion	
Mean (SD)	106 (67.9)
Median (Min, Max)	90.0 (38.0, 336)
INR prior to decanulation	
Mean (SD)	1.23 (0.338)
Median (Min, Max)	1.20 (0.900, 2.50)

BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; ECMO: Extracorporeal membrane oxygenation; ACS: Acute coronary syndrome; ICU: Intensive care unit; Hb: Hemoglobin; INR: International normalized ratio.

Table 2 Outcomes of MANTA vascular closure device post venoarterial extracorporeal membrane oxygenation decannulation, *n* (%)

Items	Overall (*n* = 19)
Survival to discharge	
Yes	16 (84.2)
No	3 (15.8)
Additional closure method	
None	17 (89.5)
Manual pressure	2 (10.5)
Bleeding	
No	17 (89.5)
Yes	2 (10.5)
Bleeding based on BARC	
No Bleeding	17 (89.5)
Type 1	0 (0)
Type 2	1 (5.3)
Type 3	1 (5.3)
Type 4	0 (0)
Type 5	0 (0)
Limb Ischemia post MANTA	
No	17 (89.5)
Yes	2 (10.5)

BARC: Bleeding academic research consortium.

This study has certain limitations, including its reliance on our single-center experience and the small number of reported patients, as well as the lack of a comparison group. Although our data aligns with other retrospective studies, more robust conclusions could be drawn from larger RCTs. Notably, calcification of the anterior femoral wall, which can be an independent risk factor for post-deployment complications, was not recorded in our study.

CONCLUSION

Overall, based on our experience and that of other centers, the MANTA VCD has proven to be a simple, safe, and effective percutaneous technique for facilitating in the OR, but most of all it opens the opportunity for bedside VA-ECMO decannulation. Post-decannulation ischemic complications are higher in this series of sick patients when compared with elective procedures like TAVR and EVAR. The crucial deployment step is to make sure the plate is inside of the vessel which was accomplished in this subset of patients by using 8 cm depth as a standard. Additionally, operators should be mindful of the incidence of ischemic complications. Distal Doppler pulse signals should always be checked, to indicate bailout options when this occurs.

FOOTNOTES

Author contributions: Milioglou I, Qian A, Salerno PRVO and Pereira GTR gathered and analyzed data; Milioglou I and Qian A contributed to the writing of the manuscript; Palma Dallan LA, Gray KE, Morrison M helped with the supervision of data analysis and gathering; Abu-Omar Y, Eldiasty M and Baeza C were responsible for the overall supervision of all steps of this research project.

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ORIGINAL ARTICLE

Observational Study

Metabolic dysfunction-associated steatotic liver disease-associated fibrosis and cardiac dysfunction in patients with type 2 diabetes

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Abstract

BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in the presence of liver fibrosis, increases the risk of cardiovascular morbidity and mortality, but the nature of the cardio-hepatic interaction in the context type 2 diabetes mellitus (T2DM) is not fully understood.

AIM
To evaluate the changes in cardiac morphology and function in patients with T2DM and MASLD-associated liver fibrosis.

METHODS
T2DM patients with MASLD underwent a medical evaluation that included an assessment of lifestyle, anthropometric measurements, vital signs, an extensive laboratory panel, and a standard echocardiography. Liver fibrosis was evaluated using two scores [Fibrosis-4 (FIB4) and Non-alcoholic fatty liver disease-Fibrosis Score (NFS)], and subjects were classified as having advanced fibrosis, no fibrosis, or an indeterminate risk. The correlations between structural and functional cardiac parameters and markers of liver fibrosis were evaluated through bivariate and multiple regression analyses. Statistical significance was set at $P < 0.05$.

RESULTS
Data from 267 T2DM-MASLD subjects with complete assessment was analyzed. Patients with scores indicating advanced fibrosis exhibited higher interventricular septum and left ventricular (LV) posterior wall thickness, atrial diameters, LV end-systolic volume, LV mass index (LVMi), and epicardial adipose tissue thickness (EATT). Their mean ejection fraction (EF) was significantly lower (49.19% ± 5.62% *vs* 50.87% ± 5.14% *vs* 52.00% ± 3.25%; $P = 0.003$), and a smaller proportion had an EF ≥ 50% (49.40% *vs* 68.90% *vs* 84.21%; $P = 0.0017$). Their total and mid LV wall motion score indexes were higher ($P < 0.05$). Additionally, they had markers of diastolic dysfunction, with a higher E/e' ratio [9.64 ± 4.10 *vs* 8.44 (2.43-26.33) *vs* 7.35 ± 2.62; $P = 0.026$], and over 70% had lateral e' values < 10 cm/second, though without significant differences between groups. In multiple regression analyses, FIB4 correlated with left atrium diameter (LAD; $\beta = 0.044$; $P < 0.05$), and NFS with both LAD ($\beta = 0.039$; $P < 0.05$) and right atrium diameter ($\beta = 0.041$; $P < 0.01$), Moreover, LVMi correlated positively with age and EATT ($\beta = 1.997$; $P = 0.0008$), and negatively with serum sex-hormone binding protein (SHBP) concentrations ($\beta = -0.280$; $P = 0.004$). SHBP also correlated negatively with LAD ($\beta = -0.036$; $P < 0.05$).

CONCLUSION
T2DM patients with markers of MASLD-related liver fibrosis exhibit lower EF and present indicators of diastolic dysfunction and cardiac hypertrophy. Additionally, LVMi and LAD correlated negatively with serum SHBP concentrations.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Type 2 diabetes mellitus; Liver fibrosis; Cardiac dysfunction; Sex-hormone binding protein

Core Tip: Metabolic dysfunction-associated steatotic liver disease (MASLD) is frequently associated with type 2 diabetes mellitus (T2DM), and both conditions are important risk factors for cardiovascular disease. However, the nature of the cardio-liver interaction, particularly in patients with T2DM, is not completely elucidated. In this study we found that T2DM patients with MASLD-associated fibrosis, quantified by accessible scores (Fibrosis-4 and Non-alcoholic fatty liver disease-Fibrosis Score), present markers of systolic and diastolic dysfunction, as well as cardiac hypertrophy, particularly increased left atrial diameter. The left ventricular mass index and left atrial dimension also correlated negatively with serum concentrations of sex-hormone binding protein, which may serve as a valuable prognostic biomarker. Mechanistic studies that explain the correlations between liver fibrosis and cardiac remodeling in MASLD patients, both with and without T2DM, are greatly needed.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined by the presence of hepatic steatosis in combination with at least one cardiometabolic risk factor, without other causes of steatotic liver disease[1]. It encompasses a spectrum of conditions from simple hepatic steatosis to steatohepatitis (which may involve varying degrees of fibrosis, from mild to severe/cirrhosis), and to hepatocellular carcinoma[1,2].

A core pathogenetic mechanism of MASLD is insulin resistance, which implies a cross-talk between the liver and peripheral tissues, favoring the accumulation of lipids in the liver[3,4]. In fact, MASLD is considered part of a multi-systemic disease, alongside other components of metabolic syndrome [*i.e.*, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, hypertension], for which insulin resistance is a key pathogenetic factor[5,6]. The relationship between T2DM and MASLD is bidirectional[6]. Literature data indicates that MASLD doubles the risk of T2DM, and the severity of hepatic fibrosis is independently correlated with a higher risk of incident diabetes[7,8]. On the other hand, T2DM increases the risk of MASLD by approximately two-fold and worsens the course of the disease toward more advanced stages (*i.e.*, advanced fibrosis/cirrhosis, hepatocellular carcinoma, liver-related hospitalizations, and deaths)[6,9-11].

Moreover, MASLD significantly increases the risk of cardiovascular disease (CVD) and mortality in both individuals with and without T2DM, independent of other risk factors[12-15]. In patients with T2DM, the presence of MASLD nearly doubles the risk of CVD, suggesting potential synergistic effects of these two conditions on cardiovascular risk[13,16]. The presence of MASLD in hospitalized patients with CVD significantly raises the risk of all-cause mortality [hazard ratio (HR): 2.08; 95% confidence interval (95%CI): 1.56-2.59, $P < 0.001$][17]. Furthermore, the severity of MASLD fibrosis is associated with a higher risk of overall mortality [unadjusted relative risk for stage F0 *vs* F4: 3.42 (95%CI: 2.63-4.46); adjusted HR for stage F0-2 *vs* F3-4: 2.24 (95%CI: 1.48-3.39)][18]. Emerging evidence also suggests that the severity of liver fibrosis has a significant impact on the risk of fatal or non-fatal CVD events, independent of other cardiometabolic risk factors [pooled random-effects HR: 2.50 (95%CI: 1.68-3.72)][15].

Nevertheless, the nature of the relationship between liver fibrosis and CVD, particularly in the context of T2DM, is not entirely clear, as the coexistence of other cardiovascular risk factors complicates the deciphering of the independent contributions of each condition to the incidence and progression of the other. Some authors even question the causal link between MASLD and CVD[19]. On the other hand, some data suggest that markers of CVD (such as carotid intima-media thickness) may predict liver fibrosis in MASLD patients with T2DM[20]. Therefore, understanding the nature of these associations is important, as early screening and intervention for one disease may potentially ameliorate the progression of the other. However, few studies have investigated the relationship between liver fibrosis and cardiac morphology and function in patients with T2DM. One study showed that liver fibrosis was independently associated with diastolic dysfunction [odds ratio (OR): 1.58 (95%CI: 1.07-2.34, $P = 0.022$), while another reported an association with subclinical myocardial remodeling in T2DM subjects[21,22].

The aim of this study was to evaluate cardiac morphology and function in relation to markers of liver fibrosis in T2DM patients with MASLD.

MATERIALS AND METHODS

Study population and data collection

The study enrolled patients with T2DM and NAFLD in the Outpatient Unit of the Emergency County Clinical Hospital of Târgu Mureș, Romania between July 2022 and July 2023. Patients were recruited from the Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, and the Gastroenterology Department of the County Clinical Hospital, Târgu Mureș. Inclusion criteria were as follows: Adult subjects aged 30 years or older, with a previous diagnosis of T2DM and NAFLD (based on patient history and liver ultrasound). NAFLD was defined by the presence of hepatic steatosis/steatohepatitis in the absence of other secondary causes of liver disease (including viral or autoimmune hepatitis, excessive alcohol intake of ≥ 30 g/day for men and ≥ 20 g/day for women, specific drugs, toxins, hemochromatosis, Wilson's disease or other known specific liver diseases). In July 2023, the term MASLD was proposed to replace NAFLD to better describe and classify the steatotic liver disease, potentially reducing stigma[23]. This new term was largely adopted thereafter, and emerging evidence indicates that the term MASLD can be used interchangeably with NAFLD[24]. Since our patients met the diagnostic criteria for MASLD (*i.e.*, had liver steatosis and at least one cardiometabolic risk factor, T2DM), we adopted the new term to describe their liver condition. Exclusion criteria for this study included other types of diabetes, other chronic liver diseases (including liver transplant), malignant diseases in the last 5 years, severe autoimmune diseases, severe valvulopathy, and significant pericardial collections. The study was approved by the Ethics Committees of the Emergency County Clinical Hospital of Târgu Mureș (nr. 8120/05.04.2022), the County Clinical Hospital of Târgu Mureș (nr. 4873/24.05.2022), and the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (nr. 1806/22.06.2022). All subjects signed an informed consent before being enrolled in the study.

The following data were collected: Demographic data, medical history (including therapy), lifestyle data (diet, coffee, tea and alcohol intake, physical exercise, sleep, smoking, stress) through general or specific questionnaires. Alcohol consumption was assessed using both a general questionnaire with secondary interview, and the AUDIT-C test. Anthropometric parameters (weight, height, waist circumference, hip circumference), heart rate, and blood pressure were measured using standard methods. The body mass index (BMI) was calculated as follows: Weight/height^2 (kg/m^2). The pO_2 was measured under standard conditions using a pulse oximeter.

Laboratory assessment

On the same day, fasting blood samples were collected between 7: 45 AM and 8: 15 AM, and serum aliquots were stored at -80 °C for subsequent analysis of the following parameters: Blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, C-peptide, uric acid, creatinine, sex-hormone binding protein (SHBP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT), direct bilirubin, albumin, ferritin, and haptoglobin. Blood for HbA1c measurement was drawn on the same occasion and stored at -80 °C for up to three months for later measurement. The biochemical tests were analyzed using a

Cobas Integra 400plus (Roche Diagnostics, Germany). Albumin, haptoglobin, and HbA1c were measured using an immunoturbidimetric method, while uric acid, ASAT, ALAT, direct bilirubin, GGT, creatinine, glucose, and lipids were measured using a spectrophotometric method. C-peptide, ferritin and SHBP were analyzed on the Immulite 2000 XPI system (Siemens) using a solid-phase, two-site chemiluminescent immunometric assay. The complete blood count was analyzed shortly after the blood was drawn using a 5-differential hematology Mindray BC6200 analyzer. The Homeostatic Model Assessment (HOMA) for Insulin Resistance (HOMA-IR) was calculated by using the HOMA calculator version 2.2.3[25]. The estimated glomerular filtration rate (eGFR) was calculated based on the CKD-EPI 2021 formula[26].

The hepatic fibrosis was estimated using two well-known and validated indices. The fibrosis-4 (FIB4) score was calculated using the formula: Age (years) × ASAT (U/L)/[platelet (10^9/L) × ALT$^{1/2}$ (U/L)]. A FIB4 score < 1.3 rules out advanced fibrosis, a score > 2.67 indicates advanced fibrosis (F ≥ 2), while FIB4 values between 1.3 and 2.67 are considered to be indeterminate risk[27]. The NAFLD-Fibrosis Score (NFS) was calculated with the following formula: -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired glucose tolerance/diabetes (yes = 1; no = 0) + 0.99 × ASAT/ALAT - 0.013 × platelet (× 10^9/L) - 0.66 × albumin (g/dL). Values > 0.676 indicate significant liver fibrosis (> F2), scores < -1.455 indicate no significant fibrosis, while values between -1.455 and 0.676 are considered undetermined[28].

Echocardiographic assessment

The echocardiographic evaluation was performed on a subsequent day (within a 2-3 weeks interval) by an experienced cardiologist who was blinded to all other aspects of the study. The ultrasonographic assessment was conducted using a VIVID9 XDClear equipment (GE HealthCare). The quantification of cardiac chamber sizes and function was carried out in accordance with the recommendations of the ASE/EAC Guidelines[29].

The left ventricular (LV) ejection fraction (EF) was evaluated using the modified Simpson's rule calculated by dividing the stroke volume by the end-diastolic LV volume. An EF was considered normal if the values were ≥ 50%[30]. The dimensions of the ventricles and atria, as well as the epicardial adipose tissue thickness (EATT), were measured in the parasternal long-axis view. The LV end-diastolic and end-systolic volumes were measured using 2D echocardiography in the apical 4-chamber view and 2-chamber view at the end of diastole and systole.

The LV mass (LVM) was calculated using the following formula: LVM (g) = 0.80 × [1.04 × (PWd (cm)+ IVSd (cm) + LVDd (cm))^3 - (LVDd (cm))^3] + 0.6, where 1.04 is the density of heart muscle (g/cm^3), PWd is the LV posterior wall thickness at end-diastole, IVSd is the interventricular (IV) septum thickness at end-diastole, and LVDd is the LV end-diastolic dimension[29,31]. The LVM was indexed to the body surface area [LVM index (LVMi)] calculated using the DuBois formula[29,32]. The upper limits for normal values of LVMi were considered to be 95 g/m^2 in women and 115 g/m^2 in men[29].

The LV outflow tract (LVOT) velocity time integral was determined in the apical 5-chamber view using the pulsed-wave Doppler technique, with the pulse wave Doppler gate positioned at the LVOT level. Using the same technique in the apical 4-chamber view, the following parameters were determined on the Doppler curve: Maximum velocities of the E wave, A wave, e' septal, e' lateral, a' septal, a' lateral, and deceleration time (DcT). The E/A ratio e'/a' septal, and e'/a' lateral ratios were calculated. The average E/e' ratio was calculated as the ratio of E to the average e' (mean of e' septal and e' lateral).

Regional LV function was assessed in a 17-segment model. The basal and midventricular segments included anterior, anterolateral, anteroseptal, inferior, inferolateral, and inferoseptal segments, while the apical segments included anterior, septal, inferior, lateral, and the ''apical cap (apex)'' (myocardium beyond the end of the LV cavity)[29]. Total and segmental kinetics scores were calculated by assigning points according to the following grading: 1 point for normal kinetics; 2 points for hypokinesia, 3 points for akinesia. Total and segmental wall motion score indexes were calculated by dividing the wall motion scores by the number of segments.

Statistical analysis

Descriptive statistics were performed for all variables, and the normality of the data was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as the mean ± SD, while non-normally distributed variables are presented as median (min-max). Categorical variables are presented as frequency (%). Comparisons between groups were conducted using one-way ANOVA with Tukey post-test for normally distributed variables or Kruskal-Wallis test with Dunn post-test for non-normally distributed variables. The χ^2 test was employed to analyze categorical variables. The relationship between two variables of interest was investigated using Spearman's test, with data presented as correlation coefficients r (95%CI). Multiple regression analyses for more than two variables were employed to test the independent associations between liver fibrosis scores and cardiac parameters, as well as to evaluate the impact of independent variables on various echocardiographic parameters of interest. Statistical analyses were performed using GraphPad InStat 3 (GraphPad Software, United States). All tests were two-tailed, and statistical significance was assumed at $P < 0.05$.

RESULTS

In this study 278 T2DM patients with MASLD were enrolled. Of these, seven patients met the exclusion criteria, and four did not return for the cardiac ultrasound evaluation. Ultimately, data from 267 T2DM-MASLD patients were analyzed. The median age of the participants was 66 (36-82) years, and the median duration of diabetes was 10 (0-33) years. Of the total cohort, 45.32% were men, 76.40% lived in urban areas, 22.84% were employed, and 75.28% were retired. Their relevant medical history, lifestyle and other clinical characteristics are presented in Table 1.

Table 1 Lifestyle and clinical characteristics of the study population

Patients' characteristics	Value
Systolic/diastolic BP (mmHg)	135.0 (95.0-190.0)/80.0 (51.0-107.5)
Heart rate (beats/min)	74.0 (50.0-112.0)
pO_2 (%)	97.0 (90.0-99.0)
Lifestyle	
Smoking status	
Current smoker	28 (10.49)
Former smoker	107 (40.07)
Never smoked	132 (49.44)
Coffee intake (cups/day)	1.25 ± 0.80
Alcohol intake (g/day)	2.85± 5.37
Anthropometric parameters	
BMI (kg/m^2)	34.11 ± 5.30
Waist circumference (cm)	109.16 ± 11.72 (F)
	114.92 ± 10.83 (M)
Hip circumference (cm)	110.21 ± 10.55 (F)
	108.86 ± 9.98 (M)
Comorbidities	
Hypertension	251 (94.00)
Dyslipidemia	247 (92.51)
Coronary artery disease	137 (51.31)
Heart failure	99 (37.01)
Atrial fibrillation	17 (6.37)
Peripheral arterial disease	18 (6.74)
Stroke	19 (7.11)
Diabetic neuropathy	106 (39.70)
Diabetic retinopathy	36 (13.48)
Chronic kidney disease	49 (18.35)
Hyperuricemia	58 (21.72)
Antihyperglycemic therapy	
Metformin	262 (98.13)
GLP-1 RA	85 (31.83)
SGLT2 inhibitors	62 (23.22)
DPP-4 inhibitors	19 (7.12)
Sulphonylureas	27 (10.11)
Insulin	66 (24.72)

Data are presented as mean ± SD, median (min-max), or as *n* (%). BP: Blood pressure; F: Female; M: Male; BMI: Body mass index; GLP-1 RA: Glucagon-like peptide-1 receptor agonists; SGLT2: Sodium-glucose co-transporter 2; DPP-4: Dipeptidyl peptidase-4.

The median FIB4 value was 1.35 (0.4-17.3), and median NFS was 0.159 (-2.783 to 6.212). One FIB4 value was a significant outlier (134.15) and was excluded from further analysis. Among the study population, 11.2% had a FIB4 score > 2.67 suggesting advanced liver fibrosis, 44.2% had a FIB4 score between 1.3-2.67 (indicating an indeterminate risk of

advanced fibrosis) and 44.6% had a FIB4 score < 1.3 (which rules out significant fibrosis). Regarding the NFS, 31.8% of subjects had a score > 0.676 indicating advanced liver fibrosis, 61% had a score between 0.676 and -1.455 (undetermined risk of liver fibrosis), while 7.1% had NFS values < -1.455, which excludes fibrosis.

Correlation between markers of liver fibrosis and heart morphology and function

To ensure a proper selection of patients in the advanced fibrosis and no fibrosis categories, we divided the study population into three groups according to the two liver fibrosis scores: Group 1 consisted of patients with both FIB4 > 2.67 and NFS > -1.455 or both NFS > 0.676 and FIB4 > 1.3 [suggestive of significant (or advanced) fibrosis], Group 3 included patients with both FIB4 < 1.3 and NFS < -1.455 (indicating no significant fibrosis, F0-1), and Group 2, included the remaining subjects (with indeterminate risk of advanced fibrosis). The laboratory data are shown according to the liver fibrosis categories in Table 2. Subjects with more advanced hepatic fibrosis exhibited higher markers of liver injury, as well as increased insulin resistance, uric acid and triglyceride levels, and lower LDL cholesterol and eGFR values. There was no significant difference among the three groups in terms of the proportion of patients receiving therapy with glucagon-like peptide-1 receptor agonists (GLP-1 RA) and/or sodium-glucose co-transporter 2 (SGLT2) inhibitors (47.6% *vs* 48.8% *vs* 52.6%, $P = 0.9244$).

We first analyzed the ultrasound cardiac parameters evaluating the heart function and structure according to the liver fibrosis category (Table 3). The E, A and DcT were not measured in patients with atrial fibrillation, as this condition alters atrial filling. T2DM patients with MASLD and advanced liver fibrosis had significantly higher LVMi, left and right atrial diameters, IV septum thickness, and LV posterior wall thickness, LV end-systolic volume, and EATT. For other measurements of the LV, a similar trend was observed, but it did not reach statistical significance.

Moreover, patients with markers of advanced liver fibrosis had significantly lower EF (Figure 1A), and higher E/e' septal, as well as higher total a LV wall motion score index (mainly due to higher mid-ventricular wall motion scores), indicative of cardiac dysfunction and dyskinesia (Table 3 and Figure 1B). A higher proportion of T2DM patients with more advanced liver fibrosis had decreased EF (50.6% *vs* 31.1% *vs* 15.8%; $P_{trend} = 0.0004$; Figure 1C and Table 3).

Additionally, over half of the patients in each liver fibrosis category had increased LVMi values, with a slightly higher percentage in the advanced fibrosis group; however, the difference between the three groups was not significant (overall prevalence: 61.65%; Table 3). Moreover, a large proportion of patients in all three groups presented lateral e' values < 10 cm/second, indicative of LV diastolic dysfunction, but the differences between groups were not significant (65.79% in group 1 *vs* 72.84% in group 2 *vs* 70.59% in group 3; $P = 0.5384$). Higher percentages of patients in the advanced liver fibrosis and indeterminate risk of fibrosis groups presented e' septal values < 7 cm/second compared to the no liver fibrosis group, but the differences were not statistically significant (19.74% in group 1 *vs* 19.75% in group 2 *vs* 5.56% in group 3; $P = 0.3308$).

We further investigated the correlation between markers of liver fibrosis (using both FIB4 and NFS) and cardiac parameters by performing bivariate correlation and multiple regression analyses. The bivariate analyses indicated an association between markers of liver fibrosis and cardiac hypertrophy (mainly LVMi and atrial diameters), and dysfunction (primarily EF and LV kinetics score; Table 4 and Table 5). FIB4 also correlated positively with the mid and apical LV segmental kinetics scores [$r = 0.14$ (0.02; 0.26), and $r = 0.12$ (-0.002; 0.24), $P < 0.05$ for both]. A similar association was found for NFS [$r = 0.15$ (0.02; 0.27), $P < 0.05$, and $r = 0.18$ (0.06; 0.30), $P < 0.01$]. The cardiac parameters not mentioned in the table did not correlate with either of the fibrosis scores.

In the multiple regression analyses, atrial dimensions were independently associated with liver fibrosis markers. In model 1, which adjusted for several independent variables (sex, smoking status, systolic blood pressure, duration of diabetes, alcohol intake, presence of atrial fibrillation, serum creatinine), both FIB4 and NFS were independently associated with left atrium diameter (LAD; FIB4: $R^2 = 7.77\%$, $P = 0.0221$; NFS: $R^2 = 15.03\%$; $P < 0.0001$; Table 5). In model 2, which included cardiac parameters, as well as serum creatinine, C-peptide and LDL cholesterol values (correlated with both FIB4 and NFS in the bivariate analyses) as independent variables, liver fibrosis markers remained correlated with LAD, and C-peptide values (for FIB4; $R^2 = 11.19\%$, $P < 0.0001$) and right atrium diameter and creatinine values (for NFS; $R^2 = 12.56\%$, $P < 0.0001$), respectively (Table 5). The remaining parameters (not mentioned in Table 5) did not correlate with either of the fibrosis scores. In the multiple regression analyses, the LVMi was not associated significantly with either liver fibrosis scores.

In a separate bivariate analysis, LVMi correlated positively with uric acid values [$r = 0.13$ (0.010; 0.253), $P = 0.0295$], age [$r = 0.16$ (95%CI: 0.038; 0.279), $P = 0.0083$], and EATT [$r = 0.15$ (0.030; 0.272), $P = 0.0122$], while the negative correlation with SHBP concentration was not quite significant [$r = -0.12$ (-0.238; 0.005), $P = 0.0538$]. No other laboratory parameters or therapies with GLP-1 RA and/or SGLT2 inhibitors correlated with LVMi. In a multivariate regression analysis that included these parameters as independent variables, along with BMI and systolic blood pressure, the latter three were significantly correlated with LVMi ($R^2 = 10.77\%$, $P < 0.0001$): Age [$\beta = 0.599$ (95%CI: 0.227; 0.971), t ratio: 3.153, $P = 0.0018$], EATT [$\beta = 1.997$ (95%CI: 0.847; 3.146), t ratio: 3.405, $P = 0.0008$], and SHBP [$\beta = -0.280$ (95%CI: -0.469; -0.091), t ratio: 2.901, $P = 0.0040$].

To better understand the interrelationship between the liver and heart, we further investigated which liver-related and -independent factors had a significant impact on the LAD. Initially we performed bivariate correlation analyses and identified several parameters that were significantly associated with LAD (Table 6). Age, duration of diabetes, BMI, smoking status, alcohol intake and the other laboratory parameters mentioned in Table 2, as well as therapy with GLP-1RA and/or SGLT2 inhibitors were not correlated with LAD. Subsequently, the multiple regression analysis (which included as independent variables those factors found to be significantly correlated with LAD in the bivariate analysis) revealed that three of them remained independently correlated with LAD ($R^2 = 15.18\%$; $P < 0.0001$; Table 7). The presence of atrial fibrillation had the strongest impact, but higher serum values of GGT and lower SHBP concentrations also influenced LAD.

Table 2 Laboratory parameters in the study population according to the liver fibrosis category

Parameter	Group 1 (advanced fibrosis), *n* = 84	Group 2 (indeterminate risk of fibrosis), *n* = 164	Group 3 (without fibrosis), *n* = 19	*P* value
Uric acid (mg/dL)	6.13 ± 1.44	5.86 ± 1.48	5.29 (3.59-8.17)	0.0484
Albumin (g/dL)	4.59 ± 0.22[a]	4.68 ± 0.23[a]	4.70 ± 0.28	0.0118
ALAT (U/L)	17.22 (2.32-80.94)	18.02 (4.18-92.79)	25.36 ± 12.56	0.0921
ASAT (U/L)	22.54 (11.48-130.85)[b]	19.91 (9.75-49.95)[b]	19.30 (13.16-39.16)	0.0034
Direct bilirubin (mg/dL)	0.21 (0.07-0.59)[a]	0.20 (0.07-0.90)	0.17 ± 0.06[a]	0.0335
GGT (U/L)	32.78 (4.97-338.18)[a]	27.51 (4.02-313.66)[a]	27.13 (9.17-173.63)	0.0360
Total cholesterol (mg/dL)	147.20 (91.38-279.48)	155.45 (96.75-376.17)	175.16 ± 51.20	0.1347
HDL cholesterol (mg/dL)	43.98 (27.86-65.09)	43.75 (22.48-75.75)	48.04 ± 11.77	0.3977
LDL cholesterol (mg/dL)	73.71 (36.57-186.09)	84.73 (31.2-270.6)	104.01 ± 39.94	0.0488
Triglycerides (mg/dL)	156.02 (70.06-573.36)[a]	155.36 (62.37-609.08)[a]	117.83 (68.15-382.84)[a]	0.0305
Blood glucose (mg/dL)	137.59 (92.09-261.68)	136.58 (87.34-326.2)	142.75 ± 18.60	0.7290
HbA1c (%)	6.80 (4.6-10.01)	6.80 (5.7-10.20)	7.02 ± 0.72	0.5780
C-peptide (ng/mL)	3.68 (0.72-10.5)[a,b]	3.00 (0.28-8.83)[a]	2.62 ± 1.43[b]	0.0039
HOMA-IR	3.04 (0.66-8.4)[a]	2.61 (0.45-7.52)	2.23 ± 1.21[a]	0.0067
eGFR (mL/min/1.73m²)	82.53 (26.70-117.25)[b,c]	91.38 (40.36-114.59)[a,b]	97.17 ± 14.60[a,c]	< 0.0001
Haptoglobin (g/L)	1.59 ± 0.57	1.73 ± 0.61	1.73 ± 0.63	0.1997
Ferritin (ng/mL)	112.00 (8.79-781.00)	92.30 (6.41-811.00)	53.90 (9.72-543.0)	0.6226
SHBP (nmol/L)	37.41 ± 15.12	32.80 (7.62-118.00)	35.38 ± 15.68	0.3811

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
For triglycerides: Group 1 *vs* group 2, and group 2 *vs* group 3. Data are presented as mean ± SD or median (min-max). ASAT: Aspartate aminotransferase; ALAT: Alanine aminotransferase; GGT: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; SHBP: Sex-hormone binding protein.

DISCUSSION

MASLD is frequently associated with T2DM and has emerged as a risk factor for CVD, yet the nature of the cardio-liver interaction, particularly in patients with T2DM is not completely understood. In this study, which included T2DM patients with MASLD, we found that a higher proportion of patients with markers of advanced liver fibrosis had a reduced EF, and the mean EF values were lower in this category. Literature indicates that MASLD is associated with an increased risk of heart failure (HF), although there is limited information regarding the association between MASLD severity/fibrosis and HF phenotypes[33,34]. A recent cohort study suggested a stronger association of MASLD with HF with preserved EF (HFpEF) rather than HF with reduced EF (HFrEF); however, this study involved a healthcare database interrogation and not a direct echocardiographic evaluation of MASLD patients[35]. Another recent study in hospitalized patients with T2DM also showed a higher risk of HFpEF in MASLD [OR: 1.59 (95%CI: 1.22-2.08)], independent of cardiometabolic risk factors, primarily associated with more advanced liver fibrosis; however, this study did not specifically investigate the correlations of liver fibrosis with EF (or the risk of HFrEF)[36]. To our knowledge this is the first report of lower EF in T2DM patients with markers of advanced MASLD-related fibrosis. Nevertheless, existing literature is congruent with our findings. A small imaging study in T2DM and in MASLD patients, that employed high-resolution magnetic resonance imaging (MRI), tagging, and spectroscopy, demonstrated alterations in cardiac structure and function[37]. T2DM patients exhibited significant systolic dysfunction (shown by reduced stroke index), and diastolic dysfunction (reduced E/A)[37]. Moreover, a recent meta-analysis of 41 papers (n = 33891 patients who underwent echocardiography) demonstrated that patients with liver biopsy- or imaging-defined MASLD had lower EF [mean difference: -0.693 (95%CI: -1.112 to -0.274); P = 0.001] compared with patients without MASLD[38]. These patients also presented indicators of diastolic dysfunction, higher LVM and increased EATT[38]. Our study population also presented markers of diastolic dysfunction: Over 70% of subjects had lateral e' values < 10 cm/second, without differences between groups, while e' septal values were lower in the more advanced liver fibrosis group. Additionally, we have found that more than 60% of T2DM-MASLD patients included in this study had increased LVMi, and LVMi values were higher in subjects with markers of advanced hepatic fibrosis. A recent meta-analysis of twenty studies showed higher LVMi in

Table 3 Echocardiographic structural and functional parameters according to liver fibrosis categories

Echocardiographic parameters	Group 1 (advanced fibrosis), *n* = 84	Group 2 (indeterminate risk of fibrosis), *n* = 164	Group 3 (without fibrosis), *n* = 19	*P* value
Morphologic parameters				
LV diastolic diameter (mm)	51.37 ± 6.04	50.00 (38.00-71.00)	48.53 ± 4.50	0.1482
LV systolic diameter (mm)	37.00 (24.00-57.00)	36.00 (24.00-60.00)	34.89 ± 6.44	0.4832
IV septum thickness (mm)	12.00 (8.00-16.00)[b]	11.00 (7.00-16.00)	10.00 (9.00-13.00)[b]	0.0029
LV posterior wall thickness (mm)	12.00 (9.00-16.00)[a]	11.00 (7.00-17.00)[a]	11.00 (10.00-14.00)	0.0277
Left atrium diameter (mm)	39.07 ± 5.15[c]	37.00 (26.00-52.00)[a]	34.31 ± 4.26[a,c]	0.0008
Right atrium diameter (mm)	36.96 ± 6.03[a]	35.47 ± 5.28	33.47 ± 4.68[a]	0.0224
Right ventricle diameter (mm)	36.34 ± 5.50	35.00 (12.00-50.00)	37.00 ± 5.18	0.5209
Aortic annular diameter (mm)	32.00 (20.00-42.00)	32.00 (23.00-40.00)	31.11 ± 3.05	0.2201
Descending aorta diameter (mm)	18.00 (13.00-33.00)[b]	19.00 (10.00-30.00)[b]	18.11 ± 1.60	0.0066
LV end-diastolic volume (mm^3)	121.64 ± 31.18	109.00 (63.00-380.00)	108.74 ± 17.85	0.1388
LV end-systolic volume (mm^3)	66.70 ± 22.25[a]	57.00 (21.00-290.00)[a]	54.35 ± 14.16	0.0101
Stroke volume (mm^3)	55.42 ± 16.60	54.00 (24.00-112.00)	52.81 ± 13.48	0.7994
EATT (mm)	8.00 (3.00-17.00)[b]	7.00 (3.00-14.00)[b]	7.26 ± 2.51	0.0027
LVMi (g/m^2)	119.16 ± 27.36	113.23 ± 24.82	104.39 ± 22.32	0.0474
Increased LVMi, *n* (%)	55 (66.27%)	99 (60.37%)	10 (52.63%)	0.4687
Functional parameters				
EF, *n* (%)	49.19 ± 5.62	50.87 ± 5.14	52.00 ± 3.25[a]	0.0030
	49.00 (27.00-65.00)[a,b]	50.00 (23.00-61.00)[a,b]	52.00 (45.00-60.00)	
EF-normal range, *n* (%)	41 (49.40)	113 (68.90)	16 (84.21)	0.0017
E wave velocity (cm/second)	72.59 ± 19.24	70.00 (32.00-158.00)	71.83 ± 18.07	0.9292
A wave velocity (cm/second)	84.31 ± 21.25	86.10 ± 22.65	81.61 ± 27.54	0.6626
Mitral valve E/A	0.79 (0.38-1.52)	0.80 (0.44-2.07)	0.94 ± 0.28	0.5683
e′ septal (cm/second)	8.00 (3.00-16.00)[b]	8.00 (4.00-15.00)	10.50 ± 2.94[b]	0.0068
e′/a′ septal	0.70 (0.43-2.0)	0.78 (0.36-3.00)	0.84 ± 0.24	0.3637
E/e′ septal	9.64 ± 4.10[a]	8.44 (2.43-26.33)	7.35 ± 2.62[a]	0.0260
e′ lateral (cm/second)	8.00 (4.00-19.00)	8.00 (4.00-18.00)	8.00 (4.00-13.00)	0.9551
e′/a′ lateral	0.73(0.40-2.00)	0.71 (0.40-2.00)	0.79 ± 0.28	0.7655
E/e′ lateral	9.15 ± 3.76	8.27 (2.83-25.0)	8.15 (3.54-20.75)	0.8768
Average E/e′ ratio	9.17 ± 3.58	8.39 (2.62-22.57)	7.77 ± 2.34	0.3208
DcT (msec)	200.73 ± 59.07	194.59 ± 51.00	192.17 ± 43.19	0.6725
LVOT VTI (cm)	30.00 (11.20-78.00)	30.00 (11.90-76.00)	28.98 ± 7.27	0.5857
LV segmental kinetics				
Total wall motion score index	1.10 ± 0.17	1.06 ± 0.13	1.02 ± 0.06	0.0352
Basal wall motion score index	1.06 ± 0.18	1.03 ± 0.12	1.02 ± 0.05	0.6358
Mid wall motion score index	1.11 ± 0.21	1.06 ± 0.15	1.03 ± 0.1	0.0240
Apical wall motion score index	1.15 ± 0.26	1.10 ± 0.24	1.02 ± 0.06	0.0548

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

For ejection fraction (%): Group 1 *vs* group 2, and group 1 *vs* group 3. Data are presented as mean ± SD or median (min-max). Ejection fraction-normal range ≥ 50%. LV: Left ventricular; IV: Interventricular; EATT: Epicardial adipose tissue thickness; LVMi: Left ventricular mass index; EF: Ejection fraction; LVOT VTI: Left ventricular outflow tract velocity time integral; DcT: Deceleration time.

Table 4 The bivariate correlations of the two liver fibrosis scores with echocardiographic parameters in type 2 diabetes mellitus patients with Metabolic dysfunction-associated steatotic liver disease

	FIB4, *r* (95%CI)	NFS, *r* (95%CI)
LV diastolic diameter	0.09 (-0.03; 0.22)	0.14 (0.02; 0.26)[a]
IV septum thickness	0.19 (0.07; 0.31)[b]	0.23 (0.11; 0.35)[c]
LV posterior wall thickness	0.12 (-0.004; 0.24)	0.18 (0.06; 0.30)[b]
Left atrium diameter	0.19 (0.07; 0.31)[b]	0.17 (0.04; 0.29)[b]
Right atrium diameter	0.17 (0.05; 0.29)[b]	0.21 (0.09; 0.32)[d]
Aortic annular diameter	0.13 (0.001; 0.25)[a]	0.09 (-0.04; 0.21)
EATT	0.12 (-0.004; 0.24)	0.13 (0.01; 0.25)[a]
LV end-systolic volume	0.08 (-0.05; 0.20)	0.14 (0.01; 0.26)[a]
LVMi	0.15 (0.02; 0.26)[a]	0.19 (0.06; 0.30)[b]
EF (%)	-0.13 (-0.25; -0.01)[a]	-0.21 (-0.33; -0.09)[d]
e′ septal	-0.24 (-0.36; -0.12)[e]	-0.19 (-0.31; -0.07)[b]
a′ septal	-0.13 (-0.25; -0.004)[a]	-0.10 (-0.22; 0.03)
e′/a′ septal	-0.14 (-0.27; -0.02)[a]	-0.12 (-0.24; 0.01)
E/e′ septal	0.19 (0.06; 0.31)[b]	0.19 (0.07; 0.31)[b]
Total LV segmental kinetics score	0.14 (0.01; 0.26)[a]	0.16 (0.04; 0.28)[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P = 0.0001$.
[d]$P < 0.001$.
[e]$P < 0.0001$.
FIB4: Fibrosis-4; NFS: Non-alcoholic fatty liver disease-Fibrosis Score; 95%CI: 95% confidence interval; IV: Interventricular; LV: Left ventricle; EATT: Epicardial adipose tissue thickness; LVMi: Left ventricular mass index; EF: Ejection fraction.

MASLD; however, in patients with T2DM the differences in LVMi according to MASLD were not significant[39]. The potentially attenuated impact of MASLD on LVMi in T2DM may be due to T2DM itself being associated with higher LVM, particularly in the context of insulin resistance, longer duration of diabetes, and the presence of hypertension[40,41]. Notably, our study group of T2DM patients with more advanced liver fibrosis also had higher HOMA-IR values, indicative of significant insulin-resistance. Nonetheless, another meta-analysis of ten studies that included 1,800 T2DM patients reported higher LVMi in the presence of MASLD, accompanied by other markers of diastolic dysfunction[42]. However, neither of the two meta-analyses evaluated the relationship between LVMi and the severity of liver fibrosis.

It has also been suggested that high LVMi might lead to early LV diastolic dysfunction, which in turn is related to changes in left atrial dimensions and function, partly due to increased filling pressures and preload[42,43]. In our study, LAD was positively correlated with markers of liver fibrosis, and was significantly higher in T2DM patients with advanced liver fibrosis. This finding aligns with the research conducted by Fan *et al*[22], which showed a positive correlation between NFS and left atrial dimension, after adjusting for confounding factors, in patients with T2DM. Additionally, the study by Decoin *et al*[44] reported that patients with MASLD and higher liver fibrosis scores had an increased risk of atrial fibrillation recurrence after catheter ablation, along with increased left atrial remodeling with impaired histopathological, electrophysiological, and hemodynamic characteristics. Liver stiffness has been associated with atrial fibrillation in various studies[45,46]. Similarly, a Japanese study that included patients with severe tricuspid regurgitation, found that FIB4 scores positively correlated with the left atrial volume index, and the risk of major adverse cardiovascular events (MACE) [HR: 1.89 (95%CI: 1.01–3.54), $P = 0.046$][47]. In fact, a large prospective study that followed 4071 patients with MASLD for 6.6 years also reported that the risk of MACE increased progressively with higher FIB4 and NFS values ($P < 0.001$)[48].

In our study, LVMi and LAD negatively correlated with serum SHBP concentrations. Emerging evidence suggests that lower SHBP levels are associated with higher cardiovascular risk in men, and with elevated LVMi in post-menopausal women[49,50]. SHBP is a glycoprotein secreted by the liver (and other tissues, including the myocardium), that acts as a

Table 5 The multiple regression analyses with fibrosis-4 and non-alcoholic fatty liver disease-fibrosis score as dependent variables in two models

	β (95%CI); *t* ratio	*β* (95%CI); *t* ratio
Model 1		
Left atrium diameter	0.044 (0.007; 0.082); 2.307[a]	0.039 (0.004; 0.074); 2.180[a]
Right atrium diameter	0.019 (-0.014; 0.052); 1.107	0.041 (0.010; 0.072); 2.628[b]
Sex	0.137 (-0.273; 0.546); 0.654	-0.560 (-0.941; -0.179); 2.881[b]
Serum creatinine	0.748 (-0.025; 1.521); 1.897	1.467 (0.747; 2.186); 3.995[c]
Model 2		
Left atrium diameter	0.037 (0.0005; 0.073); 1.990[a]	0.030 (-0.005; 0.065); 1.695
C-peptide	0.175 (0.071; 0.280); 3.282[b]	0.099 (-0.002; 1.200); 1.920
Right atrium diameter	0.013 (-0.017; 0.043); 0.851	0.030 (0.001; 0.059); 2.021[a]
Serum creatinine	0.410 (-0.328; 1.148); 1.089	0.843 (0.133; 1.533); 2.326[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.0001$.
Independent variables in Model 1: Left ventricular mass index (LVMi), left atrium diameter, right atrium diameter, sex, smoking status, systolic blood pressure, duration of diabetes, alcohol intake, atrial fibrillation, serum creatinine; in Model 2: LVMi, left atrium diameter, right atrium diameter, C-peptide, low-density lipoprotein cholesterol, serum creatinine). Only the parameters correlated with at least one score are mentioned in the table. 95%CI: 95% confidence interval; IV: Interventricular; LV: Left ventricle; LVMi: Left ventricular mass index; EF: Ejection fraction.

Table 6 Factors associated with left atrium diameter in the bivariate correlation analysis

Left atrium diameter	*r* (95%CI)
Uric acid	0.14 (0.01; 0.26)[a]
Direct bilirubin	0.15 (0.03; 0.27)[a]
GGT	0.15 (0.02; 0.27)[a]
HDL cholesterol	-0.13 (-0.25; -0.01)[a]
C-peptide	0.13 (0.005; 0.25)[a]
SHBP	-0.14 (-0.26; -0.02)[a]
Sex	0.23 (0.11; 0.34)[b]
Atrial fibrillation	0.16 (0.04; 0.28)[c]

[a]$P < 0.05$.
[b]$P = 0.0001$.
[c]$P < 0.01$.
95%CI: 95% confidence interval; GGT: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein; SHBP: Sex-hormone binding protein.

carrier for steroid hormones (androgens and estrogens, potentially influencing their availability and activity in specific tissues[51,52]. Additionally, *in vitro* experiments have shown that SHBP can bind to membrane receptors and activate intracellular signaling pathways, either through a putative G-protein-coupled receptor that increases intracellular cAMP levels, or through the megalin receptor, which induces the internalization of SHBG[51,53]. While the cardioprotective effects of sex hormones (primarily estrogens) are well established, the role of circulating SHBP in cardiovascular pathophysiology remains incompletely understood and warrants further investigation[54,55]. The findings of this research pave the way for subsequent mechanistic studies exploring the potential role of SHBP in linking liver fibrosis and cardiac remodeling.

Indeed, a mechanistic explanation for the correlation between liver fibrosis and remodeling of left atrium and left ventricle is still greatly needed. Perhaps shared pathogenetic mechanisms of cardiac and liver fibrosis, triggered by similar factors (such as inflammation/activation of inflammasomes or oxidative stress), leading to fibroblast activation and increased collagen formation, might explain these correlations (although causality remains a possibility)[56,57]. Increased visceral adiposity (particularly increased EATT), associated with insulin resistance and dysregulated adipokines, hepatokines or other molecules secreted by the liver (such as SHBP), and/or hemodynamic changes could also

Table 7 The multiple regression analysis with left atrium diameter as the dependent variable

	β (95%CI), *t* ratio
GGT	0.015 (0.003; 0.028); 2.343[a]
SHBP	-0.036 (-0.071; -0.001); 2.039[a]
Atrial fibrillation	3.481 (1.232; 5.729); 3.034[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
95%CI: 95% confidence interval; GGT: Gamma glutamyl transpeptidase; SHBP: Sex-hormone binding protein.

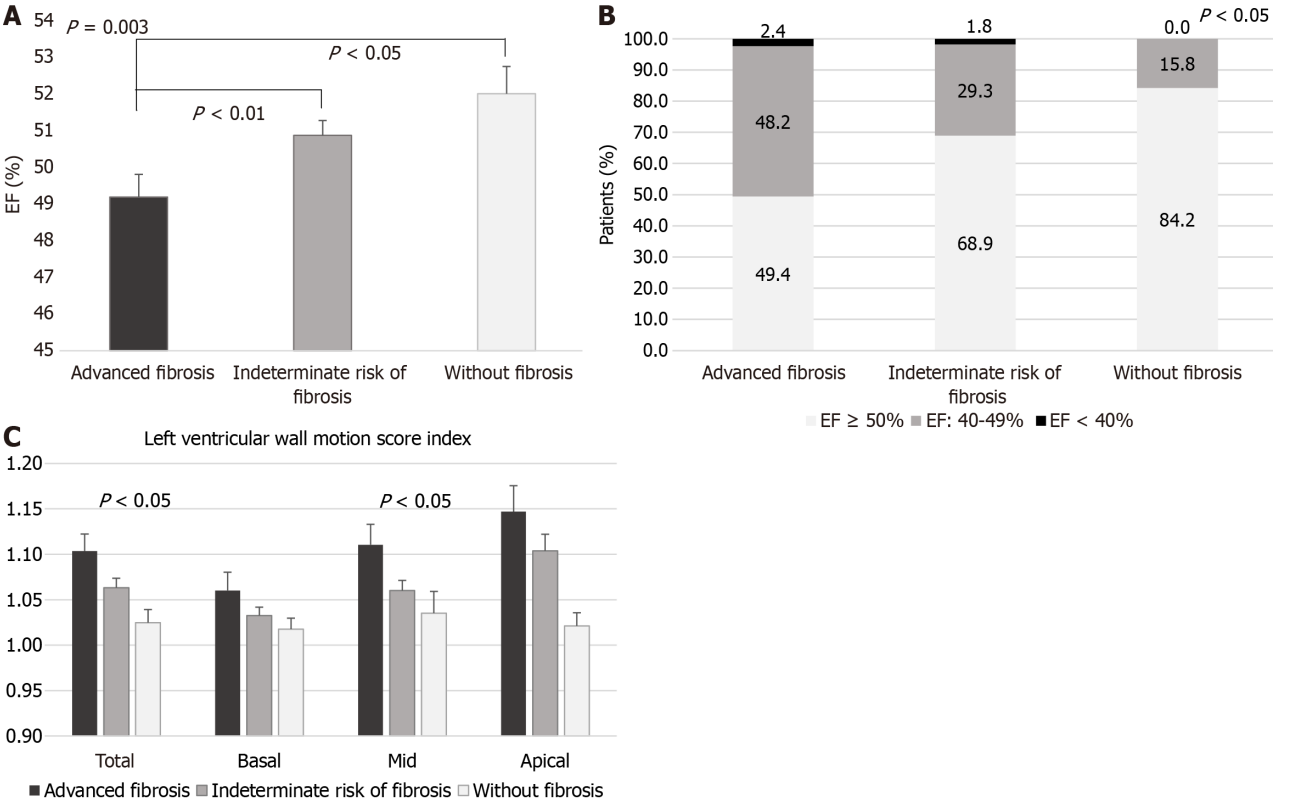

Figure 1 Association of metabolic dysfunction-associated steatotic liver disease-fibrosis categories with indicators of cardiac dysfunction and dyskinesia. A: Ejection fraction (%) according to the liver fibrosis categories in type 2 diabetes mellitus patients with metabolic dysfunction-associated steatotic liver disease; B: Proportion of patients with an ejection fraction (EF) ≥ 50% (normal), EF = 40%-49% (mild dysfunction), and EF < 40% (moderate dysfunction) in each liver fibrosis category; C: Total, basal, mid and apical left ventricular wall motion score indexes according to the liver fibrosis categories. EF: Ejection fraction.

be significant contributors[58-60]. Nevertheless, mechanistic and prospective studies are needed to better understand the interaction between liver fibrosis and cardiac remodeling and dysfunction in patients with and without T2DM. Additionally, interventional studies exploring the effects of various multidisciplinary therapeutic interventions could provide valuable insights regarding the liver-heart interaction in MASLD patients with T2DM.

We acknowledge several limitations of our study. First, the cross-sectional design did not permit a prospective evaluation of liver-heart cross-talk, and a cause-effect inference. Second, the liver fibrosis status was assessed using two fibrosis scores (FIB4 and NFS), resulting in a relatively high proportion of patients being classified as having indeterminate risk of advanced fibrosis. Nonetheless, these two scores are well validated and widely accepted in clinical practice, as FIB4 is the index of choice recommended by professional guidelines as the initial screening tool for MASLD fibrosis in patients with T2DM and other metabolic disorders[61,62]. By utilizing these two biomarkers we ensured proper classification of the advanced liver fibrosis group and the no liver fibrosis group. Another impediment of using non-invasive biological indexes was that the parameters used in the two formulas could not be included in the multivariable analyses (with the two scores as dependent variables). Thus, further studies employing different methods of liver fibrosis assessment should be undertaken. Thirdly, we did not have the opportunity to use more advanced cardiac imaging techniques (such as MRI) in this study; therefore, further research is needed to more accurately evaluate cardiac function and structure in patients with MASLD fibrosis.

CONCLUSION

T2DM patients with markers of MASLD-related liver fibrosis exhibit lower EF and present indicators of diastolic dysfunction, cardiac hypertrophy and dyskinesia. Additionally, LVMi and LAD negatively correlated with serum SHBP concentrations.

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FOOTNOTES

Author contributions: Cernea S design the study, acquired, analyzed and interpreted the data, wrote the manuscript, designed the figure; Onișor D, Roiban AL and Rat N acquired data and reviewed the paper for important intellectual content; Benedek T interpreted the data and reviewed the paper for important intellectual content.

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CASE REPORT

Unroofed coronary sinus, left-sided superior vena cava and mitral insufficiency: A case report and review of the literature

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Abstract

BACKGROUND

Unroofed coronary sinus (UCS) is a rare subtype of atrial septal defect. It is frequently associated with a persistent left superior vena cava and is often part of a more intricate cardiac malformation.

CASE SUMMARY

This report describes a rare case of an adolescent patient with UCS featuring atrial situs solitus, absence of the right superior vena cava and a persistent left superior vena cava draining into the left atrium consistent with total unroofing of the coronary sinus. This was associated with concurrent severe mitral insufficiency secondary to redundant and prolapsing leaflets, and a substantial left-to-right shunt across the coronary sinus orifice. A comprehensive examination of the existing literature is included, shedding light on the diagnostic challenges of UCS and describing the available surgical options within the context of mitral valve surgery.

CONCLUSION

UCS is a complex condition requiring careful consideration of associated anomalies and a tailored surgical approach.

Key Words: Unroofed coronary sinus; Mitral insufficiency; Single left superior vena cava; Surgical options; Absent right superior vena cava; Case report

Core Tip: In this report, we present an exceedingly rare case of a teenager with an unroofed coronary sinus and a single persistent left superior vena cava in conjugation with severe mitral regurgitation secondary to redundant and prolapsing leaflets, in the absence of other associated cardiac anomalies. This peculiar condition was detected by echocardiography and corrected by appropriate surgical intervention.

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INTRODUCTION

Unroofed coronary sinus (UCS), also known as coronary sinus (CS) septal defect, denotes a particularly rare and uncommon subtype of atrial septal defects, accounting for less than 1% of all cases within this category[1]. It arises from the incomplete development of the left atrial venous folds during embryogenesis and was first elucidated by Raghib and colleagues in 1965[2]. This anomaly manifests as a communication between the left atrium and the CS, secondary to partial or complete absence of the CS roof, resulting in a left to right shunt.

UCS is an atypical atrial septal defect as it is characterized by interatrial shunting across a normal structure, the CS ostium[3,4]. It often co-exists with a persistent left superior vena cava (LSVC) and other concomitant cardiac abnormalities, further complicating its detection[3,4]. Isolated cases of CS-to-left atrial fenestration are exceedingly rare, increasing the intricacy of the diagnostic process[3-5]. Besides, the presence of a LSVC in the absence of the right superior vena cava (RSVC) is extremely uncommon with an estimated incidence of less than 0.13%[3]. While the congenital cardiac defects associated with absent RSVC show a wide spectrum[3,6], the association of absent RSVC, persistent LSVC and UCS, in the absence of congenital heart disease is immensely rare.

In this report, we present a unique case of absent RSVC in a visceroatrial situs solitus, persistent LSVC draining into UCS, associated with severe mitral insufficiency in the absence of atrioventricular septal defect. Furthermore, we present a comprehensive examination of the existing literature, tackling the diagnostic hurdles and exploring surgical interventions, with a particular emphasis on managing mitral valve pathology simultaneously.

CASE PRESENTATION

Chief complaints

A 19-year-old female was referred to our Children's Heart Center with the diagnosis of an atrial septal defect for further evaluation and treatment.

History of present illness

The patient had minimal exercise intolerance and assumed a sedentary lifestyle. She had normal growth and development. Notably, she was known to have congenital heart disease since early childhood, yet the family did not have documented records.

History of past illness

Besides her congenital heart disease, she did not have a significant medical history.

Personal and family history

She has no family history of congenital heart disease.

Physical examination

On physical examination, her vital signs were normal except for an oxygen saturation of 95%. She had a grade 2/6 systolic murmur at the apex and another grade 2/6 systolic ejection murmur at the left upper sternal border with fixed splitting of the second heart sound.

Laboratory examinations

An electrocardiogram (ECG) revealed a normal sinus rhythm and QRS frontal axis, with a wide P wave suggestive of left atrial enlargement (Figure 1).

Imaging examinations

A chest x-ray was significant for an enlarged cardiac silhouette with prominent right atrium and increased vasculature suggestive of congestion. An echocardiogram (Figure 2) showed right atrium and ventricle dilation, with preserved right

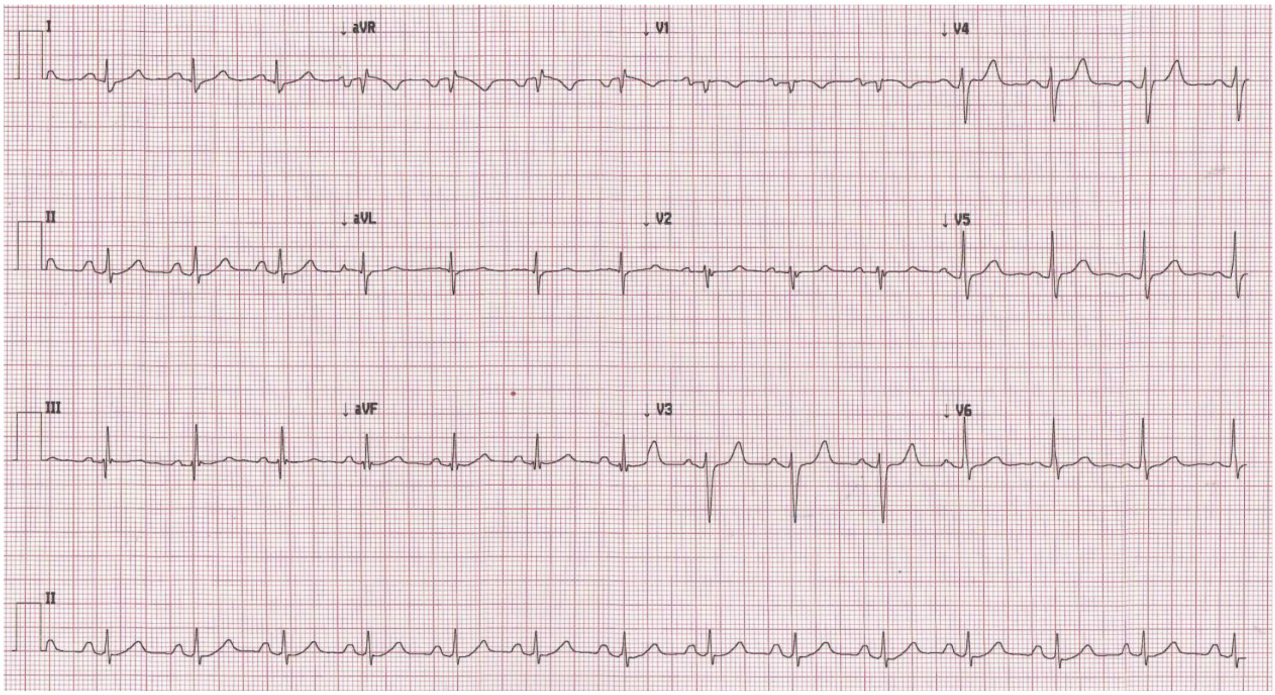

Figure 1 Pre-operative electrocardiogram. It shows normal sinus rhythm with normal P wave axis and interatrial conduction delay.

ventricular systolic function and absent RSVC. There was a right-sided brachiocephalic vein draining into a LSVC. Additionally, the ostium of the CS appeared significantly dilated with exuberant flow by color Doppler. The superior vena cava-CS continuity was interrupted consistent with UCS, while the LSVC was visualized to drain directly in the roof of the left atrium between the base of the left atrial appendage and the left upper pulmonary vein. Notably, the mitral valve leaflets were thickened, myxomatous and prolapsing resulting in multiple jets of severe mitral regurgitation. The mitral valve was bifoliate without a cleft, and the atrioventricular septum was intact without a primum atrial septal defect. Moderate tricuspid regurgitation was present and Doppler interrogation estimated the right ventricular systolic pressure to be around 30 mmHg. Contrast echocardiography, performed by injecting agitated saline through the antecubital vein of the left arm, showed sequential opacification of the LSVC, the left atrium, and the left ventricle. Concomitant with the opacification of the left ventricle, the right atrium and right ventricle opacified through the orifice of the CS (Figure 3). The inferior vena cava had a normal connection to the right atrium, and there was no evidence of a hemizygous connection. Pulmonary veins drained into the left atrium.

Subsequent computed tomography (CT) scan findings corroborated the echocardiographic diagnosis, confirming the presence of a single LSVC draining into the roof of the left atrium and complete unroofing of the CS. The ostium of the CS was dilated and served as the connection between the right atrium and the left atrium (Figure 4).

FINAL DIAGNOSIS

Workup confirmed the diagnosis of absent RSVC, persistent LSVC draining into the left atrium, and a completely UCS, in association with severe mitral insufficiency.

TREATMENT

The patient underwent surgical intervention as follows:

After median sternotomy, cardiopulmonary bypass was established *via* bi-caval venous and aortic cannulation. Upon inspection, the RSVC was absent and a persistent LSCV was noted. Antegrade cardioplegia was used. The right and left atrium were opened. Inspection of the right atrial cavity revealed a dilated and significantly enlarged CS ostium. Inspection of the left atrium showed the LSVC draining into the roof of the left atrium medial and superior to the orifices of the left pulmonary veins, and the base of the left atrial appendage was located just anterior and medial to the entrance site.

The repair of the LSVC to the left atrium was carried out using the repositioning of the atrial septum technique; a pericardial patch was sutured to the posterior rim of the LSVC using a continuous 5-0 polypropylene suture. The suture line was continued along the rim of the atrial septum and rim of the CS ostium where the caval orifice was positioned on the right side of this septum.

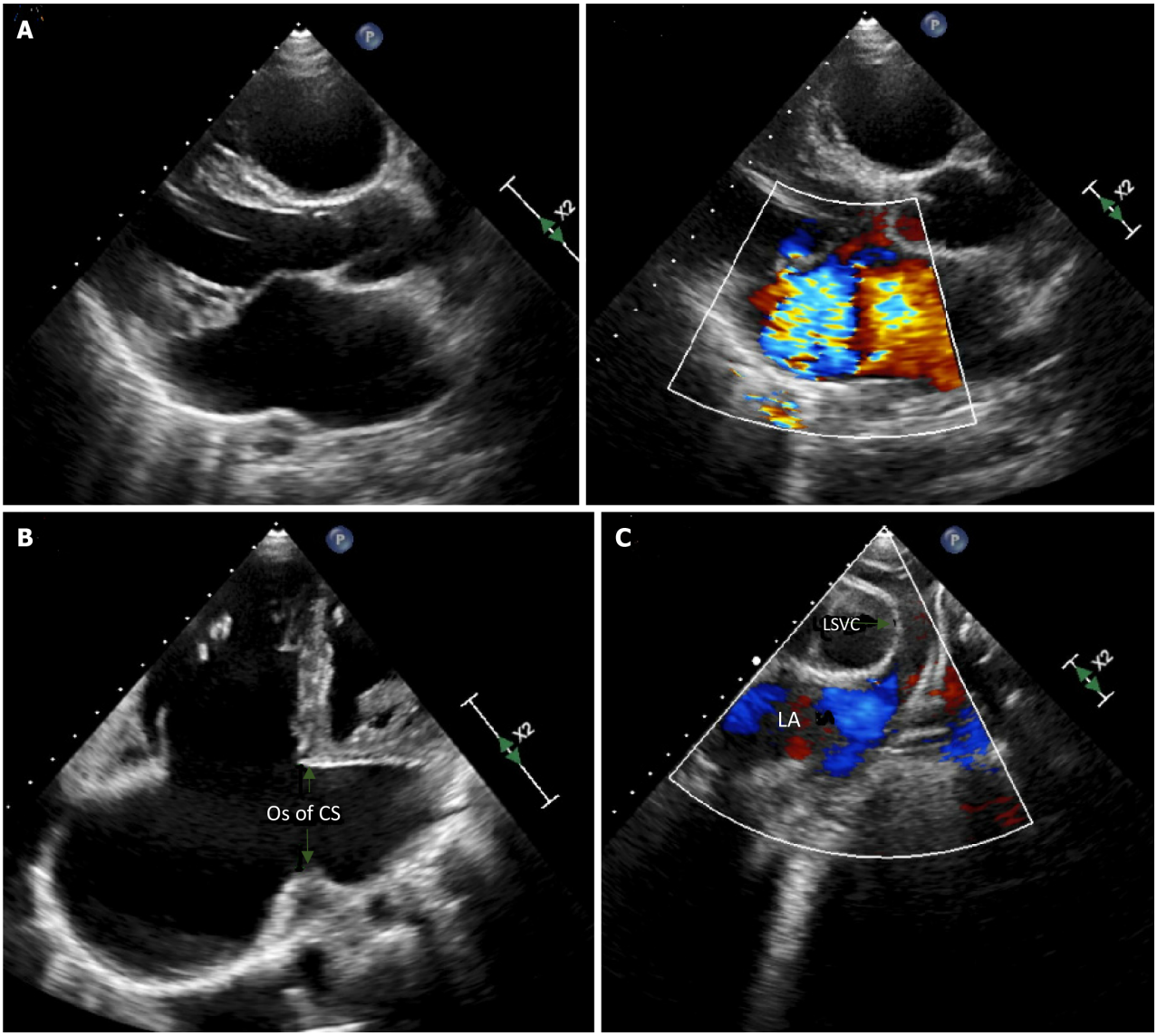

Figure 2 Echocardiographic imaging of the mitral valve. A: A parasternal long axis view of the mitral valve showing myxomatous prolapsing leaflets and severe mitral regurgitation; B: A modified 4 chamber view, with posterior angulation showing the dilated ostium of the coronary sinus; C: Modified supra coronal cut from the supra-sternal window showing a left superior vena cava draining into the left atrium. OS: Ostium; CS: Coronary sinus; LSVC: Left superior vena cava; LA: Left atrium.

Examination of the mitral valve confirmed the absence of a cleft and the severe prolapse of the anterior and posterior leaflets. The mitral valve repair was performed using the 4-chord technique with annuloplasty as described by Chemtob *et al*[7].

OUTCOME AND FOLLOW-UP

Post-operatively, a repeat CT scan and a LSVC angiogram revealed a patent intra-atrial baffle without any significant residual shunt (Figure 5).

DISCUSSION

This report describes a unique case of absent RSVC in a visceroatrial situs solitus, persistent LSVC draining into the left atrium, and a completely UCS, in association with severe mitral insufficiency in the absence of atrioventricular septal defect (AVSD). UCS is a rare condition often associated with other congenital anomalies. It exhibits various types and classifications, such as the Kirklin and Barratt-Boyes classification which utilizes the extent of the unroofing and the presence or absence of the LSVC[8].

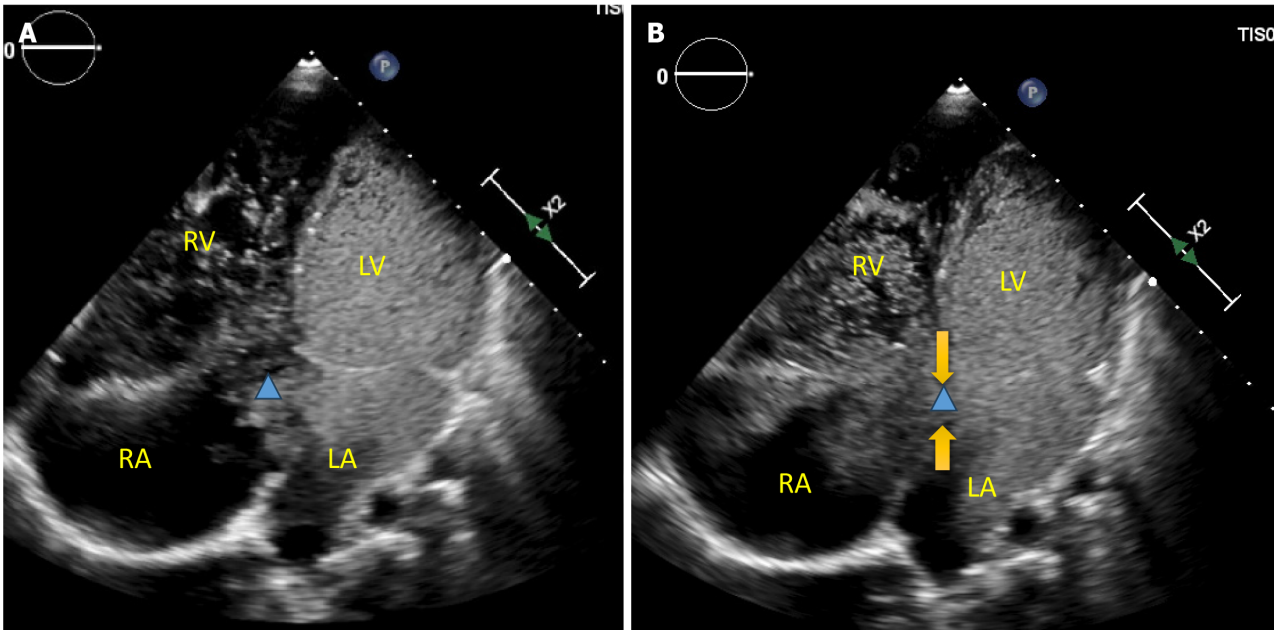

Figure 3 Agitated saline contrast injection in the left antecubital vein. A: Views taken from the 4-chamber window. Note the contrast filling the left atrium and the left ventricle before crossing the dilated ostium of the unroofed coronary sinus (triangle); B: Arrows pointing to the edges of the coronary sinus ostium. RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

The combination of an UCS, absent RSVC and a persistent LSVC is extremely rare in patients without heterotaxia syndrome. The rare obliteration of the right anterior cardinal vein and persistence of the left one during embryological development results in the absent RSVC with persistent LSVC[9]; if occurred concomitantly with failure of the formation of the left atrio-venous fold results in UCS[2]. Specific genes implicated in the association between UCS and persistence of LSVC have not been yet identified. However, both defects are linked to abnormal development of the venous system during fetal life. These anomalies are also frequently associated with genetic syndromes such as Noonan syndrome and Holt-Oram syndrome suggesting a potential genetic contribution.

Our patient had visceral and atrial situs solitus as confirmed by the P wave morphology and axis on the ECG, the drainage of the supra-hepatic portion of the inferior vena cava by imaging and ultimately the usual disposition of the atrial appendages upon direct inspection by the surgeon.

Bertram *et al*[3] reported on 121 cases, with absent RSVC, and normal cardiac lateralization, UCS was found in only seven patients: One with a ventricular septal defect, another with tetralogy of Fallot, a third with double outlet right ventricle and the remaining four did not exhibit associated congenital heart disease[10]. Martinez and his group reported an additional 12 cases, none had an UCS[7]. Doksöz *et al*[11] reported a child with absent RSVC, persistent LSVC which drained to the UCS, in association with AVSD and cor-triatriatum sinister. Kumar and his group reported a patient with absent RSVC, persistent LSVC draining into the UCS, a common atrium and an AVSD[12]. Partial UCS syndrome with persistent LSVC, absent RSVC and right-sided pericardial defect was also described in a pediatric patient[13].

UCS is rarely associated with mitral valve diseases, with only sporadic reports of mitral insufficiency in adult patients or in association with AVSD, where the regurgitation is usually through a cleft[14-17]. Mitral stenosis was reported once in the literature[18]. Detailed information on those cases is reported in Table 1.

In our patient, the presence of severe mitral insufficiency was associated with neither congenital heart disease, nor a cleft. Upon direct inspection, the mitral valve was free of a cleft, and the cause of the regurgitation was due to severe prolapse of both leaflets with elongated chords. Of interest, those changes could not have been attributed to age as is the case in adults with Barlow's disease.

UCS is occasionally misdiagnosed as a primum atrial septal defect[3,19]. To differentiate atrial septal defect from a large and dilated CS, it is crucial to note that the former shows a defect in the atrial septum near the atrioventricular valve (AVV), with a cleft in the left AVV. However, a dilated CS, secondary to either a persistent LSVC or anomalous connection of pulmonary veins, appears as a dilation in the posterior part of the right atrium, beyond the level of the AVV. Still, it should not have direct communication with the left atrium unless it is unroofed.

While transthoracic and contrast echocardiography are typically effective in the accurate diagnosis of UCS in most instances[19-24], the condition remains undetected preoperatively in approximately one-third of cases[19]. In our case the absence of the RSVC, the presence of LSVC and its draining site, the roof of the left atrium, the mitral valve pathology and degree of regurgitation as well as the unroofing of the CS were correctly identified by transthoracic and contrast echocardiography. We elected to perform a CT scan to further delineate the exact drainage of the LSVC in relationship to the left upper pulmonary vein and the base of the atrial appendage.

Although surgical repair has traditionally been the standard treatment, innovative percutaneous therapies are progressively emerging as alternatives[25,26]. In our case, the rarity of the condition, the lack of large series, and the absence of a RSVC limited the surgical options; as extra cardiac repair, be it ligation of the LSVC, in the case where a

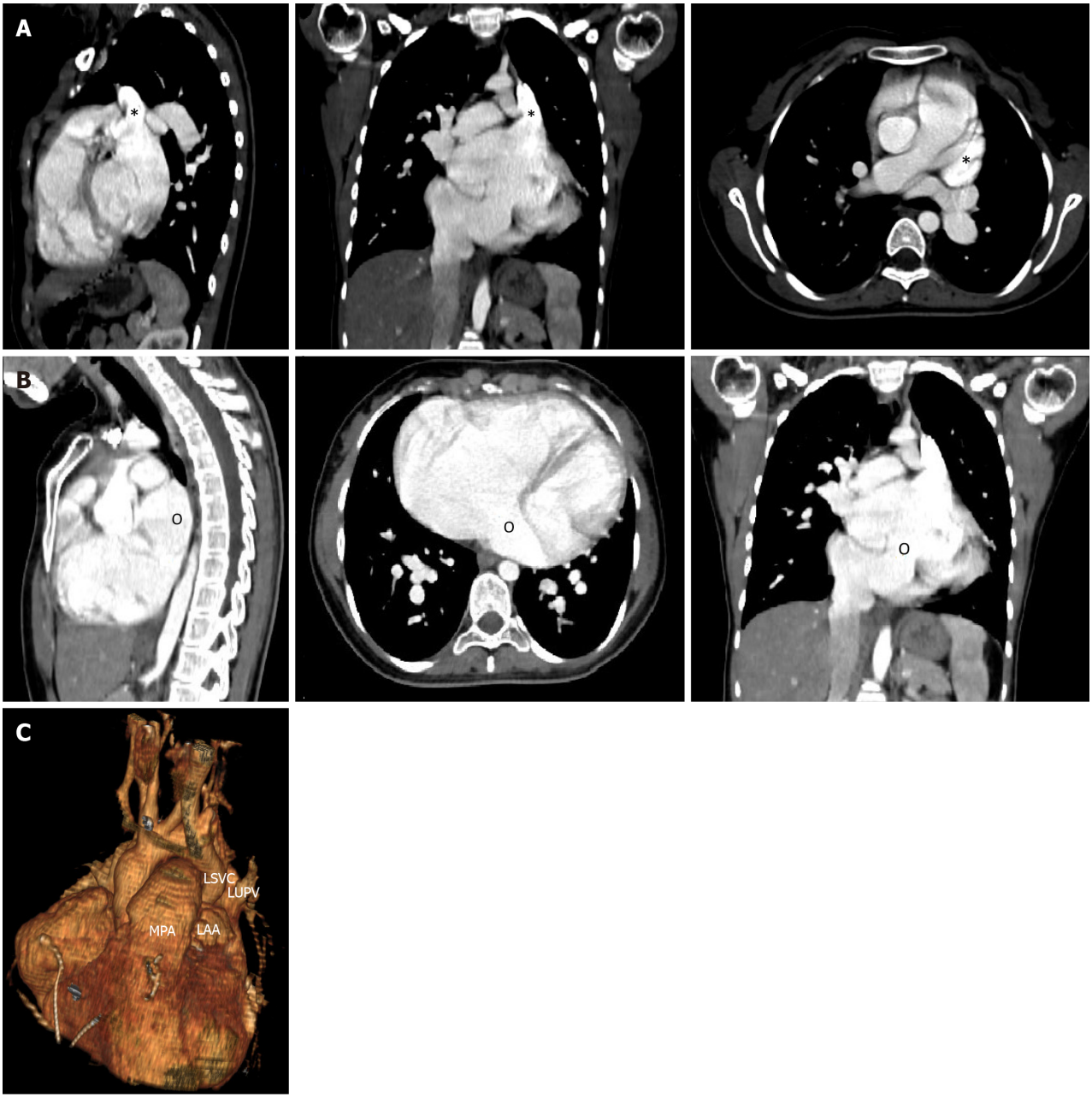

Figure 4 Preoperative computed tomography angiogram. A: The insertion site of the left superior vena cava (LSVC) is shown by an asterisk in the axial, sagittal and coronal views; B: The ostium of the coronary sinus indicated by the letter (o) is shown in the same three views; C: A three-dimensional reconstruction of the LSCV as it enters the left atrium. LSVC: Left superior vena cava; MPA: Main pulmonary artery; LAA: Left atrial appendage; LUPV: Left upper pulmonary vein.

bridging vein is present, or rerouting using a conduit to the RSVC would not be feasible. Mitral valve prolapse and redundant leaflets resulting in severe mitral regurgitation associated with LSVC to UCS may present an additional challenging surgical scenario, as roofing the CS is a concern due to its proximity to the posterior mitral valve leaflet. This proximity could compromise the surgical repair or result in replacement of the mitral valve. In cases of concurrent mitral valve repair, safely diverting the LSVC to the right atrium without obstructing the mitral valve or the pulmonary veins and closure of the CS orifice becomes a crucial aspect of the surgical approach.

Preserving the CS drainage on the left side in the context of mitral valve surgery can offer certain advantages. This simplification potential can reduce overall complexity and operative time while also minimizing the risk of potential complications or obstructions that may arise during redirection. In cases involving mitral valve repair or replacement, opting to avoid roofing of the CS may prove to be a better choice; hence, intra-cardiac baffling without roofing the CS was deemed the procedure of choice in our patient. Post-operative imaging revealed a patent intra-atrial baffle without any significant residual shunt. However, long-term follow-up *via* echocardiography is definitely needed.

Table 1 Published studies describing absent right superior vena cava, unroofed coronary sinus and associated heart lesions, in the absence of heterotaxia syndrome

Case number	Ref.	Associated cardiac disease
1	Brown *et al*[27]	None
2	Wood[28]	None
3	Sherafat *et al*[29]	None
4	Kabbani *et al*[30]	VSD
5	Choi *et al*[31]	DORV
6	Choi *et al*[31]	None
7	Pugliese *et al*[32]	TOF
8	Doksöz *et al*[11]	Cor triatriatum, AVSD
9	Kumar *et al*[12]	Common atrium, AVSD
10	Yilmaz *et al*[13]	Right sided pericardial defect
11	Bitar *et al* (current case)	Myxomatous MV

VSD: Ventricular septal defect; DORV: Double outlet right ventricle; TOF: Tetralogy of Fallot; AVSD: Atrioventricular septal defect; MV: Mitral valve.

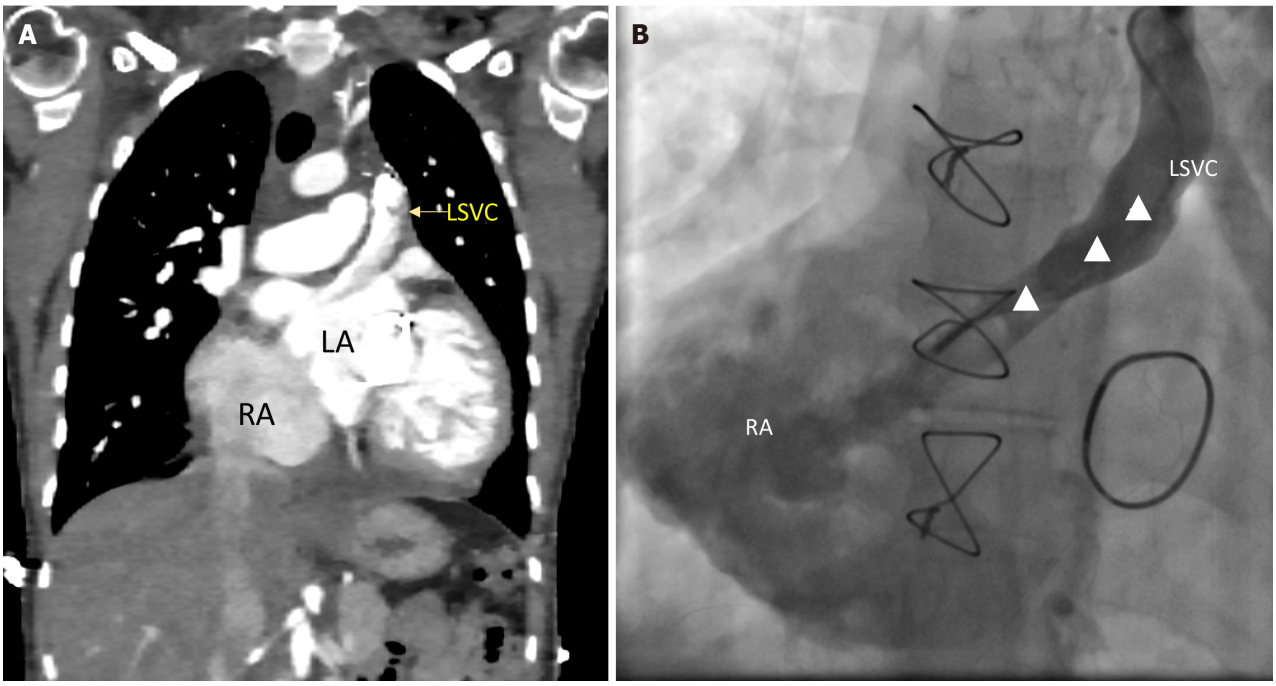

Figure 5 Post-operative imaging. A: Post-operative computed tomography angiogram; B: Antero-posterior venogram of the left superior vena cava (LSVC). Both images show the course of the intra-atrial tunnel (triangle) connecting the LSVC to the right atrium. RA: Right atrium. LA: Left atrium. LSVC: Left superior vena cava.

CONCLUSION

In conclusion, UCS is a complex condition which often requires careful consideration of associated anomalies and tailored surgical approaches, especially in cases involving severe mitral insufficiency, and single LSVC.

FOOTNOTES

Author contributions: Bulbul Z conceived the presented idea and the study framework; Bitar F, Jassar Y, Zareef R, Bulbul Z and Abboud J collected the information and wrote the first draft of the manuscript; Bitar FF, Arabi M and Bulbul Z supervised the project and performed the final editing; All authors contributed to corrections and adjustment of subsequent iterations of the manuscript; All

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LETTER TO THE EDITOR

Evaluating neuromuscular electrical stimulation for preventing and managing intensive care unit-acquired weakness: Current evidence and future directions

Annu Lisa Kurian, Brandon Lucke-Wold

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Abstract

Intensive care unit-acquired weakness (ICU-AW) is a prevalent issue in critical care, leading to significant muscle atrophy and functional impairment. Aiming to address this, Neuromuscular Electrical Stimulation (NMES) has been explored as a therapy. This systematic review assesses NMES's safety and effectiveness in enhancing functional capacity and mobility in pre- and post-cardiac surgery patients. NMES was generally safe and feasible, with intervention sessions varying in frequency and duration. Improvements in muscle strength and 6-minute walking test distances were observed, particularly in preoperative settings, but postoperative benefits were inconsistent. NMES showed promise in preventing muscle loss and improving strength, although its impact on overall functional capacity remained uncertain. Challenges such as short ICU stays and body composition affecting NMES efficacy were noted. NMES also holds potential for other conditions like cerebral palsy and stroke. Further research is needed to optimize NMES protocols and better understand its full benefits in preventing ICU-AW and improving patient outcomes.

Key Words: Neuromuscular electrical stimulation; Intensive care unit-acquired weakness; Cardiac surgery; Muscle atrophy; Functional capacity

Core Tip: Muscle weakness, termed intensive care unit-acquired weakness (ICU-AW), commonly affects limb and respiratory muscles, causing severe atrophy and functional impairment. Neuromuscular Electrical Stimulation (NMES) is a promising therapy that induces muscle contractions without patient effort. While NMES is safe and feasible, its effectiveness in improving post-surgery functional capacity is limited. It shows potential in preventing neuromyopathy and enhancing muscle strength, especially when used preoperatively. NMES may also benefit conditions beyond cardiac surgery, such as cerebral palsy and stroke. Further research is needed to fully understand and optimize NMES for preventing ICU-AW and improving outcomes in critical care settings.

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TO THE EDITOR

As emphasized by Kourek *et al*[1], to tackle the issues of diminished functional capacity and muscle function in patients recovering from cardiac surgery, and to counteract complications such as intensive care unit-acquired weakness (ICU-AW) and polyneuromyopathy, neuromuscular electrical stimulation (NMES) is advised. NMES has proven to be both safe and practical, even in high-risk patients, with a low incidence of severe complications or adverse effects. Implementing NMES as a prehabilitation strategy before cardiac surgery and continuing its use until discharge can lead to notable improvements in muscle strength, exercise tolerance, and overall mobility. This method also holds potential for reducing the length of intensive care unit (ICU) stays and minimizing complications. Nevertheless, while NMES shows considerable promise, further research with large-scale randomized controlled trials is needed to fully understand its benefits and refine its application.

WHY OPT FOR NEUROMUSCULAR ELECTRICAL STIMULATION?

Muscle weakness is a common issue in the ICU, often arising as a secondary disorder during treatment for life-threatening conditions. This condition, termed ICU-AW, primarily affects limb and respiratory muscles, with reduced muscle tone and reflexes. It can result from neurogenic or myogenic disturbances, or a combination of both known as critical illness neuromyopathy[2]. Severe muscle atrophy may occur, contributing to functional impairment. In some studies, it was shown that ICU-AW caused more than 10% loss of muscle mass, just in the first week of stay in the ICU[3]. ICU-AW stands out as the predominant neuromuscular issue encountered in patients facing critical illness in hospitals and it has been estimated to affect approximately 43% of ICU patients[4]. As this is such a common occurrence, a few therapies have emerged as possible treatments, with NMES being one of the most promising[1].

The study outlines that ICU-AW is exacerbated by prolonged ICU stays and lack of mobilization, impacting patient quality of life and mortality rates. Therapeutic strategies focus on preventing muscle atrophy and degeneration, with early mobilization showing promise but facing challenges due to patient limitations. As such, NMES has emerged as a viable alternative, promoting muscle contraction without patient effort, showing benefits in preventing neuromyopathy progression, shortening ICU stays, and improving muscle strength and functional capacity. Their systematic review aims to evaluate NMES's safety and effectiveness in improving functional capacity and mobility in pre- and post-cardiac surgery patients, with potential implications for improving patient outcomes and quality of life.

After their literature review, the study ended up looking at 10 randomized control trials with a total of 703 patients, most of them being male patients, who had undergone surgeries ranging from valve replacements to heart transplants. In these patients, NMES was consistently applied to the intervention group across all studies, with variations in intensity and session duration noted. In three studies, electrodes were placed on the control group without electricity delivery, while in seven studies, the control group received usual care post-surgery. Most studies involved at least five NMES sessions and session frequency ranged from 2 to 5 times weekly, with durations spanning from 30 to 90 minutes. Functional capacity was evaluated in nine out of ten studies on NMES. However, only two recent studies demonstrated improvement in functional capacity. One study also observed a significant increase in distance measured on the 6-Minute Walking Test (6MWT) within the NMES group as compared to the control group when it came to prehabilitation before cardiac surgery. Additionally, some studies reported significant improvements in muscle strength with NMES, while others did not find significant differences compared to controls.

Overall, NMES appears safe and feasible for pre- and post-cardiac surgery patients, potentially benefiting muscle strength to prevent ICU-AW However, its impact on functional capacity post-surgery seems limited, particularly compared to its effectiveness as prehabilitation before surgery. Muscle atrophy, a key component of ICU-AW, is influenced by various factors including age and inactivity-induced oxidative stress. NMES offers a safe alternative exercise method, potentially reducing ICU stays and improving muscle strength, particularly in the limbs, though its impact on overall functional capacity remains uncertain.

The effectiveness of NMES may be hindered by the short duration of ICU stays and limited sessions. Preoperative NMES as a form of prehabilitation shows promise in enhancing functional capacity and muscle strength, yet data on this approach are still scarce. Mechanistically, NMES activates muscle fibers directly, potentially inducing muscle growth and modulating catabolic processes. By potentially preventing ICU-AW and polyneuromyopathy, NMES could lead to better outcomes, shorter ICU stays, fewer complications, and improved exercise tolerance and mobility for cardiac surgery patients. Additionally, NMES may offer further benefits such as enhancing quality of life and improving hemodynamic and respiratory responses.

In addition to those mentioned in the paper, another limiting factor is that the review was only done on those with a body mass index (BMI) ranging from 19.3 to 29.1 kg/m^2. Obese patients, or patients with a BMI > 30.0 kg/m^2, face challenges in utilizing NMES due to their body composition[5]. The presence of excess subcutaneous fat can hinder NMES effectiveness by increasing the distance between the stimulating electrode and the axon terminals[5]. Additionally, body fat's poor conductivity means higher current intensities are needed to produce muscle contractions in obese individuals[5]. Furthermore, this heightened intensity may inadvertently activate nociceptors along with muscle fibers, which may lead to poorer outcomes[5]. Obese individuals, especially women, have also showed a lower tolerance to motor stimulation compared to non-obese individuals so this is another limiting factor to consider[6]. Furthermore, studies have shown that 4 months post-discharge from the intensive care unit, the 6MWT provided a moderately accurate prediction of long-term physical functional status after the ICU[7]. Therefore, to truly see the validity of NMES, we would need to compare the postoperative 6MWT distance with the participant's baseline 6MWT distance.

CONCLUSION

Be that as it may, NMES has a broad range of applications. There is mounting evidence that NMES can have a beneficial effect by increasing muscle strength, range of motion, and muscle function in patients with diseases such as cerebral palsy [8] or after surgeries such as total knee arthroplasties[9]. NMES has also been shown to be an excellent treatment choice in conditions such as oropharyngeal dysphagia or even stroke[10,11]. Studies have shown that NMES can have peripheral effects of boosting muscle contractility and resilience to fatigue, as well as increasing muscle mass and reducing swelling, effectively reversing muscle atrophy due to inactivity[11,12]. Certain NMES techniques may influence the central nervous system's regulation of movement, fostering motor relearning by facilitating synchronized activity between nerve endings [11]. Moreover, studies have shown that NMES-induced isometric contractions can lead to extensive brain activation patterns, similar to those observed during voluntary movements[13]. Despite discomfort being a significant constraint on NMES efficacy[13], these findings and others like it suggest the potential of NMES for developing customized stimulation protocols to target specific or impaired cerebral brain regions in future research endeavors. However, further research, particularly larger randomized controlled trials, is needed to fully understand NMES's benefits, optimize its application, and explore its potential in preventing ICU-AW after cardiac surgery.

FOOTNOTES

Author contributions: Kurian AL collaborated with the other author in conceptualization of the paper; She designed the structure of the paper, crafted the first draft, and was the primary editor; Lucke-Wold B also contributed to the conceptualization, assisted in organizing the project, provided senior oversight, and conducted quality review of the paper; He is also the co-corresponding author.

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LETTER TO THE EDITOR

Heart failure with preserved ejection fraction and the first law of thermodynamics

Robert M Peters

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Abstract

In heart failure with preserved ejection fraction, significant left ventricular diastolic abnormalities are present, despite a normal systolic ejection fraction. This article will consider whether this is consistent with the law of conservation of energy, also know as the first law of thermodynamics.

Key Words: Diastolic dysfunction; Heart failure with preserved ejection fraction; Thermodynamics

Core Tip: The term heart failure with preserved ejection fraction may be misleading, and not consistent with the first law of thermodynamics.

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TO THE EDITOR

Heart failure with preserved ejection fraction (HFpEF) has become an increasingly important entity over the last few years. However, issues regarding potential and kinetic energy have not been will studies in this syndrome. At end-diastole, the heart has a certain quantity of elastic potential energy, which is converted into kinetic energy during ventricular systole. The First Law states that energy cannot be created or destroyed, it can only be transferred from one form to another, such as potential to

kinetic energy, so in the heart, the quantity of potential energy in diastole must be equal to the quantity of kinetic energy in systole[1]. However, if the potential energy is diastole is reduced due to diastolic abnormalities/dysfunction, how can a normal quantity of kinetic energy appear in systole, and result in normal systolic function?

Potential energy

Elastic potential energy (J) is given by the equation: J = ½ KL [K represents the spring constant, in this case the left ventricular (LV) compliance, and L represents the degree of LV wall displacement in diastole]. Thus, when LV compliance and diastolic wall displacement are reduced in diastolic dysfunction, the potential energy in diastole is reduced.

Kinetic energy

Kinetic energy (K) is given by the equation: K = 1/2 MV (M represents the LV mass, And V represents the systolic wall motion velocity). Thus, with a normal LV systolic ejection fraction, it would be expected that the kinetic energy would be normal.

The problem then becomes, if both diastolic and systolic function are reduced, then a reduced quantity of potential energy would be converted to the same reduced quantity of kinetic energy. This is consistent with the first law. However, if the potential energy is reduced in diastole because of diastolic dysfunction, how can a normal quantity of kinetic energy be present in systole, as the first law tells us that energy cannot be created? Studies now show subtle abnormalities in LV function including systolic performance, even with a normal measured ejection fraction. These include Abnormal torsion, untwist, and longitudinal motion[2,5], impaired contractility and ventricular systolic stiffening[3], impaired systolic strain [4]. Also, abnormalities may be seen with exercise[5-7].

The term HFpEF may be misleading, in that is may imply that LV systolic function is completely normal when this is not the case. The first law of Thermodynamics appears to support this conclusion.

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LETTER TO THE EDITOR

Effectiveness and mechanisms of sodium-dependent glucose transporter 2 inhibitors in type 2 diabetes and heart failure patients

Yan-Xi Zhang, Hai-Sheng Hu, Bao-Qing Sun

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Abstract

We comment on an article by Grubić Rotkvić *et al* published in the recent issue of the *World Journal of Cardiology*. We specifically focused on possible factors affecting the therapeutic effectiveness of sodium-dependent glucose transporter inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM) and their impact on comorbidities. SGLT2i inhibits SGLT2 in the proximal tubules of the kidneys, lowering blood glucose levels by inhibiting glucose reabsorption by the kidneys and causing excess glucose to be excreted in the urine. Previous studies have demonstrated a role of SGLT2i in cardiovascular function in patients with diabetes who take metformin but still have poor glycemic control. In addition, SGLT2i has been shown to be effective in anti-apoptosis, weight loss, and cardiovascular protection. Accordingly, it is feasible to treat patients with T2DM with cardiovascular or renal diseases using SGLT2i.

Key Words: Sodium-dependent glucose transporter inhibitors; Type 2 diabetes mellitus; Heart failure; Treatment; Cardiovascular disease

Core Tip: Studies have revealed that type 2 diabetes mellitus (T2DM) patients often suffer from multiple comorbidities that can be effectively treated with sodium-dependent glucose transporter inhibitors (SGLT2i), which has been linked to their anti-apoptotic properties, promotion of weight loss, and cardiovascular protection. Correctly avoiding the risks of SGLT2i use and aggressive use of the drug in patients with T2DM and its complications to alleviate symptoms are feasible.

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TO THE EDITOR

Type 2 diabetes mellitus (T2DM), which is characterized by hyperglycemia, is a growing health problem worldwide[1,2]. More than 90% of people with diabetes have T2DM[3]. Heart failure (HF) is a complex chronic disease caused by impaired heart function[4]. HF increases the risk of cardiovascular, renal, and neurological complications by having T2DM[3]. As one of the most common cardiovascular complications, HF has a prevalence of 10% to 23% in patients with T2DM[5]. One study suggested that the pathophysiologic mechanism of HF in diabetes mellitus may be due to coexisting coronary artery disease, hypertension, or diabetes mellitus, which directly affects the structure and function of the heart [6,7]. Sodium-dependent glucose transporter inhibitors (SGLT2i), a new class of antidiabetic drugs, have recently been found to promote significant cardiovascular benefits in patients with diabetes or HF[8]. We have previously commented on the role of SGLT2i in cardiovascular function in patients with diabetes who take metformin but still have poor glycemic control[9]. This finding underscores the importance of SGLT2i as an effective treatment for patients with T2DM and asymptomatic HF.

INFLUENCING FACTORS AND POSSIBLE MECHANISMS OF SGLT2I TREATMENT EFFECTIVENESS

SGLT2i has many benefits in terms of treatment of patients with T2DM and combined HF. This has been explored by many researchers in order to identify why SGLT2i is effective. SGLT2 is the major transporter responsible for the reabsorption of glucose from the glomerular filtrate back into circulation. SGLT2i lower the renal reabsorption of filtered glucose and increase urinary glucose excretion, thereby lowering blood glucose levels[10]. Diabetes induces multiple molecular pathways in tissues. Evidence suggests that diabetes induces different forms of cellular damage; hyperglycemia-dependent oxidative stress leads to apoptosis, SGLT2i acts as an anti-apoptotic agent by lowering blood glucose levels, and inhibition of oxidative stress in diabetes ameliorates apoptosis[11]. Brown *et al*[12] suggested that obesity plays a key role in the development and progression of T2DM, and that the pathophysiology of T2DM is mediated by ectopic fat deposition. Therefore, weight loss has clear health benefits in patients with T2DM. Vallon *et al*[13] suggested that the mechanism by which SGLT2i reduces body weight is initially due to diuretic effects, whereas subsequently, this is due to an increase in lipolysis and fatty acid oxidation by shifting the substrate utilized from carbohydrates to lipids, resulting in a reduction in body fat, including visceral and subcutaneous fat. Multiple randomized trials have shown that SGLT2i effectively improves glycemic control in patients with T2DM, accompanied by a higher incidence of glycemic decline and weight loss. Research by Strojek *et al*[14] suggested that a 5.00 mg SGLT2i group lost 0.84 kg more than a placebo group, and this result was even more significant in a 10 mg SGLT2i group. Meanwhile, fasting blood glucose values were significantly decreased in a dapagliflozin-administered group, with a decrease of 0.82 mmol/L in a 2.50 mg (-0.93 mmol/L) group compared to a placebo group (-0.11 mmol/L), a result that was even more pronounced with an increased dosage of dapagliflozin[14]. Another randomized trial showed a mean total weight reduction of 1.61 kg in a 10.00 mg dapagliflozin group, compared with an increase of 0.43 kg in a placebo group[15]. A meta-analysis suggested that SGLT2i significantly reduces body weight and body mass index in patients with T2DM, with a mean difference in body weight of -2.73 kg and -1.13 kg/m^2[16]. In a study conducted in Japan, SGLT2i improved glycaemic control and reduced body weight in older adults with T2DM, resulting in a change in glycated hemoglobin A1C of -0.57% without affecting subjects' muscle mass[17].

In terms of cardiovascular protection, one study showed that SGLT2i reduced cardiac preload and afterload through osmotic diuresis[18]. This study concluded that SGLT2i-induced osmotic diuresis led to greater electrolyte-free water clearance, thereby relieving congestion and reducing cardiac preload. Osmotic diuresis lowers blood pressure, increases urinary sodium excretion, improves cardiovascular function, and reduces cardiac afterload. Na/H exchange (NHE) activity is low in normal healthy myocardium and high in HF myocardium, and a recent study found that empagliflozin could protect the heart in HF by mitigating cardiac hypertrophy through the inhibition of RSK-NHE1-mediated pathways [19]. Therefore, SGLT2i may be effective in the treatment of patients with T2DM complicated by HF.

TEARTMENT OF T2DM WITH CARDIOVASCULAR OR RENAL DISEASE WITH SGLT2i IS FEASIBLE

The use of SGLT2i is feasible for treating patients with T2DM because of its multiple protective mechanisms. This study showed a reduction in afterload in patients with T2DM after the use of SGLT2i[9]. Treatment with SGLT2i leads to better prognosis in T2DM patients with asymptomatic HF. In addition, SGLT2i has shown significant cardiorenal benefits in many studies. A meta-analysis suggested that the treatment of T2DM patients with SGLT2i results in significant reductions in systolic and diastolic blood pressures (by approximately 4.3 mmHg and 2.3 mmHg, respectively)[20]. A study based on data from the Asia Pacific, Middle East, and North America suggests that SGLT2i significantly reduces the risk of All-Cause Death, HF, myocardial infarction, and stroke[21]. A 2019 study showed a 0.9% reduction in cardiovascular mortality or hospitalization for HF in a SGLT2i-administered group compared to a placebo group[22]. Kluger *et al*[23] suggests that SGLT2i reduces the rate per 1000 patient-years of primary composite cardiovascular endpoints in patients by 6.5 percent compared with placebo (37.4 *vs* 43.9, respectively). A randomized controlled trial suggested that the relative risk of incident or worsening nephropathy was significantly reduced by 39% in a SGLT2i group compared to a placebo group[24]. Forbes *et al*[25] suggested that SGLT2i reduces the risk of renal failure events by 46% compared with other glucose-lowering substances. Kluger *et al*[23] also suggested that the primary composite renal endpoint occurred in 11.1% of a SGLT2i group *vs* 15.4% in a placebo group (P = 0.00001), doubling of serum creatinine from baseline (sustained for at least 30 days), end stage renal disease [dialysis, renal transplantation, or sustained estimated glomerular filtration rate (eGFR) < 15 mL/minute/1.73 m^2], or renal/cardiovascular death[23]. The effects of SGLT2i can be extended to patients with HF or chronic kidney disease (CKD) without T2DM[26].

While SGLT2i has significant benefits in treating diabetes and related cardiovascular and renal diseases, its use has certain safety concerns. The adverse effects of SGLT2i include genital infections [incidence rate ratio (IRR): 3.50, 95% confidence interval (95%CI): 3.09-3.95], hypotension, diabetic ketoacidosis (IRR: 2.59, 95%CI: 1.57-4.27), an increased risk of lower limb amputation, and an elevated risk of fractures[5,27-29]. Although the incidence of these adverse events is generally low, clinicians should conduct individualized assessments based on the health status of each patient. Therefore, while actively recommending the use of SGLT2i in patients, there is still a need to further evaluate and analyze the risks and side effects of using SGLT2i. Additionally, the use of SGLT2 inhibitors is contraindicated in some patients. For instance, SGLT2i are contraindicated in patients who are allergic to them, canagliflozin and dapagliflozin are contraindicated in patients undergoing dialysis, while all types of SGLT2 inhibitors should be avoided in patients with an eGFR < 30 mL/minute/1.73 m^2[30,31].

Moreover, due to the diversity of patients with T2DM, individual differences in age, complications, and lifestyle should also be considered. Therefore, when using SGLT2i, personalized treatment plans should also be considered. A 2023 study reported similar results for treatment efficacy and safety in older and younger patients treated with SGLT2i[32]. In addition to pharmacological interventions, lifestyle modifications tailored to a patient's individual circumstances, such as dietary adjustments, regular physical activity, and smoking cessation, are crucial for optimizing treatment outcomes and prognoses[33]. These changes not only enhance the efficacy of SGLT2i, but also contribute to better overall health management in patients with T2DM. Personalized plans that include dietary improvements and appropriate exercise can help manage weight, improve cardiovascular health, and support the renal benefits of SGLT2 inhibitors. However, another study revealed that the incremental cost-effectiveness ratio for the addition of SGLT2i therapy to standard-of-care therapy for patients with HFpEF was $141200 per quality-adjusted life-year gain compared to standard-of-care therapy [34]. Therefore, SGLT2i is not applicable for all T2DM patients in terms of economic costs. However, the ability to reduce clinical events and delay disease progression may result in cost savings. In a 2023 economic cost projection study, compared to using sulphonylureas or dipeptidyl peptidase-4 inhibitors as a second-line add-on therapy, SGLT2 inhibitors were shown to achieve cost savings more rapidly for patients with high cardiovascular risk, atherosclerotic cardiovascular disease, comorbid HF, and comorbid CKD (9, 10, 17, 20 years *vs* 14, 16, 23, 23 years)[35]. Therefore, it is necessary to reduce the cost of SGLT2i treatment and alleviate patient difficulties in using SGLT2i treatment; however, this requires further evaluation through real-world research.

CONCLUSION

In general, T2DM is likely to have HF complications, and the use of SGLT2i can effectively treat T2DM patients with asymptomatic HF, which may be related to inhibition of apoptosis or the cardiovascular protective effects of SGLT2i. Meanwhile, SGLT2i can also treat T2DM patients with other comorbidities, which is promising, but more related studies are needed to validate it.

FOOTNOTES

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LETTER TO THE EDITOR

Bioresorbable stent unloading during percutaneous coronary intervention: Early detection and management

Nabil Eid, Mohamed Abdel Wahab, Amardev Singh Thanu

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Abstract

In this letter, we comment on a recent case report by Sun *et al* in the *World Journal of Cardiology*. The report describes the successful management of a rare complication: The unloading or detachment of a bioresorbable stent (BRS) during percutaneous coronary intervention (PCI) in a male patient. The unloading of BRS was detected *via* angiography and intravascular ultrasound (IVUS) imaging of the left coronary artery and left anterior descending artery. Although this case is interesting, the authors' report lacked crucial details. Specifically, insufficient information about the type of BRS used, potential causes of BRS unloading, or whether optical coherence tomography (OCT) imaging for coronary arteries was performed before, during, or after PCI. The OCT imaging of coronary arteries before PCI can potentially prevent BRS unloading due to its higher resolution compared to IVUS. In addition, despite detecting myocardial bridging during the PCI, the authors did not provide any details regarding this variation. Here we discuss the various types of BRS, the importance of OCT in PCI, and the clinical relevance of myocardial bridging.

Key Words: Coronary artery diseases; Percutaneous coronary intervention; Optical coherence tomography; Bioresorbable/Biodegradable stents; Stent unloading/detachment; Myocardial bridge; Intravascular ultrasound; Coronary angiography

Core Tip: In a recently published case report in the *World Journal of Cardiology*, Sun *et al* reported successful management of an early and rare complication of percutaneous coronary intervention (PCI) in a male patient. This complication was the unloading or detachment of bioresorbable stent (BRS) during PCI, which was detected during PCI based on angiography and intravascular ultrasound imaging of the left coronary artery and left anterior descending artery. However, despite the rarity of this case, information regarding the type of BRS, possible causes of BRS unloading, use of optical coherence tomography (OCT) imaging for coronary arteries, and the importance of myocardial bridge during PCI were not discussed in the article. Here we shed light on the several types of BRS, the importance of OCT, and the clinical relevance of myocardial bridging.

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TO THE EDITOR

Percutaneous coronary intervention (PCI) with stent implantation is a widely accepted treatment for patients with coronary artery disease. However, the use of permanent metallic stents has been associated with various complications, including in-stent restenosis, late thrombosis, artery injury, and local chronic inflammation. To address these concerns, biodegradable or bioresorbable stents (BRSs) have emerged as a promising alternative, offering the potential for improved patient outcomes[1,2]. Compared to drug-eluting stent (DES), BRS provides temporary mechanical support until vascular remodeling and functional recovery, followed by gradual degradation, contributing to the restoration of vascular systolic function and reduces the risk of late stent thrombosis[3,4].

A recent study by Sun *et al*[5] reported successful detection and early treatment of a rare complication of PCI in a male patient. This complication was related to the unloading or detachment of BRS during PCI, which was detected during PCI based on angiography and intravascular ultrasound (IVUS) imaging of the left coronary artery and left anterior descending artery (LAD). However, despite the rarity of this case, the information provided regarding the type of BRS used during the PCI was insufficient. Several types of BRS have recently been reported, including polymer- and magnesium-based stents[1], which are important for successful loading during PCI.

Sun *et al*[5] linked the unloading of DES during PCI to calcification, angulation, and distortion of the coronary artery, in addition to device-related factors and technical operation factors, such as inadequate pretreatment. However, the authors failed to elaborate on the specific factors leading to the unloading of BRS, leaving out critical data about vessel wall pathology, anatomical vitiations such as angulation, and the technique used for intervention. Importantly, these potential factors contributing to DES or BRS detachment during PCI should be assessed using optical coherence tomography (OCT) imaging for coronary arteries[6,7]. This is based on the advantage of OCT over IVUS examination for superior delineation of calcified plaques, enabling the quantification of calcium arc and thickness[8]. In addition, OCT enables precise measurements of vessel size and lesion length, facilitating the selection of appropriate coronary stents[9].

It is crucial that authors must provide the exact size of the lesion site to be stented, as measured by IVUS/OCT prior to stent preparation so that a precisely sized BRS can be implanted. The preparation must be adequate along the entire length of the disease area; accordingly, stent expansion would be appropriate to prevent stent embolization and detachment. Even after adequate lesion preparation and stent deployment with optimum pressure, the proper deployment of the scaffold and its position to the vessel wall must be confirmed through imaging. Additionally, during removal of the deflated balloon after the scaffold is deployed, the contrast in the balloon should be properly evaluated to avoid unnecessary pulling or pushing of the stent.

Sun *et al*[5] in their discussion section suggest that the thicker lateral beam of BRS compared to DES necessitates adequate pretreatment before BRS implantation, and that PSP guarantees successful implantation and reduces poor BRS expansion. The authors fail to provide the full form of the terms DES and PSP, which should be done at first mention. The authors also found myocardial bridging during PCI, but did not touch on the finding and its impact on PCI. Myocardial bridging is a variation of the left coronary artery where a segment of the epicardial coronary artery or LAD is intramyocardial, instead of running on surface[10]. This may impact BRS loading during PCI, resulting in complications. Interestingly, new types of BRS have been recently developed, such as bioresorbable electronic stents integrated with biosensors[1].

CONCLUSIONS

PCI with stent implantation is a widely accepted treatment for patients with coronary artery disease. Compared to DES and metallic stents, BRS provide temporary mechanical support until vascular remodeling and functional recovery, followed by gradual degradation, contributing to the restoration of vascular systolic function and reduction of the risk of late stent thrombosis. Detachment or unloading of bioresorbable scaffolds during PCI is a rare complication that can be detected by angiography and IVUS imaging of the coronary artery. The successful loading of BRS and management of arising complications is a challenge in coronary intervention. The type of BRS, vessel factors, and techniques used to load

the BRS can impact the success of treatment and predict the potential for complications. OCT imaging of the coronary arteries may help successful BRS loading by identifying vessel variations, calcification, and myocardial bridging.

FOOTNOTES

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